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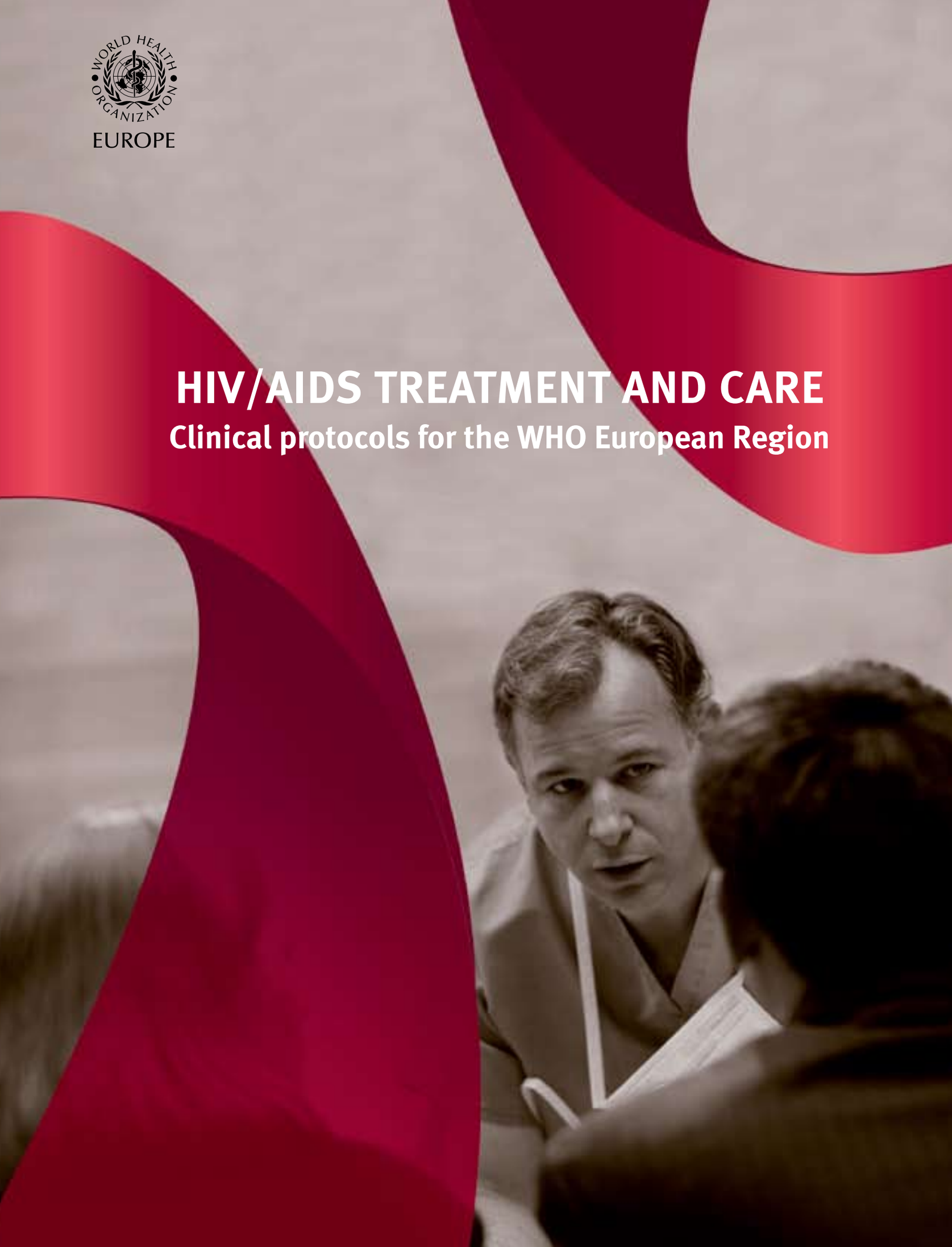
HIV/AIDS TREATMENT AND CARE

Clinical protocols for the WHO European Region



HIV/AIDS TREATMENT AND CARE

CLINICAL PROTOCOLS FOR THE WHO EUROPEAN REGION

EDITED BY:
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ABSTRACT
These 13 treatment and care protocols are the cornerstone of the strategic actions that WHO has taken on as part of its contribution to universal access to HIV/AIDS prevention, treatment, care and support services as agreed on by the member states of the United Nations. They replace *HIV/AIDS Treatment and Care: WHO protocols for CIS countries* (2004) and have been specifically developed for the entire WHO European Region. Together, the 13 protocols represent a comprehensive and evidence-based tool that offers clear and specific advice on diagnosing and managing a wide range of HIV/AIDS health related issues for adults, adolescents and children, including antiretroviral treatment, the management of opportunistic infections, tuberculosis, hepatitis, injecting drug use, sexual and reproductive health, the prevention of mother-to-child HIV transmission, immunizations, palliative care and post-exposure prophylaxis. As treatment and care for people living with HIV is a continuously evolving field, these protocols may be updated in the future; therefore the regional office encourages users to check for revisions at www.euro.who.int/aids.

KEYWORDS
CLINICAL PROTOCOLS
AIDS-RELATED OPPORTUNISTIC INFECTIONS
DISEASE TRANSMISSION – prevention and control
HEPATITIS A - prevention and control
HEPATITIS B - prevention and control
HEPATITIS C - prevention and control
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Contents

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Abbreviations

3TC	lamivudine
Ab	antibody
ABC	abacavir
ADF	adefovir
AEFI	adverse event following immunization
AFB	acid-fast bacilli
AFP	alpha-fetoprotein
AG1549	capravirin
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	antenatal care
APV	amprenavir
ARDS	acquired respiratory distress syndrome
ART	antiretroviral treatment
ARV	antiretroviral
ASC H	atypical squamous cells, cannot exclude HSIL
ASCUS	atypical squamous cells of undetermined significance
ASI	Addiction Severity Index
AST	aspartate aminotransferase
ATS	amphetamine-type stimulant
ATV	atazanavir
ATV/r	tazanavir/ritonavir
AUC	area under concentration-time curve
BAL	bronchoalveolar lavage
BCG	bacille Calmette-Guérin vaccine
BID	twice daily
BPAD	bipolar affective disorder
BPRS	Brief Psychiatric Rating Scale
BUN	blood urea nitrogen
BV	bacterial vaginosis
CAT	computerized axial tomography
CBC	complete blood count
CBT	cognitive behavioural therapy
CD4	cell cluster of differentiation antigen 4 cell (a subgroup of T lymphocytes)
CHAP	children with HIV antibody prophylaxis (a clinical trial)
CHOP	cyclophosphamide, hydroxydaunomycin (doxorubicin), and prednisolone (a chemotherapy regimen)
CI	confidence interval
CIC	combined injectable contraceptive
CIN	cervical intraepithelial neoplasia
CK	creatine kinase
Cmax	maximum blood concentration
Cmin	minimum blood concentration
CMV	cytomegalovirus
CNS	central nervous system
COC	combined oral contraceptive
CPK	creatinine phosphokinase
CrCl	creatinine clearance

CRP	C-reactive protein
CS	caesarean section
CSF	cerebrospinal fluid
CT	computerized axial tomography
Cu-IUD	copper-releasing IUD
CXR	chest X-ray
CYP	cytochrome P450
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DMPA	depot medroxyprogesterone acetate
DNA	deoxyribonucleic acid
DOT	directly observed treatment
DRV	darunavir
DSP	distal symmetric polyneuropathy
DT	diphtheria and tetanus toxoids (for paediatric use)
DTs	delirium tremens
DTaP	diphtheria, tetanus and acellular pertussis
DTP	diphtheria, tetanus and pertussis
DVT	deep venous thrombosis
E	ethambutol
EAP	expanded access programme
EASL	European Association for the Study of the Liver
EBV	Epstein-Barr virus
ECG	electrocardiogram
EE	ethinylestradiol
EFV	efavirenz
EIA	enzyme immunoassay
ELISA	enzyme-linked immunosorbent assay
ENF	enfurvitide
EPOCH	etoposide, prednisolone, Onconvin (vincristine), cyclophosphamide and hydroxorubicin (doxorubicin) (a chemotherapy regimen)
EPTB	extrapulmonary tuberculosis
ESLD	end-stage liver disease
EVR	early virological response
FDC	fixed-dose combination
FIGO	Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynecology and Obstetrics)
FPV	fosamprenavir
FPV/r	fosamprenavir/ritonavir
FSH	follicle-stimulating hormone
FTC	emtricitabine
GAD	generalized anxiety disorder
GC	gonococci
GE	gastroenteritis
GGT	gamma glutamyl transpeptidase
GHB	gamma-hydroxybutyrate
GI	gastrointestinal
GII	gastrointestinal infection
H	isoniazid
HAART	highly active antiretroviral treatment

HAV	hepatitis A virus
Hb	haemoglobin
HBcAb	hepatitis B core antibody
HBeAb	hepatitis B e antibody
HBeAg	hepatitis B e antigen
HBIg	hepatitis B immunoglobulin
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HCW	health care worker
HDL	high density lipoprotein
HDV	hepatitis delta virus
HHV6	human herpes virus 6
HHV8	human herpes virus 8
HiB	Haemophilus influenzae type b
HIV	human immunodeficiency virus
HNIg	human normal immunoglobulin
HPV	human papillomavirus
HR	harm reduction
HRIg	human rabies immunoglobulin
HSIL	high-grade squamous intraepithelial lesion
HSV	herpes simplex virus
HSV	1/2 herpes simplex virus 1 and 2
IC50	50% inhibitory concentration
ICD	immune complex-dissociated
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
IDU	injecting drug user
IDV	indinavir
IFN	interferon
Ig	immunoglobulin
IgG	immunoglobulin G
IgIV	intravenous immunoglobulin
IL-2	interleukine-2
IM	intramuscularly, intramuscular
INH	isoniazid
INR	international normalized ratio
IPV	inactivated poliovirus vaccine
IRIS	immune reconstitution inflammatory syndrome
IUD	intrauterine device
IU	international unit
IV	intravenous, intravenously
KOH	potassium hydroxide
KS	Kaposi sarcoma
KSHV	Kaposi sarcoma herpes virus
LAAM	levo-alpha acetyl methadol
LAM	lactational amenorrhea
LDH	lactate dehydrogenase
LEEP	loop electrosurgical excision procedure

LFT	liver function test
LGE	lineal gingival erythema
LGV	lymphogranuloma venereum
LH	luteinizing hormone
LIP	lymphocytic interstitial pneumonitis
LKM1	anti-liver-kidney microsome antibody
LNG-IUD	levonorgestrel-releasing IUD
LNG	levonorgestrel
LPV	lopinavir
LPV/r	lopinavir/ritonavir
LPV/r + RTV	LPV/r with extra dose of ritonavir
LSD	lysergic acid diethylmide
LSIL	low-grade squamous intraepithelial lesion
M	measles
MAC	Mycobacterium avium complex
MADRS	Montgomery Asberg Depression Rating Scale
MAI	Mycobacterium avium-intracellulare
MAO	monoamine oxidase
MCV	measles-containing vaccine
MDMA	3, 4 methylenedioxymethamphetamine
MDR-TB	multidrug-resistant tuberculosis
MEMS	Medication Event Monitoring System
MMR	measles, mumps and rubella
MOTT	mycobacteria other than tubercle bacilli (atypical mycobacteria)
MR	measles and rubella
MRI	magnetic resonance imaging
MSM	men who have sex with men
MTCT	mother-to-child transmission
MU	million units
NAM	nucleoside analogue mutation
NAS	neonatal abstinence syndrome
NAT	nucleic acid testing
NE	norethindrone
NET-EN	norethisterone-enantate
NFV	nelfinavir
NGO	nongovernmental organization
NGU	non-gonococcal urethritis
NHL	non-Hodgkin lymphoma
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside or nucleotide reverse transcriptase inhibitor
NSAID	non-steroidal anti-inflammatory drug
NVP	nevirapine
OD	once daily
OI	opportunistic infection
OLT	orthotopic liver transplantation
OPC	oropharyngeal candidiasis
OPV	oral poliovirus vaccine
ORS	oral rehydration solution
OST	opioid substitution therapy
oz	ounce

PCP	Pneumocystis jirovecii pneumonia (formerly Pneumocystis carinii pneumonia)
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PE	pulmonary embolism
PEG-IFN	pegylated interferon
PENTA	Paediatric European Network for Treatment of AIDS
PEP	post-exposure prophylaxis
PGL	persistent generalized lymphadenopathy
PID	pelvic inflammatory disease
PI	protease inhibitor
PIT	pill identification test
PLCS	pre-labour caesarean section
PLHIV	people living with HIV
PML	progressive multifocal leukoencephalopathy
PMTCT	prevention of mother-to-child transmission (of HIV)
PO	per os (orally)
POC	progestogen-only contraceptive
POP	progestogen-only pill
PPD	purified protein derivative (tuberculin skin test reagent)
PPE	personal protective equipment
PPI	proton pump inhibitor
PPV	pneumococcal polysaccharide vaccine
PTB	pulmonary tuberculosis
Q	every (e.g. Q8H = every 8 hours)
QID	four times daily
QOD	every other day
QW	once weekly
R	rifampicin
RBV	ribavirin
RCT	randomized clinical trial
RDA	recommended daily allowance
RH	reproductive health
RNA	ribonucleic acid
RPR	rapid plasma reagin
RTI	reproductive tract infection
RTV	ritonavir
S&RH	sexual and reproductive health
	S streptomycin
SMZ	sulfamethoxazole
SO2	oxygen saturation
SQV	saquinavir
SQV/r	saquinavir/ritonavir
SSRI	selective serotonin reuptake inhibitor
STI	sexually transmitted infection
SVR	sustained virological response
SW	sex worker
TAM	thymidine analogue mutation
TB	tuberculosis
Td	tetanus and diphtheria toxoids (for adult use)
TDF	tenofovir

TDM	therapeutic drug monitoring
TE	Toxoplasma gondii encephalitis
TENS	transcutaneous electrical nerve stimulation
THC	tetrahydrocannabinol
TID	three times daily
TIg	tetanus immunoglobulin
TIW	three times weekly
TLC	total lymphocyte count
TMA	transcription-mediated amplification
Tmax	time of peak concentration
TMC125	etravirine
TMP/SMX	trimethoprim-sulfamethoxazole (co-trimoxazole)
TPT	tuberculosis preventive treatment
TPV	tipranavir
TSH	thyroid-stimulating hormone
TT	tetanus toxoid
Ty21a	alive, attenuated typhoid strain
UGT	uridine 5' diphosphate glucuronosyltransferase
ULN	upper limit of normal
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Session
UNODC	United Nations Office on Drugs and Crime
UNOS	United Network for Organ Sharing
VCT	voluntary counselling and testing
VDRL	venereal disease research laboratory test
VIA	visual inspection of the cervix
VL	viral load
VLDL	very low density lipoprotein
VVC	vulvovaginal candidiasis
VZIg	varicella zoster immunoglobulin
VZV	varicella zoster virus
WHO	World Health Organization
Z	pyrazinamide
ZDV	zidovudine (also known as azidothymidine (AZT))

Foreword

HIV/AIDS is a serious public health issue in the WHO European Region, where more than 2.5 million people are estimated to be living with HIV. The epidemic continues to spread, and in 2006 the Region recorded its second highest number of newly reported cases. Fortunately, with the introduction of highly active antiretroviral treatment (HAART) more than 10 years ago, the prognosis for most infected people in the Region is no longer death but chronic disease management.

As a result, when treatment and other health care issues are addressed judiciously, people with HIV can expect to live to old age. Universal access to HIV treatment and care, where available, has not only provided people living with HIV an almost normal life expectancy and comparable quality of life; it has also significantly reduced the risk of further transmission.

High-quality HIV treatment and care must therefore address the issue of long-term care, as well as the complex interaction of various conditions and diseases that can simultaneously affect a person with HIV. The tremendous challenge that European health providers face is integration – integrating HIV treatment and care with mental health and substance use services, with treatment and care of major coinfections such as hepatitis and tuberculosis, with prevention and treatment of sexually transmitted infections, with other reproductive health services and with palliative care. These treatment and care protocols can help by providing an evidence-based package of interventions for chronic case management that is effective and patient-centred.

The United Nations has charged WHO with leading the health sector response to the HIV/AIDS epidemic, particularly in promoting effective treatment and care. A major part of this role has been helping countries where treatment was just a dream a few years ago to scale up access to antiretroviral therapy. HAART is now available in every state of the European Region; the task at hand is to ensure that the best medicines in the correct dosages reach everyone in need.

These 13 protocols form the cornerstone of strategic efforts by the WHO Regional Office for Europe to achieve universal access to HIV/AIDS prevention, treatment, care and support services. They replace *HIV/AIDS treatment and care: WHO protocols for CIS countries* (2004) and have been specifically developed for the entire European Region, based on current knowledge and the skills, technical capacity and health infrastructure found in the Region.

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WHO Regional Office for Europe

Introduction

HIV is a chronic infection with no known cure, and people living with HIV have to be followed medically for the rest of their lives. WHO promotes a comprehensive approach to the management of people living with HIV that addresses the individual's full range of health-related needs, many of which may change during his or her lifetime. The underlying principle may be described as "treating the individual and not the disease".

The core component of this approach is the provision of antiretroviral treatment (ART). The optimal form of ART, known as highly active ART (HAART), combines three or more drugs, and it increases the length and quality of life for infected individuals while reducing the onward transmission of the virus. Evidence over the past decade from western Europe and other industrialized countries shows that what was once an almost universally fatal disease has become a manageable chronic condition, and that the medicines available today can ensure people living with HIV a life expectancy comparable to that of uninfected people.

These treatment and care protocols for the WHO European Region are part of a global effort to achieve universal access to HIV prevention, treatment, care and support services by 2010, an effort led by the United Nations. The protocols provide normative guidance and technical tools that should strengthen health care providers' ability to scale up HIV treatment and care services.

These protocols have been specifically developed for clinicians and health care workers involved in diagnosing, treating, caring for and offering other health-related support and services to people living with HIV on a daily basis. They encourage collaboration and cooperation among health programmes.

Together, the 13 protocols provide a comprehensive evidence-based tool offering clear, specific advice on diagnosing and managing a wide range of HIV/AIDS health-related issues for adults, adolescents and children. Major topics include ART, the management of opportunistic infections, tuberculosis coinfection, hepatitis coinfection, injecting drug use, sexual and reproductive health, prevention of mother-to-child transmission, immunizations, palliative care and post-exposure prophylaxis.

At times, the protocols diverge from the normative documents that WHO headquarters has developed for resource-limited settings around the world. In particular, we have taken into account specific epidemiological features of the HIV epidemic in the European Region that merit special attention – such as the significant role of injecting drug use, which has created a need for clinical guidance in managing hepatitis and other complex comorbidities, and the substantial population requiring the provision of not only ART but also specific mental health and substance use interventions. The fact that hundreds of thousands people with HIV in this Region are living long, active, productive lives has also created a need for detailed guidance on how to ensure not only basic survival but also good quality of life. For example, one of the areas specifically addressed here is the sexual and reproductive health of people living with HIV, including reproduction and the ability to enjoy safe, fulfilling sexual lives.

The organization of health systems in the European Region, their capacities and their technological, institutional and human resources all differ from those of health systems in other WHO regions. These differences have dictated that we not only set minimum requirements for quality

HIV treatment and care in these protocols, but that we also guide providers in the rational use of the complex technology that is widely available in the European Region Member States.

We strongly believe that establishing standards that are optimal – and not merely minimal – is critical to an effective public health approach to HIV treatment and care. We have accordingly sought to incorporate the perspectives of people living with HIV and risk group members in developing these protocols, thereby enabling clinical providers to make rational choices that simultaneously ensure desirable population outcomes, such as reduced HIV-related morbidity and mortality, and tangible individual benefits.

Considering the well-being of both the entire treatment population and the infected individual is a fundamental ethical obligation for medical professionals. Principles of medical ethics formulated since 1945 underline the responsibility of every physician to advocate, advance and protect the individual interest of each patient. As a citizen, the medical service provider should consider the greater societal good, but as a medical professional, he or she is obliged to serve the best interests of the individual. Cost-containment efforts, cost–effectiveness concerns and resource limitations are sometimes directly opposed to the dictates of medical professional ethics. In these protocols, we have attempted to reconcile these two often-divergent sets of priorities.

As there is great diversity among the Member States in the European Region, we encourage individual ministries of health to adapt these protocols to meet their specific needs, or to use them as foundations for the development of their own national protocols. Finally, it should be remembered that HIV/AIDS treatment and care is a rapidly evolving field. We encourage users to check for protocol revisions at www.euro.who.int/aids, and to contribute to the further improvement of these protocols by providing us with feedback on their technical usefulness.

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EUROPE

1 Patient Evaluation and Antiretroviral Treatment for Adults and Adolescents

Clinical Protocol for the WHO European Region

Contents

I. Introduction

HIV/AIDS is chronic lifelong disease with no known cure, and therefore, people living with HIV (PLHIV) have to be followed medically for the rest of their lives *(1–3)*. The core component of treatment and care of PLHIV is provision of antiretroviral treatment (ART). Optimal ART increases the length and quality of life of HIV-infected patients, and reduces the onward transmission of the virus. WHO promotes a public health approach to ART *(4)*, which promotes the rational selection and sequencing of different drug classes into first and second-line regimens with salvage options; simplified and standardised clinical management; and standardised record keeping in order to preserve therapeutic options, minimize drug toxicity and side-effects, maximize adherence and to support the goals of ART.

The goals of ART are:
- clinical: prolongation of life and improvement of its quality;
- immunological: quantitative and qualitative immunological reconstitution, in order to prevent the onset of opportunistic infections;
- virological: maximum possible reduction of the viral load for the longest possible time, in order to halt the progression of disease and prevent and delay the development of drug resistance;
- epidemiological: reduction, ideally the prevention of onward HIV transmission *(5)*.

WHO has produced a series of guidelines to support ART delivery in national programmes and by treatment implementers, which are available on the WHO website http://www.who.int/hiv/universalaccess2010/en/index.html. Particular reference is made in this protocol to the guidelines and recommendations for clinical and immunological staging and to ART guidelines for ART in adolescents and adults.

Medical history, examination findings, exact history of ART, laboratory results, results of other medical procedures and social circumstances need to be documented for the entire treatment period, which may be years or even decades long. Such records are crucial for the individual patient as well as for retrospective analysis (for example, in endoscopic procedures, CT scanning, advanced microbiologic testing or viral load (VL) testing). For such purposes, an electronic record-keeping system is advisable, especially at the clinical level. Confidentiality of medical information should be ensured.

Optimal HIV-related treatment and care should be delivered by clinical teams. The core clinical team providing basic medical case-management of a patient should ideally consist of a physician (often an infectious disease specialist), a nurse and a social worker or a non-medical service provider. Each of the team members has distinctive roles in providing treatment and care, and their services should be complementary. A network of other specialists and self-help groups should be available in supporting PLHIV *(6)*.

II. Management of patients with HIV

Proper management of patients living with HIV is a comprehensive lifelong process focused on the patient's needs. It should include:
- initial HIV testing and confirmation of the result;
- appropriate counselling during the process of identifying HIV infection;
- clinical evaluation;
- patient counselling;
- monitoring patient health;
- initiating ART and its maintenance;
- prevention and treatment of opportunistic infections (OIs), other coinfections and comorbidities;
- psychological support;
- adherence support; and
- referrals to provide continuity of care.

Clinical evaluation of patients should include testing and counselling for health maintenance issues related to HIV as well as to other conditions that may interact with the management of HIV infection, especially potential interactions with ART.

1. Initial patient evaluation

The initial evaluation of a patient aims at determining the full status of his/her HIV infection, to develop a basis for further clinical management and for referral to non-medical services as appropriate.

Initial patient evaluation should include:
- confirmation of HIV infection status with potential time of infection established, if possible;
- a detailed personal, family and medical history;
- physical examination;
- laboratory and other examinations;
- specialist examinations, as appropriate; and
- clinical and immunological staging.

1.1. Personal, family and medical history

Patients newly diagnosed with HIV infection or patients who are transferred in, having had their long-term care and ART being initiated elsewhere, should provide a complete history before physical examination *(7)*. See Table 1.

Table 1.	Medical history information required at initial patient evaluation

General information:
- patient's name
- date of birth
- sex
- date of assessment

Testing information:
- date of first positive HIV test
- reason for being tested
- last HIV-negative test, if known

HIV exposure risk and transmission category (if known):
- injecting drug use
- sexual (heterosexual, homosexual, types of sexual contact: oral, vaginal, anal)
- blood or blood product transfusion, organ and tissue transplantation
- mother-to-child transmission
- occupational exposure (describe)
- unknown
- HIV status of sexual partner(s), if known
- risk factor of sexual partner(s), if known

Time and place (country) of infection most probable or known[a]

History of HIV treatment and care: (see Annex 1)
- time and place of previous treatment or HIV-related services, including treatment interruptions
- drug regimens
- side-effects
- adherence
- laboratory data (CD4 count, VL, electrolytes, liver function, renal function, full blood count, in chronological order for patients with longer infections (several years' duration) *(8)*)
- documented results of previous resistance tests (if performed)

HIV-related illnesses and conditions and HIV clinical staging:
- tuberculosis
- respiratory infections
- viral, other bacterial and fungal infections
- hepatitis C and B
- neoplasms
- other

Other illnesses and conditions:
- hospitalizations
- surgery
- mental health conditions (e.g. depression)
- kidney or liver diseases
- endocrinological disorders
- sexually transmitted infections (STIs)
- vaccinations
- allergies
- body changes
- current medications

Family medical history (diabetes, hypertension, skin disorders, malignancies, etc.)

Cardiovascular disease and disease risks (obesity, smoking, hypertension, etc.)

Exposure to tuberculosis (TB) (personal and household TB contacts)[b]

Current medications (including opioid substitution therapy (OST))

Substance use:
- illicit drug use (past and present)
- alcohol consumption

Reproductive and sexual health:
- contraceptive methods in female patients
- pregnancies (past, current, planned)
- sexual practices (oral, anal, vaginal)

Social history
- living situation (partners/spouses/family members, children, etc.)
- employment and occupation
- support networks (social and medical insurance, community groups, who knows of patient's HIV status, etc.)

[a] Useful for epidemiology, subtype of virus and possibly a drug resistance profile.
[b] For further evaluation on TB please refer to Protocol 4, *Management of tuberculosis and HIV coinfection*.

1.2. Physical examination

The physical examination should document presenting symptoms and signs and reproducible results so that other physicians can determine changes in status. A standardized history and examination questionnaire is preferable; see Table 2.

Table 2. Initial physical examination

General appearance: • height and weight • body morphology (lipodystrophy) • Karnowsky index or other standardized scale for general fitness
Vital signs: • blood pressure • temperature • pulse • respiratory rate
Lymph nodes
Skin (entire body): • in particular, assess for ◦ active or former herpes zoster ◦ liver disease ◦ Kaposi sarcoma ◦ seborrhoeic dermatitis ◦ injection sites in injecting drug users (IDUs) The documentation of skin disorders such as discoloured brown or dark patches is best made with photos; other possibilities include drawing the area of a patch on transparent foil, to be able to compare in future in examinations.
Oro-pharynx: • oral health and dental status • signs for: ◦ oral candidiasis ◦ oral hairy leukoplakia ◦ primary syphilis
Thorax and lungs: • signs (breathing, cough, dyspnoea) • form of thorax • control for risk of emphysema
Mamma examination (in female *and* male patients) to control for risk of carcinoma
Cardiac examination for baseline information when there may be higher risk for cardiovascular complications with ART *(9, 10)* or risk for endocarditis in IDUs
Abdominal examination (for baseline information for ART side-effects, especially in cases of chronic hepatitis, alcohol toxicity and cirrhosis): • consistency, size and shape of liver and spleen • bowel movement • tenderness • rigidity • nausea, vomiting, disphagia
Genital and anal region examination: • signs for: ◦ herpes simplex ◦ cytomegalovirus (CMV) ◦ syphilis ◦ Human papilloma virus (HPV), (condylomata acuminatae, anal carcinoma) *(11)*, other STIs ◦ erectile dysfunction
Legs (movement, mobility, lipodystrophy) to provide baseline information for ART side-effects
Neurological status (also signs of neuropathy)
Mental status
Eye and ear functions

1.3. Laboratory and other examinations

Table 3.	Laboratory testing

HIV-related testing:
- HIV serological testing (typically an enzyme-linked immunosorbent assay (ELISA) or rapid blood test), followed by confirmatory test (typically western blot) *(12)*
- CD4 cell count to determine the severity of immunodeficiency; in pregnant women CD4 *% (13, 14)*
- viral load testing by polymerase chain reaction (PCR), to determine level of viral replication[a]

Other infectious disease testing:
Routine testing:
- venereal disease research laboratory (VDRL) test for syphilis
- serological tests for hepatitis C and B viruses (HCV and HBV) – i.e. HCV antibodies and hepatitis B surface antigen (HBsAg)[b]
- toxoplasma immunoglobulin G (IgG) serological test and information about risk of infection if negative

If indicated:
- vaginal, penile or anal (as appropriate) swab for gonorrhoea and *Chlamydia trachomatis*
- *Cryptococcus* antigen titre when CD4 cell count is <200/mm^3 with clinical signs of cryptococcosis
- CMV antigenaemia (pp65 early antigen), when CD4 cell count is <100/mm^3.[c]

General laboratory testing:
- electrolytes (sodium, potassium)
- liver function (alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase)
- bilirubin
- renal function (blood urea nitrogen (BUN), creatinine)
- lactate dehydrogenase (LDH) (general turnover of cells in lymphomas, signs of pulmonary infections, myocardial infarction, muscle damage, etc.)
- quick (international normalized ratio (INR) test or prothrombine time)
- full blood count with differential and platelets
- pregnancy test before initiating ART

If available:
- fasting glucose
- cholesterol (high-density lipoprotein (HDL), very-low-density lipoprotein (VLDL))
- triglycerides
- lipase
- C-reactive protein (CRP)
- thyroid-stimulating hormone (TSH)

[a] Performance of tests by the same laboratory is preferable to rule out technical discrepancies.
[b] For further information on testing of hepatitis, please refer to Protocols 6 and 7, *Management of hepatitis C* and *HIV coinfection* and *Management of hepatitis B and HIV coinfection*.
[c] Very early detection of CMV infection is possible, and is a good marker for treatment response in CMV infection.

Table 4.	Other examinations

- tuberculin skin test for those with no TB symptoms or no known TB exposure[a]
- sputum-smear microscopy and chest X-ray if signs and symptoms of active TB are present[a]
- ECG – optional (might be useful as a baseline for comparison due to greater risk for cardiovascular disease with ART) *(15)*

[a] For further information please refer to Protocol 4, *Management of tuberculosis and HIV coinfection.*

Other examinations may be necessary, depending on individual comorbidities, for example, in HCV/HIV or HBV/HIV coinfection, abdominal ultrasound to assess lymph nodes, size and shape of liver and spleen; or in presence of clinical signs of gastrointestinal (GI) tract disease, endoscopy of the upper and lower GI tract. Endoscopic findings should be documented with photos.

Table 5.	Specialist consultations if required
• neurological examination (for peripheral polyneuropathy) • ophthalmological examination (useful to repeat every three months for CMV retinitis when CD4 count is <100/mm^3) • gynaecological examination including a Pap smear every six months (for human papillomavirus-mediated (HPV-mediated) carcinoma)[a] • other specialist consultations as needed	

[a] There is no hard evidence to recommend routine rectal PAP smears at the time of writing this protocol. For more information please refer to Protocol 9, *Support for sexual and reproductive health of people living with HIV.*

2. Counselling on issues related to living with HIV

Patient counselling is an essential component of patient management strategy and patient-health care provider relationships. It should start with the assessment and discussion of the patient's social conditions, which may be predictors of cooperation during treatment. These include:

- partnership status and quality
- employment status, type of work and conditions
- people who are informed and should be informed of the HIV status
- people with whom health care workers can discuss the patient's health-related matters
- familial relationships
- availability of safe refrigerated storage for medications
- lifestyle factors that might interfere with treatment *(16–18)*.

Health care providers who counsel PLHIV should ensure that certain information is discussed and understood by the patient.

- Risk reduction (safe sex, injecting practices, etc.) must be explained, including the danger that unprotected sex with HIV-positive partners could lead to super-infection with another HIV strain and possible resistance to antiretrovirals (ARVs) *(19)*.
- Importance of disclosure to sexual partner(s), friends and family members for a few reasons:
  - obtaining psychological and treatment support
  - prevention of HIV transmission
  - testing of sexual partner(s).
- Availability of treatment, its benefits, preparedness to it, long-term consequences and importance of adherence should be discussed with every patient.
- Patients need to be informed about signs of possible OIs, and encouraged to have further evaluation. For further information, see Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS.*
- The importance of stopping illicit drug use needs to be discussed with users. If a patient is unable or unwilling to stop, the merits of harm-reduction measures should be discussed, including the merits of reducing drug use; not injecting; not sharing needles, syringes or other injecting paraphernalia; and drug dependence therapy (such as OST). For more information, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*
- Prevention of other infections should be discussed. Please refer to section 3 below.
- Based on the assessment of social conditions, healthy daily habits – sleep, nutrition, exercise – should be encouraged.
- Patients about to initiate ART should be counselled on:
  - adherence (see section II.4.3 below)
  - possible antiretroviral (ARV) toxicity (see section II.5.5 below)

  - drug interactions (see section II.5.6 below)
  - reliable contraception when the ARV regimen will contain efavirenz (EFV) (for further information refer to Protocol 9, *Support for sexual and reproductive health in people living with HIV)*
  - patient understanding of treatment process and related to it issues should be ensured by the health care provider.
- Patients should also be informed about legal responsibilities (if applicable) and their rights and be referred to other appropriate services.
- Patients should be informed of issues related to immunization (including travel) and occupational risks.

3. Prevention of opportunistic and other infections

- Prevention of active tuberculosis is among the first priorities. For more information on management of TB/HIV coinfected patients and prevention of active TB please see Protocol 4, *Management of tuberculosis and HIV coinfection.*
- As HBV/HIV and HCV/HIV coinfections are common and present further medical difficulties, their prevention must be emphasized. It is equally important to advise on reducing the risk of liver-related harm and preventing mother-to-child transmission (MTCT).[2]
- PLHIV should be immunized against hepatitis B and A and influenza. For further information, please refer to Protocol 12, *Immunization of people living with HIV and people at risk for HIV.*
- Every patient with a CD4 cell count less than 200 cells/mm^3 should be given prophylaxis against certain opportunistic infections, in particular *Pneumocystis jirovecii* pneumonia (PCP) and other infections. Co-trimoxazole should be given until the CD4 cell count is >200/ mm^3 for more than three months after initiating ART. For more information please refer to Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS.*
- In case of negative toxoplasma serology, the transmission route and ways to prevent infection should be explained (including risks associated with pets). For futher information see Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS.*

4. Antiretroviral treatment

4.1. Initiation of ART

The best point at which to start ART is under discussion *(20)*. A review of several cohort studies and guidelines shows a widespread view that clinical staging (stage 3 or 4) and CD4 counts are the best primary markers and viral load the secondary marker for this decision *(21–31)*. Prior to starting ART, support to ensure adherence should be initiated; see section II.4.3 below.

[2] For further information see Protocol 6, *Management of hepatitis C and HIV coinfection*, Protocol 7, *Management of hepatitis B and HIV coinfection*, Protocol 8, *Prevention of hepatitis A, B, C and other hepatotoxic factors in people living with HIV*, and Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants.*

4.1.1. Clinical and immunological considerations

WHO recommends initiation of ART using clinical and immunological criteria as per Table 6.

Table 6. Recommendations for initiating ART in PLHIV

WHO clinical stage[a]	CD4 cell count	Recommendation
1	<200/mm^3	Treat
	200–350/mm^3	Consider treatment[b]
2	<200/mm^3	Treat
	200–350/mm^3	Consider treatment[b]
3	200–350/mm^3	Treat
4	Regardless of CD4 count	Treat

[a] See Annex 2 for a description of the clinical stages.
[b] When the CD4 count is around 350 cells/mm^3, begin discussions with the patient on the advancing need for initiating ART and on preparations for starting.

The decision to initiate ART should be based on two different CD4 counts, ideally at least 7 days apart because of variability in the CD4 count itself and to rule out laboratory mistakes and other variances (for example, concurrent illnesses). In case of a concurrent acute illness, CD4 cell count should be repeated only after the illness is cured. Therapy should not however be delayed if a patient is unwell or if the second count cannot readily be performed. If the CD4 count is not available, the decision to initiate ART can still be made on clinical grounds alone – with clinical stage 3 or 4 illness.

Baseline CD4 count at the onset of ART (ideally determined when the patient is free from any active major opportunistic infection) is a critical value in determining prognosis, response to ART and for monitoring the subsequent immunological response to ART.

4.1.2. Considerations for viral load

Viral load is associated with loss of CD4 cells. Though on its own it is not a marker for initiating ART, in case of viral load >100 000 copies/ml (this can go as high as 1 million copies), the probability of rapid CD4 cell count decline is very high. Therefore, it is recommended to consider initiation of ART at CD4 cell count of 350/mm^3 if the viral load is higher than 100 000 copies/ml.

While viral load testing is more expensive and may be less accessible, it is important to have a baseline viral load if at all possible, as this value is relevant for monitoring ART. The absence of viral load data should not be a criterion for delaying the start of treatment, or used as a reason for treatment exclusion.

4.1.3. Considerations for drug resistance test

Prevalence of HIV drug resistance varies in different countries and is linked to several factors, including the duration of ART availability, history of treatment (mono- and dual therapy) and adherence. In western Europe, multicentric studies showed a 10% overall prevalence of resistance in newly diagnosed HIV-infected individuals between 1996 and 2002 *(32)*. A study of 40 cities in the United States revealed a resistance rate of 14% *(33)*. The highest results from these studies were 26% in Spain *(34)* and 19% in San Francisco *(35)*. In countries with a short or no history of ART, risk of HIV drug resistant virus transmission is significantly lower, and the first-line highly active antiretroviral treatment (HAART) regimen recommended below (section II.4.2) is effective for treatment of naïve patients. It is important to have population-based HIV drug resistance strategies in place to monitor for the appearance and spread of HIV drug resistance; and to act on the early warning indicators for drug resistance emergence in order to minimize its appearance and onward spread.

WHO does not recommend individual drug resistance testing prior to initiation of ART in settings where only one first-line regimen is provided in the public sector because any results will not influence ART. Instead, sentinel surveys that demonstrate resistance at population level above the threshold of 5% *(36, 37)* should be taken into consideration in adapting national recommendations for first-line ART. Refer to Annex 3 for additional information on resistance testing. Where resources permit, and the public sector provides more than one first-line regimen, then drug resistance testing at baseline may help determine the choice of optimal ART; cost and availability will likely limit the widespread use of this in many settings (*38–40)*.

4.2. First-line HAART regimen

It is recommended that two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) be combined in the first-line HAART regimen.

Table 7. Recommended first-line HAART

ARV drug classes	HAART regimens
2 NRTIs + 1 NNRTI	ZDV + 3TC + (**EFV**[a] or NVP) or TDF + FTC + (**EFV**[a] or NVP) or ABC + 3TC + (**EFV**[a] or NVP)

[a] EFV is highlighted as the preferred NNRTI.

(For recommended dosages, please refer to Annex 4.)

4.2.1. Considerations for NRTI component

- The "backbone" of first-line ART is a combination of two NRTIs. One should be lamivudine (3TC) or emtricitabine (FTC); FTC is considered an equivalent drug to 3TC in both efficacy and toxicity *(41)*. The second is most often the thymidine analogue zidovudine (ZDV also known as AZT). A large body of data and provider experience is available for ZDV, as it was the first known ARV drug.
- Stavudine (d4T) is another thymidine analogue. It is available in several fixed-dose combinations (FDCs), is cheaper than ZDV and consequently widely used in many countries. However, it has a poor toxicity profile and recent studies have shown a higher rate of long term side-effects with d4T (*42–49)*. Many national and international recommendations are moving away from recommending it for initial therapy. It is increasingly being reserved as an alternative for ZDV (a within class substitution) when ZDV has to be substituted or changed for side effects or toxicity. The lower dose 30 mg is now recommended for all weights to reduce long-term toxicity.
- Other possible non-thymidine analogues for first-line are tenofovir (TDF) or abacavir (ABC) in combination with 3TC or FTC. Recently, one study has shown a slight superiority of TDF/FTC over ZDV/3TC when used in combination with EFV *(42)*, probably due to a lower rate of side-effects in the TDF arm. Further studies are needed. It should be noted that ABC has a risk of dangerous hypersensitivity syndrome; and, TDF can cause renal damage, so pre-screening for renal function is usually recommended.
- The advantage of TDF and ABC is their resistance profile, which potentially allows more NRTI combinations to support second-line protease inhibitors (PIs). The disadvantages are cost, avail-

ability and licensing, and the relative lack of programmatic experience and effectiveness data, which is less comprehensive than the data for the thymidine analogues *(43)*.

- NRTIs are available (or are likely soon to be prequalified and available) in the following FDCs, or one-pill formulations from originator and generic manufacturers:
  - ZDV + 3TC
  - TDF + FTC, TDF + 3TC
  - ABC + 3TC
  - d4T + 3TC
- An additional advantage of TDF/FTC and ABC/3TC is the availability of a once-daily regimen.

Other NRTIs and combinations are not recommended for first-line ART *(44)*. Certain rules pertain to the use of NRTIs.

- Do not combine "d-drugs" (ddI (didanosine), d4T).
- Do not give single d-drugs with pre-existing polyneuropathy.
- Do not combine ZDV and d4T.
- Do not combine 3TC and FTC.

4.2.2. Considerations for NNRTI component

- There are two NNRTIs, EFV and nevirapine (NVP), which are available and recommended for first-line ART. The effectiveness of NVP is comparable to that of EFV *(50)*. Both have important toxicities and side-effects which limit how they can widely be used.
- The best available data are for the regimen of ZDV + 3TC + EFV *(51–53)*. This three-pill combination is given in two doses per day. It is fast acting, the viral load falls rapidly in the first two weeks with EFV, the increase of CD4 count is comparable to other regimens and problems are limited.
- EFV should be avoided in patients with a history of severe psychiatric illness, in women of childbearing age who do not use effective contraceptives, and during the first trimester of pregnancy. NVP is an alternative option for these cases.
- NVP can cause severe hepatic toxicity which seems to be related to the level of immunosuppression *(54)* so its use is limited to female patients with CD4 count <250 cells/mm^3 and males with CD4 count <400 cells/mm^3. CD4 counts higher than these are associated with more risk of hepatic toxicity.
- NVP needs to be dose-escalated. There is a recommended 14-day lead-in period with 200 mg NVP once daily (OD) when starting this regimen, for better tolerance. After 14 days, the dosage should be increased to the standard regular 200 mg twice daily (BID).
- EFV is usually preferred when the patient is being co-treated for TB with rifampicin (see Protocol 4, *Management of tuberculosis and HIV coinfection* for further information).
- The combination of two NNRTIs with one NRTI is not recommended *(55)*.

4.2.3. Alternative first line HAART regimens

- Triple NRTI-based first-line regimens such as ZDV+3TC+ABC and ZDV+3TC+TDF can be recommended in specific circumstances where NNRTI is contraindicated or too complex to manage and have the advantage that they still preserve the PI class for second-line ART. These regimens can be used in the following circumstances:
  - intolerance or resistance to NNRTIs;
  - psychiatric disorders;
  - pre-existing liver disease – an increase of the ALT level by more than 3–5 fold–and established cirrhosis;
  - coinfection with HBV or HCV;
  - HIV-2 infection due to intrinsic resistance to NNRTI class; and
  - cotreatment of TB in women of child-bearing age and where adequate contraception cannot be guaranteed, and when NVP and boosted PIs cannot be used.

- ZDV+3TC+ABC has short-term inferior virological efficacy at least in patients with high initial viral loads but comparative immunological efficacy to ZDV+3TC+EFV regimen *(51, 56)*. ZDV+3TC+TDF is a promising regimen but there are limited data to date (see the following Protocols: 4, *Management of tuberculosis and HIV coinfection;* 6, *Management of hepatitis C and HIV coinfection;* and 7, *Management of hepatitis B and HIV coinfection*).
- Other triple NRTI-based regimens, such as ZDV+TDF+ABC or TDF+3TC+ddI have unacceptably high virological failure rates and high incidence of the K65R mutation *(57, 58)* and should not be used.
- Boosted PIs are usually reserved for second-line ART. They can exceptionally be used as part of first-line ART in combination with two NRTIs when triple NRTI regimen is not available or deemed inappropriate or when there are contraindications for NNRTIs (i.e. neither EFV nor NVP can be prescribed) including:
  - psychiatric disorders;
  - an increase of the ALT level by more than 3–5 fold;
  - cirrhosis;
  - pregnancy with CD4 count of 250–350 cells/mm^3, particularly in the 1st trimester of pregnancy (as EFV is contraindicated);
  - HIV-2 infection due to intrinsic resistance to NNRTI class; and
- If a first-line ART regimen containing a PI fails, there are very limited options for subsequent regimens at least within a public health approach and within the public sector in many countries. A failing PI regimen has, in consequence, more resistance patterns than a failing NNRTI regimen (point mutation in NNRTI class). In general therefore, it is recommended that PIs be left to second-line ART.

4.3. Adherence to ART

Optimal treatment benefits require strict adherence to ART. It is well recognized that when adherence is high, there is a dramatic reduction in HIV-associated morbidity and mortality *(59)*, whereas low adherence leads to rapid development of drug resistance *(60)*. Effective adherence levels have not been fully defined for ART (there being differences between a number of regimens), but levels lower than 95% have been associated with poor virological and immunological response, while levels of 100% seem to achieve even greater benefit than 95% *(61, 62)*. The most recent data show a correlation between drug resistance in various classes of ARVs and adherence *(63)*.

Low or insufficient adherence has consequences for patients, public health and national economies.

- Patients are in danger of developing significant viral resistance, treatment failure and disease progression *(64, 65)*. Changing to a new regimen after treatment failure results, in most cases, in more difficult adherence (more pills, side-effects, dietary restrictions, toxicity and dosing complexity).
- The increase in resistant viruses is likely to result in their transmission to newly infected individuals. Data from the United States *(66)* and Europe *(67)* suggest that such primary resistance is increasing, and that acquired resistance has a negative effect on ART response.
- Economically, the presence of resistant strains will result in increased use of second-line and salvage regimens, which are in general more expensive than first-line regimens.
- Low adherence also means a higher risk of disease progression, resulting in higher costs for treating opportunistic infections *(68)*.

4.3.1. Barriers to high adherence and counteracting strategies

Health care workers should identify possible factors which might lead to poor adherence to treatment and address it accordingly.

4.3.1.1. Patient factors and supportive methods

The role of patients themselves is fundamental. One cannot predict patients' adherence potential. Studies investigating the role of gender, race, age, mode of transmission and educational level as indicators of adherence have produced inconsistent results *(69)*. Individual adherence rates also vary over time *(70)*. Most PLHIV under treatment will exhibit low adherence at some time.

Barriers to adherence include:
- drug and alcohol use (may impair routine use of medication)
- poor diet due to poverty or due to other reasons
- religious beliefs *(71)*
- fear of disclosing HIV status through routine medications
- psychiatric conditions *(72)*
- fear of side-effects and doubts about the necessity of medication *(73)*.

Methods to support adherence include:
- education on the need for ART
- addressing patient misconceptions promptly
- regular evaluation of patient commitment to ART
- peer intervention (groups, friends, patient supporters)
- regular assessment of mental health problems
- assessing behavioral skills needed for adherence[3]
- contacting specialized social care services and other institutions.

4.3.1.2. Provider factors

Health care providers should clearly understand adherence and its role in resistance development when providing adherence support. Professionals working in the area of HIV/AIDS require continuous education in adherence issues. There are several strategies that health care workers should employ to increase adherence:
- Every HIV treatment centre should have a written and regularly reviewed adherence strategy.
- Health professionals need to be engaged in adherence support programmes *(74)*.
- Exploring patient preferences for involvement may act as a catalyst to adherence.
- Adherence services should be offered to all patients, taking into account the varying degrees of adherence that all patients show over the course of treatment.
- Adherence support should be continued for second-line and salvage regimens. Treatment failure is a key point for reinforcing adherence and support interventions *(75)*.
- As high adherence is a process and not a single event *(76)*, support must be offered when starting ART, changing ART and as a routine follow-up.
- Providers must ensure that patients have sufficient understanding of HIV, the relationship between adherence and resistance, the requirements of their regimen and potential side-effects. Verbal information should be supported by written information.
- Pill diaries, pill charts, medication containers, electronic reminders, and enlistment of family and friends as reminders can all be recommended by health care providers *(77)*.
- Adherence to ART is improved where patients view their relationship with their doctor and other health care providers positively *(78)*.

[3] These can be augmented by contacting people who can help (nurses, pharmacy, family), and by using timetables, pill boxes with clocks, pill-taking routines, strategies for travel and managing disclosure or discovery by others.

- Early follow-up should occur two days after initiating or changing a regimen, to evaluate whether the patient needs more information or has unregistered problems.
- The partnership between clinics and community-based organizations can improve the uptake of information, especially among hard-to-reach populations and some ethnic groups.

4.3.1.3. Regimen factors and strategies

- Dosing more than two times a day is associated with lower adherence levels *(79)*, while there is probably no adherence difference between one or two daily doses *(80)*. In regimens with single or double daily dosing, more of the doses are taken at a time. Taking the dose later than prescribed has been associated with treatment failure in multivariate analysis *(81)*.
- A low pill burden is associated with the likelihood of having a viral load below 50 copies/ml after 48 weeks *(80)*.
- Adherence levels are not correlated with any ARV class. However, conflicting dietary rules for different drugs can be a problem *(82)*.
- Harmful drug interactions and side-effects can influence adherence. Doses can be missed due to vomiting or diarrhoea, and fatigue can cause patients to sleep past doses *(83)*.

Methods to support adherence include:

- evaluating lifestyle factors like eating, sleeping and working patterns and adjusting the regimen accordingly;
- assessing individual preferences for regimen characteristics such as pill size, formulation, burden, dietary restrictions, etc.;
- showing patients the pills prior to regimen selection;
- education about side-effects, prompt palliation of them and information about support;
- dispensing medication in small amounts at frequent intervals, which can facilitate:
  - opportunities to address adherence problems before they lead to resistance;
  - limiting treatment disruptions and misuse;
- utilization of once-daily options and FDCs, which can lower the pill burden and be beneficial early in treatment; and
- directly observed treatment (DOT), particularly in hospitals.

4.4. ART success and failure

All patients should be regularly monitored by skilled clinicians. Ideally all should have access to both immunological and virological tests. Successful ART can be defined by clinical, immunological or virological criteria (see Table 8).

Table 8. Criteria for treatment success

	Virological		**Immunological**	**Clinical**
Marker	Viral Load		CD4 cell count	Clinical stage
Time[a]	24 weeks	48 weeks	24–48 weeks	By 12 weeks of treatment initiation should be asymptomatic or have few symptoms
Suggested ranges[a]	<400 copies/ml	<50 copies/ml	Increase from baseline by at least 50-100 cells/mm^3	Stage 1 or 2[b]

[a] Time and suggested ranges should not be seen as absolute and strict numbers.
[b] Please see section II.5.3 below for more information on immune reconstitution inflammatory syndrome (IRIS).

Failure of first-line ART can be defined and identified in three different ways: clinically, immunologically and virologically. The three may reflect different aspects of failure. Further, it is proving difficult in the absence of good clinical end-point data on the subsequent durability of second-line responses, to know which is the best indicator of when to switch and what value or level should be used. There are differing views about whether a patient with a "failing" regimen, regardless of

criterion used, should switch to second-line ART, and when to do so. There is no clear consensus globally on the definition of treatment failure. Currently, different biological end-points are used to represent virological, immunological and clinical failure in different settings.

4.4.1. Virological response

- VL is the earliest indicator of treatment success or failure, followed by CD4 cell count approximately a month later. In rare cases, a paradoxical reaction of virological response and immunological failure occurs; consequently, VL should be seen in combination with CD4 cell count.
- Failure to decrease viral load to <400 copies/ml by week 24 of treatment or <50 copies/ml by week 48 means incomplete virological response.
- When the viral load has already decreased to an undetectable level, but two measurements are >400–1000 copies/ml in 4 to 8 weeks, it means there is a risk of virological failure *(84)*.[3]
- "Blips" are slight elevations of viral load, from under the testing threshold to around 50–200 copies/ml. They may happen without the development of resistant virus strains (laboratory errors), but should be an indicator for a discussion of adherence *(86)*. In this situation, therapeutic drug monitoring (TDM) may also be helpful, if available. Any blip should be controlled within four weeks.
- If no reason is found for virological failure (poor adherence, suboptimal drug levels, drug–drug interactions, etc.), a second-line regimen should be discussed.

4.4.2. Immunological response

- CD4 cell count response on its own can be used as an indicator of treatment failure or success.
- On average, a CD4 cell increase of about 150 cells/mm³ occurs in the first year in treatment-naive patients *(87, 88)*. Failure to increase CD4 cell count more than 50 cells/mm³ during the first year of ART is considered immunological failure.
- If the CD4 cell count does not increase for six months, adherence to treatment should be reassessed and ensured.

4.4.3. Clinical response

- Patients will usually reverse their clinical stage and become asymptomatic (stage 1) or have minimal or minor HIV-related signs and symptoms (stage 2).
- Some stage 3 or 4 OIs can recur and the prognostic significance of oral and oesophageal candida in particular is not always clear-cut.
- Usually however, presentation of a new or recurrent stage 3 or 4 event (OI or other HIV-related illness) after initiation of ART is an indicator of clinical failure.

4.4.4. Dissociated virological and immunological responses

Despite the persistence of low but detectable viremia (VL suppressed to less than the natural set point), CD4 cell count may remain stable or even increase in some patients taking HAART *(89–91)*. In a large intercohort analysis even in those people who had experienced 3-class virological failure and continue to take HAART, viremia less than 10 000 copies/ml or suppression of at least 1.5 log copies/ml less than the pretherapy value, was not associated with a decline in CD4 cell count *(92, 93)*.

[4] WHO headquarters notes that the optimal viral load value at which ART should be switched has not been defined. However, values of more than 10 000 copies/ml have been associated with subsequent clinical progression and appreciable CD4 cell count decline. In resource-limited settings, WHO, at the global level, has provisionally opted for 10 000 copies/ml, as an interim recommendation for switching to second-line HAART, if the VL indicator is used as a criterion *(85)*.

4.5. Second-line HAART regimen

- When failure of the first-line regimen has been identified, it is recommended that all drugs are changed and then the patient switches to second-line treatment.
- Second-line ART is the next regimen used in sequence immediately after first-line ART has failed. The PI class is reserved for second-line use. Ideally, ritonavir-boosted PIs are recommended, supported by two agents from the NRTI class. See Table 9 for second-line ARV regimens.

Table 9. Recommended second-line HAART for adults and adolescents

First-line HAART regimens	Second-line HAART regimens after treatment failure
ZDV + 3TC + (EFV or NVP)	**LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ABC or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + TDF + ABC or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + TDF + (ZDV + 3TC)[b]
TDF + FTC + (EFV or NVP)	**LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ABC or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ZDV
ABC + 3TC + (EFV or NVP)	**LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ddI + ZDV or **LPV/r**[a] (or ATV/r, SQV/r, FPV/r, IDV/r) + ZDV + TDF (+ 3TC)[b]

[a] LPV/r is listed as the preferred RTV-boosted PI in this table, but other boosted PIs can be substituted, based on individual programme priorities. ATV/r, SQV/r, FPV/r and IDV/r are all possibilities. In the absence of a cold chain, NFV can be employed as the PI component, but it is considered less potent than an RTV-boosted PI.

[b] ZDV + 3TC are listed here for strategic use since resistance to both is predicted following failure of the listed first-line regimen. ZDV may prevent or delay the emergence of the K65R mutation; 3TC will maintain the M184V mutation, which may decrease viral replicative capacity as well as induce some degree of viral resensitization to ZDV. It must be stressed that the clinical efficacy of this strategy has not been proven.

(For recommended dosages of ARVs, please refer to Annex 4.)

4.5.1. Considerations for NRTI component

- Minimum changes for a second-line regimen are two new NRTI drugs. Never change only one drug in cases of suspected resistance.
- If the first-line ART included ZDV + 3TC, then ABC in combination with ddI (or TDF with dose-adjusted ddI and close monitoring) may be an option *(94)*.
- Patients who began with TDF or ABC may now benefit from ZDV *(95)*, due to the higher likelihood of resistance. For instance, the K65R mutation promoted by TDF and ABC increases susceptibility to ZDV *(96, 97)*.
- 3TC is also useful in cases of 3TC resistance, as the regularly acquired 184V mutation reduces viral fitness and also increases susceptibility to ZDV *(96)*.

4.5.2. Considerations for PI component

- With a first-line regimen containing a NNRTI, second-line ART should include a PI.
- In the PI class, the majority of drugs are boosted with a low dose of RTV, itself a PI, 100 mg BID – except nelfinavir (NFV), which is boosted not chemically but with food. The means of boosting is ritonavir's inhibition of the cytochrome P450 (CYP) 3A4 isoenzyme. Subsequently, the drug levels of the main PIs (except NFV) are increased *(98)*. RTV is used only for boosting other PIs and is not effective as a stand-alone ARV.
- The differences among the PIs lie in the number of mutations needed to develop resistance and in the profile of their side-effects.
- One of the highest genetic barriers for resistance is documented for LPV/r *(99)*.
- The resistance profiles of ritonavir-boosted atazanavir (ATV/r), fosamprenavir (FPV/r), indinavir (IDV/r) and SQV/r show slight differences that have little or no clinical impact.

- NFV seems to be inferior to the other PIs, but it is well documented in pregnant women. In case of failure, the D30N mutation is usually selected; it does not encode for cross-resistance for other PIs *(100, 101)*.
- LPV/r is the PI of choice due to its well-documented potency *(102)*, availability as a FDC and relatively low pill burden and good tolerance. A new tablet formulation of LPV/r has been approved in Europe requiring two pills BID and no refrigeration *(103)*.
- Recent studies *(104, 105)* showed similar efficacy of SQV/r and FPV/r to LPV/r, but in ARV naive patients. The pro-drug formulation of amprenavir (APV) in the form of FPV, the once-daily PI ATV and the new formulation of SQV (500 mg tablets) have not been directly tested against LPV/r. Therefore, only indirect data are available. Further studies with head to head comparisons among boosted PIs in ARV experienced individuals are needed.
- Possible side effects, comorbidities, drug interactions and individual preferences should influence the choice of PI.
- If first-line ART regimens containing PIs fail, the choice of a second-line regimen is mainly based on resistance profiles. If resistance profiles are not available, then resistance to the PIs contained in the first-line regimen must be assumed to be the cause of the regimen's failure (see section II.4.4 above for success and failure criteria).
- Possible options in the event a first-line regimen with a PI fails:
  - ZDV + 3TC + PI/r → ABC + ddI + NNRTI
  - or one of the salvage options (see section II.4.6 below).

4.6. Salvage regimens

In case of confirmed second-line ARV treatment failure (using virological, immunological or clinical criteria), a salvage regimen should be considered. Salvage regimens are combinations of drugs that will probably work even against viruses that are partly drug resistant. Every regimen after second-line treatment is complicated and requires a high level of ART knowledge and skill on the part of the healthcare provider. Performing a resistance test in these circumstances is highly desirable. It is at times better to wait several months before initiating salvage treatment, although this strategy can be dangerous, particularly if the CD4 cell count is low.

- If possible two effective drugs should be added, for example the fusion inhibitor enfuviztide (ENF) *(106)*, which is administered twice daily with subcutaneous application, and the new boosted PIs TPV/r *(107, 108)* or boosted darunavir (DRV/r) *(108–112)*.
- The genetic barrier of TPV/r seems to be even higher than that of LPV/r, and data show its efficacy to be comparable or better than the latter's *(113)*. This PI is presently used only for salvage regimens.
- Another option is a combination of two PIs *(114–117)*, except boosted tipranavir (TPV/r), which is not to be combined with any other PIs.

(For recommended dosages, please refer to Annex 4.)

4.7. Structured treatment interruption

Most ART providers are opposed to planned interruptions, but there are conditions that may justify them. For example, constant CD4 count >500 cells/mm^3 with completely suppressed virus for years may offer such an opportunity. Although it is not necessary to interrupt, it is better to do so than to face poor adherence followed by the development of resistant strains. During structured treatment interruption, the CD4 cell count normally falls rapidly to pre-ART levels; thus, it is imperative to monitor monthly counts during the first three months, then once every three months. Some patients continue to maintain satisfactory CD4 cell count (usually >350 cells/mm^3) with a low VL (1000–5000 copies/ml) for months and years. The scientific investigation of this issue is continuing *(118–122)*, and involves discussions particularly among the self-help groups and ART providers. However, a recent multicentric trial conducted in the United States demonstrated that this strategy can be associated with an increased risk of HIV disease progression, occurrence of non-AIDS re-

lated complications (kidney, liver and cardiovascular disease) and death *(123)*, which motivated the interruption of the specific arm study using the structured treatment interruption strategy. Because of these results and the lack of definitive evidence of the benefits of structured treatment interruptions strategies in other studies, WHO does not recommend this approach outside clinical trials.

5. Clinical monitoring of patients with HIV

Once a person has been diagnosed with HIV infection, a continuum of care and monitoring should be ensured.

5.1. Monitoring of laboratory indicators before ART

- CD4 cell count
  - Repeat every six months, unless there are unexpected results (rapid fall of CD4 cells count or diagnosis of opportunistic infection).
  - If starting ART is under discussion (CD4 count is 350 cells/mm^3 or less), repeat CD4 count every three months. Statistically, every patient has a median average loss of 50 CD4 cells/mm3 per year, but they can also drop very quickly, especially with concomitant infection.
- Viral load
  - Although viral load testing is expensive, the costs of unmonitored ART are much higher (useless drugs, hospital admission in case of failure), as well as bringing a much higher risk for further transmission of HIV due to higher infectivity from an elevated viral load.
  - If possible, viral load should be monitored in the same interval as CD4 cell count. The result gives a hint about the intensity of viral replication; low viral load (1000–5000 copies/ml) indicates slow progression, high viral load (>100 000 copies/ml) indicates a high risk for rapid progression.
- The general laboratory testing panel (see Table 3 above) should be repeated every six months if there are no changes with regard to initiation of ART or other circumstances (comorbidities, pregnancy, etc.).

5.2. Monitoring of laboratory indicators in ART patients

Successful ART is first reflected by the decrease of viral load; immunological response is a result of viral load, and thus occurs later. ART monitoring is best done with viral load and CD4 count both.

- Viral load
  - VL should be measured after 4–8 weeks for assessment of whether the regimen is successful. Viral load usually falls below the assay's limits of detection within 16–24 weeks.
  - Subsequent monitoring of viral load should be done in intervals of three to four months.
  - Once viral load is below the testing threshold which is <50 copies/ml (or 60 or 70 copies/ml, depending on the available test), it should remain there.
- CD4 cell count should be repeated every six months, except in case of clinical failure.
- The general laboratory testing panel (see Table 3 above) should be repeated every six months if there are no changes in ART or other circumstances.
- Depending on specific ARVs used, the frequency for laboratory testing might differ. See Table 10.

Table 10.	Frequency of laboratory testing, generally and with specific ARV use							
	Baseline	**Week 2**	**Week 4**	**Week 8**	**Week 16**	**Week 24**	**Week 36**	**Week 48**
Viral load	X			X		X	X	X
CD4 count	X			X		X	(X)	X
Complete blood count	X		X	X	X (ZDV)	X	(X)	X
Liver Function Test (LFT)	X	X (NVP)	X	X (NVP, ZDV, PIs)	X (NVP, PIs)	X	(X)	X
Cholesterol triglycerides	X (PIs)				X (PIs)			X (PIs)
Renal function test	X	X (TDF)	X (TDF, IDV)			X	(X)	X

X: laboratory tests to be performed irrespective of the ARVs being administered; **X (ARV)**: laboratory tests to be performed if an ARV in parentheses is being administered; (**X**): optional test.

5.3. Immune reconstitution inflammatory syndrome

IRIS happens after initiating ART, more often with CD4 counts <100 cells/mm^3. If a dormant opportunistic infection is not diagnosed because of missing clinical symptoms, there may be an inflammatory reaction after initiating ART, due to an improved and activated immune system, leading to diagnosis of the OI *(124, 125)*. This may occur in up to a third of persons with TB who initiate ART *(85)* (for further information on IRIS in TB/HIV coinfected patients, refer to Protocol 4, *Management of tuberculosis and HIV coinfection*). The OI often presents differently than usual, for example, in abscesses with *Mycobacterium avium-intracellulare* (MAI) or curious chest X-rays with PCP. The incidence of IRIS is probably about 10%. MAI and CMV are the most common OIs, but worsening of a treated PCP may also occur *(126)*. In principle, ART should be continued along with treatment of the OI. Low-dose prednisone or prednisolone (20–60 mg/day) may help. ART should be discontinued if irregularly taken due to side-effects of OI treatment or if there is pain with oesophagitis (CMV, herpes, candidiasis).

5.4. Monitoring adherence

Every patient's adherence to ART should be measured and recorded during routine clinical visits. While there are tools for monitoring adherence (see Annex 5), the preferred method is a standardized questionnaire for 14 days or one month.

Viral load rebound should always prompt physicians to discuss adherence behavior with their patients. The use of open questions that acknowledge customary low adherence is more likely to elicit full responses.

Optimizing adherence in the first four to six months of treatment is crucial to ensuring long-term immunovirological success *(127)*. Several interventions are possible, but priority should be given to interventions aimed at improving adherence in the early months of ART *(127–131)*.

Staff should provide individualized support to adherence, based on the needs of each patient at any time during treatment. At every patient visit, health care providers have to ensure that every patient:

- has emotional and practical living support
- fits the drug regimen into a daily routine
- understands that non-adherence leads to resistance
- recognizes that all doses **must** be taken
- feels comfortable taking drugs in front of others
- keeps clinical appointments

- understands ARV interactions and side-effects
- knows alarm signals and when to see a doctor about them *(132, 133)*.

Once a patient is already on ART, additional issues may arise which also need to be addressed in a timely fashion:
- treating depression to enhance adherence and improve long-term outcomes *(134)*; and
- management of drug interactions and dosages.

5.5. Management of ARV toxicity and side-effects

Side-effects are common with ARVs, especially PIs. See Table 11.
- LPV/r and NFV can cause severe diarrhoea.
- LPV/r is associated with hyperlipidaemia (especially high triglycerides).
- Problems with lipid metabolism can occur with nearly all PIs.
- Long-term studies of side-effects and increased risk for cardiovascular complications are needed.

Toxicity might be a reason for substitution of prescribed ARV to another ARV drug within the same regimen. Switching to another treatment regimen due to toxicity is not recommended.

Table 11. Documented toxicity of ARVs and suggestions for management

ARV	Toxicity	Management
Hepatic necrosis (life-threatening)		
NVP	• Fever, rash (50%), nausea, vomiting, eosinophilia, elevation of ALT/AST • Usually in first 6–18 weeks, rare after 48 weeks • 1–2% of all NVP treated individuals, higher if CD4 count >250 in females and >400 in males	• Monitor LFT at weeks 2, 4, 8 and 16, and then every three months. • Treatment is symptomatic. • Hepatic necrosis is life threatening; in severe clinical situations, stop drugs at once.
Lactic acidosis (life-threatening)		
From highest to lowest risk: • d4T with ddI • ddI • d4T • ZDV	• Nausea, vomiting, wasting, fatigue, pancreatitis, multiorgan failure, acute respiratory distress syndrome (ARDS) • 1–10 per 1 000 patients/year for ddI and d4T	• Monitor lactic acid clinically. If suspected, look for early indicators (creatine kinase (CK), HCO_3). • The symptomatic treatment is bicarbonate against acidosis. • Change to ABC, TDF, 3TC, FTC.
Hypersensitivity (life threatening in case of re-exposure: anaphylactic shock)		
ABC	• Nearly always fever and rash, also fatigue and nausea • 5%, rare after six weeks	• Monitor skin, do not start together with other rash-producing drugs. • Stop ABC, do not use again if diagnosis is firmly suspected. • Change to ZDV, TDF or d4T.
Stevens–Johnson syndrome, toxic epidermal necrolysis		
NVP Less with EFV	• Fever, rash with blistering, myalgia • NVP: 0.3%, EFV: 0.1%	• Monitor skin. • Administer antibiotics and intensive care of wounds, perhaps in a burns centre.
Pancreatitis		
From highest to lowest risk: • d4T with ddI • ddI • d4T	• Pain, high levels of lipase • ddI 1–7%, less with dose adjustment	• Monitor lipase level. • The symptomatic treatment is pain medication, parenteral nutrition, drug stoppage. • Change to ZDV or TDF or ABC.

ARV	Toxicity	Management
Nephrotoxicity		
TDF	• Renal failure and Fanconi syndrome • More frequent in individuals with baseline renal dysfunction *(135)*	• Monitor creatinine, history of renal failure. • Treatment is symptomatic. • Eventually try again with dose adjustment of TDF (creatinine clearance is needed: TDF every second day). • Change TDF to ZDV, ABC or d4T.
Anaemia		
ZDV	• Anaemia and neutropenia (slight decrease is normal with ZDV) • 1–4%, dose dependent	• Monitor blood count after 2, 4, 8 and 12 weeks. Macrocytosis with light anaemia (haemoglobin up to 10 g/dl or 100 g/litre) is common. • Treatment is a transfusion of erythropoetin (very expensive) or changing ZDV to another NRTI (TDF, ABC or d4T).
Peripheral neuropathy		
d-drugs: ddI, d4T	• Pain/paraesthesia of extremities • 10–30%, also after years	• Monitor peripheral nerves, warn patient. • Treatment is pain management, change of ART. Stop d-drug, change to another NRTI (ZDV, TDF, ABC).
Fat atrophy		
d4T and other NRTIs	• Reduced buccal fat and extremity fat • Common with long use (mitochondrial toxicity)	• Monitor and compare to previous pictures. • Change d4T to TDF or ABC. If atrophy is irreversible, plastic surgery is indicated.
Fat accumulation		
PIs	• Increased abdominal fat ("crixi belly"), breast size, buffalo hump • 20–80%	• Measure and compare to previous pictures. • Change to NNRTI if lipodystrophy/lipoatrophy is not tolerable. Plastic surgery may be indicated.
Rash		
NNRTI > APV/FPV > ABC	• Maculopapular itching • 15% NNRTI, APV ~20%, ABC 5%	• Monitor fever, LFT, CK in close visits. • Think of other allergenic drugs (sulfamethoxazole/trimethoprim and other antibiotics, prophylaxis). Rashes sometimes resolve spontaneously with continued ART. • Change NVP to EFV or vice versa. If no improvement, try a new regimen.
Elevation of transaminase		
NNRTIs (all) and PIs (all)	• Otherwise unexplained elevation of LFT • 8–15% with PI and NNRTI • More frequent in patients with chronic HBV or HCV	• Monitor ALT every three months, look for other reasons (drugs, hepatitis). • Elevation often resolves with continuation of NNRTI or PI. • Discontinue NNRTI or PI.
Gastrointestinal intolerance		
PIs (all), ZDV, ddI	• Nausea and vomiting, diarrhoea • Common	• Rule out other reasons (IRIS with CMV colitis, cryptosporidiosis, microsporidiosis, also weeks after initiating ART). • Treatment is loperamide if there is no other reason for diarrhoea; metoclopramide, Zofrane for nausea and vomiting.

ARV	Toxicity	Management
Central nervous system (CNS) toxicity		
EFV	• Nightmares, impaired concentration, depression (risk of suicide) • 50%	• Warn patient, take psychiatric history, refer to psychiatric consultation. • Treatment usually not necessary, resolves in 5–21 days.
Insulin resistance		
PIs (all but ATV), especially IDV	• Elevated glucose tolerance, elevated glucose with morning fasting • 5%	• Monitor fasting blood glucose. • Treatment is via diet and exercise, metformin or Glitazone. • Change PI to NNRTI.
Hyperlipidaemia		
d4T > PIs (all but ATV)	• Increased lipids, increased LDL, cholesterol, triglycerides (for the last, d4T is particularly prominent) • % varies	• Monitor fasting lipid levels at initiation of ART and every six months. • Treatment is per lipid, cholesterol and triglyceride guidelines. • Use statins and fibrates. Be careful with interactions (no simvastatin, no lovastatin).
Hyperbilirubaemia		
ATV > IDV	• Elevation of bilirubin (harmless; possible itching, no prolonged liver damage, reversible) • Frequency varies	• Monitor bilirubin and clinical symptoms. • Stop drug only if not tolerated. Change PI.
Nephrolithiasis		
IDV	• Abdominal pain, haematuria, renal colic • 10–20% per year, less with >3 litre fluid/day	• Monitor urinalysis, creatinine. • Treatment is the same as for nephrolithiasis.

Source: *Bartlett (136).*

5.6. Drug interactions

Drug interaction can be a severe problem in ART. PLHIV need to take a good deal of different agents due to concomitant diseases or manifestation of HIV and AIDS.

Though some drugs are genuinely contraindicated, most drugs that show interactions can still be given in combination; however, the probability of side-effects is then greater, and they should be closely monitored. The effectiveness of contraceptives could also be jeopardized. (See also Protocol 9, *Support for sexual and reproductive health of people living with HIV.*) Tables 12 and 13 illustrate interactions of drugs with NNRTIs and with PIs.

Table 12. NNRTI interaction with selected drugs

NNRTI (drug A)[a]		With … (drug B)	Effect	Significance [b]
EFV	NVP			
+		Ergotamine	↑ level of B	++(avoid)
	+	Antiarrhythmics: lidocaine, amiodarone, others	↑ and ↓ level of B	++(caution)
+	+	Anticonsulvants: carbamazepine, phenytoin, phenobarbital	↓ level of B and/or A; use gabapentin instead	++
(+)[c]	+	Itraconazole, ketoconazole	(–)[c] level of B	+
	+	Cyclosporine, tarolimus, Rapamycin	↑ level of B	++
	+	Calcium channel blockers	↑ level of B	++
+	+	Sildenafil, vardenafil, tadalafil	↑ level of B	++
	+	Fentanyl	↑ level of A	++
+	+	Methadone	↓ level of B	++
+	+	Contraceptives	↑ and ↓ level of B	++
+	+	Rifampin, rifabutin	↑ and ↓ level of B, ↓ level of A (caution)	++
+	+	St John's wort	↓ level of B	++
+	+	Warfarin	↑ level of B	++

[a] + *or* ++ under drug A shows the drug strength in changing the level of drug B.
[b] Significance: + probable importance, ++ definite clinical importance.
[c] (+) or (–) indicates inconsistent results.
Sources: Sande & Eliopoulos; Gilbert, Moellering & Eliopoulos; Antoniu & Tseng *(137–139)*.

Examples of how the tables should be read are as follows.
1. In Table 12 line 6: EFV strongly increases the levels of midazolam, alprazolam and triazolam while NVP does so less strongly. The significance of this is that there is a definite clinical importance; however, these drugs can still be coadministered.
2. In Table 13 line 4: APV, IDV LPV, NFV, RTV and SQV all increase the levels of carbamazepine, clonazepam, phenytoin and phenobartial while these drugs in turn decrease the levels of the those PIs. The significance of this is that there is definite clinical importance. The combination of any of these should be avoided.

Table 13. Protease inhibitors interactions with selected drugs

Protease inhibitor (drug A) [a]							With … (drug B)	Effect	Significance [b]
APV	ATV	IDV	LPV	NFV	RTV	SQV			
					+		Fentanyl, tramadol, hydrocodon	↑ level of drug B	+
			+		+		Codeine, morphine, methadone	↓ level of drug B	+
+	+	+	+	+	+	+	Amiodaron, lidocaine, flecainide	↑ level of drug B	+
+		+	+	+	+	+	Carbamazepine, clonazepam, phenytoin, phenobarbital	↑ level of drug B ↓ level of drug A	++(avoid)
+	+	+			+		Tricyclic antidepressants	↑ level of drug B	+
	+				+		All other antidepressants	↑ level of drug B	+
					+		Loratadine	↑ level of drug B	++

Protease inhibitor (drug A) [a]							With … (drug B)	Effect	Significance [b]
APV	**ATV**	**IDV**	**LPV**	**NFV**	**RTV**	**SQV**			
			+				Atovaquone	↓ level of drug B	+
+	+	+	++	+	+	++	Benzodiazepine	↑ level of drug B	++
					+		Beta blockers	↑ level of drug B	+
+	+	+	+	+	+	+	Calcium channel blockers	↑ level of drug B	++
	+				+	+	Clarithromycin, erythromycin in renal impairment	↑ level of drug B	+(caution)
+		+		+	+	+	Clarithromycin, erythromycin	↑ level of drug B and drug A	+
	+		+	+	+		Contraceptives	↑ level of drug B	++
+			+		+	+	Corticosteroids	↑ level of drug B ↓ level of drug A	+
+	+	+	+	+	+	+	Cyclosporine	↑ level of drug B	+
+	+	+	+	+	+	+	Ergot derivatives	↑ level of drug B	++(avoid)
+	++	+	+	+	+	+	Proton pump inhibitors (PPIs)	↓ level of drug A	+(caution) (++, ATV-avoid)
+	++	+	+	+	+	+	H_2 antagonists	↓ level of drug A	++ (caution) (++, ATV-avoid)
+	+	+	+	+	+	+	Lovastatin, simvastatin	↑ level of drug B	++(avoid)
	+						Irinotecan	↑ level of drug B	++(avoid)
+		+	+	+		+	Ketoconazole, itraconazole	↑ level of drug B ↑ level of drug A	+
+	+	+	+	+	+	+	Pimozide	↑ level of drug B	++(avoid)
+	+	+	+	+	+	+	Rifampin	↑ level of drug B ↓ level of drug A	++(avoid)
+	+	+	+	+	+	+	Rifabutin	↑ level of drug B ↓ level of drug A	+(caution, dose adjustment)
+	+	+	+	+	+	+	Sildenafil	Some ↑, some ↑ level of drug B	++
+	+	+	+	+	+	+	St John's wort	↓ level of drug A	++(avoid)
	+						Tenofovir	↓ level of drug A	++(add RTV)
		+	+		+		Theophyline	↓ level of drug B	+
+	+		+		+		Warfarin	↑ level of drug B	+

[a] + *or* ++ under drug A shows the drug strength in changing the level of drug B.
[b] Significance: + probable importance; ++ definite clinical importance.
Sources: Sande & Eliopoulos, Gilbert, Moellering & Eliopoulos, Antoniu & Tseng *(137–139)*.

III. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to treatment and its success. Such indicators assist managers in decision-making on ways to strengthen and expand these services to all who need them.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV patients "seen for care" (seen at least once in the previous 12 months);
- number of HIV patients seen for care who are eligible for ART (CD4 <350 cells/mm^3);
- number of HIV patients seen for care initiating HAART;
- number of HIV patients seen for care receiving first-line HAART;
- number of HIV patients on HAART changing from first-line HAART to second-line HAART;
- number of HIV patients on HAART changing from second-line HAART to salvage HAART;
- number of HIV patients interrupting ART treatment, including the reason (e.g. death, toxicity/side effects, loss to follow-up, ARVs not available, etc.);
- number of patients who died while on HAART, including cause of death (e.g. HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide);
- number of HIV patients who died within the first 12 months of initiating HAART; and
- number of deaths among all HIV patients including cause of death (e.g. HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

Annex 1. Essential information on personal history of HIV/AIDS treatment

Table 14.	Essential information on personal history of HIV/AIDS treatment					
Date	CD4 cells/ mm^3	%	VL copies/ml	Current ART	Resistance (genotype or phenotype)	Previous ART regimens, reasons for changing

Annex 2. Revised WHO clinical staging of HIV/AIDS for adults and adolescents

(Interim European Region version for people aged ≥15 years with positive HIV antibody test or other laboratory evidence of HIV infection)

Acute HIV infection
- Asymptomatic
- Acute retroviral syndrome

Clinical Stage 1
- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Clinical Stage 2
- Seborrhoeic dermatitis
- Angular cheilitis
- Recurrent oral ulcerations (two or more episodes in six months)
- Herpes zoster (extensive zoster across one dermatome)
- Recurrent respiratory tract infections (two or more episodes in any six-month period of sinusitis, otitis media, bronchitis, pharyngitis, tracheitis)
- Fungal nail infections
- Papular pruritic eruptions

Clinical Stage 3
- Oral hairy leukoplakia
- Unexplained chronic diarrhoea for longer than one month
- Recurrent oral candidiasis (two or more episodes in six months)
- Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)
- Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Clinical Stage 4a
- Pulmonary tuberculosis
- Extrapulmonary tuberculosis (excluding lymphadenopathy)
- Unexplained weight loss (more than 10% within six months)
- HIV wasting syndrome
- Pneumocystis pneumonia
- Recurrent severe or radiological bacterial pneumonia (two or more episodes within one year)
- CMV retinitis (±colitis)
- Herpes simplex virus (HSV) (chronic or persistent for at least one month)
- HIV-associated encephalopathy
- HIV-associated cardiomyopathy
- HIV-associated nephropathy
- Progressive multifocal leukoencephalopathy (PML)
- Kaposi sarcoma and HIV-related malignancies
- Toxoplasmosis
- Disseminated fungal infection (e.g. candida, coccidomycosis, histoplasmosis)
- Cryptosporidiosis
- Cryptoccocal meningitis
- Non-tuberculous mycobacterial infection or disseminated mycobacteria other than tubercle bacilli (MOTT)

[a] Possibly to be included in Stage 4 if supported by sufficient evidence: anal cancer and lymphoma (T-cell Hodgkin lymphoma).
Source: WHO Regional Office for Europe *(140).*

Annex 3. Resistance tests

Resistance testing needs a minimum of 500–1000 copies/ml; it is not possible with completely suppressed virus.

Genotypic resistance testing is based on the analysis of RNA mutations. The amplified genome is sequenced. Known mutations are encoded for changed susceptibility of the virus. It is an indirect proof of drug resistance. The resistant virus population has to be higher than 20% of the whole population.

Virtual phenotypic resistance testing uses computer-based algorithms of genotypic tests connected with large data banks for interpreting results.

Phenotypic resistance testing, like microbiological susceptibility testing, examines the ability of viruses to replicate in cell culture in the presence of different agents. It is compared to the same ability of wild-type virus. The 50% inhibitory concentration (IC50) is a marker of drug potency. The results of the test show different grades of susceptibility.

Which resistance test to use

All tests are presently very expensive. Genotypic tests cost €400, phenotypic tests cost €800 (2005). The time between taking the sample and achieving results can be weeks. Basic genotypic testing should show enough evidence for further planning of regimens. First- and second-line regimens do not require the more expensive phenotypic test. When there is a confused ART history, with a lot of already known mutations or an inexplicable treatment failure, a phenotypic test might be justified. For all tests, the individual has to continue taking the failing regimen; otherwise, wild-type virus will overgrow the resistant strains. There are no standardized recommendations for the use of either phenotypic or genotypic resistance testing.

Annex 4. Essential information about ARVs

Table 15. Essential ARV drug information

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile (major and minor)
NRTIs						
Abacavir	ABC	300 mg	300 mg tablet BID or 600 mg OD	No re-exposure if history of hypersensitivity reaction.	Hypersensitivity reaction (fever, rash, and influenza-like symptoms such as GI and pulmonary symptoms)	65R, 74V, 115F, 184V/I
Didanosine	ddI	250 mg 400 mg	Patients ≥60 kg: 400 mg tablet OD Patients <60 kg: 250 mg tablet OD	Two hours after meal, dose reduction with TDF; not in combination with ribavarin.	Peripheral polyneuropathy, pancreatitis, lactic acidosis	65R, 74V
Emtricitabine	FTC	200 mg	200 mg capsule OD		Same as 3TC	65R, 184V/I
Lamivudine	3TC	300 mg 150 mg	300 mg tablet OD or 150 mg tablet BID		Rare diarrhoea	65R, 184V/I
Stavudine	d4T	30 mg	30 mg capsule BID	Not with ZDV.	Peripheral neuropathy, lipodystrophy, elevation of ALT/AST	41L, 67N, 70R, 75T/M/S/A, 210W, 215Y/F, 219Q/E
Tenofovir	TDF	300 mg	300 mg tablet OD	Dose reduction of ddI, not in combination with d4T; careful with renal insufficiency (dose reduction).	Renal insufficiency	41L, 65R, 210W
Zidovudine	ZDV	300 mg	300 mg tablet BID	Not with d4T; better susceptibility when 65R and 184V.	Anaemia, GI, headache	41L, 67N, 70R, 210W, 215Y/F, 219Q/E
ABC + 3TC	KVX	600 mg ABC, 300 mg 3TC	1 tablet OD			
TDF + FTC	TVD	300 mg TDF, 200 mg FTC	1 tablet OD			
ZDV + 3TC	CBV	300 mg ZDV, 150 mg 3TC	1 tablet BID	Higher (historical) dose of ZDV (higher risk of side-effects).		
ZDV + 3TC + ABC	TZV	300 mg ZDV, 150 mg 3TC, 300 mg ABC	1 tablet BID	Not once daily.		

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile (major and minor)
NNRTIs						
Efavirenz	EFV	600 mg	600 mg tablet OD	Start in the evening.	Dizziness, sleeping disorders, psychiatric disorders (depression, risk of suicide)	100I, 101E, 103N, 106A/M, 108I, 181C, 188L, 190A/S, 225H, 230L
Nevirapine	NVP	200 mg	200 mg tablet BID	First 14 days 200 mg OD, then 200 mg BID.	Rash, liver enzyme elevation	100I, 101E, 103N, 106A/M, 108I, 179D/E, 181C/I, 188C/H, 190A/S, 230L
Delaverdine	DLV	200 mg 100 mg	200 mg × 2 tablets TID or 100 mg × 4 tablets TID	Not used in Europe.	Rash, GI symptoms, diarrhoea	K103N/S, Y181C/I, P236L, G190A/S/E/Q/C, Y188L/H/C, V106A/M, K101E/P, M230L, K238T/N, F318L, V179D/E
PIs						
Atazanavir	ATV	300 mg	300 mg capsules OD plus 100 mg capsules RTV OD	Dosage for treatment experienced patients. Use with RTV.	Bilirubin elevation (harmless)	24I, 33F/I/V, 36I/L/V, 46I/L, 50L, 54V/L/M/T, 82A/F/T/S, 84V, 88S, 90M
Fosamprenavir	FPV	700 mg	700 mg tablet BID plus 100 mg capsule RTV BID	Dosage for treatment experienced patients. Use with RTV.	Rash, headache, diarrhoea, dyslipidaemia	32I,47V, 50V, 54L/M, 82A/F/T/S, 84V
Indinavir	IDV	400 mg	400 mg capsules BID plus 100 mg capsule RTV BID	Use with RTV.	Kidney stones, dyslipidaemia	24I, 32I, 36I, 46I/L, 54V, 82A/F/T/S, 84V, 90M
Lopinavir/ritonavir fixed combination	LPV/r	133 mg/33 mg 200 mg/50 mg	(133 mg/33 mg) × 3 capsules BID or (200 mg/50 mg) × 2 tablets BID	Old formulation required refrigeration; new formulation does not; once daily under discussion.	Diarrhoea, meteorism, dyslipidaemia	10I/R/V, 20M/R, 24I, 32I, 33I/F/V, 46I/L, 53L, 54V/L, 63P, 71V, 82A/F/T, 84V, 90M
Nelfinavir	NFV	250 mg 625 mg	625 mg × 2 tablets BID or 250 mg × 5 tablets BID	With meal, resorption increases 270%; no booster with RTV.	Diarrhoea, meteorism	30N, 36I, 46I/L, 54V/L/M/T, 82A/F/T/S, 84V, 88D/S, 90M
Ritonavir	RTV	100 mg	Only as a booster		Dyslipidaemia, liver enzyme elevation, diarrhoea	
Saquinavir	SQV	500 mg	500 mg × 2 capsules BID plus 100 mg capsule RTV BID	New 500 mg tablets; was in 200 mg tablets until 2004. Use with RTV.	Diarrhoea and other GI symptoms, dyslipidaemia	48V, 53L, 54V/L, 82A/F/T, 84V, 90M
Tipranavir	TPV	250 mg	250 mg × 2 capsules BID plus 100 mg × 2 capsules RTV BID	Dosage for treatment experienced patients. Do not combine with other PIs. Use with RTV.	Dyslipidaemia (severe), liver enzyme elevation, diarrhoea	13L/V, 20M/R/V, 33F/I, 35D/N, 36I, 45R, 46I/L, 47V, 54A/M/T/V, 58E, 66F, 69K, 71I/K, 74P, 82F/L/T, 84C/V, 90M, 91S

ARV	Abbr.	Size	Dosage	Remarks	Major side-effects (cf. Table 11)	Resistance profile (major and minor)
Fusion inhibitors						
Enfuvirtide	ENF	90 mg	90 mg/ml subcutaneous injection BID	No oral formulation.	Skin reaction (itching, swelling, pain)	gp41 single point mutation or gp 41 double and triple point mutations between positions 36 and 45; gp 41 mutation outside of position 36-45

Sources: Adapted from Sande & Eliopoulos, Gilbert, Moellering & Eliopoulos, Antoniu & Tseng, IAPAC *(137–139, 141)*.

Annex 5. Tools for adherence monitoring

Self-reporting is a good adherence marker, but it is not perfect. It seems to overestimate ART adherence more than other methods *(142)*. To be effective, the patient must be willing to disclose problems, particularly face to face. This method may be important in reinforcing the central role of patients in managing their own adherence, as opposed to provider-controlled methods.

Provider estimates of adherence have been demonstrated to be poor *(143)* and are not advisable.

Drug-level monitoring is expensive and not yet possible for all ARVs. It is not a method for routine control of adherence, and can only reveal a snapshot of the time the sample is taken *(144)*. In case of low plasma drug levels, adherence has to be discussed. Laboratory markers like mean corpuscular volume of erythrocytes might show adherence to ZDV and to a lesser extent d4T.

Medication Event Monitoring System (MEMS) is frequently used in research settings. An electronic device fitted to pill boxes records the removal of the cap. It is associated with predictable virological response to ART *(145)*. It is not possible with blister packs.

Pill counts and pharmacy records may be seen as an unwelcome attempt of health care providers to police adherence. They are time-consuming and require patients to bring their medication with them.

Pill identification test (PIT) is a novel method that correlates with validated self-reporting measures *(146)*. Patients are invited to distinguish the pills of their regimen from a display of ARVs, including two "twin pills", which are similar but not identical to their own.

The use of **surrogate markers** is reliable but too late when poor adherence is revealed. Individuals with virological failure on a PI-containing regimen had low PI blood levels, low adherence levels by pill count and an absence of genotypic resistance to PIs, suggesting their treatment failure had been caused by low adherence *(147, 148)*. Providers have to be careful with interpretation of these markers, however, because of other possible reasons for low drug levels *(145)*.

Annex 6. List of antiretroviral drugs[5]

Table 16. Antiretroviral drug list

International non-proprietary name (INN)	Proprietary name	Pharmaceutical company
NRTIs		
Abacavir (ABC)	Epzicom *US*, Kivexa *United Kingdom* (lamivudine/abacavir) Trizivir *Europe, United Kingdom, US* (zidovudine/lamivudine/abacavir) Ziagen *United Kingdom, United States*	*GlaxoSmithKline*
	Abavir	*Genixpharma*
	Virol Virol LZ (abacavir/lamivudine/zidovudine)	*Ranbaxy*
Didanosine (ddI)	Videx, Videx EC	*Bristol-Myers Squibb*
	Dinex EC Odivir Kit (didanosine/lamivudine/efavirenz)	*Cipla*
	Aviro-Z Virosine Viro-Z	*Ranbaxy (India)*
	Divir	*Thai Government*
Emtricitabine (FTC)	ATRIPLA (efavirenz/emtricitabine/tenofovir)	*Bristol-Myers Squibb and Gilead Sciences*
	Emtriva Truvada (tenovovir/emtricitabine)	*Gilead Sciences*
Lamivudine (3TC)	Combivir *United Kingdom, United States* (lamivudine/zidovudine) Epivir *United Kingdom, United States*, Zeffix *United Kingdom* Epzicom *United States*, Kivexa *United Kingdom* (lamivudine/abacavir) Trizivir *United Kingdom, United States* (zidovudine/lamivudine/abacavir)	*GlaxoSmithKline*
	Lamivox Stavex-L (lamivudine/stavudine) Stavex-LN (lamivudine/nevirapine/stavudine) Zidovex-L (lamivudine/zidovudine) Zidovex-LN (lamivudine/nevirapine/zidovudine)	*Aurobindo*
	Duovir (lamivudine/zidovudine) Duovir-N (lamivudine/nevirapine/zidovudine) Lamivir Odivir Kit (didanosine/lamivudine/efavirenz) Triomune (lamivudine/nevirapine/stavudine)	*Cipla*
	Heptavir Lamistar 30, Lamistar 40 (lamivudine/stavudine) Nevilast (lamivudine/nevirapine/stavudine) Zidolam (lamivudine/zidovudine)	*Genixpharma*
	Virolam Virocomb (lamivudine/zidovudine) Virolans (lamivudine/nevirapine/stavudine) Virolis (lamivudine/stavudine) Virol LZ, Abac-ALZ (abacavir/lamivudine/zidovudine)	*Ranbaxy*

[5] This list is a compilation of those ARVs that are widely used, and should not be construed to be exhaustive. It was accurate as of 31 July 2006. ***Disclaimer:*** The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.

International non-proprietary name (INN)	Proprietary name	Pharmaceutical company
Stavudine (d4T)	Zerit, Zerit XR	*Bristol-Myers Squibb*
	Stavex Stavex-L (lamivudine/stavudine) Stavex-LN (lamivudine/nevirapine/stavudine)	*Aurobindo*
	Stavir Lamivir-S (lamivudine/stavudine) Triomune (lamivudine/nevirapine/stavudine)	*Cipla*
	Lamistar (lamivudine/stavudine) Nevilast (lamivudine/nevirapine/stavudine) Stag	*Genixpharma*
	Stavir	*GPO (Thailand)*
	Avostav Triviro-LNS (lamivudine/nevirapine/stavudine) Virolans (lamivudine/nevirapine/stavudine) Virolis, Coviro (lamivudine/stavudine) Virostav	*Ranbaxy*
Tenofovir (TDF)	Truvada (tenofovir/emtricitabine) Viread (tenofovir)	*Gilead Sciences*
	ATRIPLA (efavirenz/emtricitabine/tenofovir)	*Bristol-Myers Squibb*
Triple nuceoside (TRZ)	Trizivir *United Kingdom, United States* (zidovudine/lamivudine/abacavir)	*GlaxoSmithKline*
Zidovudine (ZDV or AZT)	Combivir *United Kingdom, United States* (lamivudine/zidovudine) Retrovir *United Kingdom, United States* Trizivir *United Kingdom, United States* (zidovudine/lamivudine/abacavir)	*GlaxoSmithKline*
	Zidovex	*Auribindo*
	Zidovir Duovir (lamivudine/zidovudine)	*Cipla*
	Zido-H (zidovudine)	*Genixpharma*
	Antivir	*GPO (Thailand)*
	Aviro-Z Virocomb (lamivudine/zidovudine) Virol LZ (abacavir/lamivudine/zidovudine) Viro-Z	*Ranbaxy*
NNRTIs		
Delavirdine (DLV)	Rescriptor	*Pfizer, Inc*.
Efavirenz (EFV)	Sustiva *Europe, United Kingdom*, Stocrin *Australia, Europe, Latin America, South Africa* ATRIPLA (efavirenz/emtricitabine/tenofovir)	*Bristol-Myers Squibb*
	Viranz	*Aurobindo*
	Efavir	*Cipla*
	Estiva	*Genixpharma*
	Efferven	*Ranbaxy*

International non-proprietary name (INN)	Proprietary name	Pharmaceutical company
Nevirapine (NVP)	Viramune	*Boehringer Ingelheim*
	Nevirex Stavex LN (lamivudine/nevirapine/stavudine)	*Aurobindo*
	Duovir-N (lamivudine/nevirapine/zidovudine) Nevimune Triomune (lamivudine/nevirapine/stavudine)	*Cipla*
	Nevilast (lamivudine/nevirapine/stavudine)	*Genixpharma*
	GPOVir	*GPO (Thailand)*
	Nevipan Triviro LNS (lamivudine/nevirapine/stavudine) Virolans (lamivudine/nevirapine/stavudine) Zidovex-LN (lamivudine/nevirapine/zidovudine)	*Ranbaxy*
Fusion inhibitors		
Enfuvirtide, T-20	Fuzeon *United Kingdom, United States*	*Roche Pharmaceuticals & Trimeris, Inc.*
Protease inhibitors		
Amprenavir (APV)	Agenerase *United Kingdom, United States*	*GlaxoSmithKline*
Atazanavir (ATV)	Reyataz *Europe, United States*	*Bristol-Myers Squibb*
Fosamprenavir (FPV)	Lexiva *United States*, Telzir *United Kingdom*	*GlaxoSmithKline and Vertex*
Indinavir (IDV)	Crixivan	*Merck & Co.*
	Indivex	*Aurobinda*
	Indivir	*Cipla*
	Indivir	*Genixpharma*
	Virodin	*Ranbaxy*
Lopinavir/ritonavir combination (LPV/r)	Kaletra	*Abbott Laboratories*
Nelfinavir (NFV)	Viracept	*Pfizer, Inc., Roche Pharmaceuticals*
	Nelvex	*Aurobinda*
	Nelvir	*Cipla*
	Nelfin	*Genixpharma*
	Nefavir	*Ranbaxy*
Ritonavir (RTV)	Norvir	*Abbott Laboratories*
	Ritovir	*Hetero/Genix*
Saquinavir (SQV)	Fortovase *Europe, United Kingdom, United States* Invirase *United Kingdom, United States*	*Roche Pharmaceuticals*

Annex 7. Glossary

Adherence is patient ability to take ARV drugs as prescribed at specific time. High adherence is defined as taking over 95% of doses; low adherence is anything under this level.

Backbone is the part of ARV treatment, usually consisting of two NRTIs which are used in combination with an NNRTI or a PI or a PI and fusion inhibitor. “Optimized backbone” means an adjusted combination of probable working NRTIs based on results of resistance testing.

Genetic barrier is a description of the number of mutations needed for the virus to be resistant to a drug. Resistance with 1 mutation means a low genetic barrier; resistance with 10 mutations means a very high genetic barrier, though this characterization is subject to change.

Major mutations are the changes in viral RNA that encode for resistance to particular ART drugs or ART classes.

Minor mutations work in combination and can lead to resistance or counteract disadvantages of other major or minor mutations.

Nucleoside analogue mutations (NAMs) reveal cross-resistance for most NRTIs.

A **point mutation** is one change in the RNA code resulting in resistance to a drug or class of drugs. For example, in ART treatment mutation 103 means a resistance to all NNRTIs, resulting from changes in virus at specific point.

Resistance is the result of changing amino acids in the RNA strain of the virus. This happens due to the poor replication abilities of HIV. Most changes lead to the death of the virus; other changes are viable, and the resultant virus has the ability to survive the mechanisms of ART. In most cases, resistance leads to poorer viral fitness, meaning a slower HIV replication rate. Though a benefit for the patient at the beginning, it will result in total resistance and high replication rates of the less fit viruses. However, several combinations of resistance patterns can balance this disadvantage, so that some resistance patterns result in a fitter virus in the end.

Thymidine analogue mutations (TAMs) are usually a result of ZDV treatment.

Annex 8. Beyond the horizon

Research on ART continues. New viral mutations and drug resistance occur regularly – as do new understandings of the interactions between drugs and the virus. The following are some of the latest ARVs to be approved or to be pending approval, along with new combinations of older drugs.

- A once-daily fixed-dose combination of TDF + FTC + EFV has been recently developed and appears to be slightly more effective than the standard ZDV + 3TC + EFV combination *(42)*.
- TMC125 (etravirine) is a new NNRTI that has potencies despite existing mutations which encode for NNRTI class resistance *(149)*.
- DRV (darunavir) is a new PI with an even higher genetic barrier than LPV/r. Development of resistance is slower than with NFV, APV or LPV/r in vitro. TMC114 is available through an expanded access programme (EAP) *(150)*. It has been recently approved by the US Federal Drug Administration (FDA).
- AG1549 (capravirin) is also a second-generation NNRTI, which is effective despite classical NNRTI mutations.
- New coreceptor inhibitors in the fusions molecule are coming. CXCR4- and CCR5-expressing viruses are being fought with drugs that can inhibit one or both of them. New tests for the coreceptor expression of the virus are needed for this treatment. Side-effects are limited for now, though initial experience with this new class has revealed cardiotoxic effects. On August 6, 2007, FDA granted accelerated approval to Selzentry (maraviroc) for combination antiretroviral treatment of adults infected with only CCR5-tropic HIV-1 detectable, who have evidence of viral Replication and have HIV-1 strains resistant to multiple antiretroviral agents.

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EUROPE

2 Management of Opportunistic Infections and General Symptoms of HIV/AIDS

Clinical Protocol for the WHO European Region

Contents

I. Principles

- Management of opportunistic infections (OIs) is an essential component of comprehensive HIV/AIDS treatment and care.
- *All* patients with OIs – irrespective of gender or social class and including injecting drug users (IDUs), sex workers, prisoners, immigrants and other vulnerable populations – should be treated. The decision of whom to treat should be based exclusively on medical considerations.
- Treatment for comorbidities should not stop while OI prevention and/or treatment is being provided.

II. Management of opportunistic infections

1. General information

HIV-related infections and illnesses include the following (Table 1).

Table 1. HIV-related infections and illnesses

Bacterial infections	Fungal infections	Viral infections	Parasitic infections	Other illnesses
Tuberculosis Bacterial respiratory infections Bacterial enteric infections Atypical mycobacteriosis Bartonellosis	*Candida* oesophagitis Cryptococcosis Histoplasmosis *Pneumocystis jirovecii* pneumonia (PCP) Coccidioidomycosis	Herpes simplex virus (HSV) disease Varicella-zoster virus (VZV) disease Cytomegalovirus (CMV) disease Human herpesvirus 8 (HHV8) infection, also known as the Kaposi sarcoma herpes virus (KSHV) Human papillomavirus (HPV) infection Progressive multifocal leukoencephalopathy Hepatitis B and C (natural course of infection is worsened by HIV coinfection)	Toxoplasmosis Cryptosporidiosis Microsporidiosis Isosporiasis Leishmaniasis	Kaposi sarcoma (KS) Non-Hodgkin lymphoma (NHL) Cervical cancer Encephalopathy Vacuolar myelopathy

The most common OIs in the WHO European Region include:
- tuberculosis (TB)
- bacterial infections
- PCP
- herpes infections (including herpes zoster, CMV, HSV 1 and 2 (HSV 1/2)
- *Candida* oesophagitis
- *Cryptococcus* meningitis
- toxoplasmosis.

Less frequent opportunistic infections and cancers include:
- *Mycobacterium avium* complex (MAC or MAI) disease
- KS
- NHL
- CMV infection (retina, gastrointestinal (GI) tract, encephalitis).

The order of infections and cancers in the list may change, due to factors that may or may not be related to the HIV/AIDS epidemic.

2. Initial evaluation

Patients with unknown HIV status who present with infections or illnesses that are associated with HIV infection should be offered HIV testing and counselling. The physician should explain to the patient the reasons for offering an HIV test and the importance of knowing the results for correct clinical management. However, patients have the right to refuse testing (opt out).

The initial assessment of HIV status should include:
- HIV pretest counselling;
- serological testing (typically ELISA and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test (which indicates HIV infection if the result is positive); and
- post-test counselling – whether the result is positive or negative – including information on reducing risky behaviour.

If the patient is HIV-positive, an initial clinical evaluation should be made to determine the clinical stage of the infection and identify comorbidities and conditions. (For more information please refer to Protocol 1, *Patient evaluation and antiretroviral treatment of adults and adolescents*).

3. Counselling patients on OIs and other conditions

- Physicians and nurses should counsel all patients and/or families about the chronic nature of HIV infection and the possible appearance of OIs.
- Patients should be informed that some OIs can be prevented (see Table 2 below).
- They should know that it is essential to diagnose an opportunistic infection early, so that they consult their physician when they suspect any disease progression may be occurring.
- They should be counselled on symptoms that might indicate OIs and the need to inform their physician about them:
  - dyspnoea: *Pneumocystis jirovecii* pneumonia (PCP), TB, pneumonia;
  - cough: PCP, TB, pneumonia;
  - bloody sputum: TB, pneumonia;
  - neurological changes: cerebral toxoplamosis, cerebral lymphoma or meningitis/ encephalitis;
  - weight loss, fever, night sweats: TB, atypical TB, lymphoma;
  - visual impairment: CMV retinitis;
  - painful swallowing: candida oesophagitis; or
  - diarrhoea: CMV colitis, infection with cryptosporidiae, microsporidiae, salmonellosis, etc.
  - visual field loss (reading a newspaper is a good and sensitive test);
  - weakness of arms or legs: cerebral toxoplasmosis;
  - any change of mental status or behavioural signs that may signal mental health problems (as observed by friends and family members): herpes meningitis, toxoplasmosis, progressive multifocal leukoencephalopathy (PML), etc.
  - change in skin conditions or (more often) oral thrush (possible antiretroviral treatment (ART) failure).
- Patients should know the importance of monitoring their chronic conditions.
  - Patients with chronic hepatitis should have an abdominal ultrasound twice a year because of the risk of hepatocellular carcinoma.
  - Patients with a history of tuberculosis should have a chest X-ray once a year.
  - Older overweight HIV patients who have hypertension and are on an ART regimen that includes a protease inhibitor (PI) must be checked for cardiovascular disease, diabetes and other conditions.
- Patients should be given a checklist that includes a schedule of laboratory and clinical tests to be undertaken on a regular basis. The content of this list may vary due to comorbidities.

For further information on counselling issues please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

4. OI prophylaxis in HIV-infected patients

- Certain OIs that may develop in people living with HIV (PLHIV) can be prevented.
- Prophylaxis of OIs in PLHIV should be an integral part of OI management.
- After initiating ART, it is possible to discontinue primary prophylaxis if the CD4 count has risen over the relevant indication level for 3–6 months (e.g. PCP: >200 cells/mm^3, toxoplasmosis: >100 cells/mm^3, MAI: >50 cells/mm^3). See Table 2 below. Discontinuation of secondary prophylaxis should also be possible in the same situation with close monitoring. Always restart prophylaxis when CD4 counts fall below the indication level.

Table 2 summarizes the most recent recommendations for prophylaxis strategy.

Table 2. OI prophylaxis for HIV-infected patients

Pathogen	Indication	First choice	Alternatives
Pneumocystis jirovecii	CD4 count <200 cells/mm^3 *or* oropharyngeal candidiasis	TMP-SMZ (cotrimoxazole) double-strength tablet PO[a] OD[b]	• TMP-SMZ single-strength tablet PO OD *(1)* • TMP-SMZ double-strength tablet PO TIW[c] (Monday, Wednesday and Friday) • Dapsone 50 mg PO BID[d] • Dapsone 100 mg PO OD *(2)* • Pyrimethamine 50 mg + dapsone 50 mg + folinic acid 15 mg OD • Pentamidine inhalation 300 mg every three weeks *(3)* • Also possible: clindamycin or atovaquone *(4, 5)*
M. tuberculosis	Purified protein derivative (PPD) reaction ≥5 mm *or* recent contact with a case of active TB	Isoniazid (INH) 300 mg PO + pyridoxine 50 mg PO OD for 6 months *(6)*	Further research is needed for developing alternative prophylaxis treatment for TB in areas with high prevalence of INH resistance.
Toxoplasma gondii, primary	CD4 count <100 cells/mm^3	TMP-SMZ double-strength tablet PO OD	• TMP-SMZ single-strength tablet PO OD *(7, 8)* • Dapsone 50 mg PO OD + pyrimethamine 50 mg PO QW[e] + folinic acid 25 mg PO QW
Toxoplasma gondii, secondary	CD4 count <100 cells/mm^3	TMP-SMZ double-strength tablet PO OD	Dapsone 50 mg PO OD + pyrimethamine 50 mg OD + folinic acid 15–25 mg OD
M. avium complex	CD4 count <50 cells/mm^3	Azithromycin 1200 mg PO QW	Clarithromycin 500 mg PO BID *(9, 10)*
Cryptococcus neoformans	CD4 count <50 cells/mm^3	Fluconazole 100–200 mg PO OD *(11)*	

[a] PO: per os.
[b] OD: once daily.
[c] TIW: three times weekly.
[d] BID: twice daily.
[e] QW: once weekly.

5. Diagnosis and treatment of OIs

5.1. Respiratory infections

- Lower respiratory tract infections are the most common recurrent infections in PLHIV. They are usually life-threatening and can be caused by bacteria, viruses (rarely) and fungi (also rarely).

- Patients may present early in the course of HIV infection with bacterial pneumonias, which respond readily to antibiotics *(12)*.
- Patients with HIV infection appear to be particularly prone to infections with encapsulated organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae (13)*.
- Later, and with the onset of immune suppression, patients may develop opportunistic pulmonary infections, the most important of which is pulmonary TB.
- As cell-mediated immunity deteriorates, patients may develop life-threatening opportunistic infections such as PCP and severe fungal and viral pneumonias. Table 3 summarizes the respiratory illnesses associated with HIV infection.

Table 3. Respiratory illness in PLHIV

Type of infection	Possible complications[a]
Bacterial	
Pneumococcal pneumonia	Empyema[b], pleural effusion, lung abscess
H. influenza pneumonia	Pleural effusion[b], lung abscess, empyema,
Klebsiella pneumonia	Empyema[b], pleural effusion
Staphylococcal pneumonia	Lung abscess[b], empyema, pleural effusion
M. tuberculosis pneumonia	Pericardial effusion, lung abscess, empyema, pleural effusion
MAC pneumonia	Rare complications: Abscesses especially with IRIS
Viral	
Cytomegalovirus	Pneumonitis[b] (highly lethal)
Herpes simplex virus	Pneumonitis[b] (highly lethal)
Fungal	
Pneumocystis pneumonia	Pneumothorax
Cryptococcosis	
Histoplasmosis	
Aspergillosis	Lung abscess
Other conditions	
KS	Pleural or pericardial effusion
Lymphoma	Pleural or pericardial effusion
Carcinoma (non-HIV-related)	Pericardial effusion

[a] Possible complications are in the order of the frequency the occur.
[b] Complications that occur most frequently.

5.1.1. Bacterial respiratory infections

- Bacterial lower respiratory tract infections are common in the general population, but they are more frequent and more severe in immunosuppressed persons with HIV infection.
- *S. pneumoniae* is the most common lower respiratory tract pathogen.
- Patients with bacterial pneumonia present with cough and fever and often have chest pain, difficulty in breathing and tachypnoea.
- Chest X-rays may show classic lobar pneumonia, bronchopneumonia or atypical (or absent) infiltrates.

5.1.1.1 Diagnosis

The diagnosis of pneumonia is usually made on clinical grounds and by a chest X-ray, which may reveal:

- lobar or patchy consolidation
- diffuse lung infiltrates or
- atypical changes, including cavitary disease.

5.1.1.2. Treatment

- If the patient is not severely ill and no PCP is suspected, treatment may be provided at home according to Tables 4 and 5 below.

Table 4. First-line antibiotic treatment of bacterial pneumonia

Antibiotic	Dose	Frequency	Route	Duration
Amoxicillin (Use a penicillin in combination with beta lactamase inhibitor if there is a chance of penicillin/ampicillin resistance.)	500–1000 mg	TID[a]	PO	7 days or longer until resolved
or:				
Erythromycin	500 mg	QID[b]	PO	7 days
or:				
Clarithromycin	500 mg	BID	PO	7 days
or:				
Azithromycin	500 mg	OD	PO	3–4 days
or:				
Quinolone with pneumococcal activitiy (e.g. moxifloxacin)	400 mg	OD	PO	7 days
or:				
Doxyciclin	100 mg	BID	PO	7 days

[a] TID: three times daily.
[b] QID: four times daily.

- If patients do not respond to first line treatment over a period of 72 hours (no fever, C-reactive protein (CRP) elevation resolved, leukocyte count is not reliable), the patient should be referred to the hospital and second line treatment prescribed as indicated below. Patients may also require oxygen (in this case PCP should be suspected).
- Severely ill patients should be referred for hospital admission immediately.

Table 5. Second-line treatment of bacterial pneumonia

Antibiotic	Dose	Frequency	Route	Duration
Ceftriaxone + erithromycin	2 g 500 mg	OD QID	IV*	7 days
or:				
Ampicillin + sulbactam + erythromycin	1500 mg 500 mg	TID QID	IV	7 days
or:				
Quinolone with pneumococcal activitiy (e.g. moxifloxacin)	400 mg	OD	IV/PO	7 days
or:				
Chloramphenicol (if other drugs are not available)	12.5 mg (base) per kg of body weight	QID	IV	7 days

*Intravenously.

- If patients do not respond to this treatment, consider PCP or TB as a possible diagnosis. The diagnostic gold standard is lavage by bronchoscopy to define the pathogen before starting antibiotics *(14)*. Also helpful are blood cultures, which have a higher rate of pneumococcal identification and may be done up to five times.

5.1.2. Atypical mycobacteriosis

Mycobacterium avium complex (MAC or MAI) disease is less common than some other OIs. It presents with:

- fever
- weight loss
- night sweats
- diarrhoea
- wasting.

MAC organisms may be found in the blood and excreta of infected persons. A definite infection can be shown with acid-fast bacilli (AFB) in sterile fluids or specimens (blood, cerebrospinal fluid, bone marrow and liver).

5.1.2.1. Diagnosis

- Blood cultures on special media are the cornerstone of MAC diagnosis.
- In most symptomatic patients, the intensity of mycobacteraemia is such that most or all blood cultures are positive.
- Because the liver and bone marrow are often involved in disseminated MAC infection, the bacteria may be visible in acid-fast-stained biopsy samples from these sites.
- Presumptive diagnosis by examination of a biopsied liver specimen saves time.

5.1.2.2. Treatment

Table 6. Atypical mycobacteriosis treatment

Antibiotic	Dose	Frequency	Route	Duration
First-line treatment *(15, 16)*				
Clarithromycin + ethambutol + rifabutin	500 mg–1000 mg	BID	PO	6 months; decide on clinical grounds
	15 mg/kg	OD	PO	6 months; decide on clinical grounds
	300–450 mg	OD	PO	6 months; decide on clinical grounds
Other drugs active against MAC[a]				
Azithromycin	500–1200 mg	OD	PO	6 months
Ciprofloxacin	500 mg	BID	PO	6 months
Amikacin	15 mg/kg/day or 7.5 mg/kg/day	OD BID	IV IV	No longer than 4 weeks

[a] Rifampicin is not effective against MAC.

- Once MAC treatment has been started, and there is indication that the condition is improving and the drugs are well tolerated, ART should be initiated.
- Standard procedure is to start on ART 4–6 weeks after MAC treatment has begun. After six months with an improved immune response (CD4 count >100 cells/mm^3), reduce MAC treatment or stop it and use a secondary prophylaxis.
- Stopping the secondary prophylaxis is possible when the immune system is stable and responsive for more than 3–6 months.
- MAC treatment or secondary prophylaxis should be administered for six months to ensure a successful treatment and avoid relapse.
- It is important to begin with treatment for MAC to avoid confusion about whether any side-effects come from MAC drugs or ART.

- There is the possibility of immune reconstitution inflammatory syndrome (IRIS) after starting ART (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, sections Clinical failure and Immune reconstitution inflammatory syndrome).

5.1.3. Pneumocystis pneumonia

- PCP is a common HIV-associated OI, caused by the fungus *Pneumocystis jirovecii* (formerly known as *Pneumocystis carinii)*.
- Patients usually present with cough, shortness of breath and fever.
- Occasionally patients with PCP have no chest signs.
- Patients with PCP often have features of respiratory failure such as shortness of breath and cyanosis.
- Symptoms may be very severe; an attack of PCP may lead to death if not treated early and effectively.

5.1.3.1. Diagnosis

- Diagnosis is often made on clinical grounds when a febrile PLHIV presents with respiratory distress, with or without cyanosis.
- The patient may have a non-productive cough, but the main feature of the condition is shortness of breath, with minimal or absent chest signs on physical examination.
- Chest X-rays:
  - There is not always a ground-glass opacification in the lower zones of both lung fields.
  - There may be evidence of patchy infiltrates in both lung fields that mimics bacterial pneumonia or TB.
  - A considerable proportion of patients with confirmed PCP show no changes at all on the X-ray.
- Bronchial lavage is the gold standard of diagnosis *(14)*. Diagnosis is confirmed upon finding cysts of *Pneumocystis* in forced sputum or in bronchial lavage aspirate.
- If diagnosis cannot be established due to the lack of a bronchoscope, deteriorating pulmonary function tests or blood gas analysis can be used as indicators.
- Treatment should be started immediately upon diagnosis.

5.1.3.2. Treatment

Patients should be admitted to hospital for management. Supportive therapy including oxygen may be necessary. Details of treatment are given in Tables 7 and 8 below.

Table 7. PCP first-line treatment

Antimicrobial agent	Dose	Frequency	Route	Duration
TMP-SMZ	240/1200 mg <60 kg 320/1600 mg ≥60 kg	QID	PO/IV	21 days

Table 8. PCP second-line treatment

Antimicrobial agent	Dose	Frequency	Route	Duration
Clindamycin + primaquine	600 mg 15 mg	QID BID	PO/IV PO	21 days *(17)*
or:				
Pentamidine (in combination with a broad-spectrum antibiotic to prevent bacterial superinfection, e.g. ampicillin + sulbactam for 10 days)	4 mg/kg IV daily. Dose reduction to 2 mg/kg after 5 days of treatment *(18)*	OD	IV	21 days

- Severely ill patients will require prednisolone, 80–250 mg PO/IV daily for 1–2 weeks (reduces interstitial oedema).
- Combination treatment should also be considered in severe cases, for example, TMP-SMZ and pentamidine. This treatment has incurred a high risk of toxicity according to case reports only. A severe case of PCP requires artificial ventilation or an oxygen saturation (SO_2) <92%.

Side-effects should be monitored, especially the kidneys (both), pancreas (with pentamidine) and bone marrow (with TMP-SMZ). Lab analysis should be required twice weekly.

After successfully treating an acute episode of PCP:
- it is necessary to continue secondary prophylaxis with TMP-SMZ 160/800 mg PO OD on a long-term basis;
- prophylaxis may be discontinued when the patient's CD4 count remains stable at >200/mm^3 for at least three months.

5.1.4. Other causes of pneumonia in immunosuppressed people

- Other causes of pneumonia include fungal and viral infections. They are difficult to diagnose without sophisticated laboratory facilities and are difficult to treat.
- Viral pneumonia may be caused by herpes simplex virus, varicella-zoster virus or cytomegalovirus.
- In addition to PCP, other fungal causes of pneumonia include *Histoplasma capsulatum*, *Cryptococcus neoformans* and *Aspergillus*.

5.1.4.1. Diagnosis

- When pneumonia fails to respond to standard treatment, TB or pneumonia caused by viruses, fungi or protozoa should be suspected.
- Making a specific diagnosis of fungal or other infections requires sophisticated laboratory tests:
  - pp65 early CMV antigen from peripheral blood or bronchial lavage;
  - polymerase chain reaction (PCR) for viruses of the herpes family (CMV, HSV 1/2, VZV, Epstein-Barr virus (EBV), human herpes virus 8 and 6 (HHV8, HHV6))
  - special cultures for slow-growing pathogens, such as nocardia.
- Close collaboration between physician and microbiologist is needed.

5.1.4.2. Treatment

Treatment will depend on the cause, for example foscarnet for CMV infection or long-term antibiotics (eight weeks) for nocardia.

5.2. Gastrointestinal infections (GIIs)

- GIIs in PLHIV may be the result of any of the following infections:
  - HIV (direct infection of the GI tract)
  - bacterial
  - fungal
  - viral
  - protozoal
  - parasitic.
- Some of the problems may arise from atrophy of the intestinal villi, which commonly leads to malabsorption.
- The most common GI problem encountered is diarrhoea, which can be acute, acute-on-chronic or chronic.
- Diarrhoea is persistent or chronic in people with AIDS, and an important cause of death among them.
- Acute diarrhoea leads to dehydration unless properly treated.
- The passing of bloody or blood-stained stools occurs in persons with shigellosis or amoebic dysentery.
- Other common GI problems in PLHIV include:
  - poor appetite
  - nausea
  - vomiting
  - progressive weight loss.

Table 9 summarizes the clinical features, diagnosis and treatment of some of the more common gastrointestinal infections seen in immunosuppressed PLHIV.

Table 9. Gastrointestinal infections commonly encountered in PLHIV

Infection	Clinical features and diagnosis	Treatment
Non-typhoid salmonelloses	Fever, abdominal pain, diarrhoea with or without blood, weight loss, anorexia, hepatosplenomegaly Diagnosis upon blood or stool culture	Ciprofloxacin 500 mg PO BID for >2 weeks *(19)*
Shigelloses	Fever, abdominal pain, bloody diarrhoea Diagnosis upon blood or stool culture	Ciprofloxacin 500 mg PO BID for 7–10 days *or:* Nalidixic acid 500 mg PO QID for 7–10 days *or:* TMP-SMZ 160/800 mg PO BID for 7–10 days
Cryptosporidiosis	Watery diarrhoea, loss of appetite; afebrile Diagnosis upon stool microscopy	Paromomycin 1 g PO BID + azithromycin 600 mg PO OD for 4 weeks *then:* Paromomycin alone for 8 weeks *(20, 21)*. Treatment often fails *(22)*.
Microsporidiosis	Watery diarrhoea, loss of appetite; afebrile Diagnosis upon stool microscopy	Albendazole 400 mg PO BID for 4 weeks. *If this does not work try:* Mebendazole 200 mg PO TID (albendazole tends to be more successful) *(23)*.

5.3. Candidiasis

- *Candida albicans* colonizes primarily the GI tracts of both men and women. Up to one third of all normal women also carry *C. albicans* in the vagina.
- Women with vaginal candidiasis may develop a vaginal discharge and vulvovaginal pruritus.

- Men with genital candidiasis will develop balanitis or balanoposthitis and will complain of a subpreputial discharge and itchiness of the penis and foreskin.
- Oral candidiasis (thrush) leads to inflammation of the mucosal surface together with the appearance of adherent white plaques.
- *C. albicans* can infect the skin and cause pruritic dermatitis.
- Depending on the level of immune suppression, oral infection may extend to involve the oesophagus.
- Bronchial and disseminated infections are rare.

5.3.1. Symptoms

- Oral thrush can include infection of the:
  - buccal mucosa
  - tongue
  - oropharynx
  - gums
  - hard and soft palates.
- Patients may have no symptoms at all or may complain of a burning sensation in the mouth when eating.
- Some patients may complain of white patches in the mouth.
- If the thrush has extended into the oesophagus, patients may complain of:
  - pain on swallowing food
  - retrosternal pain
  - excessive salivation.

Patients in whom candidiasis occurs most frequently are:

- healthy pregnant women and healthy women on oral contraceptives
- healthy neonates, especially pre-term infants
- those on prolonged courses of broad-spectrum antibiotics
- those receiving steroids systemically
- those with diabetes mellitus
- those with congenital or acquired immunodeficiencies
- those suffering from chronic debilitating conditions
- the severely malnourished
- those with cancer and those receiving chemotherapy or radiotherapy.

5.3.2. Diagnosis

- The diagnosis of oropharyngeal candidiasis is made on clinical grounds, based on direct observation and microscopic examination of material obtained from lesions.
- Examination of the oral cavity may reveal redness and inflammation of the mucosa, with or without patches of white plaques.
- Inflammation may be seen on the palate, throat, gums, tongue and/or the inside of the cheeks. When the tongue is affected, it may be smooth and red, and the papillae normally found on the tongue may be absent.
- Diagnosis has to be confirmed by histological examination of tissue biopsies only in cases of suspected *Candida* oesophagitis or aspergillosis of the lungs.
- The symptoms of *Candida* oesophagitis are:
  - difficulty in swallowing
  - pain in the chest that increases with swallowing.
- Disseminated candidiasis causes fever and symptoms in the affected organs (for example, blindness when it affects the eyes).

5.3.3. Treatment

- Localized candidiasis is treated first with relatively inexpensive topical drugs such as nystatin, miconazole or clotrimazole.
- In patients with disseminated candidiasis and in those in whom topical treatment has failed, systemic antifungal agents such as ketoconazole, fluconazole, itraconazole or amphotericin B may be given.
- For treatment of drug-dependent patients receiving methadone as opioid substitution therapy, see Table 4 of Protocol 5, *HIV/AIDS treatment and care for injecting drug users*, for the interactions of fluconazole, itraconazole and ketoconazole with methadone.

Table 10. Oral candidiasis

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment *(24)*				
Myconazole	Buccal tablets	Once a day	Gum patch	7 days
or:				
Fluconazole	100 mg	BID for 3 days followed by OD for 4 days	PO	7 days
Second-line treatment *(25)*				
Itraconazole	200–400 mg	OD	PO	7 days

Table 11. Vaginal candidiasis

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment				
Fluconazole	100 mg	Single dose	PO	Once
Clotrimazole	500 mg	Single dose	Vaginal	Once
Second-line treatment				
Ketoconazole	200 mg	BID	PO	3 days
Ketoconazole	200 mg	OD	PO	7 days
Maintenance therapy				
Nystatin	2–4 million IU	BID	PO	10 days
or:				
Fluconazole	50–200 mg	OD	PO	10 days
Third-line treatment				
Ketoconazole	200 mg	OD	PO	Depends on response, usually 7–10 days
Itraconazole	100 mg	OD	PO	Depends on response, usually 7–10 days

Table 12. Oesophageal and disseminated candidiasis

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment				
Ketoconazole	200–400 mg	BID	PO	21 days
or:				
Fluconazole (more effective than ketoconazole)	200–400 mg, reduce on clinical grounds after 3 days to 100 mg/day	OD	PO/IV	14 days
Second-line treatment				
Amphotericin B	0.3–0.5 mg/kg		IV	10–14 days
or:				
Itraconazole	200–400 mg	OD	PO	2 weeks

- Long-term maintenance treatment with fluconazole 50–100 mg OD PO, itraconazole 100 mg OD PO or ketoconazole 200 mg OD PO may be necessary for patients who have been treated for candidal oesophagitis.
- If the patient fails to respond to this treatment, a diagnosis of CMV or HSV oesophagitis should be considered, and the patient should be referred for an oesophagoscopy.
- *Candida glabrata*, *C. krusei* and *C. tropicalis* are resistant to fluconazole to some extent. A specimen is needed for culture; susceptibility testing is possible and prescribing of amphotericin B makes more sense. Voriconazole, posaconazole and caspofungin are new drugs encountering rare resistance in any fungi, including *Aspergillus*; all are very expensive. Voriconazole can interact with ARV drugs, and it should not be prescribed to patients taking efavirenz (EFV) or ritonavir (RTV). Patients receiving both PIs and voriconazole should be closely monitored for possible side-effects *(26)*.

5.4. Cryptococcal meningitis

- Cryptococcosis most often appears as meningitis, and occasionally as pulmonary or disseminated disease.
- Cryptococcal meningitis is a common systemic fungal infection in PLHIV.
- **Without treatment, the life expectancy of patients with cryptococcal meningitis is probably less than a month.**

5.4.1. Diagnosis

Cryptococcosis is relatively easy to diagnose. Patients usually present with headache, fever, neck stiffness and/or cranial nerve palsies, or they may be comatose. However, signs of meningeal inflammation such as fever and neck stiffness often do not occur. A centrifuged deposit of the cerebrospinal fluid (CSF) should be examined microscopically after adding a drop of India ink.

- The yeasts are visible as organisms surrounded by thick capsules.
- The CSF may be cultured for cryptococci.
- The cryptococcal antigen test is useful in assessing patients for cryptococcosis and can be performed on serum or cerebrospinal fluid.

5.4.2. Treatment

Table 13. Cryptococcal meningitis treatment

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment *(27)*				
Amphotericin B + 5-flucytosine	0.7–1.0 mg/kg 25 mg/kg	OD QID	IV IV	14 days
then: fluconazole	400 mg	OD	PO	At least 10 weeks
then: fluconazole	200 mg	OD	PO	Lifelong
Second-line treatment				
Amphotericin B + 5-flucytosine	0.7–1.0 mg/kg 25 mg/kg	OD QID	IV IV	6–10 weeks
or:				
Amphotericin B	0.7–1.0 mg/kg	OD	IV	6–10 weeks
or (in mild cases):				
Fluconazole	400–800 mg	OD	PO	10–12 weeks
then: fluconazole	200 mg	OD	PO	Lifelong

5.4.3. Secondary chemoprophylaxis or maintenance therapy

- Lifelong secondary chemoprophylaxis is necessary; it may be achieved with fluconazole 200 mg orally once daily for life.
- Alternate long-term secondary prophylaxis may be achieved with itraconazole 200 mg orally once daily for life.
- The need for maintenance therapy with patients who have an improved immune system (CD4 count >200) is presently neither supported nor refuted by concrete evidence.
- For treatment of drug-dependent patients receiving methadone as opioid substitution therapy, see Table 4 of Protocol 5, *HIV/AIDS treatment and care for injecting drug users*, for the interaction of fluconazole with methadone.

5.5. Histoplasmosis

This uncommon acute or chronic infection is caused by inhaling spores from the fungus *Histoplasma capsulatum*.

- The outcome of exposure depends on the immune status of the host as well as the size of the inoculum.
- Intact cell-mediated immunity is essential for preventing its dissemination. The acute illness is influenza-like, with:
  - fever
  - anorexia
  - arthralgia
  - myalgia
  - dry cough
  - chest pain.
- Dissemination occurs soon after initial infection in immunosuppressed patients, who develop:
  - weight loss
  - oral and skin lesions
  - chest symptoms
  - liver, spleen and lymph node enlargement.

- Oral lesions may appear as protruding, necrotic ulcers. There may also be perforation of the palate and extensive soft tissue destruction.

5.5.1. Diagnosis

Diagnosis is made on clinical grounds and is confirmed by fungal cultures or histological examination of biopsied tissues.

- A chest X-ray in acute illness may show:
  - hilar lymphadenopathy
  - scattered infiltrates
  - lower lobe nodules.
- Blood and skin tests have been developed for the diagnosis of histoplasmosis, but they are not widely available.

5.5.2. Treatment

In normal immune systems, acute histoplasmosis is self-limiting and does not require treatment. In immunosuppressed patients it may be treated as shown in Table 14.

Table 14. Treatment of histoplasmosis

Antifungal agent	Dose	Frequency	Route	Duration
Amphotericin B	0.7–1 mg/kg	OD	IV	10 days

Source: Johnson et al. *(28).*

This initial treatment is followed, three months after immunoreconstitution with >100 CD4 cells, with one of the following long-term treatments:

- itraconazole 200 mg BID PO
- fluconazole 200 mg BID PO
- amphotericin B 1 mg/kg IV weekly.

An alternative is itraconazole 200 mg TID PO x 3 days, then 200 mg PO BID x 12 weeks (taken with a meal and an acidic drink).

5.6. Kaposi sarcoma (KS)

- KS is caused by the human herpes virus type 8 (HHV8), also known as the Kaposi sarcoma herpes virus (KSHV).
- Any patient suspected of KS should be examined by an oncologist and referred to an oncology clinic as needed.
- In HIV-associated immunosuppression, KS is more aggressive, disseminated and rapidly progressive than the endemic disease found in people without HIV infection.

5.6.1. Diagnosis

The diagnosis of KS is made on clinical suspicion and confirmed by histological examination of biopsied tissue.

Clinical signs include the following.

- Lesions may be found anywhere on skin and on any mucosal surface. Skin lesions are hyperpigmented, blue or purplish papules or nodules and can be associated with lymphoedema. Systemic lesions are commonly found on the palate, gastrointestinal tract, lungs or lymph nodes.
- Oral lesions of KS may be found on the hard palate and occasionally on the tongue, throat, tonsils or gums. The lesions are purple papules, usually painless and sometimes large and pedunculated.

- Pulmonary lesions are infiltrative with pleural effusion and often lead to respiratory failure. The condition may be confused with bacillary angiomatosis (bartonellosis), an infective condition seen in PLHIV.

5.6.2. Treatment

- KS is a cancer and should accordingly be treated by an oncologist.
- It is treatable with radiotherapy if lesions are localized and with cytotoxic chemotherapy if it is generalized.
- Cytotoxic drug combinations that have been used with varying degrees of success include:
  - liposomal doxorubicin monotherapy (best results) *(29–31)*
  - bleomycin
  - vincristine
  - daunorubicin
  - vinblastine
  - etoposide.
- Remission is difficult to achieve, and relapses are common.
- Localized lesions may be surgically excised or treated with liquid nitrogen (high relapse rate), laser therapy or radiation. Intralesional injection with bleomycin has also been shown to be effective.
- KS is usually treatable with ART alone; after successful initiation of ART, KS becomes inactive and slowly disappears.

5.7. Cervical cancer

- Cervical cancer is one of the most common types of cancer, causing deaths among women worldwide. The estimated number of new cases per year is 500 000 *(32)*.
- Human papillomavirus (HPV) infection is the leading etiologic agent in the development of premalignant and malignant lower genital tract disease, including cervical cancer.
- The relative risk of cervical intraepithelial neoplasia (CIN) is 5–10 times higher for women with HIV/AIDS, and abnormal pathology is observed in 20–40% of their Pap smears *(33, 34)*.

5.7.1. Diagnosis

When a woman is diagnosed with HIV, a gynaecologic evaluation with pelvic examination and Pap smear should be performed. The examination and Pap smear should be repeated at six months and then annually.

For further information, please refer to Protocol 9, *Support for sexual and reproductive health of people living with HIV*.

5.8. Other cancers

Lymphomas – including non-Hodgkin, intracranial and Burkitt types – and squamous cell carcinoma are more commonly found in immunosuppressed PLHIV than in people who do not have HIV. Any patient suspected of cancer should be examined by an oncologist and referred to the oncology clinic as needed.

5.8.1. Non-Hodgkin lymphoma (NHL)

NHL – usually B-cell, very rarely T-cell – occurs commonly in immunosuppressed PLHIV, but its appearance is independent of CD4 cell count. It is thought that EBV or some other virus plays a role in the pathogenesis of this disease.

- Malignant NHL cells may be detected in all locations, most often in the lymph nodes, as well as the muscles; organs such as the liver, spleen, lung, heart, brain and GI tract; and (more rarely) the bones.
- Symptoms may vary.
- Swollen lymph nodes may be palpable in different locations.

- Fever, weight loss and fatigue are common, but not inevitable.
- Determining the stage of the disease (I–IV) requires thorough examination – cerebral, cervical, thoracic and abdominal computerized axial tomography (CAT) scans, bone marrow and cerebrospinal fluid biopsies and gastroscopy.
- Diagnosis is performed by biopsy of a suspect (enlarged) lymph node, followed by histological examination.

5.8.2. Burkitt-type lymphoma in PLHIV

Burkitt-type lymphomas, actually a subgroup of NHLs, are associated with HIV infection and may occur before advanced immunosuppression sets in. This type of tumour is associated with EBV.

5.8.2.1. Diagnosis

The diagnosis of Burkitt-type lymphoma is made on careful examination of lymph node and tumour biopsies, confirmed by histological examination.

5.8.2.2. Treatment of non-Hodgkin, Burkitt-type and CNS lymphomas

- For NHL, the CHOP regimen is effective and should be administered through six cycles (the number usually needed for complete remission) of the following:
  - prednisolone 100 mg/day OD for five days
  - vincristine (Oncovin) 1.4 mg/m²/day (maximum 2 mg/day) in one dose on Day 1 of treatment
  - cyclophosphamide 750 mg/m²/day in one dose on Day 1
  - doxorubicin (hydroxydaunomycin) 50 mg/m²/day in one dose on Day 1.

Begin a new cycle every 21 days (Day 22 becomes Day 1, etc.).

- The EPOCH regimen, which includes etoposide, prednisolone, vincristine, cyclophosphamide and daunorubicin or doxorubicin, has been shown to be effective in combination with ART. It is based on a regimen of continuous infusion for 96 hours, as follows:
  - etoposide 50 mg/m² per day (via central venous line)
  - doxorubicin 10 mg/m²/day (via central venous line)
  - vincristine 0.4 mg/m²/day (max 2 mg/week) (via central venous line)
  - cyclophosphamide 375 mg/m² on Day 5 only, in a bolus (via IV)
  - prednisolone 100 mg/day on Days 1–5 OD PO.

Repeat the regimen every 21 days until six cycles have been performed.

- Burkitt-type lymphoma is managed in the same manner as other lymphomas, and responds to CHOP or EPOCH. Treating this fast-growing lymphoma with more aggressive chemotherapy (such as the B-ALL regimen) is under discussion so there are no specific recommendations at the present time *(35, 36)*.
- In Burkitt-type lymphomas, chemotherapy should be followed by radiation of the suspected primary location.
- It is possible to treat NHL independently of CD4 cell count, but for prolonged success, ART should be started early. Even during chemotherapy with CD4 count >350, there is a high rate of relapse without ART *(37)*.
- For intracranial lymphoma (metastasis), cranial radiation in conjunction with cytotoxic chemotherapy and steroids is advised *(38)*.
- For primary central nervous system (CNS) lymphoma, radiation is the only effective evidence-based therapy. Most patients show CD4 counts <50 with diagnosis. In multivariate analysis, highly active antiretroviral treatment (HAART) is the only additional factor in prolonged remission. There are some reports of the effectiveness of HAART alone, so it should be started immediately *(39, 40)*.

5.9. Neurological infections

Invasion of the nervous system by HIV leads to encephalopathy, myelopathy and peripheral neuropathy. Numerous neurological syndromes have been ascribed to HIV, including:

- cerebral atrophy and degeneration
- AIDS dementia complex
- cerebellar atrophy
- vacuolar myelopathy
- facial nerve paralysis
- Guillain-Barre syndrome
- painful sensory and motor peripheral neuropathy.

A number of opportunistic infections, including bacterial, viral and fungal infections, also affect the central nervous system. (For cryptococcal meningitis, please refer to section II.5.4 above.)

5.9.1. Toxoplasmosis

Toxoplasmosis is frequently encountered in PLHIV in industrialized countries. It leads to the development of multiple inflammatory lesions in the brain. In PLHIV, it mainly appears as encephalitis or as disseminated disease.

5.9.1.1. Diagnosis

- Toxoplasmosis may be suspected through clinical findings, and patients may present with:
  - altered mental status
  - fever
  - seizures
  - headaches
  - focal neurological findings, including motor deficits, cranial nerve palsies, movement disorders, dysmetria, visual-field loss and aphasia.
- Patients who present with evidence of diffuse cortical dysfunction develop evidence of focal neurological disease as the infection progresses.
- CAT or MRI brain scans may reveal multiple ring-enhancing lesions.
- Serological tests for *Toxoplasma* antibody (immunoglobulin G, or IgG) may help in establishing the diagnosis in the absence of neuro-imaging techniques.
- Most patients with cerebral toxoplasmosis have serological evidence of prior infection with *Toxoplasma gondii* (IgG-positive).
- If toxoplasmosis is suspected, patients should be given a trial of treatment.
- Only if they do not respond to this treatment within two weeks should a brain biopsy be considered.
- The diagnosis can be confirmed by histological examination of tissue obtained by brain biopsy.

5.9.1.2. Treatment

Table 15. Treatment of toxoplasmosis

Drug	Dose	Frequency	Route	Duration
Pyrimethamine	200 mg	Once (loading dose)	PO	Single dose
Then: pyrimethamine + folinic acid + sulfadiazine	25 mg or 50 mg	TID BID	PO	6–8 weeks
	15 mg	OD	PO	6–8 weeks
	1 g	QID	PO	6–8 weeks

Sources: Katlama et al., Dannemann et al. Chirgwin et al. *(41–43).*

- In the regimen above, sulfadiazine may be replaced by any of the following:
  - clindamycin 600 mg QID IV/PO for six weeks
  - azithromycin 1200 mg OD PO for six weeks
  - clarithromycin 1 g BID PO for six weeks
  - atovaquone 750 mg QID PO for six weeks.
- Some patients need a very long period of acute treatment. There is no rule for treatment duration. The decision has to be made on clinical grounds and CAT scan if available.
- Secondary prophylaxis is given using half the dosage of the acute treatment from the effective regimen, until CD4 count is over 200 cells/mm^3 for three months.

5.9.2. Herpes simplex virus (HSV)

- HSV infection is commonly encountered in clinical practice.
- Following an initial attack, there are frequent recurrences.
- In immunosuppressed people the infection may be extensive and persistent and possibly disseminated.
- Dissemination may lead to infection of the lungs, oesophagus and brain.
- HSV may also cause meningoencephalitis and meningitis.

5.9.2.1. Diagnosis

- The diagnosis of HSV infection is usually made based on the typical clinical presentation of vesicles and painful superficial sores around the mouth, nose, lips and/or genitals.
- It is often difficult to make a diagnosis of disseminated herpes. Special laboratory tests – such as viral culture, radio-immunoblot assay and fluorescent and monoclonal antibody tests – may be necessary.
- Typical changes may be seen on CAT scans of the brain, where herpes simplex encephalitis leads to multiple lesions.

5.9.2.2. Treatment

Table 16. Treatment of herpes simplex virus: mild infection

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	400 mg	TID	PO	7–10 days
or:				
Famciclovir	250 mg	TID	PO	7–10 days
or:				
Valaciclovir	1 g	BID	PO	7–10 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

Table 17. Treatment of herpes simplex virus: recurrences

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	800 mg	5 times per day	PO	7–10 days
or:				
Famciclovir	500 mg	TID	PO	7–10 days
or:				
Valaciclovir	1 g	BID	PO	7–10 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

Table 18. Treatment of herpes simplex virus: severe infection

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	10 mg/kg	TID	IV	7–10 days
or:				
Valaciclovir	1 g	BID	PO	7–10 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

Table 19. Treatment of herpes virus: severe and visceral infection

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	10 mg/kg	TID	IV	14–21 days
Second-line treatment				
Foscarnet (when resistance to aciclovir is suspected)	40–60 mg/kg	TID	IV	14 days

Source: *Conant et al., Ionnadis et al., Chang, Absar & Beall, Safrin (44–47).*

5.9.3. Herpes zoster *(48)*

- Varicella-zoster virus (VZV) often causes disseminated infection after initial exposure.
- In children, initial infection results in the development of chicken pox, though most who become infected develop no symptoms or signs of infection.
- The virus lies dormant in the paraspinal ganglia for years.
- With immune suppression, regardless of cause, the virus replicates and produces lesions along the length of a cutaneous nerve in a dermatomal distribution.

- Dissemination can also occur at the same time, with involvement of skin, nervous system, lungs and mucous membranes.
- In immunosuppressed patients, zoster is often multidermatomal in distribution, persistent, extensive and associated with severe pain and debility.

5.9.3.1. Diagnosis

The diagnosis is usually made on clinical grounds.

5.9.3.2. Treatment

Table 20. Treatment of dermatomal zoster

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	800 mg	5 times a day	PO	7–10 days or until lesions crust
or:				
Famciclovir	500 mg	TID	PO	7–10 days

Table 21. Treatment of disseminated, visceral or ophthalmic zoster

Antiviral agent	Dose	Frequency	Route	Duration
First-line treatment				
Aciclovir	10 mg/kg	TID	IV	7–10 days
or:				
Famciclovir	500 mg	TID	PO	7–10 days
Second-line treatment				
Foscarnet	60 mg/kg or 40 mg/kg	BID TID	IV	7–10 days

- Post-herpetic neuralgia is a common and seriously debilitating problem. It causes severe pain in dermatomal distribution, usually at the site of the lesions.
- Pain control is often necessary and may be achieved with non-steroidal anti-inflammatory drugs (NSAIDs).
- If pain control is not achieved, amitryptiline, carbamazepine or phenytoin may be tried.

5.9.4. Cytomegalovirus (CMV) infection

CMV may affect multiple systems and organs in immunosuppressed individuals. Symptoms may include:

- fever and diarrhoea from CMV colitis
- dyspnoea from CMV pneumonitis
- blindness caused by CMV retinitis
- the appearance of painful ulcers in the mouth, resulting in difficulty eating.

5.9.4.1. Diagnosis

- The most frequent localization is the retina and is diagnosed by a specialized ophthalmologist.
- Other localizations require sophisticated equipment and costly tests, such as tissue biopsies and deoxyribonucleic acid (DNA) hybridization studies.

5.9.4.2. Treatment

Treatments for CMV GI disease, neurological disease and retinitis are found in Tables 22–24.

Table 22. First-line treatment of CMV GI disease, neurological disease and retinitis

Antiviral agent	Dose	Frequency	Route	Duration
Ganciclovir	5 mg/kg	BID	IV	2–3 weeks

Source: *Whitley et al., AIDS Research Group, Martin et al., Jacobson et al., Martin et al. (49–53).*

For secondary prophylaxis, long-term treatment with ganciclovir 5 mg/kg given IV daily may be necessary.

Table 23. Second-line treatment of CMV GI disease, neurological disease and retinitis

Antiviral agent	Dose	Frequency	Route	Duration
Foscarnet	90 mg/kg	BID	IV	3 weeks

Source: *Whitley et al., AIDS Research Group, Martin et al., Jacobson et al., Martin et al. (49–53).*

For secondary prophylaxis, long-term treatment with foscarnet 90 mg/kg given IV daily may be necessary.

Table 24. Secondary prophylaxis of CMV retinitis

Antiviral agent	Dose	Frequency	Route	Duration
Ganciclovir eye implant + Valganciclovir (to prevent infection in the other eye)	900 mg	OD	PO	Until CD4 count is over 100-150 cells/ mm^3 for minimum 3 months

Source: *Whitley et al., AIDS Research Group, Martin et al., Jacobson et al., Martin et al. (49–53).*

Secondary prophylaxis can be stopped after six months and immune reconstitution to 100–150 CD4 cells/mm^3.

5.9.5. Epstein-Barr-virus-related conditions

- Infection with EBV, a herpesvirus, is common in PLHIV and others.
- PLHIV have increased amounts of EBV in their oropharyngeal secretions and higher EBV antibody titres than HIV-negative people.
- EBV is thought to cause a number of conditions including:
  - oral hairy leukoplakia
  - lymphocytic interstitial pneumonitis (LIP)
  - non-Hodgkin lymphoma (see section II.5.8.1 above)
  - Burkitt-type lymphoma (see section II.5.8.2 above)
  - nasopharyngeal carcinoma.

5.9.5.1. Oral hairy leukoplakia

- Oral hairy leukoplakia occurs in PLHIV as well as some immunosuppressed transplant recipients.
- It is a non-malignant lesion of epithelial cells, presenting as raised, white, corrugated lesions of the oral mucosa, especially on the lateral aspect of the tongue.
- It is commonly mistaken for oral candidiasis, as they are frequently found together.
- No specific treatment is available for the condition. Patients are generally advised on good oral hygiene.

5.9.5.2. Lymphocytic interstitial pneumonitis (LIP)

- LIP occurs primarily in children, but it also occurs in adult PLHIV.
- It is characterized by diffused interstitial pulmonary infiltrates that may be confused with TB or PCP. However, patients with LIP often do not have signs of severe respiratory illness.
- No specific treatment is available for LIP.

III. General symptoms

1. Persistent generalized lymphadenopathy (PGL) in adults

- The most common clinical manifestation of HIV infection is symmetric generalized lymph node enlargement.
- Enlarged lymph nodes are generally painless, firm, mobile and rubbery and are most easily palpated in the neck, submental area, axillae and the groin.
- The patient may or may not have other associated symptoms of HIV infection.
- PGL is defined as the presence for more than one month of lymph nodes measuring more than 1 cm in diameter in more than one area of the body other than the groin.
- PGL is a very common feature of HIV infection. In most cases a lymph node histology only reveals “reactive hyperplasia” or “follicular hyperplasia”. A lymph node biopsy is necessary to establish a cause.

1.1. Diagnosis

It is important to palpate lymph nodes specifically in the following areas:

- anterior and posterior triangles of the neck
- submental area
- suboccipital area
- anterior and posterior auricular areas
- both axillae
- epitrochlear areas
- both inguinal regions.

Patients with PGL caused by HIV infection may have other features of HIV infection, including:

- oral thrush
- oral hairy leukoplakia
- pruritic skin rash
- hyperpigmented nails
- oral or genital herpes
- involuntary weight loss
- unexplained fever.

PGL may be caused by a number of conditions other than HIV infection, including TB, leukaemia, lymphoma, KS, syphilis, *Chlamydia trachomatis* (lymphogranuloma venereum), CMV, toxoplasmosis, EBV, cryptococcosis, histoplasmosis and septic skin conditions, bubonic plague and hepatitis B.

1.2. Criteria for performing a lymph node biopsy

A patient with PGL should be referred for a lymph node biopsy if presenting with any of the following:

- asymmetrical lymph node enlargement
- massive lymph node enlargement (at least one lymph node >3 cm in diameter)
- lymph node enlargement over a period of observation
- evidence of TB on a chest X-ray
- evidence of hilar lymph node enlargement on a chest X-ray
- evidence of KS elsewhere
- fever, night sweats and weight loss for more than one week.

A diagnosis of HIV-related lymphadenopathy does not rule out other serious diseases like lymphoma in unbiopsied lymph nodes. Therefore, with any change in condition, persistent fever or other suspicious circumstance, a biopsy or lymphadenectomy should be repeated.

2. Fever

- Fever can occur as a result of infection, inflammation or malignancy. Persistent fever in adults is defined as a body temperature of more than 38°C lasting for more than two weeks.
- In PLHIV, the only clinical presentation of HIV infection may be fever. Thus, it is important to keep in mind a possible diagnosis of HIV infection when managing a patient who presents with a persistent fever and no obvious cause.
- In PLHIV, persistent fever may be accompanied by features of the possible underlying cause, for example pneumonia, TB, gastrointestinal infection or lymphoma. In adults with persistent fever, the following factors may suggest the presence of HIV infection:
  - a history of unsafe sexual behaviour
  - a partner or child known to be HIV-infected
  - other features suggestive of HIV infection, such as:
    - PGL
    - oral or genital thrush
    - oral hairy leukoplakia
    - pruritic skin rash
    - oral or genital herpes
    - involuntary weight loss
    - darkening of the nails (melanonychia)
    - hypopigmentation of the lips
    - thinning and straightening of the hair.

3. Weight loss in adults

- HIV infection is a common cause of weight loss.
- Severe weight loss is defined as involuntary loss of more than 10% of one's body weight.
- Severe involuntary weight loss in PLHIV is known as HIV-associated wasting syndrome or "slim disease".
- The cause of such wasting is not fully understood. Possible unsubstantiated causes include:
  - chronic and recurrent infections
  - chronic diarrhoea
  - malabsorption
  - HIV-induced myopathy
  - HIV-induced poor appetite.

3.1. Clinical features

- The patient may complain of involuntary weight loss or loss of appetite, with or without fever and diarrhoea.
- Patients with HIV-associated wasting disease are ill and emaciated and may be feverish and dehydrated.
- Oral candidiasis is commonly found in such patients.
- The patient may have other features of AIDS, including features of neurological involvement such as encephalopathy and AIDS dementia complex.

4. Chronic diarrhoea in adults

- Adults with chronic diarrhoea complain of frequently passing three or more consecutive loose stools over 28 days. During the course of the illness the patient may also have episodes of acute diarrhoea.
- The stool does not usually contain blood, except if there is concomitant dysentery.
- The patient usually also has a poor appetite and weight loss.
- The patient may also be dehydrated, anaemic and wasted.

- Adults with chronic diarrhoea often have:
  - skin and hair changes typically associated with malnutrition
  - hypopigmentation of the lips
  - darkly pigmented nails
  - oral thrush, hairy leukoplakia or lymph node enlargement.

Details on the management of chronic diarrhoea and assessment of dehydration in adults are provided in Protocol 3, *Palliative care for people living with HIV*.

5. Oral lesions

Besides candidiadis (see section II.5.3 above), a large number of other oral lesions may be found in patients with HIV infection. Some of these are described in Table 25.

Table 25. Description and treatment of oral lesions common in PLHIV

Condition	Description	Treatment
Gingivitis	Swollen and red gums that tend to bleed easily	Metronidazole 400 mg PO BID for 7 days or erythromycin 500 mg PO QID for 7 days
Pyorrhoea	An accumulation of pus in the gingival margin around the teeth	Gargling with warm salty water after every meal and brushing the teeth BID
Periodontitis	A painful condition with rapid loss of the bone and soft tissue supporting the teeth, bleeding of the gums, tooth loss and possible ulceration	Local debridement, chlorhexidine mouth washes Amoxycillin 500 mg PO TID or metronidazole 200 mg PO TID for 5 days
Aphthous ulcers	Painful punched-out ulcers on the mucosal surface, usually covered in a purulent exudate and tending to bleed when touched	Oral hygiene and treatment with topical steroids
Stomatitis	Inflammation of the mucosa in the oral cavity, often associated with poor oral hygiene and invasion of anaerobic bacteria	Gargling with warm salty water after every meal and brushing the teeth BID
Cheilitis	Inflammation, redness and eventual pallor of the lips, common in patients with advanced immunosuppression	No specific treatment available; vitamins A, B and C and advice on oral hygiene
Secondary syphilis	Lesions on the buccal mucosa, including moist papules, "snail track" ulcers and condylomata lata at the angles of the mouth and around the nostrils. (In secondary syphilis, all serological tests for syphilis are positive.)	Benzathine penicillin 2.4 milliunits IM QW for three weeks *or* doxycycline 100 mg PO BID for 28 days *or* erythromycin 500 mg PO QID for 28 days

6. Skin and nail conditions

6.1. Dermatomycosis

- Fungal skin rashes (dermatomycoses) occur commonly in PLHIV and others.
- Rashes are usually itchy and dry, with visible scales of dead skin.
- The lesions may be found anywhere on the body.

6.1.1. Diagnosis

Fungal elements may be found on microscopic examination of skin scrapes.

6.1.2. Treatment

Topical applications of antifungal ointments and creams will usually clear the lesions. The following may be used for treating dermatomycoses.

Table 26. Treatment of dermatomycosis

Antifungal preparation	Dose	Frequency	Route	Duration
First-line treatment				
Topical miconazole		TID	Topical	21 days
or:				
Topical clotrimazole		TID	Topical	21 days
Second-line treatment				
Ketoconazole	200 mg	OD	PO	1–3 months
or:				
Itraconazole	100 mg	OD	PO	1–3 months

6.2. Onychomycosis

Nails may also become infected with fungi (onychomycosis). The infection can result in discoloration, distortion or destruction of the nails.

6.2.1. Diagnosis

- Diagnosis is usually made on clinical findings.
- Microscopic examination of potassium hydroxide (KOH) preparations of subungual material may reveal fungal elements.

6.2.2. Treatment

Table 27. Treatment of onychomycosis

Antifungal preparation	Dose	Frequency	Route	Duration
First-line treatment				
Terbinafine	250 mg	OD	PO	6 weeks for fingers 12 weeks for toes
or:				
Itraconazole	200 mg	BID	PO	For fingers, 1 week each month for 2 months For toes, 1 week each month for 3–4 months

6.3. Seborrhoeic dermatitis

- Seborrhoeic dermatitis is a common presenting feature in PLHIV. It is probably caused by a fungus known as *Pityrosporum ovale* (also known as *Malasezia furfur*).
- The rash is erythematous and scaly. In persons with HIV infection it may be extensive, persistent and recurrent.

6.3.1. Diagnosis

- Diagnosis is made on clinical grounds. The rash appears commonly on the:
  - face
  - area around nostrils
  - nasolabial folds
  - eyebrows

- scalp
- chest
- axillae
- upper trunk
- genital area.

Diagnosis can be confirmed by finding fungal elements on microscopic examination of skin scrapes.

6.3.2. Treatment

- Frequent skin washing to remove scales is advised.
- Shampooing with selenium sulfide shampoo is effective.
- Topical applications of 1% hydrocortisone are probably the most effective. Ketoconazole 2% cream has also been shown to be effective.

6.4. Scabies

Scabies is caused by the mite *Sarcoptes scabei*. The female mite burrows into the skin, and the burrows appear as raised lines up to several centimetres long.

- When a person is infested with scabies mites for the first time, there is usually little evidence of infestation for the first 2–6 weeks.
- In subsequent infestations, people usually have become sensitized to the mites, and the symptoms generally occur within 1–4 days.
- The burrowing of the mites under the skin causes a rash, most frequently found on the:
  - hands (particularly the web spaces between the fingers)
  - folds of the wrist, elbow or knee
  - ulnar margins of the forearms
  - penis
  - breast
  - shoulder blades
- Burrows and mites may be few in number and difficult to find in some cases.
- Severe itching is common, especially at night and frequently over much of the body, including areas where no mites are living.
- Norwegian scabies, a more severe form more common among immunocompromised patients, is characterized by vesicles and the formation of thick crusts on the skin, accompanied by abundant mites but only slight itching.
- Complications due to infestation are usually caused by secondary bacterial infections from scratching.

6.4.1. Diagnosis

- The diagnosis is usually made on finding the rash and burrows.
- Skin scrapes may reveal mites or mite ova on microscopic examination.

6.4.2. Treatment

- The treatment of choice is the topical use of gammabenzene hexachloride 1%, applied to the whole body from the neck down and washed off after 24 hours in adults and 8 hours in children. A single application is sufficient.
- Permethrin 1% applications are also useful. Both are applied to affected areas and washed off after 8 hours.
- These agents should not be used during pregnancy or lactation or on children until 2 ½ years old.
- Ivermectin in a single oral dose of 200 µg/kg is an alternative that is effective for crusted scabies in immunocompromised people.
- All members of the household and sexual partners should also be treated.
- All clothes, bedding and towels should be washed in hot water, dried and ironed.

6.5. Staphylococcal folliculitis

- Folliculitis is a skin infection that is localized in the hair follicles.
- A pustular perifolliculitis occurs commonly in PLHIV.
- Usually the condition is caused by *Staphylococcus aureus,* though other organisms may also be responsible.

6.5.1. Diagnosis

- Diagnosis is made on clinical findings.
- Lesions are small (less than 5 mm in diameter), and found in multiple erythematous follicles that may have a purulent centre.
- Lesions are itchy and often found in clusters.

6.5.2. Treatment

Treatment is with antibiotics, such as cephalexin or cloxacillin 500 mg PO QID for 7–21 days.

6.6. Molluscum contagiosum

- Molluscum contagiosum is a superficial skin infection caused by the molluscum contagiosum virus.
- The infection is spread through close body contact and may occur through sharing clothing, bedding or towels or through sexual transmission.
- The incubation period varies from several weeks to several months.
- Shaving or scratching may cause the infection to spread.
- The infection occurs more commonly in immunosuppressed PLHIV.
- In comparison to the lesions found on HIV-negative people, those found on PLHIV are:
  - more widespread
  - more persistent
  - much larger
  - more difficult to treat.

6.6.1. Diagnosis

- The diagnosis is based on the characteristic appearance of the bumps.
- The virus invades the skin, causing the appearance of firm, flesh-coloured papules 2–5 mm in diameter. The lesions contain a white sebaceous material.
- The papules can occur anywhere on the body and often remain unchanged for many months, after which they disappear and may or may not reappear.
- No diagnostic test for this virus is available.

6.6.2. Treatment

The goal of treatment is to remove the soft centre, after which the papule resolves. As such, each lesion needs to be treated individually. Various methods are available for the destruction of the lesion, including:

- curettage
- chemical destruction with concentrated phenol
- cryotherapy
- electrocautery.

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3 Palliative Care for People Living with HIV

Clinical Protocol for the WHO European Region

Contents

I. Policy, principles and organization of services

1. Policy

Palliative care is an approach that improves the quality of life of patients and their families when facing the problems of life-threatening illness. While disease-specific (or "curative") treatment is directed at reversing the course of an illness, palliative care is primarily focused on the prevention and relief of suffering in progressive, incurable disease. Early identification, sound assessment and effective treatment of pain and other physical, psychosocial and spiritual problems are essential elements in assuring quality palliative care *(1–5)*. Ideally, palliative care and disease-specific treatment should be integrated throughout the course of chronic, life-limiting illness, rather than being divided into two completely disconnected treatment approaches. The balance between palliative and curative therapy should depend in a given situation on the etiology of the patient's symptoms and suffering, the possibility of improving these symptoms through disease-specific and/or palliative interventions, and the availability of resources in the particular country *(6)*.

- Palliative care is a core component of comprehensive HIV/AIDS care.
- Access to palliative care should not be artificially restricted due to political or social constraints. All patients needing and wanting it should receive it, without exception.
- Palliative care should be provided in accordance with the needs of the patient and WHO standards of care.
- Treatment for illnesses and conditions should not be withheld at any stage of the disease (for example, tuberculosis (TB) treatment, antiretroviral treatment (ART) or substitution therapy for injecting drug users).
- Palliative care should be incorporated as appropriate at every stage of HIV disease, and not only when the patient is dying.

2. Principles

The guiding principles of palliative care are to:

- provide relief from pain and other distressing symptoms to enhance quality of life;
- integrate the psychological and spiritual aspects of patient care;
- offer support to help patients live as actively as possible;
- offer support to help families cope during illness and bereavement;
- draw on experience and communication between the patient and health care provider (nurse, physician, family member, etc) to provide the best combination of interventions and medications;
- affirm life and regard dying as a normal process;
- strive neither to hasten nor postpone death.

3. Organization of services

- The needs of patients and their families can be addressed by a team approach, including bereavement counselling if indicated.
- Palliative care services can be provided as consultative services in hospitals at both inpatient units and outpatient clinics.
- Palliative care services can also be provided in the community, in outpatient settings and as home-based care, coordinated with hospital services as needed.
- Where available, palliative care specialists should be available to AIDS clinical services. In situations where such access is difficult, AIDS clinics should refer to other institutions where palliative care specialists and services are available.
- AIDS care providers should also be familiar with basic principles of palliative care and be able to manage routine problems without needing to refer to palliative care specialists.
- Nongovernmental organizations should be involved in delivering palliative care.

II. General considerations for palliative home care of people living with HIV (PLHIV)

Care of patients at home and in the community is an essential component of palliative care. Caregivers' questions and concerns about safety and infection control can be readily addressed by references to simple and longstanding practices which decrease risk of contamination with HIV and other bloodborne pathogens. Standard infection control measures to prevent the transmission of HIV have been well established since the 1980s *(7, 8)*. Precautions that should be taken when caring for someone with HIV/AIDS, whether it be in the hospital, clinic or at home, should be the same. These precautions are based on the principles of standard infection control and should be in place and respected at all times. These principles minimize the risk of contamination through infected blood or other body fluids by considering all such fluids as potentially infectious and applying simple and consistent techniques for handling and disposing of them.

1. Precautionary measures at home

When palliative care is offered at home, the health care provider (doctor or nurse) should counsel the home care provider (family member, friend or other service provider) on the following points:

- Family members and other caregivers can safely care for AIDS patients. There is an extremely low risk of HIV transmission to health care providers and household contacts if the following hygienic practices are respected.
  - Wear latex gloves when in contact with blood and bodily fluids.
  - Keep wounds covered (on both caregivers and PLHIV); if they become wet with blood or other body fluids, change dressings and dispose of properly.
  - Clean up blood, faeces and urine with ordinary household bleach while wearing gloves.
  - Keep clothing and sheets that are stained with blood, faeces or other body fluids separate from other household laundry. Use a piece of plastic or gloves to handle soiled items.
  - Do not share toothbrushes, razors, needles or other skin-piercing instruments.
  - Wash hands with soap and water after changing soiled bedsheets and clothing and after any contact with bodily fluids.
- There is no risk from casual household contact (no gloves needed).
- Cutlery and other food items, unsoiled clothing and linens, toilets, baths, showers, etc. can be cleaned with ordinary cleaning products.

2. Education on management of symptoms

The attending doctor or nurse should provide clear instructions to home caregivers on the management of symptoms, including:

- explanation of symptom management;
- education in the most immediately necessary areas, teaching a few skills at a time;
- demonstration of skills, such as how to safely give an injection;
- verification of skills and knowledge by asking questions and requesting demonstrations;
- encouraging the care provider to return if there are any questions or concerns;
- ensuring that the caregivers know when and whom to call for help and how to provide back-up, especially in case of side-effects or drug interactions.

3. Psychosocial issues for affected families

When recommending palliative home care for PLHIV, the health care worker needs to consider the family's emotional state, the home environment and any socioeconomic issues that may affect the patient and family. Significant factors may include:

- frustration, sadness, grief;
- family members' fear of becoming infected if they are not already known to be;
- anger and blame for the infection that are directed towards the patient;
- stigmatization and discrimination of the patient, family members, friends and other caregivers; and
- concerns about the economic impact of life-threatening illness on the main family wage-earner(s), and the possibility of orphaning any children.

Actions to be taken include:

- assessing if the family is physically and emotionally capable of caring for the patient and other home responsibilities (may include age-related concerns);
- counselling and educating family caregivers;
- providing psychological support, referrals to HIV/AIDS psychologists and/or peer support groups;
- assisting in planning for and ensuring care of orphans;
- referral to social service agencies for financial, legal and other assistance.

III. Initial evaluation

The initial evaluation of PLHIV in need of palliative care, like the initial clinical evaluation of newly diagnosed PLHIV, should include a complete history, physical examination, general staging of the illness (i.e. WHO Categories I–IV), and assessment of any active problems or other issues requiring intervention or follow-up (see Box 1). (See Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.) In addition, the palliative care-focused evaluation should identify any significant physical symptoms; the types and degree of pain; any emotional, psychological or spiritual issues; and any family or social problems.

Box 1. Initial evaluation of PLHIV in need of palliative care

History

- Present illnesses and treatments administered
- Past medical history, including all comorbidities and past HIV-related complications, other major illnesses, hospitalizations, surgeries and date of HIV diagnosis
- Medication history
- Substance use and dependence history, including treatment (see Protocol *5, HIV/AIDS treatment and care for injecting drug users*)
- Family history
- Social history
- Social resources
- Financial issues
- Current symptoms (i.e. pain, weight loss, anorexia, fatigue, fevers, night sweats, insomnia, sadness, anxiety, dyspnoea, cough, nausea/vomiting, diarrhoea)
- Chronology of symptoms
- Exacerbating and relieving factors
- Current medications or other treatment for symptoms
- Cause, type and grade of pain[a]
- Symptom cause, type and characteristics
- Impact:
  - of symptoms on functional capabilities
  - of symptoms on each other
  - of specific therapies on each symptom
  - of symptoms on patient's quality of life
- Mental health history and treatment (e.g. depression, anxiety disorder, delirium, psychosis), and any current mental health problems

Physical examination

- Full clinical examination
- Systems review including:
  - constitutional (fatigue, anorexia, fevers, weight loss)
  - neurological
  - mental status
  - dermatological

Other examinations and tests as required

[a] Grading of pain should be on a 0 to 10 scale, with 0 being no pain and 10 being the worst pain imaginable.

The initial palliative care assessment should result in a staging of the HIV infection; identification of comorbidities and other relevant medical, mental health, social and environmental conditions; classification and grading of pain and other symptoms; and an initial plan for addressing the multiple needs of the patient and the patient's family in accordance with the conceptual framework of palliative care outlined in section I above.

IV. Treatment

Since early in the HIV/AIDS epidemic, patients with HIV have been found to have a high prevalence of pain and other symptoms *(9–24)*. The source of pain (and most of the other common symptoms of HIV/AIDS) can be HIV itself, specific opportunistic infections or malignancies, medications used in the treatment of HIV, and/or other coexisting conditions. Accordingly, the most effective approach to symptom management may be treating an underlying condition, controlling HIV infection, changing medications to reduce toxicity and/or treating the symptoms themselves.

1. Pain management

Pain is generally categorized as nociceptive or neuropathic.

Nociceptive pain results in the stimulation of intact nociceptors (pain receptors), and it is subdivided into:

- somatic pain (involving skin, soft tissue, muscle and bone)
- visceral pain (involving internal organs and hollow viscera) *(25)*.

Nociceptive pain generally responds to non-opioid and opioid analgesics.

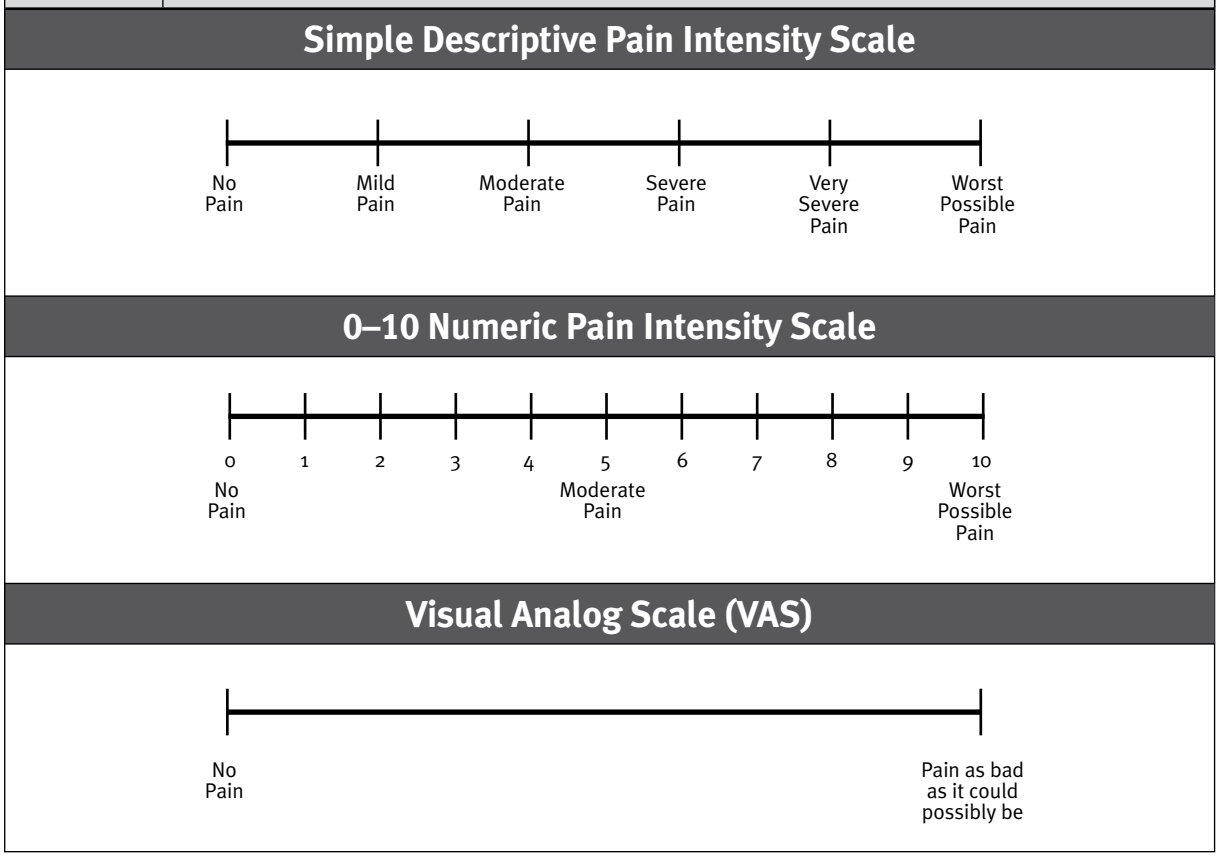
In PLHIV, neuropathic pain occurs in at least 40% of patients with advanced disease *(21)*. It is mostly due to the syndrome of distal symmetric polyneuropathy (DSP), which is an axonal neuropathy apparently caused by HIV infection itself and characterized by numbness, tingling, a "pins and needles" sensation and allodynia, especially involving the distal lower extremities and feet *(26–31)*. Neuropathic pain generally responds to non-opioid or opioid analgesics together with adjuvant medications such as antidepressants or anticonvulsants *(1, 2, 24, 29, 31, 32)*.

In addition, certain antiretroviral agents used in ART, e.g. didanosine (ddI) and stavudine (d4T), have been associated with a similar toxic neuropathy with comparable symptoms that also affect the distal lower extremities. In these cases, a change in antiretroviral agent(s) may result in some improvement, though that is not always the case.

Pain management should begin with a thorough and systematic assessment of pain, including possible etiologies, and the specific nature of pain. Important characteristics include intensity, type, interference and relief.

- **Pain intensity.** Use of a 10-point numeric scale is standard, with 0 as no pain and 10 the worst possible pain. It is particularly helpful to use the same scale over time in an individual patient, to monitor any changes on a continuing basis (see Fig. 1 below) *(33)*.
- **Pain type.** Nociceptive pain may be described as aching, stabbing, deep, dull, pulsating; neuropathic pain may be described as burning, tingling, "pins and needles", numbness or otherwise abnormal sensations. Such characterizations can help guide analgesic choice, especially for suspected neuropathic pain.
- **Pain interference.** The impact of pain on patients' functional status, ability to perform usual daily activities and emotional state should also be documented.
- **Pain relief.** Conditions or interventions which increase or decrease pain should be elicited.

Fig. 1. Pain Intensity Scales

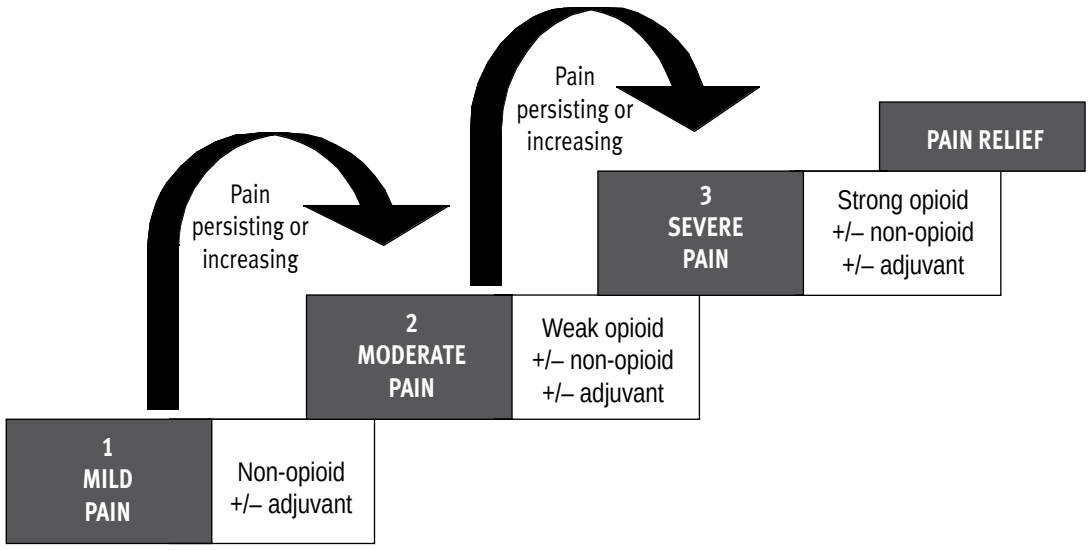


Note: a 10-cm baseline is recommended for any graphic representation of these scales.
Source: Acute Pain Management Guidelines Panel *(33)*.

Severe chronic pain most often occurs with malignancies, chronic pancreatitis, joint problems and severe neuropathy.

A graded approach for using analgesics to treat mild, moderate and severe pain, along with the potential use of adjuvant medications at each stage, can be helpful (see Fig. 2) *(1)*. Table 1 below, expands on this approach indicating starting doses and other recommendations.

Fig. 2. WHO analgesic ladder for management of pain in PLHIV



+/–: with or without.
Mild pain: 1–3 on the 0–10 Numeric Pain Intensity Scale; moderate pain: 4–6; severe pain: 7–10.
Non-opioid analgesics: ibuprofen, indomethicin, acetylsalicyclic acid, paracetamol.
Adjuvants: amtriptyline, imipramine, gabapentin, carbamazepine, valproic acid.
Weak opioids: codeine, hydrocodone.
Strong opioids: morphine, oxycodone, methadone, hydromorphone, fentanyl.
Notes: Adjuvant medications are particularly helpful for neuropathic pain. Not all analgesics will be available in all settings.
Source: adapted from WHO *(1)*.

Some specific considerations are worth noting:

- If possible, administer analgesics orally or (assuming no history of rectal abscesses, rectal infection, etc.) rectally. Intramuscular pain management, though sometimes required for severe pain not responding to oral regimens, can be painful in itself and may pose a risk of infection. If necessary and available, intravenous or subcutaneous infusion of strong analgesics can be used as an alternative route of administration, especially in hospital settings but also in the home if resources permit.
- Tailor the analgesic regimen to patterns of sleep, i.e. if possible do not awaken the patient to give pain medication.
- Administer analgesia before the effects of the previous dose have worn off.
- Start with a low dose and increase gradually until the patient is comfortable.
- For breakthrough pain,[1] give an extra dose (50–100% of the 4-hourly dose) in addition to the regular schedule.
- While aspirin can be effective in controlling mild-to-moderate pain, care should be taken in using it due to the increased bleeding tendencies of PLHIV, especially in patients with clinically significant liver disease. Paracetamol may also be problematic in patients with active liver disease and should be used cautiously, generally not exceeding 2 g/day in such patients.

[1] Breakthrough pain is pain that "breaks through" a regular pain medicine schedule. Breakthrough pain comes hard and fast and can last up to an hour. It may be an intensified all-over dull pain, or come as a localized sharp stab or fiery sensation. Breakthrough pain differs from person to person and is often unpredictable.

Table 1. Pain management

Type of pain or treatment	Usual starting dose (adults)	Recommendations
A. Medical treatment[a]		
Step 1: *mild pain*		
Non-opioids	**Paracetamol** 500–1000 mg every 4–6 hours (also available in rectal suppositories)	Do not exceed 4 g/day. Use with careful monitoring in patients with liver disease; toxicity is dose-related.
	Ibuprofen 400 mg every 6 hours	Maximum 2.4 g/day. Contraindicated in patients with gastrointestinal bleeding and/or bleeding disorders. Use with caution in patients with liver disease.
	Aspirin (acetylsalicylic acid) 325–500 mg every 4 hours, or 1000 mg every 6 hours	Do not give to children under 12 years old. Contraindicated in patients with gastrointestinal bleeding and/or bleeding disorders. Use with caution in patients with liver disease.
Step 2: *moderate pain*[b]		
Non-opioids **Plus** **Opioids**[c]	**Paracetamol** 500–1000 mg every 4–6 hours (also available in rectal suppositories)	Do not exceed 4 g/day. Use with careful monitoring in patients with liver disease; toxicity is dose-related.
	Ibuprofen 400 mg every 6 hours	Maximum 2.4 g/day. Contraindicated in patients with gastrointestinal bleeding and/or bleeding disorders. Use with caution in patients with liver disease.
	Aspirin (acetylsalicylic acid) 325–500 mg every 4 hours, or 1000 mg every 6 hours	Do not give to children under 12 years old. Contraindicated in patients with gastrointestinal bleeding and/or bleeding disorders. Use with caution in patients with liver disease.
	Codeine 25–50 mg every 4 hours If codeine is not available consider alternating aspirin and paracetamol. Codeine is available in fixed-dose combinations with aspirin or paracetamol, with 325–500 mg paracetamol or aspirin and 25–60 mg codeine.	Maximum daily dose for pain 180–240 mg due to constipation, otherwise switch to morphine. Prevent constipation through use of a stool softener and bowel stimulant, use laxatives if needed. For IDUs, use a non-steroidal anti-inflammatory (ibuprofen) before offering codeine. Be aware of possible abuse of codeine or morphine-related drugs. Refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users*.
	Tramadol 50–100 mg every 4–6 hours	—

Type of pain or treatment	Usual starting dose (adults)	Recommendations
***Step 3:** severe pain*		
Non-opioids **Plus**	**Paracetamol** 500–1000 mg every 4–6 hours (also available in rectal suppositories)	Do not exceed 4 g/day. Use with careful monitoring in patients with liver disease; toxicity is dose-related
	Aspirin (acetylsalicylic acid) 325–500 mg every 4 hours, or 1000 mg every 6 hours	Do not give to children under 12 years old. Contraindicated in patients with gastrointestinal bleeding and/or bleeding disorders. Use with caution in patients with liver disease.
Opioids[c]	**Oral morphine**[d] 10–20 mg every 3–4 hours in tablet or liquid form	If oral morphine is not available, and injectable morphine is used rectally, use 5 mg/5 ml or 50 mg/5 ml, according to need and rate of respiration (no ceiling; consider withholding if respiration rate is <6/minute).
	IV or IM morphine 5–10 mg every 3–4 hours	Prevent constipation through use of a stool softener and bowel stimulant; use laxatives if needed.
	Dose can be increased by 50% after 24 hours if severe pain persists. There is no ceiling dose.	Pain management for IDUs is the same as for non-IDUs, only the needed dose of the analgesic is usually higher.
	Oxycodone[d] 5–10 mg, every 4 hours	In case of opioid substitution therapy (OST), the substitution dose should be maintained and opioid analgesics added.
	Dose can be increased by 50% after 24 hours if severe pain persists.	Be aware of possible abuse of codeine and of morphine-related drugs. Refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*
	Hydromorphone 2–4 mg every 4 hours	Approximately 4–6 times more potent then morphine.
	Fentanyl transdermal patch 25 mcg, replaced every 72 hours	Not for use in opioid-naive patients.
B. Treatment for special pain problems		
Neuropathic pain Burning pains, abnormal sensation pains, shooting pains, "pins and needles" sensation. Common causes include HIV-related peripheral neuropathies and herpes zoster.	*Use opioids with or without non-opioid analgesics, as above, along with one of the following adjuvants*	
	Amitriptyline 25 mg at night (because of side-effects, e.g. fatigue) or 12.5 mg twice daily (BID)	Wait 2 weeks for response, then increase gradually to 50 mg at night or 25 mg BID. As there is no sudden relief, wait 5 days minimum for a response.
	Gabapentin Maximum 2.4 g/d if on highly active antiretroviral treatment (HAART) regimen with protease inhibitor (PI)	Refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, section on Drug interactions with ARVs.
	Carbamazepine 200–400 mg every 6 hours	Monitor white blood cell count and drug interactions.
	Clonazepam 0.5–1.0 mg 2–3 times daily	—

Type of pain or treatment	Usual starting dose (adults)	Recommendations
Muscle spasms	**Diazepam** 5–10 mg 2–3 times daily **Tetrazepam** 50 mg/day, up to 200 mg/day in 2 doses **Baclofen** Begin with 5 mg three times daily (TID), increase every 3 days up to 25 mg TID.	IDUs: before administering consider carefully the possibility of polysubstance misuse. Should only be used in the short term (6–8 weeks maximum).
In terminal care, with no referral and: • **swelling around tumour;** • **severe oesophageal candidiasis** with ulceration and swallowing problems; • **nerve compression;** or • **persistent severe headache** due to increased intracranial pressure.	**Dexamethasone** 2–6 mg per day **Prednisolone** 15–40 mg for 7 days or as provided by trained health worker	Helpful in terminal care; improves appetite and makes patient feel comfortable. Reduce dose to lowest possible. Withdraw if no benefit in 3 weeks. Dexamethasone is about seven times stronger than prednisolone. If prednisolone needs to be used, multiply the dexamethasone dose by seven. Corticosteroids may cause candidiasis.
Gastrointestinal pain from colic	**Butylscopolamine** 10-20 mg 2-3 times daily	Butylscopolamine has different half-lives: IV is more rapid, while per os (PO) is slower, though dosage remains the same for both. Start with IV, followed by PO; if stable PO, dose with IV for peaks.
	Codeine 30 mg every 4 hours	Codeine can cause constipation and worsening of symptoms in injecting drug users (IDU). Be aware of possible abuse of codeine or morphine-related drugs.
	Trimebutin 100–200 mg TID before meals	—
C. Non-medical treatment		
Psychological, spiritual and/or emotional support and counselling to accompany pain medication	Not applicable	Pain may be more difficult to bear when accompanied by guilt, fear of dying, loneliness, anxiety or depression. Relieve fear and anxiety by explaining events.
Relaxation techniques, including physical methods, such as massage and breathing techniques; and cognitive methods, such as music	Not applicable	Contraindicated if the patient is psychotic or severely depressed.

[a] Administer only one drug from the non-opioid and opioid choices at a time; aspirin every 4 hours can be given along with paracetamol every 4 hours by offsetting the schedule so that the patient is being given one of the two every 2 hours.
[b] See equianalgesic dose chart in Annex 1, which can be used to help select or substitute for specific opioid analgesics.
[c] If pain is controlled, reduce morphine rapidly or stop if used for only a short time; reduce gradually if used for more than 2 weeks.
[d] Morphine and oxycodone are frequently available in long-acting (sustained-release) forms; the guidelines above refer to acute pain management, which should be initiated with short-acting preparations and then converted to long-acting formulations if the need for chronic analgesia persists.

Morphine and other opioids commonly cause side-effects which can generally be prevented or treated easily through dose adjustment or other simple symptom-specific interventions, as outlined in Table 2. Many of these symptoms may diminish on their own over time. Occasionally, if symptoms are persistent and treatment-limiting with a particular opioid, it may be necessary to change to another opioid medication. For equianalgesic dose equivalents for opioids, please refer to Annex 1.

Table 2. Management of side-effects of morphine and other opioids

Side-effect	Managmenet
Constipation	Increase consumption of fluids and fibre with fruits and vegetables or bran supplements. Give stool softener **(docusate 200–800 mg/d)** at time of prescribing plus stimulant (**senna** 7.5–8.6 mg tablets, 2–4 BID). If no improvement, add laxative such as **macrogol** 13.125 g/dose once or twice a day, or **lactulose** 10–20 ml TID, and if still no improvement, **bisocodyl** 5–15 mg oral tablets or rectal suppositories as needed. Prevent by using some or all of the above measures for prophylaxis (unless chronic diarrhoea).
Nausea and/or vomiting	An antiemetic usually resolves the problem in several days; may need round-the-clock dosing.
Respiratory depression (rare if oral morphine is titrated against pain)	Usually no need to intervene if respiratory rate >6–8/min. If severe, consider withholding next opioid dose, then halve the dose.
Confusion or drowsiness (due to the opioid)	Usually occurs at start of treatment or dose increase. Usually resolves within a few days. Can occur at end of life with renal failure. Halve dose or increase interval between doses.
Itching/twitching (myoclonus – if severe or present during waking hours)	If on high dose, consider reducing or alternating doses or using two opioids. Re-evaluate pain and treatment; pain may not be morphine responsive.
Somnolence	Extended sleep can be from exhaustion due to pain. If condition persists more than 2 days after starting, reduce dose by half.

Note: Reducing morphine when the cause of pain is under control depends on the length of use. If morphine has been used only for a short time, stop or rapidly reduce dosage. If it has been used for >2 weeks, reduce dosage gradually and watch for withdrawal symptoms.

Table 3. Oral morphine instructions for family and community care providers

Purpose	Instructions

To teach family and community care providers how to give small amounts of oral morphine with a syringe and how to deal with side-effects.	Oral morphine is a strong painkiller that is only available from specially trained health workers.
	• To administer oral morphine:
	  ◦ pour a small amount of morphine liquid into a cup;
	  ◦ draw up the exact dose into a syringe (using the ml marks); and
	  ◦ drip the liquid from the syringe into the mouth (there should be no needle on the syringe).
	• Give prescribed dose regularly every 4 hours – do not wait for pain to return.
	• Give a double dose at bedtime.
	• If the pain is getting worse or reoccurs before the next dose is due, give an extra dose and inform the health worker – the regular dose may need to be increased.
	• **Nausea** usually goes away after a few days of morphine and does not usually come again.
	• **Constipation** should be prevented in all patients except those with diarrhoea; give local remedies or a laxative such as **senna**. If constipation does occur, see Table 2 above and section IV.11 below for management.
	• **Dry mouth:** give sips of water.
	• **Drowsiness** usually goes away after a few days of morphine. If it persists or gets worse, halve the dose and inform the health worker.
	• **Sweating or muscle spasms:** notify health worker.

Table 4. Pain management instructions for family and community care providers

Purpose	Instructions
To teach family and community care providers how to administer pain medication	• Explain frequency and importance of administering pain relief medicine regularly and of not waiting for the pain to return. • Stress that dose should be given before the previous dose wears off. • Write out instructions clearly.
To advise family and community care providers on additional methods of pain control.	Discuss how to control pain through: • emotional support; • physical methods: touch (stroking, massage, rocking, vibration), ice or heat, deep breathing; • cognitive methods: distraction, music, imagery, etc.; and • spiritual support, including meditation and prayer, while respecting the patient's beliefs.

2. Symptom management

Patients with HIV/AIDS may experience a wide range of symptoms, involving virtually every major organ system, as a result of specific opportunistic infections, malignancies, comorbidities, medication toxicity, substance abuse or HIV infection itself. Many studies from different countries have documented a high prevalence of symptoms in patients with AIDS (see Table 5) *(34)*. Table 6 summarizes some of the common symptoms in HIV/AIDS and their possible causes, grouped primarily by organ system, and it also indicates some of the disease-specific and/or palliative care interventions that may be applied in individual cases. Tables 7–26 present symptom-specific palliative care interventions in more detail, along with suggestions that may be useful for home care providers. Whenever possible, the particular condition causing the symptom should be treated (e.g. cryptococcal meningitis that is causing headaches), but often it is just as important to treat the symptom itself (for example, loperamide or codeine for chronic diarrhoea that is not due to a specific pathogen).

Table 5. Prevalence of symptoms in patients with AIDS

Symptoms	Prevalence
Fatigue or lack of energy	48–45%
Weight loss	37–91%
Pain	29–76%
Anorexia	26–51%
Anxiety	25–40%
Insomnia	21–50%
Cough	19–60%
Nausea or vomiting	17–43%
Dyspnoea or other respiratory symptoms	15–48%
Depression or sadness	15–40%
Diarrhoea	11–32%
Constipation	10–29%

Source: based on available descriptive studies of patients with AIDS, predominantly with late-stage disease, 1990–2002, in Selwyn & Forstein *(34)*.

Table 6. Common symptoms in patients with AIDS and possible disease-specific and symptom-specific interventions

Type	Symptoms	Possible causes	Disease-specific treatment	Symptom-specific treatment
Constitutional	Fatigue, weakness	AIDS Opportunistic infections Anaemia	HAART Treat specific infections Erythropoietin, transfusion	Corticosteroids (prednisone, dexamethasone) Psychostimulants (methylphenidate, dextroamphetamine)
	Weightloss/anorexia	HIV Malignancy	HAART Chemotherapy Nutritional support/enteral feedings	Corticosteroids Megestrol acetate Anabolic agents (oxandrolone, testosterone)
	Fevers/sweats	DMAC Cytomegalovirus (CMV) HIV Lymphoma, malignancy	Azithromycin, ethambutol Ganciclovir, foscarnet HAART Chemotherapy	NSAIDs[a] (ibuprofen, indomethicin) Corticosteroids Anticholinergics (hyoscine, thioridazine) H_2 receptor antagonists (cimetidine)
Pain	Nociceptive pain: • somatic • visceral	Opportunistic infections, HIV-related malignancies, non-specific causes	Treat specific disease entities	*For nociceptive pain* • NSAIDs[a] • Opioids • Corticosteroids

	Neuropathic pain	HIV-related peripheral neuropathy
		CMV
		Varicella-zoster virus (VZV)
		Possible toxicity from dideoxynucleosides (didanosine, stavudine)
		Other medications (isoniazid)
			HAART
			Ganciclovir, foscarnet,
			Aciclovir, famciclovir
			Change antiretroviral drug
			Change drug
				For neuropathic pain
				• NSAIDs[a]
				• Opioids
				• Adjuvants
				  ◦ Tricyclic antidepressants (amitriptyline, imipramine)
				  ◦ Benzodiazepines (clonazepam)
				  ◦ Anticonvulsants (gabapentin, carbamazepine)
				• Corticosteroids
				• Acupuncture

Type	Symptoms	Possible causes	Disease-specific treatment	Symptom-specific treatment
Gastrointestinal	Nausea/vomiting	Esophageal candidiasis CMV HAART	Fluconazole, amphotericin B, Ganciclovir, foscarnet Change antiretroviral regimen	Dopamine antagonists (haloperidol, prochlorperazine) Prokinetic agents (metoclopromide) Antihistamines (promethazine, diphenhydramine, hydroxyzine) Anticholinergics (hyoscine, scopolamine) H_2 receptor antagonists (cimetidine) Proton pump inhibitors (omeprazole) Serotonin antagonists (ondansetron, granisetron) Benzodiazepines (lorazepam) Corticosteroids
	Diarrhoea	MAI Cryptosporidiosis CMV Microsporidiosis Other intestinal parasites Bacterial gastroenteritis, malabsorption	Azithromycin, ethambutol Paromomycin Ganciclovir, foscarnet Albendazole Other antiparasitic agents Other antibiotics	Bismuth, methylcellulose, kaolin Diphenoxylate + atropine Loperamide Tincture of opium (paregoric)
	Constipation	Dehydration Malignancy Anticholinergics, opioids	Hydration Radiation/chemotherapy Medication adjustment	Activity/diet Prophylaxis on opioids Softening agents: • surfactant laxatives (docusate) • bulk-forming agents (bran, methylcellulose) • osmotic laxatives (lactulose, macrogol, sorbitol) • saline laxatives (magnesium hydroxide) Peristalsis-stimulating agents: • anthracenes (senna) • polyphenolics (bisacodyl)

Type	Symptoms	Possible causes	Disease-specific treatment	Symptom-specific treatment
Respiratory	Dyspnoea	PCP Bacterial pneumonia Anaemia Pleural effusion/mass/ obstruction, decreased respiratory muscle function	Trimethoprim/sulfamethoxazole, pentamidine, atovaquone etc. Other antibiotics Erythropoietin, transfusion Drainage/radiation/ surgery	Use of fan, open windows, oxygen Opioids Bronchodilators Methyl xanthines Benzodiazepines (lorazepam)
	Cough	PCP, bacterial pneumonia TB	Anti-infective treatment (as above) Antituberculosis chemotherapy	Cough suppressants (dextromethorphan, codeine, other opioids) Decongestants, expectorants (various)
	Increased secretions (“death rattle”)	Fluid shifts, ineffective cough, sepsis, pneumonia	Antibiotics as indicated	Atropine, hyoscine, transdermal or subcutaneous scopolamine, glycopyrrolate, fluid restriction Discontinuation of intravenous fluids
Dermatologic	Dry skin	Dehydration End-stage renal disease End-stage liver disease malnutrition	Hydration Dialysis Nutritional support	Emollients with or without salicylates Lubricating ointments
	Pruritus	Fungal infection End-stage renal disease End-stage liver disease dehydration Eosinophilic folliculitis	Antifungals Dialysis Hydration Steroids, antifungals	Topical agents (menthol, phenol, calamine, capsaicin) Antihistamines (hydroxyzine, cetirizine, diphenhydramine) Corticosteroids Antidepressants Anxiolytics
	Decubiti/pressure sores	Poor nutrition Decreased mobility, prolonged bed rest	Improve nutrition Increase mobility	Prevention (nutrition, mobility, skin integrity) Wound protection (semi-permeable film/hydrocolloid dressing) Debridement (normal saline, enzymatic agents, alginates)

Type	Symptoms	Possible causes	Disease-specific treatment	Symptom-specific treatment
Neuropsychiatric	Delirium/agitation	Electrolyte imbalances, dehydration	Correct imbalances, hydration	Neuroleptics (haloperidol, risperidone, chlorpromazine)
		Toxoplasmosis, cryptococcal meningitis	Sulfadiazine/pyrimethamine antifungals	
		Sepsis	Antibiotics	Benzodiazepines (lorazepam, midazolam)
	Dementia	AIDS-related dementia	HAART	Psychostimulants (methylphenidate, dextroamphetamine) Low dose neuroleptics (haloperidol)
	Depression	Chronic illness, reactive depression, major depression	Antidepressants (tricyclics, SSRIs, monoamine oxidase (MAO) inhibitors, other)	Psychostimulants (methylphenidate, dextroamphetamine) Corticosteroids (prednisone, dexamethasone)

[a] NSAIDs: non-steroidal anti-inflammatory drugs.
Note: not all medications will be available in all settings.
Source: Selwyn & Forstein *(34)*.

3. Management of weight loss

Table 7. Management of weight loss

Condition	Treatment and dosages (for adults)	Suggestions for home care
General weight loss	Encourage the patient to eat, but do not force as vomiting may result. Offer more frequent smaller meals of the patient's preferred foods.	Consider possible reasons for weight loss (tumours, *Candida* oesophagitis, TB, atypical mycobacteria, CMV colitis, cryptosporidiosis). Avoid cooking close to the patient. Let the patient choose the foods he/she wants to eat from what is available. Accept that intake will decrease as the patient becomes more ill. Seek help from trained health worker in case of rapid weight loss, consistent refusal to eat or inability to swallow.
Anorexia and severe fatigue	**Prednisolone** 5–15 mg daily for up to 6 weeks	Try to stimulate appetite.
Nausea and vomiting	Provide antiemetics (see Table 9).	Offer more frequent smaller meals of the patient's preferred foods; do not force the person to eat.
Thrush or mouth ulcer	See Table 10.	—
Diarrhoea	See Table 13.	—

4. Management of fever

Fever may be a side-effect of antiretroviral (ARV) regimens; if suspected, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, Table 11.

Table 8. Management of fever

Condition	Treatment and dosages (for adults)	Suggestions for home care
General fever	Assess and treat cause. Give **paracetamol** or **acetylsalicylic acid** every 4 hrs (no more than 8 tablets paracetamol in 24 hours). Make sure the patient remains hydrated.	Encourage the patient to drink water, diluted tea or fruit juice frequently. Use physical methods like wet compresses or ice packs.

5. Management of nausea and vomiting

Nausea and abdominal discomfort may be side-effects of ARV regimens or due treatment of opportunistic infections; if suspected, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, Table 11, and Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS*, section on Gastrointestinal infections.

Table 9. Management of nausea and vomiting

Condition	Treatment and dosages (for adults)	Suggestions for home care
Nausea and vomiting	**Metoclopromide** 10 mg every 4–8 hours **Haloperidol** 1–2 mg once daily (OD) or BID **Chlorpromazine** 25–50 mg every 6–12 hours **Cyclizine** 50 mg up to four times daily **Clemastine** 1 mg BID **Cetirizine** 10 mg OD **Hydroxyzine** 25–50 mg three or four times daily **Ondansetron** 8 mg OD or BID	Seek foods the patient likes that cause less nausea. Offer smaller meals and have the patient drink frequently and slowly. Seek help from trained health worker for: • vomiting more than once a day • dry tongue • passing little urine • abdominal pain.

6. Management of mouth ulcers or pain on swallowing

Be aware that mouth ulcers or painful swallowing may be caused by CMV ulcers of the mouth or oesophagus, herpes infection or candida oesophagitis.

Table 10. Management of mouth ulcers or pain on swallowing

Condition	Treatment and dosages (for adults)	Suggestions for home care
General	—	Use soft toothbrush to gently scrub teeth, tongue, palate and gums. Rinse mouth with diluted salt water (a pinch of salt in a glass of water) after eating and at bedtime (usually 3–4 times daily). Topical anaesthetics can provide some relief. Dissolve 2 aspirin in water and rinse the mouth with it up to four times a day. Pain relief may be required (see Table 1). Remove food leftovers with gauze/cloth soaked in salt water. Soft foods may decrease discomfort. Textured foods and fluids may be swallowed more easily. Avoid very hot, cold or spicy foods.
Candida (oral thrush)	**Miconazole** buccal tablets 1 tablet OD for 7 days If severe and/or no response: **Fluconazole** initial loading dose: 200 mg (1 day); maintenance: 100 mg daily for 10–14 days or until symptoms resolve	
Aphthous ulcers	**Prednisolone** applied as crushed grains **Dexamethasone** solution as mouthwash **Kenalog** cream applied to sores	
Herpes simplex	**Aciclovir** 400 mg PO 5 times a day	
Foul-smelling mouth due to oral cancer or other lesions	**Metronidazole** mouthwash: crush 2 tablets in water and rinse mouth.	

7. Management of dry mouth

Table 11. Management of dry mouth

Condition	Treatment	Suggestions for home care
Dry mouth	Review medications; condition could be a side-effect.	Give frequent sips of drinks. Moisten mouth regularly with water. Let the person suck on fruits such as oranges (citrus fruits should be avoided in cases of sores).
Significant lack of saliva	Refer to dentist.	—

8. Management of hiccups

Table 12. Management of hiccups

Condition	Treatment and dosages (for adults)	Suggestions for home care
General, or with oral thrush	**Fluconazole** 100 mg/d, if severe start with 200 mg followed by 100 mg per day until symptoms resolve)	First try manoeuvres to control hiccuping. Have the patient stimulate the throat by: • quickly eating 2 heaped teaspoons sugar; • drinking cold water; • eating crushed ice; or • rubbing the upper palate with a clean cloth (towards the back where it is soft). Or have the patient interrupt normal breathing by: • holding breath or breathing into paper bag, stopping if discomfort occurs; or • pulling the knees to the chest and leaning forward (compressing the chest).
Advanced cancer with distended stomach	**Simethicone** (up to 100 mg TID (reduces flatulence)	
If no response to simethicone or recurrence of condition	**Metoclopromide** (10 mg tablet, 1–2 tablets 3–4 times daily) **Haloperidol** (5 mg tablet: from ¼ to 1 tablet 1–3 times daily)	
Brain tumour	Anti-epileptic medication	

9. Management of diarrhoea

Diarrhoea may be a side-effect of ARV regimens (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, Table 11); other causes include CMV colitis, cryptosporidiosis, microsporidiosis, giardiasis, Kaposi sarcoma, other infective agents, etc.

Table 13. Management of diarrhoea

Condition	Treatment and dosages (for adults)	Suggestions for home care
General	Increase fluid intake, to prevent dehydration. Use oral rehydration solution (ORS) if large volume of diarrhoea. Suggest a supportive diet. Give constipating drugs, unless there is blood in stool or fever, or if patient is younger than 5 or elderly. **Loperamide** 4 mg to start, then 2 mg after each loose stool (maximum 12 mg/day, though some patients need more) Or (if approved): • **codeine** 10 mg TID (up to 60 mg every 4 hours); or • **oral morphine** 2.5–5.0 mg every 4 hours (if severe)	Encourage the patient to drink plenty of fluids to replace lost water (given in small amounts, frequently). Increase frequency of small amounts of food intake, such as rice soup, porridge, ORS, bananas, other soups. Be careful with milk and chocolate. Special care for rectal area: • after the person has passed stool, clean with toilet paper or soft tissue paper; • wash the anal area three times a day with soap and water; and • if the patient feels pain when passing a stool, apply petroleum jelly around the anal area. Seek help of a trained health worker for any of the following: • vomiting with fever • blood in stools • diarrhoea for more than 5 days • increasing weakness • broken skin around the rectal area • perianal ulcers.
Rectal tenderness	Local anaesthetic ointment or petroleum jelly	
Incontinence	Petroleum jelly to protect perianal skin	

10. Assessment of dehydration in adults

An assessment of the state of hydration is essential in the management of persons with chronic diarrhoea.

Table 14. Assessment of dehydration in adults

Clinical features	Dehydration		
	Mild	**Moderate**	**Severe**
General condition	Weak	Weak	Restless, irritable, cold, sweaty, peripheral cyanosis
Pulse	Normal	Slight tachycardia	Rapid, feeble
Respiration	Normal	Normal	Deep and rapid
Skin elasticity	Normal	Pinch retracts slowly	Pinch retracts very slowly
Eyes	Normal	Sunken	Deeply sunken
Mucous membranes	Slightly dry	Dry	Very dry
Urine flow	Normal amount; urine dark	Reduced amount; dark amber in colour	No urine; bladder is empty

11. Management of constipation of more than two days

Table 15. Management of constipation of more than two days

Condition	Treatment and dosages (for adults)	Suggestions for home care
Impacted	Perform rectal exam and remove manually.	Offer drinks often. Encourage consumption of fruit (including dried fruit), vegetables, linseed porridge, soft foods. Give a tablespoon of vegetable oil before breakfast. Have the patient gently put petroleum jelly or soapy solution into the rectum, or do it yourself if the patient cannot. For this procedure, as for any contact with potentially infective matter, use protective gloves.
Other constipation	Give stool softener/bulk agents, varying the dose for the individual: • a bulk-enhancing agent the first time, e.g. bran 4 tablets/day or **psyllium** 2–3 tablespoons in water/juice up to TID; • **macrogol**, 13.125 g/dose, 1–2/day; • **lactulose**, 10–20 ml TID; • **bisocodyl** 5–15 mg at night; or • **senna** 2 tablets to start (7.5–8.6 mg each) TID, up to 2 tablets every 4 hours). **Remember:** always provide a bowel regimen with stool softener, with or without a stimulant, to patients being treated with opioids such as morphine or codeine.	

12. Management of incontinence

Table 16. Management of incontinence

Condition	Treatment and dosages (for adults)	Suggestions for home care
Incontinence of urine or faeces	• Assess for possible neurological reasons (cerebral toxoplasmosis or other opportunistic infections (OI)). • For males: use urine bottle, condom or catheter. • For females: consider catheterization. • In general consider diapers, regardless of patient sex. • Keep stools firm with **loperamide** (see Table 13).	• Change pads or diapers regularly. • Keep skin clean and dry; apply protective ointments as needed.

13. Management of itching

Skin rashes, both mild and severe, can be a side-effect of ARV regimens; if suspected, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, Table 11.

Table 17. Management of itching

Condition	Treatment and dosages (for adults)	Suggestions for home care

Scabies, prurigo, eczema, ringworm, dry itchy skin, psoriasis, icterus	Assess whether condition is a side-effect of medication.
	
	General care
	• Local steroid creams may be useful if inflammation is present in absence of infection (bacterial, fungal or viral).
	• Antihistamines:
	  ◦ **chlorpheniramine** 4–5 mg BID, **cetirizine** 10 mg OD, **hydroxyzine** 25–50 mg TID;
	  ◦ **diphenhydramine** 25–50 mg at bedtime or up to TID, possibly useful for severe itching.
	• For skin infections, use **0.05% chlorhexidine** rinse after bathing.
	• For itching from obstructive jaundice, try **prednisolone** (20 mg OD) or **haloperidol** (2 x 1 mg OD).
	• For eczema, gently wash with warm water and dry skin. Do not use soap. Topical steroids may be used for the short term (but not on face).
	• For ringworm, use compound benzoic and salicylic acid ointment (**Whitfield ointment**) or other antifungal cream. If extensive, use **fluconazole** (start with 200 mg on first day, followed by 100 mg OD).
	• Consider treatment for scabies even if there are no typical lesions **(ivermectine** 200 µg x 1 dose; see Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS*, section on General symptoms, scabies.)
	• For psoriasis, use coal tar ointment 5% in 2% salicylic acid and expose to sunlight 30–60 minutes per day.
		Try any of the following:
		• applying petroleum jelly to the itchy area;
		• putting one spoon of vegetable oil in 5 litres of water to wash the patient;
		• diluting one teaspoon of **chlorhexidine** in a litre of water and applying after bathing; or
		• using warm water for bathing.
		
		Seek help from a trained heath worker for painful blisters or extensive skin infection.

14. Management of bedsores

Table 18. Management of bedsores

Condition	Treatment and dosages (for adults)	Suggestions for home care
Signs of infection	All patients need skin care to avoid pressure sores. • Ensure infection is not from another source. • If redness, tenderness, warmth, pus or crusts present, assess for fever; if systemically unwell, or if infection extends to muscle, refer to hospital, start IV/IM antibiotics (or oral **cephalexin** or **dicloxacillin**). • Start **cephalexin** or **dicloxacillin** 500/1000 mg four times daily (QID) if any of the following present: ◦ lesion greater than 4 cm ◦ red streaks ◦ tender nodes ◦ more than 6 abscesses. • Drain pus if fluctuant, elevate limb and follow up next day. • If sores are only red, tender and warm, clean them with antiseptic, drain pus if fluctuant and follow up in two days. • For ill-smelling tumours or ulcers use crushed **metronidazole** to cover the affected area.	*Soothing the pain of bedsores and hastening their healing* • For small sores, clean gently with salty water and allow to dry. • For bedsores that are not deep, leave the wound open to the air. • If painful, give painkillers such as paracetamol or aspirin regularly. • For deep or large sores, gently clean and cover with clean light dressing daily to encourage healing. • Seek help from a trained health worker for any discoloured skin, or if bedsores worsen. *Preventing bedsores in bedridden PLHIV* • Help the patient to sit up in a chair from time to time if possible. • Lift patient up in the bed – do not drag patient, as it can break the skin. • Change the patient's position on the bed often, if possible every 1–2 hours – use pillows or cushions to maintain position. • After bathing, dry skin gently with a soft towel. • Oil the skin with cream, body oil, lanolin or vegetable oil. • Massage back, hips, elbows and ankles with petroleum jelly. • If there is leakage of urine or stools, protect the skin with petroleum jelly applied around the genital area, back, hips, ankles and elbows. • When passing urine or stool in bed, the patient should be supported over the receptacle so as to avoid injury and soiling of linen. *Bedding suggestions* • Keep bedding clean and dry. • Put extra soft material, such as a soft cotton towel, under the patient. • For incontinent PLHIV, use plastic sheets under the bed sheets to keep the mattress dry.

15. Management of mental health problems

For individuals living with HIV, attention to and care of mental health is of particular significance. For example, studies suggest that people living with HIV who suffer from depression have lower levels of adherence to HIV medication. On the other hand, antidepressant treatment improves adherence to antiretroviral treatment among depressed PLHIV *(35)*.

Mental health issues in PLHIV may arise independently of HIV as part of an associated illness (organic cause), or as a reaction to the HIV diagnosis or related stressors and social issues, such as stigmatization and health uncertainty.

Anxiety disorders cover a broad spectrum. Anxiety can be non-pathological, or it can present as part of another illness, such as depression or thyrotoxicosis. In other cases, it presents as an independent entity, ranging from anxiety that is pervasive and persistent (generalized anxiety disorder, or GAD) to anxiety in specific situations, either with an identifiable source (a traumatic event or phobic entity) or without, as in panic attacks. For each type, severity may also vary from mild to severe.

Table 19. Management of anxiety

Condition	Treatment and dosages (for adults)	Suggestions for home care
GAD	Counsel on managing anxiety in accordance with the specific situation, teach relaxation techniques, listen carefully and provide emotional support. Self-help based on **cognitive behavioural therapy** (CBT) principles should be encouraged, or a CBT referral made if available. CBT involves a short course of sessions with a psychologist or psychiatrist to explore the origins and warning signs of depression and learn skills to manage it. A **selective serotonin reuptake inhibitor** (SSRI) is an appropriate first-line pharmacological treatment, e.g. **citalopram** 10 mg OD for the first week, increasing to 20 mg or higher (max. 60 mg/day) for several weeks. A **benzodiazepine** can provide rapid symptomatic relief from anxiety but because of tolerance and dependence should not be used beyond 2–4 weeks. It may be useful at the start of SSRI treatment to prevent an initial worsening of symptoms.	*Helping with anxieties* • Take time to listen to the patient. • Discuss the problem in confidence. • Soft music or massage may help the patient to relax. • Connect the patient with appropriate support groups. • In case of increasing anxiety or depression, refer to a health care provider.
Panic disorder	An **SSRI** should be used as a first-line treatment. If the SSRI is contraindicated or ineffective, **clomipramine** can be used (25 mg OD to start, increased over 2 weeks to daily dose 100–150 mg) Self-help based on CBT principles should be encouraged, with referral for CBT if available.	
Phobic disorders	An **SSRI** may be begun. CBT is particularly important, for example, using graded exposure techniques.	

16. Management of sleeping problems

Insomnias are disorders in initiating or maintaining sleep. They may be divided into initial insomnia, middle insomnia and early-morning wakening. In many cases the insomnia is a symptom of another mental or physical disorder, such as:

- unmanaged pain
- anxiety
- depression
- drug withdrawal (e.g. from alcohol, diazepam or heroin).

Insomnia, nightmares and somnolence can all be side-effects of certain ARV regimens, especially those with efavirenz; if suspected, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, Table 11.

Table 20. Management of insomnia

Condition	Treatment and dosages (for adults)	Suggestions for home care
Insomnia	Ascertain whether the underlying cause of insomnia has been addressed, e.g. depression, anxiety, mania, pain or substance withdrawal. In the absence of such causes, better sleep hygiene should be considered. • Exercise in the daytime, use relaxation techniques such as meditation or listening to calming music, and observe a routine of retiring and rising at the same time each day. • Daytime napping and using the bed for daytime activities should be discouraged and caffeine and alcohol intake reduced, especially at nighttime. For initial insomnia, getting up after 20 minutes and engaging in a relaxing activity before returning to bed may be recommended. In some individuals, short term use of a benzodiazepine (e.g. **temazepam** 5–10 mg at night) or another hypnotic (such as 3.75–7.5 mg **zopiclone**) can be taken at least one hour before retiring. Either one can be continued for a maximum of 3–4 weeks, to avoid tolerance and dependence. Longer term treatment may be beneficial in a small number of cases, but may cause rebound insomnia; hypnotics should be tapered slowly.	Listen to the fears that may be keeping the patient wake, and respond to these fears in a reassuring manner. Reduce noise where possible. Do not give the patient strong tea or coffee late in the evening. Treat pain if present.

17. Management of affective disorders

17.1. Depression

Symptoms of depression include:

- low moods, reduced energy, decreased activity and diminished capacity for enjoyment;
- reduced interests and concentration, and marked tiredness after even minimum effort;
- disturbed sleep and diminished appetite; and
- reduced sense of self-esteem and self-confidence (even in mild depression), often with some feelings of guilt or worthlessness.

The lowered mood varies little from day to day, is unresponsive to circumstances and may be accompanied by so-called "somatic" symptoms, such as early-morning awakening, marked psychomotor retardation, agitation, loss of appetite, weight loss and loss of libido.

Table 21. Management of depression

Condition	Treatment and dosages (for adults)	Suggestions for home care
Depression (general)	Assess and classify as to suicide risk, major or minor depression, complications from loss or other difficult life events. • Consult with a psychiatrist for treatment • Consider whether the condition may be due to effects of medication, e.g. efavirenz; see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, Table 11.	Provide support and counselling. Mobilize family and friends for support, and refer patient to PLHIV support groups or religious support groups. Do not leave alone if suicide risk: • counsel; • help patient find a solution if sleep-disturbed; and • follow up.
Mild depressive episode Symptoms from two or three of the symptom groups listed in the text are usually present. The patient is usually distressed by them but is probably able to continue with most activities.	Antidepressants are not recommended, as monitoring, problem-solving and exercise are more important.	—
Moderate depressive episode Symptoms from all four groups listed in the text are usually present, and the patient is likely to have great difficulty in continuing with ordinary activities.	For a single moderate episode of depression, it is advised that treatment be continued for 4–6 months; longer for multiple episodes. *First-line treatment* should be an SSRI, e.g. **citalopram** 10–20 mg/d, increasing with monitoring over several weeks to a maximum of 60 mg/d. The lowest possible therapeutic dose should always be used. In the early stages of SSRI use, the patient should be closely monitored for restlessness, agitation and suicidal tendencies. Many PLHIV find the potential side-effect of reduced libido unacceptable.	—
	Second-line therapy should be considered if SSRI is poorly tolerated or ineffective after 6–8 weeks. An antidepressant from another class (usually a tricylic or an MAO inhibitor, e.g. **amitryptyline** initially 25 mg TID) can then be used, with reference to a standard text for guidelines on withdrawing or substituting. However, it must be borne in mind that tricylics are very toxic in overdose, so they should not be considered if there is a risk of self-harm. An alternative SSRI could also be tried, e.g. **sertraline** commencing at 50 mg daily.	
	Caution: The herbal antidepressant **St John's wort** interacts with PIs and NNRTIs, leading to low levels of these drugs in the blood and risking the development of drug-resistant HIV. It is thus not recommended for patients taking PIs or NNRTIs.	

Condition	Treatment and dosages (for adults)	Suggestions for home care
Severe depressive episode without psychotic symptoms Several of the above symptoms are marked and distressing, typically loss of self-esteem and feelings of worthlessness or guilt. Suicidal thoughts and acts are common, and several "somatic" symptoms are usually present.	For severe or resistant depression, a combination of antidepressants and CBT is recommended. Depending on the severity of the depression and the risk to the patient, a mental health specialist may consider **lithium** (enough to achieve a plasma level of 0.4–1.0 mmol/litre), electroconvulsive therapy or **venlafaxine** (starting dose 75 mg/day), with appropriate advice to the patient, including baseline tests: a minimum of electrocardiogram (ECG), thyroid and renal function for lithium, and ECG and blood pressure for venlafaxine.	Educate patient and family about medication. Refer for counselling. Ensure follow-up.
Severe depressive episode with psychotic symptoms A severe episode of depression with hallucinations, delusions, psychomotor retardation or stupor.	Psychotic symptoms may require commencement of an antipsychotic, following review by a mental health specialist.	—
Suicidal thoughts	Assess if the person has a plan and the means to carry out suicide. If so, consider patient to be high risk and refer for hospitalization.	Do not leave alone. Remove harmful objects. Mobilize family and friends.

17.2. Mania and bipolar affective disorder (BPAD)

- Individuals with HIV may suffer comorbidly from BPAD, which is characterized by two or more episodes of mood disturbance, including one that is manic or hypomanic.
- Mania has been documented as occasionally presenting in individuals with no personal or family history of BPAD, but with advanced HIV or very low CD4 counts.

Typical signs of mania and BPAD:

- Mood is elevated out of keeping with the patient's circumstances and may vary from carefree joviality to almost uncontrollable excitement.
- Elation is accompanied by increased energy, resulting in overactivity, pressure of speech and a decreased need for sleep. There is often marked distractibility. Self-esteem is often inflated with grandiose ideas and overconfidence.
- Loss of normal social inhibitions may result in behaviour that is out of character as well as reckless or inappropriate.
- In addition, delusions (often grandiose) or hallucinations may be present.

Table 22. Management of mania and BPAD

Condition	Treatment and dosages (for adults)	Suggestions for home care
Mania and BPAD	Mood stabilizers – including lithium (plasma level 0.4–1.0 mmol/litre), **valproate semisodium, lamotrigine** and **gabapentin** – can be used with caution. **Valproate semisodium** is an enzyme inhibitor, so that as with most psychotropics to varying degrees, its potential effect on ARV levels should be considered when starting or stopping valproate semisodium. *Caution:* **carbamazepine** should generally not be used because of interactions with ARVs and risk of agranulocytosis. CBT can also play an important role in helping provide the patient with the skills to recognize the warning signs and triggers of mood swings. Psychotic symptoms may require commencement of an antipsychotic, following review by a mental health specialist.	Caregivers can help with medication compliance and identification of early warning signs of mood disorders.

18. Management of dementia

Dementia is a syndrome due to brain disease, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. It should be noted with dementia that:

- consciousness is not clouded; and
- impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour (e.g. disinhibition) or motivation.

Individuals with HIV may also present with cognitive impairment or apparent dementia for other reasons.

- Depression and anxiety can present with forgetfulness and concentration difficulties, so should be excluded from a diagnosis of dementia.
- Acute infection may also present with confusion (delirium), and should also be excluded.
- In addition, some people with advanced HIV and very low CD4 counts may present with cognitive impairment that is thought to be due to the effects of HIV on the CNS, or possibly to the immune response to the virus.

Table 23. Management of dementia

Condition	Treatment and dosages (for adults)	Suggestions for home care
Dementia	• Assess for alternative explanations, such as depression and delirium. • Assess for reversible causes of dementia, such as normal pressure hydrocephalus, operable tumours, hypothyroidism, neurosyphilis and vitamin B12 and folate deficiencies. Treat accordingly. • Consider pain or fear as possible causes, and treat accordingly. • The mainstay of treatment for HIV-associated dementia is HAART.	As far as possible, keep patient in a familiar environment. • Keep things in the same place, easy to reach and see. • Keep a familiar pattern to the day's activities. • Remove dangerous objects. • Speak in simple sentences, one person at a time. • Keep noise down. • Make sure somebody is always present to look after the patient.
Dementia with behavioural changes such as aggression or restlessness	Non-pharmacological strategies are preferable, such as attempts to communicate patiently. Medication may also be considered, e.g. low dose **quetiapine** (12.5 mg daily), if the patient is distressed. When the patient is being cared for at home, carer support, including relief for the caregiver, should be offered where resources allow. Reducing restlessness may also be more critical in the home environment, since the family may be adversely affected by this behaviour over time.	
Paranoia, severe agitation or distress at night Distress, particularly if patient is experiencing paranoid delusions or other psychotic symptoms	Again, non-pharmacological strategies are preferable, such as attempts to communicate patiently. Medication may be considered, e.g. low dose **quetiapine** (12.5 mg daily), if the patient is distressed, following careful psychiatric assessment of the nature of the patient's symptoms and experiences. Due attention should be given to the increased risk of falls if medication is given.	

19. Management of cough or difficulty breathing

Cough or difficulty breathing may be due to common opportunistic infections seen in HIV/AIDS or to immune reconstitution syndrome, which is usually seen within two to three months of starting ART. If the latter is suspected, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, section on immune reconstitution syndrome.

Table 24. Management of cough or difficulty breathing

Condition	Treatment and dosages (for adults)	Suggestions for home care
Dyspnoea with bronchospasm	Give oxygen via mask if possible. *Asthma protocols* • Give bronchodilators by metered-dose inhaler with spacer/mask or nebulizer. Continue until patient is not able to use them or has very shallow or laboured breathing. • Give **prednisolone** 1 mg/kg per day (usually 60 mg in one dose in the morning); wait one week to assess response, than slowly reduce by 10 mg over a week.	*For simple cough* • Use local soothing remedies, such as honey, lemon or steam (plain or with eucalyptus). • If patient has a new productive cough for more than two weeks, it may be tuberculosis. Arrange with health worker to send three sputum samples for examination for TB. *In addition to treatment given by a health worker* • Help the patient into the best position to ease breathing – usually sitting up. • Leaning slightly forward and resting arms on a table may help. • Use extra pillows or some back support. • Open windows to allow in fresh air. • Fan with a newspaper or clean cloth. • Give patient water frequently to loosen sputum. *For safe handling and disposal of sputum* • Handle with care to avoid spreading infection. • Use a tin for spitting and cover it. • Empty the container in the toilet and wash the tin with a detergent or clean with boiled water. *For easing use of remaining lung function* • Plan activities to accommodate breathlessness. • Avoid crowding, cooking and smoking in the patient's room.
Heart failure or excess fluid	**Furosemide** 40–160 mg/day in a single or divided dose until symptoms improve (monitor for overdiuresis)	
Cough with thick sputum	• Administer nebulized **saline**. • If more than 30 ml/day, try expiratory technique ("huffing") with postural drainage. • Avoid tracheal suction, which is very distressing to the patient.	
Excessive thin sputum	**Hyoscine** (make use of its anticholinergic side-effect) 10 mg every 8 hours	
Pleural effusion (due to Kaposi sarcoma, pneumonia, etc.)	Aspirate pleural fluid if possible (see also Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS).*	
Dry cough	**Codeine** 5–10 mg QID or, if no response, oral **morphine** (2.5–5 mg) as long as needed (try to reduce after one week)	
New productive cough more than 2 weeks **TB**	• Send three sputum samples for acid-fast bacilli (AFB) testing. • See Protocol 4, *Management of tuberculosis and HIV coinfection.* • Continue treatment to prevent transmission.	
Dyspnoea in terminal patients	• Oral **morphine/tramadol** in small dose. • For patients not already on oral morphine for pain, give 2.5 mg every 6 hours; if no relief increase dose progressively by clinical measures; treat pain and anxiety. • For patients already on oral morphine, increase dose progressively by 25%.	

20. Prevention of contractures and stiffness

Table 25. Prevention of contractures and stiffness

Condition	Treatment and dosages (for adults)	Suggestions for home care
Stiffness and contractures **Muscle spasms**	**Diazepam** 5–10 mg 2–3 times daily **Tetrazepam** 50 mg/day, up to 200 mg/day in 2 doses **Baclofen** starting 5 mg TID, increasing every 3 days up to 25 mg TID	Do not confine – encourage mobility. Do the following simple range-of-motion exercises if patient is immobile. • Exercise limbs and joints at least twice daily. • Protect joints by holding the limb above and below and support it as much as possible. • Bend, straighten and move joints as far as they normally go. Be gentle and move slowly without causing pain. • Stretch joints by holding as before but with firm steady pressure. • Bring the arms above the head and lift the legs to 90 degrees – let the patient do it as far as possible and help the rest of the way. Massage the patient.

21. Management of vaginal discharge from cervical cancer

Table 26. Management of vaginal discharge from cervical cancer

Condition	Treatment and dosages (for adults)	Suggestions for home care
Vaginal discharge from cervical cancer	**Metronidazole** 100 mg tablets as pessary OD	Provide daily hygiene. Patient can sit in basin of water with pinch of salt, twice daily if possible.

22. Drug interaction considerations

There are a few instances in which medications used in palliative care are not recommended for use with antiretroviral agents such as the more potent PIs (e.g. ritonavir and indinavir) or NNRTIs (e.g. nevirapine and efavirenz), due to drug interactions mediated through the cytochrome P450 enzyme system involved in hepatic metabolism. These substances to avoid include triazolam, midazolam, terfenadine, astemizole and St John's wort *(36–40)*. In most other cases, such as longer-acting benzodiazepines, anticonvulsants and tricyclic antidepressants, it is recommended rather that clinicians monitor patients closely for evidence of under- or overmedication, and that therapeutic drug level monitoring be used in instances where it is available and may provide useful additional information.

V. Special advice for terminal care

It is very helpful in the care of dying patients for family members to understand and anticipate some of the medical, emotional and spiritual changes that can occur as part of the normal process of dying in the last months of life. The health care team can play an important role in educating family members and other caregivers about end-of-life issues, including what to expect over the final course of the illness. At the end of this section, Table 27 presents a general prognostic timeframe for approaching the end of life, describing typical patient features and interventions that may be helpful in the last months, weeks, days and hours of life. General recommendations for working with patients' families in end-of-life care are presented immediately below.

1. Preparing for death

- Encourage communication within the family. A family meeting may be useful to identify the fears and worries and of the patient and of the family.
- Talking with the patient to establish the patient's understanding and prognosis of the disease is important.
- Discuss worrisome issues such as custody of children, family support, future school fees, old quarrels and funeral costs.
- Let the patient know he/she will be loved and remembered.
- Talk about death if the person so wishes. Find out if the patient has ever seen anyone die and his or her own fears about death. Such fears may have a basis in physical and/or psychological ones.
- Make sure the patient gets help in addressing any feelings of guilt or regret.
- Respond to spiritual needs as the patient requests, providing connections with spiritual counsellors or religious institutions of the patient's choice.

2. Presence

- Be present with compassion.
- Visit regularly, hold hands, listen and talk.

3. Caring

Provide comfort measures, such as:

- moistening lips, mouth and eyes
- keeping patient clean and dry
- treating fever and pain (around the clock if necessary)
- controlling other symptoms and relieving suffering with medical treatment as needed
- providing liquids and small amounts of food as needed
- providing physical contact.

4. Bereavement

After the death of the patient, it is important to acknowledge and attend to the bereavement needs of survivors. Particular issues for families affected by HIV include:

- the relatively young age at which most patients die, which can be a more difficult loss for families than the death of an older family member;
- the immediate and longer term risk of financial and social losses;
- the stigmatized nature of the disease, which may complicate the grieving process; and
- the possibility that other family members have already have died from HIV/AIDS, or that survivors may be HIV-infected and at risk for dying from it.

All of these issues make it necessary for HIV/AIDS care providers to be sensitive and responsive to the needs of survivors and orphans to help them deal with the grief and multiple losses which HIV/AIDS often inflicts on families.

Table 27. Common manifestations in PLHIV approaching the end of life, and suggestions for family and caregiver support

Type of manifestation	Last months	Last weeks	Last days	Last 24–28 hours
PLHIV end-of-life manifestations				
Physical	• Increased fatigue • Increased sleep • Decreased interest in eating • Increase in pain or other symptoms	• More time in bed • Insomnia • Less interest in food and drink • Decreased energy • Difficulty walking	• Incontinence • Sleep pattern reversal • Sweats • Confusion • Cognitive failure • Changes in skin (pallor) • Respiratory changes	• Somnolence • Restlessness • Agitation • Gradual or sudden loss of consciousness • Further changes in skin colour • Periodic breathing • Gurgling • Moaning • Delirium
Emotional	• Increased need for closeness, talking, physical contact • Social withdrawal • Increased sadness, crying • Seeking closure, expressing feelings of love	• Desire to talk about funeral arrangements • Periods of intense emotional expression • Bargaining • Life review, discussion of past events • Desire to reassure family • Fear of sleep	• Greater peacefulness, quiet • Increased communication • Signs of closure/saying goodbye • Increased anxiety	• May be unresponsive or minimally responsive • Confusion, delirium, inability to express emotions clearly
Spiritual	• Increased interest in spiritual matters • Prayer • Desire for contact with religious/spiritual leader • Questioning of faith	• Dreams or visions of deceased loved ones • Increased faith in God • Periods of quiet reflection	• Increased clarity in thinking and emotions • Increased sense of peace and transcendence	• Perception of other dimensions of experience • Increased sense of peace • Deep peaceful sleep

Type of manifestation	Last months	Last weeks	Last days	Last 24–28 hours
Suggestions for family/caregiver support				
All	• Allow patient to dictate food preferences. • Offer and encourage food/fluids (never pressure or force). • Offer assistance with walking. • Help create a comfortable, safe environment. • Work closely with treatment team and report any new or worsening symptoms or problems. • Provide emotional support; listen. • Try not to deny patient's acceptance of illness by saying everything will be okay. • Allow patient to cry and vent emotions. • Do not minimize sad feelings. • Pray with patient if possible. • Assist patient in contacting spiritual leader.	• Support patient's choice to rest as needed. • Continue to report any increase in pain or symptoms to the treatment team. • Monitor any changes in sleep patterns, eating, etc. • Support discussion of end- of-life wishes. • Moderate visiting so patient can rest. • Allow for life review discussion, reminiscing. • Provide physical contact, e.g. back rubs, foot massages. • Communicate feelings of love, acceptance. • Leave bedroom light on if patient is fearful of the dark. • Reassure patient frequently that loved ones will be present whenever possible. • Participate in discussion of spiritual issues.	• Keep patient clean and dry. • Reposition patient frequently if unable to move. • Offer but don't force foods and fluids. • Be aware of level of consciousness, ability to swallow prior to feeding. • Provide physical contact. • Moisten lips with ice chips, swabs. • Continue verbal communication, play favourite or soothing music. • Allow family and friends to keep bedside vigil. • As a caregiver, remember to rest and eat whenever possible. • Pray with patient.	• Provide warm/cool compresses as needed if cold/sweating. • Talk to patient (even if unresponsive). • Report changes in breathing to treatment team (and be reassured about abnormal breathing changes at end of life). • Notify team if patient appears uncomfortable (frowning, furrowed brow). • Provide medications as needed/directed. • Talk with patient and express emotions. • Provide verbal and nonverbal support through words and actions. • Say goodbye and give permission to go. • Reassure patient. • Express love and acceptance. • Participate in supportive rituals.

Note: The symptoms and signs listed in this table are meant to be typical rather than universal. Patients do not necessarily exhibit all of them, and the final course of illness differs significantly among PLHIV. The timeframe for individual manifestations will also vary substantially in individual cases from what is shown.
Source: Selwyn & Rivard *(41)*.

VI. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected is important in the development of key indicators on access to palliative care and its success. Such indicators assist managers in decision making on ways to strengthen and expand these services to all PLHIV who need them.

The following data should be collected on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV/AIDS patients requiring palliative care[2]
- number of HIV/AIDS patients receiving palliative care
- number of HIV/AIDS patients receiving any pain management
- number of HIV/AIDS patients receiving opioid pain management

[2] Defined as the PLHIV who exhibit the signs and symptoms described in this protocol.

Annex 1. Equianalgesic dose equivalents for opioids

Table 28. Equianalgesic dose equivalents for opioids

Opioid agonist	Approximate equianalgesic dose	
	Oral	Parenteral
Morphine	30 mg every 3–4 hours	10 mg every 3–4 hours
Hydromorphone	7.5 mg every 3–4 hours	1.5 mg every 3–4 hours
Methadone	15 mg every 6–8 hours	10 mg every 6–8 hours
Fentanyl	25 mcg (transdermal)[a] every 72 hours	0.01 mg
Hydrocodone[b]	30 mg every 3–4 hours	—
Oxycodone[b]	30 mg every 3–4 hours	—
Codeine[b]	180–200 mg every 3–4 hours	130 mg every 3–4 hours

[a] Not for use in opioid-naive patients.
[b] May be available in fixed-dose tablet combination with paracetamol or aspirin.
Source: Jacox et al. *(32)*.

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4 Management of Tuberculosis and HIV Coinfection

Clinical Protocol for the WHO European Region

Contents

I. Epidemiology of TB, TB/HIV/AIDS and reciprocal influence of TB and HIV

1. Epidemiology of TB

Tuberculosis (TB) is a serious public health problem in the WHO European Region, where according to the most recent WHO estimates, almost 445 000 new cases and more than 69 000 related deaths occurred in 2004. The overall TB incidence rate for the Region is 50 per 100 000 population, ranging nationally from 2/100 000 in Monaco to 177/100 000 in Tajikistan. By subregion, the rates are 12/100 000 for western Europe, 27/100 000 for central Europe and 96/100 000 for eastern Europe. Among the 22 high-burden TB countries in the world, the Russian Federation ranks 12th *(1, 2)*.

As noted, the highest rates of TB are reported in the countries of eastern Europe, where weakened economies and public health efforts are the main causes of its resurgence, and where internationally recommended control strategies need further expansion and strengthening. In western Europe, there are pockets of increasing incidence, particularly in major cities with socially marginalized immigrants from high-burden TB countries *(3, 4)*.

The European Region has the highest prevalence rates in the world for multidrug-resistant TB (MDR-TB); it includes seven of the nine countries in the world with >6.5% prevalence of MDR-TB in new cases (Estonia, Israel, Kazakhstan, Latvia, Lithuania, the Russian Federation and Uzbekistan), as well as five of the nine countries with >30% prevalence of MDR-TB in previously treated cases (Estonia, Kazakhstan, Lithuania, the Russian Federation and Uzbekistan) *(5)*.

TB is more frequently found among prisoners than in the outside population. The average prison population rate in the European Region is about 100 prisoners per 100 000 inhabitants, with higher rates in the eastern part of the Region. In the Russian Federation, the 2003 rate was approximately 600/100 000 *(6)*. In 2003, more than 7% of the new TB cases reported to WHO Regional Office for Europe were detected in prisons, with large variations among countries (range 0.1–30.4%) *(7–10)*.

2. Epidemiology of TB/HIV coinfection

In eastern Europe there are independent epidemics of TB and HIV/AIDS, and a large majority of TB patients developed their disease without HIV-related immunosuppression. Among people living with HIV (PLHIV), the risk of acquiring TB is higher where the TB prevalence is high. In 2004, western and eastern European countries reported TB as the most frequent AIDS-indicative disease, with respective rates of 24% and 56% of newly reported AIDS cases *(11, 12)*. Unfortunately, knowledge of the real extent of TB/HIV coinfection in Europe is limited due to insufficient surveillance data. As the result of the recent dramatic increase of HIV prevalence in eastern Europe, as well as the high prevalence of TB there, it is expected that the number of TB/HIV patients will dramatically increase in the next few years *(12–14)*.

Prisoners are more vulnerable to becoming infected with TB and HIV due to environmental and nutritional factors that increase their exposure, vulnerability and risk-taking behaviour. Prisons, with their often crowded and enclosed conditions, poor ventilation, inadequate lighting and continuous exposure to TB-infected people, facilitate airborne TB transmission. Malnutrition also contributes to the higher risk for prison transmission. In addition, common prison behaviours – unsafe injecting drug practices, tattooing and unprotected sex – expose prisoners to HIV infection, as well as hepatitis B and C *(15)*.

3. Reciprocal influence of HIV and TB

3.1. Influence of HIV on the development of active TB

HIV promotes the progression of infection with Mycobacterium tuberculosis to active TB, both in people with recently acquired infections and those with latent infections. Undeniably, HIV is the most powerful risk factor known for activation of latent M. tuberculosis infection. For an HIV-infected person-coinfected with M. tuberculosis, the risk of developing active TB reaches 5–10% annually, instead of the 5–10% lifetime risk for an individual not infected with HIV. This discrepancy is clearly linked to the immunodeficiency caused by HIV. Furthermore, HIV infection increases the rate of recurrent TB, which can be due to either endogenous reactivation or exogenous reinfection *(16, 17)*.

3.2. Influence of HIV on the transmission of TB

TB is one of the most common infections in HIV-infected people, especially in high TB prevalence areas. HIV greatly increases the number of TB patients, which in turn increases TB transmission from family members (the highest TB transmission risk is from household contacts, such as children and HIV-positive partners) and community members (through contact in work-places, schools and hospitals) where there is a risk of nosocomial infections from both patients (whether HIV-positive or -negative) and health care workers. Moreover, the risk of MDR-TB transmission may be increased if effective and uninterrupted TB treatment is not ensured *(18–20)*.

3.3. Influence of HIV on the clinical presentation of TB

As HIV infection progresses, CD4 lymphocytes decline by about 50–80 cells/mm^3/year, and the immune system becomes less able to prevent the growth and local spread of *M. tuberculosis*.

Pulmonary TB (PTB) remains, especially in adults, the commonest form of TB, but its presentation depends on the degree of immunosuppression. The clinical pictures, sputum-smear results and chest X-rays are often different in the early stage of HIV infection (CD4 >350 cells/mm^3) and the late stage (CD4 <200 cells/mm^3). The clinical presentation of TB cases in early HIV infection is similar to that of individuals without HIV infection, resembling post-primary PTB, that is, with positive sputum smears (defined as two or more initial smear examinations that are positive for acid-fast bacilli (AFB), or one plus consistent radiographic abnormalities) and often with cavities in the chest X-ray. In contrast, the clinical presentation in late HIV cases resembles primary PTB: the sputum smear is often negative and radiological infiltrates are present instead of cavities *(21–23)*. In case of severe immunodeficiency, the rate of extrapulmonary TB (EPTB) increases in both adults and children. Because of difficulties in diagnosis, disseminated TB may account for a high proportion of misattributed hospital deaths.

3.4. Influence of TB on HIV morbidity and mortality

Active TB itself is responsible for a mild immune deficiency. In countries with independent epidemics of TB and HIV/AIDS, TB does not always indicate severe deterioration of the immune system in HIV-infected people because it may occur before HIV infection or in its early stages, before the immune system has deteriorated. When active TB occurs in HIV patients, a worsening of the HIV-related deficiency is commonly observed, facilitating the progression of other opportunistic infections such as *Candida albicans* oesophagitis, *Cryptococcus* meningitis and, particularly, *Pneumocystis jirovecii* (formerly *P. carinii)* pneumonia. Any of these opportunistic infections may be lethal. If so, TB is indirectly responsible for the death *(24)*.

In addition, TB has been found directly responsible for an average mortality rate of 30% among HIV/AIDS cases in many reports *(22, 23, 25)*. These data emphasize the need of early diagnosis and specific treatment of TB in all HIV-infected patients, especially when the clinical pattern of CD4 cells count shows a severe degree of immunodeficiency.

II. Identification of TB/HIV in adults and adolescents

All HIV-positive people should be assessed for risk factors for having or acquiring TB, just as all patients with active TB disease should be offered HIV testing and counselling. The major reasons for this are:

- HIV-positive people are at higher risk for having or developing active TB, one of the major opportunistic infections causing death in PLHIV;
- HIV infection influences the clinical progression of TB and its treatment;
- TB disease influences the clinical progression of HIV/AIDS and its treatment; and
- TB may be an indicative sign of advanced HIV/AIDS disease.

1. TB risk assessment and diagnosis in PLHIV

In assessing PLHIV for TB risk, particular attention should be paid to:

- people with respiratory symptoms;
- household contacts of anyone with an active case of pulmonary TB; and
- coexisting risk factors and vulnerability-increasing factors (e.g. injecting drug use, alcohol abuse and incarceration).

The initial assessment for TB should include:

- a history of TB exposure (individual and household); and
- a history of possibly related symptoms (especially a cough of more than two weeks duration without any clear explanation).

If an HIV-infected person does not have an obvious risk for TB (recent exposure or clinical symptoms), a tuberculin skin test[1] should be performed to identify the status of any latent TB infection that may evolve into TB disease due to HIV-related immunosuppression. (See Fig. 1 below.)

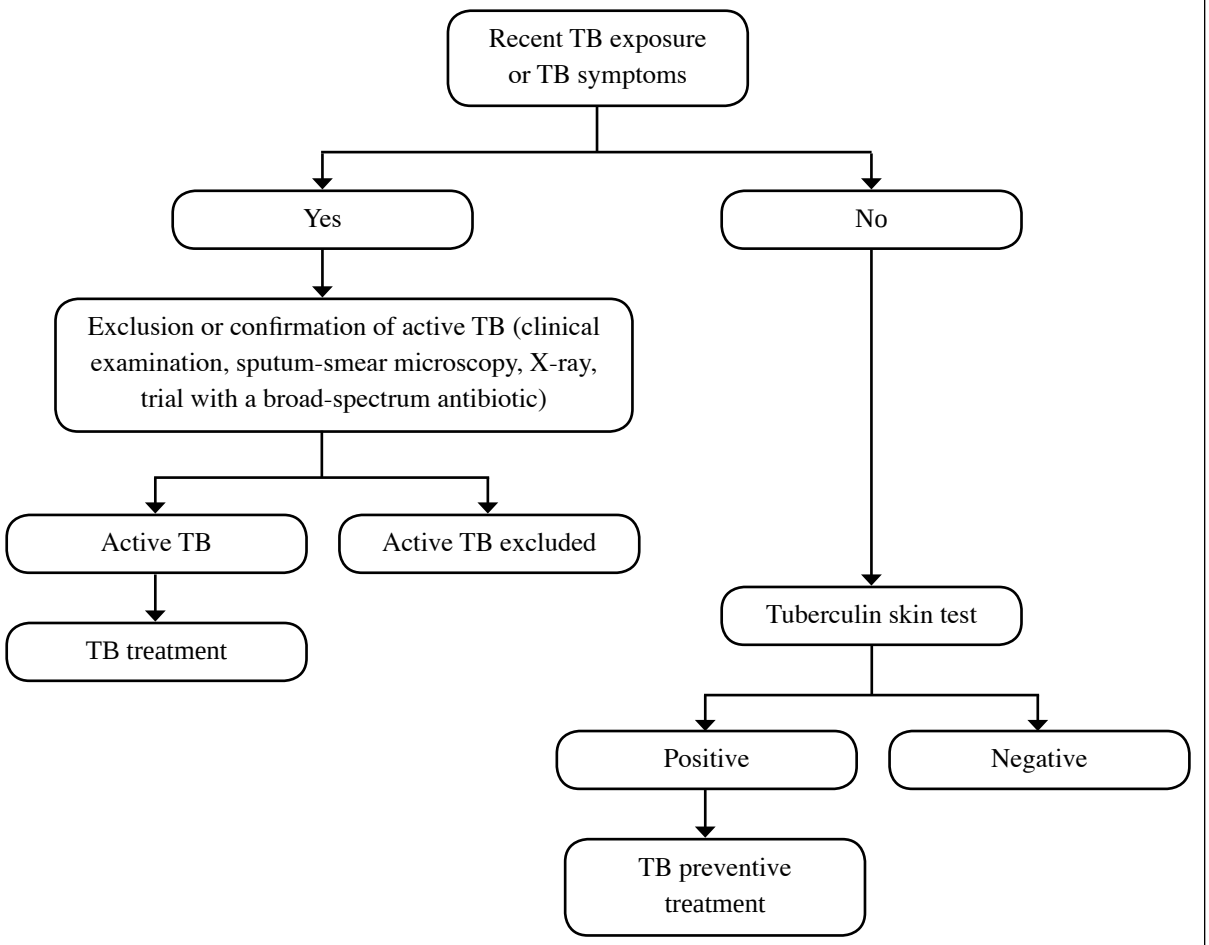
A positive tuberculin skin test is indicative of past or recent TB infection, which is a condition for starting TB preventive treatment (TPT). A negative tuberculin skin test in PLHIV usually means no risk of TB (except in those with severe immunosuppression).

If an HIV-infected person has been recently exposed to TB or has clinical symptoms indicative of pulmonary or extrapulmonary TB disease, the status of active TB disease should be explored. Active TB can be excluded through careful clinical examination, bacteriological investigation (sputum microscopy and culture) and X-ray. In case of infiltrate in the chest X-ray, a clinical trial with a full course of broad-spectrum antibiotics may be necessary to make a diagnosis differentiating between TB and nonspecific pneumonia. When active TB disease is excluded, the possibility of latent TB infection should be explored through a tuberculin skin test.

If an HIV-infected person has active TB disease, he or she should be treated as described in section III below.

[1] Tuberculin is a purified protein derived from tubercle bacilli. Tuberculin injected into the skin of a TB-infected person produces a delayed local reaction after 24 to 48 hours, which is quantified by measuring the diameter of the related skin induration (thickening). The test is usually considered positive in HIV-infected people when induration exceeds 5 mm. The reaction only shows that the person has at some time been infected with *M. tuberculosis (15, 17).*

Fig. 1. Algorithm for assessing TB risk and disease in an HIV-positive person



2. HIV risk assessment and diagnosis in patients with TB

Offering HIV testing and counselling should be a routine procedure in health care settings dealing with patients who have active TB. Health care providers should explain to the patients the reasons for offering the test and the importance of knowing the results for correct clinical management. However, all patients have the right to refuse an HIV test. The initial assessment of a patient's HIV status should include:

- HIV pretest counselling;
- serological tests (typically, ELISA and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test; and
- post-test counselling, including information on reducing risky behaviour, irrespective of the results of the HIV test.

Further evaluation of patients found to be HIV-infected is required to decide on a clinical management strategy. For more detailed information, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

III. Clinical management of TB/HIV in adults and adolescents

For clinical management of TB/HIV-coinfected patients, a major consideration is when to start treatment.

After initial assessment of TB and HIV status, a patient with TB/HIV would fit in one of two TB categories, each requiring a different clinical management strategy, and each of which may or may not require ART:
1. TB-infection (positive tuberculin skin test)
2. active TB disease.

1. Management of coinfected patients

HIV-infected patients coinfected with TB have a higher risk of developing active TB; therefore, tuberculosis preventive treatment (TPT) should be initiated with isoniazid 5 mg/kg (300 mg maximum) once daily (OD) for six months.

Alternative schedules have been suggested to improve adherence, but further research is needed to prove their efficacy. Further research is also needed for developing alternative TPT in areas with high prevalence of isoniazid resistance *(26–28)*. The addition of 6 mg pyridoxine daily can prevent peripheral neuropathy, especially in pregnant women, alcoholics and the malnourished.

The decision of when to start ART is based on a number of indicators, of which the most important are the HIV/AIDS clinical stage and immunological criteria (please refer to the section on Initiation of HAART and WHO Clinical staging of HIV/AIDS for adults and adolescents, in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*).

TPT can also be given simultaneously with ART. More evidence is required to identify the threshold of CD4 count above which TPT can be considered less necessary.

2. Management of coinfected patients with active TB

2.1. TB treatment

TB treatment in HIV-infected patients is a priority and should be started as soon as active TB has been diagnosed. Treating TB promptly will reduce TB-related mortality and the risk of transmission *(15, 29, 30)*.

Treatment of TB, regardless of its concomitance with ART, should be based on drugs of known bioavailability. TB treatment regimens consist of two phases: an initial phase and a continuation phase. Each TB drug has an abbreviation (ethambutol: E, isoniazid: H, pyrazinamide: Z, rifampicin: R, streptomycin: S); for further information on drug dosages see Annex 1. The duration of the initial phase is 2–3 months, the continuation phase, 4–5 months. Present evidence clearly shows that TB relapse in HIV-infected patients is minimized by a regimen containing rifampicin throughout the course of treatment.

Table 1. Recommended TB treatment regimens for PLHIV with active TB

Type of TB case	TB treatment regimen[a]	
	Initial phase[b]	Continuation phase
New TB patient	HRZE 2 months[c]	HR 4 months
Previously TB-treated patient, including: • relapse • treatment after default • treatment failure[d]	HRZES 2 months or HRZE 1 month	HRE 5 months
Chronic or MDR-TB cases (still sputum-positive after supervised re-treatment)	A specially designed regimen, whether standard or ad hoc	

E: ethambutol; H: isoniazid; R: rifampicin; S: streptomycin; Z: pyrazinamide.
[a] Daily TB treatment is recommended for HIV-positive patients with active TB.
[b] Direct observation of drug intake is recommended during the entire course of therapy, particularly in the initial phase.
[c] Streptomycin may be used instead of ethambutol. In meningeal TB, ethambutol should be replaced by streptomycin, which diffuses more in the meninges.
[d] Whenever possible, drug sensitivity testing should be done to enable an individualized treatment regimen.

2.2. Initiation of antiretroviral treatment

Many patients with active TB have advanced HIV disease and are therefore eligible for ART, which should not be withheld simply because a patient is receiving or is about to receive TB treatment. Nevertheless, it is preferable not to initiate treatment for HIV and TB simultaneously, and when possible to delay ART (see Table 2) *(31–34)*. This strategy:

- simplifies patient management
- avoids antiretroviral (ARV) and TB drug interactions
- avoids overlapping toxicities
- limits risk of immune reconstitution inflammatory syndrome (IRIS)
- minimizes confusion about what drugs to take when, and for which disease
- increases adherence.

Table 2. Strategy for initiation of treatment for both TB and HIV infection

Criteria	TB treatment	ART
Extrapulmonary TB (regardless of CD4 count)	Start immediately	Start ART as soon as TB treatment is tolerated (between two weeks and two months)[a].
Pulmonary TB CD4 <200 cells/mm^3	Start immediately	
Pulmonary TB CD4 = 200–350 cells/mm^3	Start immediately	Start ART after completion of initial TB treatment phase (start earlier if severely compromised).
Pulmonary TB CD4 >350 cells/mm^3	Start immediately	Monitor CD4 count. Consider ART if CD4 cell count drops below 350 cells/mm^3.

[a] The decision to start ART should also be based on clinical evaluation of other signs of immunodeficiency.

2.3. First-line HAART regimens

Highly active antiretroviral treatment (HAART) is the standard recommended ART. It includes three or in some cases more ARV drugs. The main factors to consider in selecting the best ARV regimens for TB patients are:

- potency
- side effects and toxicity
- simplicity, to allow better adherence.

ART during TB treatment requires giving special consideration to:

- interactions between rifampicin and some ARVs
- pill burden
- the importance of high adherence
- drug toxicity
- the risk of immune reconstitution syndrome.

Table 3. Recommended first-line HAART for patients being treated for TB with rifampicin[a]

	ARV drug classes	HAART regimes
Preferred	2 NRTIs + 1 NNRTI	ZDV (or TDF) + 3TC (or FTC) + EFV[b]
Alternative	3 NRTIs (triple-nuke regimen)	ZDV + 3TC + ABC (or TDF)

[a] See Annex 2 for dosages

[b] Recommended efavirenz (EFV) dose is 600 mg/day especially in patients with <60 kg body weight *(35–37)*. Increasing the dose to 800 mg/day can be considered in patients with >60 kg body weight, though further research is needed. If EFV is not available, Nevirapine (NVP) can be used [200 mg OD for 2 weeks followed by 200 mg twice daily (BID)] with close monitoring of liver function and drug toxicity. [ZDV + 3TC + NVP is available in an fixed-dose combination (FDC).]

2.3.1. Key considerations for first-line regimens

ZDV (or TDF) + 3TC (or FTC) + EFV (see Table 3)

- No rifampicin dose adjustment is required
- EFV decreases methadone levels significantly; this is important to remember for treatment of injecting drug users (IDU) on opioid substitution therapy. For further information please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*

ZDV + 3TC + ABC (or TDF) (see Table 3)

- No rifampicin dose adjustment is required.
- Pregnant women with TB can safely use ZDV + 3TC + ABC.

For additional considerations regarding first-line ART regimens, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

2.3.2. Treatment failure

Response to ART is monitored by clinical symptoms, CD4 count and viral load. For further information on treatment failure criteria please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

TB is not a criterion for treatment failure in itself and if it occurs without other evidence of immunodeficiency in patients on a first-line regimen, they should not be switched to a second-line regimen. If a patient on a second-line ART develops TB during treatment, the protease inhibitor (PI) component needs to be adjusted.

2.4. Second-line HAART regimens

Table 4. Recommended second-line HAART for patients receiving TB treatment with rifampicin

	ARV drug classes	HAART regimens
Preferred	2 NRTIs + 2 PIs (one of them boosted)	ABC + ddI + LPV/r + RTV or TDF + ddI + LPV/r + RTV
Alternative	2 NRTIs + 2 PIs	ABC + ddI + SQV + RTV or TDF + ddI + SQV + RTV

2.4.1. Key considerations for second-line regimens

ABC (or TDF) + ddI + LPV/r + RTV (see Table 4)

- If ddI is administered with TDF, its dosage should be adjusted due to toxic pancreatic and negative immune effects. The recommended dose of ddI when administered with TDF (300 mg OD) is:
  - 250 mg OD for patients with >60 kg body weight
  - 125–200 mg OD for patients with <60 kg body weight *(38, 39)*.
- When LPV/r 400/100 mg BID is administered, RTV 300 mg BID should be added, with close monitoring of liver functions and lipid levels.

ABC (or TDF) + ddI + SQV + RTV (see Table 4)

- When SQV is administered, the recommended daily dosages of SQV and RTV are each 400 mg, and close monitoring of liver functions is required.
- No rifampicin dosage adjustment is required with these regimens.

2.5. ARV and TB drug interactions and management

- Rifampicin stimulates the activity of the hepatic cytochrome P450 (CYP) enzyme system that metabolizes NNRTIs and PIs (see Annex 2 for ARV classes). This mechanism leads to a reduction in the blood levels of NNRTIs and PIs, and consequently the incomplete suppression of HIV replication and the emergence of drug resistance. Rifampicin causes up to a 75% reduction in the serum levels of PIs, thus necessitating dosage adjustment.
- NNRTIs and PIs can also enhance or inhibit CYP and lead to altered blood levels of rifampicin. Therefore, when rifampicin is used concomitantly with NNRTIs and PIs, a daily regimen is preferred *(40–42)*.
- The effects of rifampicin and NNRTIs and PIs on the CYP are both complex and common, but unless a definitive contraindication exists, rifampicin is the preferred TB drug. The reason is that the rate of TB relapse in HIV-positive patients becomes as low as in HIV-negative patients when treated for ≥6 months with rifampicin-containing regimens.
- Rifampicin has no effect on the serum levels of nucleoside reverse transcriptase inhibitors (which are not metabolized by CYP), and no dosage adjustment of these drugs is necessary.
- In patients on second-line ART, rifabutin 150 mg every other day (QOD) or 3 times/week can be used safely as an alternative to rifampicin. Rifabutin may be preferred in settings with a limited capacity to adjust PI dosage; however, it is more expensive than rifampicin.
- Rifabutin should not be prescribed with unboosted SQV, but it can be used with combination of SQV with RTV.

2.6. Cotrimoxazole primary prophylaxis

TB/HIV-coinfected patients may die soon after the commencement of treatment if it is started at too advanced an HIV/AIDS stage. Death may be related to the progression of TB itself, but in many cases the death is related to the progression of other opportunistic infections, such as *Pneumocystis jirovecii* pneumonia (PCP) or *Toxoplasma gondii* encephalitis (TE) *(32)*. Therefore, primary prophylaxis with cotrimoxazole (trimethoprim-sulfamethoxazole) is needed as prophylaxis against PCP and TE.

- Patients with a CD4 count <200 cells/mm^3 or who are at Clinical Stage 3 (with oropharyngeal candidiasis, for example) or Clinical Stage 4 should receive cotrimoxazole simultaneously with TB treatment (if indicated) until the CD4 cell count has stabilized for 4–6 months, or at least 3 months at >200 cells/mm^3.
- The recommended prophylaxis with cotrimoxazole in adults is one double-strength tablet: 160/800 mg OD.
- Adherence to cotrimoxazole is critical, and direct observation of its administration, together with the administration of TB drugs, may be useful, particularly in very ill patients.

For more information, please refer to Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS*, section on OI prophylaxis in HIV infected patients.

3. Clinical management of TB/HIV in special conditions

3.1. Renal failure

- Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can therefore be given in normal dosage to patients with renal failure.
- Patients with severe renal failure should receive pyridoxine with isoniazid in order to prevent peripheral neuropathy.
- Streptomycin and ethambutol, however, are excreted by the kidney. They should be given in reduced doses, and renal function should be monitored closely (creatinine level monthly).
- TDF should be avoided in ARV regimens due to its known nephrotoxicity.

Table 5. Recommended TB regimens for patients with renal failure[a]

	Initial phase	Continuation phase
Preferential	HRZ 2 months	HR 4 months
Alternative (if monitoring of renal function is possible)	HRZE 2 months	HR 4 months

[a] Renal failure is defined as occurring when the creatinine level increases to 130–160 micromoles/litre.

3.2. Liver disease

- Isoniazid, rifampicin and pyrazinamide are all associated with drug-induced hepatitis.
- Pyrazinamide is the most hepatotoxic, followed by rifampicin. Rifampicin is less likely to cause hepatocellular damage, although it is associated with cholestatic jaundice.
- Patients with liver disease should not receive pyrazinamide. Alternative TB treatment regimens are listed in Table 6.
- Clinical monitoring of the liver and laboratory monitoring of liver enzymes should be performed to detect any exacerbation of the condition. They should be done on a regular basis, at a frequency that depends on the patient's condition.

Table 6. Recommended TB regimens for patients with liver disease[a]

	Initial phase	Continuation phase
Preferential	SHRE 2 months	HR 6 months
1st Alternative	SHE 2 months	HE 10 months
2nd Alternative	RE 9 months	–

[a] Liver disease is defined as an alanine aminotransferase (ALT) exceeding three times the normal level, or the presence of chronic hepatitis or cirrhosis.

3.3. Women of childbearing age

- Rifampicin and some ARV drugs (mainly PIs) can reduce estrogen levels, so oral contraceptives containing estrogen may not be effective. For more information on contraception choices, please refer to Protocol 9, *Support for sexual and reproductive health of people living with HIV.*
- If effective contraception is ensured, TB/HIV-coinfected women may receive a regular TB treatment regimen and the same ARV regimen as men, including EFV; otherwise, EFV must be avoided. ABC is a recommended alternative to EFV.

3.4. Pregnant women

- The strategy for initiating TB treatment and ART in pregnant women is the same as in men and non-pregnant women (please see Table 2 in section III.2.2 above).
- Condoms should be recommended to TB/HIV-coinfected pregnant women as well as to all HIV monoinfected women to reduce risk of HIV superinfection (additional infection with the same or another HIV subtype) and other STIs.
- Most first-line TB drugs are safe for use in pregnancy. The exception is streptomycin, which is ototoxic to the fetus and should not be used during pregnancy (except for meningeal infections) or lactation due to the potential for serious adverse reactions in nursing infants *(43).*
- If a TB/HIV-coinfected woman decides to carry a pregnancy to term, she should receive ARV prophylaxis for prevention of mother-to-child transmission. For further information please refer to Protocol 10, *Prevention of HIV infection transmission from HIV-infected mothers to their infants*.
- If proper case management of TB and ART is carried out, the monitoring of treatment should be the same as for other adults.

3.5. Injecting drug users

The clinical management of TB/HIV in IDUs is challenging and requires more effort due to the following factors:

- interaction of TB and ARV drugs with illicit drugs and resultant increased hepatotoxicity in those IDUs receiving opioid substitution therapy;
- a decrease in methadone levels (33–68%) or withdrawal caused by rifampicin (the methadone dose may need to be increased);
- larger likelihood of coinfection with hepatitis C and/or B, and therefore of potential drug interactions with hepatitis drugs;
- decreased adherence levels; and
- decreased access to the health care system.

Collaboration with harm-reduction programmes *(44, 45)* may be essential in organizing effective outreach services such as education, screening, TB preventive treatment, directly observed treatment (DOT) for TB and the tracing of treatment defaulters.

It is important to keep in mind the following.

- Rifampicin should not be administered with LPV/r, NFV or SQV in patients receiving methadone substitution therapy. Rifabutin is an option, administered as 150 mg 3 times/week with

LPV/r or 300 mg 3 times/week with NFV.
- Rifabutin should not be used together with SQV.

For more information, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users*.

4. Monitoring TB/HIV-coinfected patients

4.1. Monitoring TB treatment

For most patients, unless there is drug resistance, TB treatment is effective, and their clinical status improves starting in the second or third week. In TB patients with advanced HIV infection or with late diagnoses for both diseases, a clinical or radiological worsening may be observed. Moreover, treatment with normally effective TB drugs may be unable to reverse clinical course in the late stages of HIV.

During the initial 2–4 weeks of TB treatment, during which patients are preferably hospitalized, a complete clinical evaluation should be done at least weekly. ALT must be assessed at least once at the end of the first month. Hepatotoxicity may be observed in up to 5–10% of coinfected patients.

A patient's ability to swallow a pills should be verified, and adherence should be checked regularly. Exceptionally, severe chronic diarrhoea can be responsible for drug malabsorption and treatment failure; such a condition requires the use of injectable TB drugs. Even without diarrhoea, HIV-infected patients may not absorb rifampicin adequately. In case of severe gastrointestinal intolerance, which occurs in up to 10% of HIV patients, priority should be given to TB treatment and ART stopped until recovery from gastrointestinal symptoms.

TB treatment stops at the end of the continuation phase. There is still not enough evidence supporting the utility of secondary TB treatment in preventing further relapses.

For patients who adhere to TB regimens, the prognosis for TB itself is good. Exceptions are:
- patients with MDR-TB, who should be referred to specialized treatment centres because of their complex management; and
- patients who are just beginning TB treatment at an advanced HIV/AIDS stage.

4.2. Monitoring antiretroviral treatment

Monitoring patients receiving ART should include clinical signs and symptoms, immunological and virological criteria, and ARV toxicity and side-effects. After initiation of ART, immune reconstitution inflammatory syndrome (IRIS) can occur, especially in severely immunosupressed patients. Such worsening of clinical HIV/AIDS disease after initial improvement may occur in up to a third of patients with TB who have started ART. The average time of onset is two months after ART initiation, but it can occur as early as five days after. IRIS is thought to be the result of immune restitution due to administration of antiretroviral and/or TB drugs. IRIS is more common if ART is started early in the course of TB treatment, and if the patient has a very low CD4 count *(46, 47)*.

The exacerbated signs and symptoms are due to a more effective local tissue reaction to infection, due to *M. tuberculosis* or some other opportunistic infection(s). These signs and symptoms include a combination of:
- high fever
- occurrence or enlargement of peripheral or mediastinal lymphadenopathy
- expanding lesions in the central nervous system
- worsening of chest radiographic findings.

The diagnosis of IRIS should be made only after a thorough evaluation has already excluded other etiologies, particularly a failure of the TB treatment. Most cases resolve without any intervention, and ART can be safely continued. Serious reactions, such as tracheal compression due to massive adenopathy or respiratory therapy, may require a short course of steroids. Prednisone may be given at the dose of 20–60 mg/day for at least two or three weeks, gradually decreasing in dose over at least one month *(48, 49)*.

For information about ARV drug toxicity and its management please refer to the section Management of ARV toxicity and side-effects in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

Patients treated for TB and HIV should be followed regularly for clinical evaluation of tolerance to treatment. The tests to be performed are summarized in Table 7.

Table 7. Monitoring of patients on ARV and TB treatment

Assessment	Week				Month									
	0	2	4	8	3	4	5	6	7	8	9	10	11	12
TB and HIV disease history	X													X
Physical examination	X	X	X	X	X			X						X
Comorbidities	X				X			X						X
Gynaecological examination	X							X						X
Routine laboratory tests: • haemoglobin • full blood count with differential and platelets • liver function tests (ALT, possibly AST and bilirubin) • creatinine • urine	X	X	X	X	X			X						
CD4 count	X			X				X						X
Viral load (if available)	X			X				X						X
Chest X-ray	X													X
Pregnancy test	X													X
Sputum-smear examination[a]	X			X	X		X	X		X				
Adherence (both TB and ART treatment)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Required at the end of the third and eighth month only when on 8-month TB treatment regimen.

4.3. Adherence to TB treatment and ARV treatment

Adherence is crucial for the success of both TB and ARV treatment. Patients with poor adherence are at very high risk for developing drug-resistant strains of M. tuberculosis and HIV. Drug-resistant TB and HIV are very difficult to treat effectively and can be transmitted to others. DOT is recommended to reinforce adherence to TB treatment, combined with context-specific and patient-sensitive support *(50)*. For ART, more than 95% adherence is required to achieve optimal HIV suppression and treatment outcome *(51)*. The importance of adhering to treatment and consequences of poor adherence should be fully understood by patients and properly covered during patient counselling.

Adherence to treatment of TB and HIV/AIDS should be closely monitored and explored at every visit. The effective management of adverse reactions to drugs is very important and considered an essential condition for ensuring adherence to treatment (For more information on adherence please see the sections Adherence to ART and Monitoring adherence both in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*).

For both TB and ART, adherence may be challenging in special population groups, such as IDUs. (For detailed information about factors influencing adherence in IDUs, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*)

IV. Identification of TB/HIV in infants and children

Children are usually infected with TB through contacts with an adult or another child with sputum smear-positive PTB, often a family member. In the absence of interventions to prevent its transmission, infants typically acquire HIV when exposed to HIV-infected fluids (principally blood) in utero or during labour.

Without preventive TB treatment, 40–50% of HIV-positive infants and 15% of HIV-positive older children will present with symptoms of TB disease within one or two years of becoming infected with TB. In infants, the time between TB infection and TB disease may be as little as 6–8 weeks. Special considerations should be given to infants born to HIV-positive women who start TB treatment less than two months before delivery. These infants should be evaluated for signs and symptoms of congenital TB and be treated if appropriate.

Children older than 7 and adolescents usually develop adult-type pulmonary TB disease with classic presentation. Many children younger than 4, however, show atypical presentations of extrapulmonary dissemination with hepatomegaly, prolonged fever, lymphadenopathy, anaemia and weight loss, clinical manifestations of more advanced phases of immune suppression.

1. Identification of TB in HIV-infected infants and children

Diagnosis of TB in infants and children is difficult, whether or not they are infected with HIV, because they rarely have cavitary pulmonary disease and do not produce sputum for bacteriological examination. Other methods of obtaining material, such as gastric lavage, can be problematic. Consequently, bacteriological confirmation is usually not possible, and the diagnosis of pulmonary TB in children is often presumptive. The diagnosis of TB in HIV-infected children is even more difficult, as several HIV-related diseases may present in a manner similar to TB, and the interpretation of the tuberculin skin test is also less reliable. TB diagnosis is thus often based on a combination of a history of contact with an adult TB infectious case, TB clinical signs and symptoms and the results of the investigations. See Table 8 *(15)*.

Table 8. Conditions linked to active TB disease in children

Suspected tuberculosis • A history of contact with a confirmed case of pulmonary TB • Failure to regain normal health after measles • Weight loss, cough and wheeze that do not respond to antibiotic treatment for respiratory disease • Painless swelling in a group of superficial lymph nodes
Probable tuberculosis Suspected TB with any of the following: • positive (≥5 mm) induration on tuberculin skin test • suggestive appearance on chest radiograph • suggestive histological appearance on biopsy material • favourable response to TB-specific therapy.
Confirmed tuberculosis • Detection by microscopy or culture of tubercle bacilli from secretions or tissues • Identification of tubercle bacilli as Mycobacterium tuberculosis by culture characteristics

2. Identification of HIV in children with active TB

HIV infection may be suspected in children with TB. Diagnosis of HIV infection in infants <18 months old should be done using the HIV DNA polymerase chain reaction (PCR) test. In children 18 months and older, the ELISA serological test followed by a confirmatory western blot test is recommended. For further information please refer to Protocol 11, *Paediatric HIV/AIDS treatment and care*.

V. Clinical management of TB/HIV in children

1. Treatment of TB

TB treatment of HIV-infected children is a priority and should start as soon as active TB disease is diagnosed.

The recommended TB treatment regimens for children are the same as those recommended for adolescents and adults (see Table 1 in section III.2.2.1. above). The drug dosages per kilogram of body weight are also the same (see Annex 1).

2. Treatment of HIV/AIDS

2.1. Initiation of ART

In HIV-infected children with confirmed TB disease, initiating TB treatment should be a priority. ART should be initiated as soon as possible *(52)*, taking into consideration the clinical and immunological criteria summarized in Table 9.

Table 9. Strategy for initiation of ART in HIV-infected children with active TB

Criteria		TB treatment	ART
Paediatric Clinical Stage 4[a, b]		Start immediately	Start ART soon after TB treatment (2–8 weeks after starting TB treatment).
Paediatric Clinical Stage 3[a]	Advanced immunodeficiency[c]		
	Mild or no immunodeficiency[d]	Start immediately	ART may be delayed and the need for it reassessed after completion of TB therapy. Closely monitor response to TB therapy; if there is no improvement, consider starting ART.

[a] For paediatric clinical staging, see Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 1.
[b] All children with Clinical Stage 4 should be initiated on ART, regardless of CD4 criteria.
[c] Advanced immunodeficiency is assumed to be a CD4 percentage of 5% above the age-specific CD4 threshold for severe immunodeficiency, or a CD4 count of 200–350 cells/mm^3 for children ≥5 years of age (see Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 2).
[d] Mild or no immunodeficiency is assumed at CD4 levels above those defining advanced immunodeficiency (again, see Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 2).

2.2. Recommended HAART regiments

The ART regimens recommended for TB/HIV-coinfected children differ slightly from recommendations for HIV-monoinfected children. The choice of ART regimen is complicated by the limited options for paediatric drug formulations and/or dosing information (particularly for children younger than 3).

2.3. Key considerations for ARV drugs

- In case of ZDV toxicity or intolerance, stavudine (d4T) can be substituted.
- If NVP is administered concomitantly with rifampicin, potential liver toxicity needs to be monitored clinically and with a liver function test.
- EFV is not currently recommended for children <3 years of age, nor should it be given to sexually active girls who do not use adequate contraception or are in the first trimester of pregnancy.
- Following completion of TB treatment, it is preferable to maintain the ART regimen outlined in Table 10.

Table 10. HAART regimens for TB/HIV-coinfected children being treated with rifampicin

Age of child	ARV drug classes	ARV drug combination
<3 years	*Preferred* 3 NRTIs (triple-nuke regimen)	ZDV + 3TC + ABC
	Alternative 2 NRTIs + NVP	ZDV + 3TC + NVP
≥3 years	*Preferred* 2 NRTIs + 1 NNRTI	ZDV + 3TC + EFV
	Alternative 3 NRTIs (triple-nuke regimen)	ZDV + 3TC + ABC

2.4. Cotrimoxazole primary prophylaxis

TB/HIV-coinfected children should receive cotrimoxazole prophylaxis during the whole TB treatment phase, independent of their level of immune suppression. For cotrimoxazole formulations and dosages, please see Protocol 11, *Paediatric HIV/AIDS treatment and care,* section on prevention and management of OIs.

3. Monitoring of TB/HIV-coinfected children

Routine monitoring of TB/HIV-coinfected children and their response to treatment should include monitoring of clinical signs and symptoms, laboratory indicators, adherence and growth (nutrition). Sputum-smear assessments should be performed the same as for adults: week 8, month 5, month 6, month 8 and month 12 after initiation of TB treatment.

For more information on the clinical management of HIV/AIDS in children, please refer to Protocol 11, *Paediatric HIV/AIDS treatment and care.*

VI. Suggested minimum data to be collected at the clinical level

It is recommended *(52)* that the following data be collected on a regular basis (e.g. monthly, quarterly or semi-annually) at the clinical level to improve clinical management of TB/HIV-coinfected patients and to monitor the implementation of collaborative TB/HIV activities:

- number of registered TB patients;
- number of registered TB patients who are tested for HIV;
- number of registered TB patients testing positive for HIV;
- number of HIV patients seen for treatment and care who are screened for TB symptoms;
- number of HIV patients who have TB infection:
  - number of HIV patients with TB infection who have received tuberculosis preventative treatment (TPT) with izoniazid;
- number of HIV patients who are newly diagnosed with TB disease:
  - number of HIV patients newly diagnosed and registered with TB disease who have CD4 ≥350 cells/mm^3;
  - number of HIV patients newly diagnosed and registered with TB disease who have CD4 <350 cells/mm^3;
  - number of HIV patients newly diagnosed with TB disease who have received cotrimoxazole preventive therapy[2] (CPT);
- number of HIV/TB patients who are receiving TB treatment;
- number of HIV/TB patients receiving both TB treatment and ART;[3]
- number of HIV/TB patients in each category of TB treatment outcome;[4]
- number of HIV/TB patients who have died, including cause of death (e.g. TB-related deaths, other HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

[2] Defined as at least one dose during their TB treatment.
[3] Including the number of patients who have started on ART or are continuing previously initiated ART during or at the end of TB treatment
[4] This indicator should be calculated for each of the following possible outcomes: cure, treatment completion, treatment failure, death, default and transfer out. For definitions of these outcomes please refer to *Treatment of tuberculosis: guidelines for national programmes (53).*

Annex 1. TB drugs (adults, adolescents and children)

Table 11. Recommended dosage of first-line TB drugs

Drug	Recommended dose	
	Daily dose[a] (usual dose or range)	**Thrice-weekly dose (usual dose or range)**
Isoniazid (H)	5 mg/kg	10 mg/kg
Rifampicin (R)	10 mg/kg (450 mg if <50 kg; 600 mg if ≥50 kg)	10 mg/kg (450 mg if <50 kg; 600 mg if ≥50 kg)
Pyrazinamide (Z)	25 mg/kg (20–30 mg/kg)	35 mg/kg (30–40 mg/kg)
Ethambutol (E)	15 mg/kg (15–20 mg/kg)	30 mg/kg (20–35 mg/kg)
Streptomycin (S)	15 mg/kg (12–18 mg/kg)	15 mg/kg (12–18 mg/kg)

[a] When rifampicin is used concomitantly with antiretroviral drugs in TB/HIV patients, a daily TB treatment regimen is preferred *(20)*.

Table 12. Recommended formulations of first-line TB drugs

Drug(s)	Dose form	Strength (mg)
Single drugs		
Isoniazid (H)	Tablet	100, 300
Rifampicin (R)	Tablet or capsule	150, 300
Pyrazinamide (Z)	Tablet	400
Ethambutol (E)	Tablet	100, 400
Streptomycin (S)	Powder for injection in vial	750, 1000
Fixed-dose combinations		
Isoniazid + rifampicin	Tablet Tablet Tablet Tablet or pack of granules Tablet or pack of granules	75 + 150 150 + 300 30 + 60 150 + 150 (thrice weekly) 60 + 60 (thrice weekly)
Isoniazid + ethambutol	Tablet	150 + 400
Isoniazid + rifampicin + pyrazinamide	Tablet or pack of granules	75 + 150 + 400 30 + 60 + 150 150 + 150 + 500 (thrice weekly)
Isoniazid + rifampicin + pyrazinamide + ethambutol	Tablet	75 + 150 + 400 + 275

Annex 2. ARV drugs (adults and adolescents)

Table 13. Recommended formulations of first-line ARV drugs

Drug(s)	Recommended dose (mg)
NRTIs	
Abacavir (ABC)	300 BID
Didanosine (ddI)[a]	400 OD (250 if <60 kg) or 200 BID
Lamivudine (3TC)	150 BID or 300 OD
Zidovudine (ZDV)	300 BID
Tenofovir (TDF)	300 OD
NNRTIs	
Efavirenz (EFV)	600 OD
PIs	
Lopinavir/ritonavir + ritonavir (LPV/r + RTV)	(400/100 + 300) BID
Saquinavir + ritonavir (SQV + RTV)	(400 + 400) BID

[a] When ddI is administered concomitantly with TDF, the recommended dose is ddI 250 mg OD for patients with a body weight of >60 kg and 125–200 mg OD for patients with a body weight of <60 kg.

Table 14. Recommended ARV formulations for TB/HIV-coinfected adults and adolescents

Drug(s)	Dose form	Strength
Single drugs		
Abacavir (ABC)	Tablet Oral solution	300 mg 20 mg/ml
Didanosine (ddI)	Tablet Single-dose packets of buffered powder for oral solution Paediatric powder for oral solution Delayed-release capsules	25, 50, 100, 150, 200 mg 100, 167, 250 mg 4- and 8-ounce glass bottles containing respectively 2 and 4 g didanosine 125, 200, 250, 400 mg
Lamivudine (3TC)	Tablet Oral solution	150, 300 mg film coated 10 mg/ml
Zidovudine (ZDV)	Tablet Capsule Oral solution/syrup Retrovir IV infusion/sterile solution for IV infusion	250, 300 mg 100 mg 50 mg/5 ml 10 mg/ml
Tenofovir (TDF)	Tablet	300 mg
Efavirenz (EFV)	Capsule Tablet film coated	50, 100, 200 mg 600 mg
Lopinavir/ritonavir (LPV/r)	Tablet Capsule Oral solution (contains 42.2% alcohol)	200/50 mg 133.3/33.3 80/20 mg/ml
Saquinavir (SQV)	Capsule Tablet	200 mg 500 mg
Ritonavir (RTV)	Capsule Oral solution	100 mg 80 mg/ml
Fixed-dose combinations		
Zidovudine + lamivudine (ZDV + 3TC)	Tablet film coated	300 + 150 mg
Zidovudine + lamivudine + abacavir (ZDV + 3TC + ABC)	Tablet	300 + 150 + 300 mg
Tenofovir + emtricitabine (TDF + FTC)	Tablet	300 + 200 mg
Abacavir + lamivudine (ABC + 3TC)	Tablet	600 + 300 mg

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WORLD HEALTH ORGANIZATION
EUROPE

5 HIV/AIDS Treatment and Care for Injecting Drug Users

Clinical Protocol for the WHO European Region

Contents

I. Policy and principles

Substance dependence is a complex condition, with profound consequences for the health of drug users, for public health and for health care systems, particularly when the substances are injected. The World Health Organization (WHO) and others have committed to scaling up access to highly active antiretroviral treatment (HAART and have confirmed that injecting drug users IDUs) should have equitable and universal access to HIV/AIDS prevention, treatment and care, including HAART *(1)*. While this protocol has been produced specifically for countries in the WHO European Region, it should be equally useful for countries in other regions where injecting drug users require HIV/AIDS treatment and care.

Although the overwhelming majority of HIV cases in eastern Europe are IDUs, they are the least likely to receive HAART *(2–4)*. Drug users have suboptimal access to and utilization of HAART and initiate it at more advanced stages of infection *(5)*. Patients with a history of injecting drug use have lower rates of access to HAART, even in developed countries with relatively good access for the general population *(6–9)*. Many studies show that clinicians are reluctant to prescribe antiretrovirals (ARVs) to HIV-infected IDUs, due to the common belief that they may have lower levels of adherence that may in turn lead to elevated rates of ARV resistance, whereas studies show that resistance levels are similar among IDUs and non-IDUs *(10)*. Where comprehensive HIV care has been provided to IDUs in an accessible and non-judgemental way, large proportions of them have been attracted to, and retained in, effective treatment. Combining HIV/AIDS care with substance dependence treatment services (including harm reduction, detoxification and substitution therapy) and psychosocial services has been particularly successful *(1, 4, 11–13)*.

WHO has a long tradition of working in HIV/AIDS prevention, treatment and care for IDUs and prisoners, guided by a broad range of WHO and United Nations resolutions, commitments, policies, position papers and technical documents. The work is now solidly evidence-based on the concept of harm reduction. The 1974 report of the *WHO Expert Committee on Drug Dependence* statement that programmes should be more concerned about preventing and reducing problems related to drug use rather than preventing drug use itself, predates HIV/AIDS and provides the rationale for WHO's public health approach to addressing drug-related problems within a harm-reduction framework *(14)*.

The term "harm reduction" is sometimes used to refer to all drug-related harm, but in the context of HIV/AIDS, WHO also uses the term to describe a comprehensive package of evidence-based interventions that reduce HIV transmission and the HIV/AIDS impact associated with drug use, particularly drug injecting. However, a harm-reduction approach is also effective against other bloodborne infections (notably hepatitis C), overdosing and other individual and public harms. A comprehensive strategy for the prevention of drug-use-related HIV epidemics must include programmes aimed at the primary prevention of drug use. Yet the comparative advantage of the WHO approach rests with interventions delivered through the health sector,[1] particularly those targeting current users and, increasingly, prisoners. WHO recognizes that HIV/AIDS prevention, treatment and care for drug users and prisoners requires a comprehensive approach with a range of interventions.

[1] "The health sector is wide-ranging and encompasses organized public and private health services (including those for health promotion, disease prevention, diagnosis, treatment and care), health ministries, nongovernmental organizations, community groups and professional associations, as well as institutions which directly input into the health care system (e.g. the pharmaceutical industry, and teaching institutions)." *The Global Health Sector Strategy for HIV/AIDS 2003–2007 (15).*

In May 2003 the 56th World Health Assembly endorsed the *WHO Global Health Sector Strategy (GHSS) for HIV/AIDS 2003–2007*, which lists the core components of a comprehensive health sector response to HIV/AIDS, including "promoting harm reduction among injecting drug users, such as wide access to sterile injecting equipment, and drug dependence treatment and outreach services to help reduce frequency of injecting drug use" *(15)*.

WHO has recently renewed its commitment to providing universal access to HIV/AIDS prevention, care and treatment for all who need it, in which harm reduction is a priority intervention guided by a number of technical papers and policy briefs *(1, 14–23)*.

The WHO Regional Office for Europe has been at the forefront of harm-reduction efforts. In 1998, the Regional Office, in cooperation with UNAIDS and the Council of Europe, published its basic principles for effective prevention of HIV infection among IDUs. It was among the first United Nations publications to set out basic principles for effective prevention among IDUs, explicitly mentioning provision of sterile injecting equipment and opioid substitution therapy (OST). The current mandate for the Regional Office work on harm reduction in Europe is provided in the 2002 resolution of the WHO Regional Committee for Europe (EUR/RC52/R9), *Scaling up the response to HIV/AIDS in the European Region of WHO*, which urges Member States:

> … to promote, enable and strengthen widespread introduction and expansion of evidence-based targeted interventions for vulnerable/high-risk groups, such as prevention, treatment and harm reduction programmes (e.g. expanded needle and syringe programmes, bleach and condom distribution, voluntary HIV counselling and testing, substitution drug therapy, [sexually transmitted infection] STI diagnosis and treatment) in all affected communities, including prisons, in line with national policies.

In February 2004, the Regional Office also helped draft the landmark Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia, in which all European Region Member States committed to:

> Scale up access for injecting drug users to prevention, drug dependence treatment and harm reduction services through promoting, enabling and strengthening the widespread introduction of prevention, drug dependence treatment and harm reduction programmes[2] (e.g. needle and syringe programmes, bleach and condom distribution, voluntary HIV counselling and testing, substitution drug therapy, STI diagnosis and treatment) in line with national policies… *(17)*.

The following principles should be applied to IDUs living with HIV.

- HAART is as effective for HIV-positive IDUs as it is for other people with HIV/AIDS.
- Given appropriate support, former and active IDUs can adhere just as well as others and should have equal access to HAART.
- Current or past drug use should not be a criterion for deciding who should receive antiretroviral treatment (ART).
- Special attention should be paid to the particular needs of former and active IDUs when administering HAART, including those related to substance dependence, comorbidities and coinfections.
- A public health policy that addresses the need to treat both substance dependence and HIV/AIDS improves patient well-being, reduces stigmatization and promotes delivery of comprehensive, ethical medical care.

[2] WHO recommends that at least 60% of IDUs have access to drug dependence treatment and harm-reduction programmes in order to have an impact on the epidemic among this group.

- The most effective response consists of a combination of prevention, treatment, care and support within a harm-reduction framework.
- Harm reduction is highly effective for IDUs in supporting prevention, treatment and care.
- Provision of good quality OST is an essential component of HIV/AIDS treatment and is highly effective in addressing opioid dependence.
- A supportive environment that upholds the human rights and dignity of IDUs and helps expand and improve access to drug dependence treatment should be ensured.
- Countries with HIV epidemics fuelled by injecting drug use should respond immediately to the needs of IDUs with preventive and treatment services, including harm reduction, opioid substitution therapy and equitable access to HAART.

II. Background and general considerations

1. HIV and injecting drug use epidemiology

Estimates suggest that by the end of 2003 there were approximately 13.2 million IDUs worldwide, the majority, 10.3 million (78%), in developing and transitional countries. The number of IDUs in western Europe has been estimated at 1.2 million, with 3.2 million in eastern Europe and central Asia *(24)*. HIV epidemics in many parts of the world are driven by injecting drug use and sexual contact with IDUs. Estimates indicate that at least 10% of all new HIV infections in the world – 30% if Africa is excluded – can be attributed to injecting drug use, and that approximately 3 million past and current IDUs are living with HIV *(25, 26)*.

In eastern Europe, HIV epidemics have been driven almost entirely by injecting drug use. Estonia, the Russian Federation and Ukraine have the largest and most widespread epidemics *(27, 28)*. HIV prevalence rates among IDUs differ widely in western Europe, with the highest rates in Spain, Italy and Portugal *(24)*. The countries most affected are those where access to prevention, treatment and care is limited, where needle and syringe programmes and drug substitution therapy are not widely available or illegal, and where law enforcement is the dominant approach to drug use *(29, 30)*.

Explosive growth is characteristic of drug-driven HIV epidemics. In some cases, HIV prevalence among IDUs has risen from around 1% to as much as 70% in a few years *(31, 32)*. Rapid increases of injecting drug use also often coincide with the most rapid increases in HIV/AIDS. Drug use-driven HIV epidemics typically start with IDUs who are young, male and sexually active, and are then followed by sexual transmission to male and female partners as well as to children through mother-to-child transmission (MTCT). Commercial sex work can act as a bridge between populations through the exchange of sex for drugs or through sex work to support drug use *(33)*.

These explosive epidemics can be explained by the lack of access to prevention and treatment (notably harm reduction), together with the efficacy of bloodborne transmission through sharing needles, syringes and other drug paraphernalia. An additional factor is the elevated level of viraemia characteristic of the first weeks and months after seroconversion, which may contribute to the high HIV-transmission rates typical of these epidemics *(4)*. Social and environmental factors also contribute to IDU/HIV epidemics *(34)*.

2. Health and social consequences of injecting drug use

Substance dependence is a complex condition that has both physical and psychosocial components and is associated with severe morbidity and a high risk of death. Substance dependence (particularly opioid dependence) is a chronic relapsing condition, which is difficult to control due to compulsive drug use and craving, leading to repetitive use, even in the face of negative health and social consequences *(35)*. There are a number of medical, psychiatric and social problems common among substance-dependent people that are important considerations in designing and delivering HIV/AIDS care.

2.1. Health problems

In addition to HIV, IDUs usully have a wide range of coinfections, coinfections, comorbidities and injecting related health issues.

The most common health problems among IDUs are:

- infection with bloodborne viruses, including hepatitis B, C and D (delta) leading to liver diseases
- bacterial infections: *(36)*
    - tuberculosis

  - bacterial pneumonia
  - endocarditis
  - septicaemia
- overdoses
- alcohol dependence and alcohol-related liver disease
- polysubstance dependence
- psychiatric comorbidity, including depression.

Some IDUs have a long history of mental illness without proper diagnosis or treatment. There are some mental conditions that may result from, or be exacerbated by, the use of substances such as alcohol, cocaine and opioids. These substances may also be used by individuals as a form of self-medication for symptoms of mental illness and substitute for effective treatment. A substantial increase in the frequency of major depression and suicide in HIV-positive IDUs is apparent, even above the elevated rates associated with advanced HIV infection and AIDS *(37–39)*.

Other frequent injecting related prolems include:
- deep venous thrombosis (DVT) or pulmonary embolism (PE)
- local soft tissue and vascular injuries, including skin abscesses and thrombophlebitis
- increased risk of respiratory and smoking-related illnesses and chronic diseases.

2.2. Social problems

Common perceptions that drug users do not adhere to HAART may overlook the confounding effects of social instability, poverty, psychiatric morbidity, human rights violations and poor patient–physician relationships that characterize many drug users' lives.

IDUs' most prevalent social problems include:
- stigmatization, discrimination and social marginalization
- poverty
- homelessness
- unemployment
- family and social dysfunction
- criminal behaviour and imprisonment.

2.2.1. Stigmatization, discrimination and social marginalization

Drug use is a prevailing source of stigmatization and discrimination beyond that associated with positive HIV status.
- The stigma attached to drug use is often reinforced because it is typically an illegal and covert activity, with no legal protection available to people who use drugs.
- Drug users are often reluctant to attend medical facilities because of stigmatization and discrimination. Fear of discrimination may discourage HIV-infected drug users from revealing their drug use to HIV/AIDS care specialists, leading to a greater risk of misdiagnosis, or of pharmacological interactions between the HIV treatment regimens and the substances used *(4)*.
- Many IDUs live on the economic and social fringes, and may be rejected by their families.
- People who are most vulnerable to the impact of poverty, racial discrimination, poor health, lack of education and employment are also those most vulnerable to drug use.
- Social problems, including the stigma and discrimination associated with drug use and being HIV-positive, in turn exacerbate drug use.

2.2.2. Prison

The economic pressure of supporting drug dependence and the crime that results mean that in most countries, a large proportion of drug users are periodically incarcerated. Many countries have some form of compulsory detoxification or abstinence-based treatment in closed settings as the predominant type of treatment for drug use. There is no evidence that such approaches are effective as forms

of drug dependence treatment; furthermore, they bring a range of problems with them. Health problems associated with incarceration include:

- unsafe drug use with the risk of disease infection and transmission for other communicable diseases, including hepatitis;
- tuberculosis (TB) (particularly multidrug-resistant TB);
- unprotected sex between prisoners, with risk of transmitting HIV and other STIs;
- increased risk of overdose after release;
- physical and sexual assault;
- depression and anxiety; and
- suicide.

Explosive HIV epidemics within prisons have been reported in a number of countries, and can trigger or significantly affect broader HIV epidemics.

3. Opioid substitution therapy practice

The global number of opioid dependants receiving prescribed methadone is estimated to be over half a million – including nearly 400 000 in the European Region *(19, 40)* – and it is increasing in practically all regions. Originally implemented in Australia, the United States and western Europe, methadone maintenance treatment is expanding eastwards to central and eastern Europe, to the eastern Mediterranean region and Asia. Methadone covers up to 80% of estimated treatment needs in some European countries, in others much less. In the European Region, 76% of substitution treatment programmes use methadone *(41)*. In the United States, 179 329 patients were enrolled in methadone maintenance treatment programmes at the end of 1998; more recent estimates range from 200 000 to 300 000. Methadone is also being used in Argentina, Australia, Canada, China, Indonesia, the Islamic Republic of Iran, New Zealand and Thailand, among other countries. It is estimated that a million opioid dependants will be in methadone treatment within the next five years.

The global number of opioid dependants receiving prescribed buprenorphine is estimated to be close to 200 000 and increasing in practically all regions. The greatest level of experience with buprenorphine has been in France, where it has been widely available through general practitioners since 1995. In 1998, approximately 65 000 patients there per year were in buprenorphine treatment. By 2001, 74 000 were in buprenorphine treatment while 9600 were treated with methadone *(42)*. In Australia, buprenorphine was registered for the treatment of opioid dependence in 2001, and there were 8641 patients receiving it by June 2003. In 2005 it was available in countries including Australia, Austria, Belgium, China (Hong Kong Special Administrative Region), the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Iceland, India, Indonesia, Israel, Italy, Lithuania, Luxembourg, Malaysia, the Netherlands, Norway, Portugal, Singapore, Slovakia, Slovenia, South Africa, Sweden, Switzerland, Ukraine, the United Kingdom and the United States.

III. Organization and management considerations

1. Services

The organization of HIV prevention, treatment and care services and their linkage are important determinants of successful treatment of IDUs. HIV treatment programmes should be linked to harm-reduction services to facilitate enrolment and retention of IDUs, and to ensure that those in treatment can readily access risk reduction advice, counselling and relevant commodities (clean needles and syringes, condoms, etc). Harm-reduction strategies, including drug substitution therapy, can limit medical and psychosocial complications of drug use and can facilitate HIV care by stabilizing IDU behaviour.

Four types of linked services are crucial in the treatment of substance dependence and HIV/AIDS:
- general medical care and/or clinical infectious disease care
- harm reduction
- drug dependence treatment
- psychosocial support.

Outreach strategies can form strong links with community-based organizations representing affected groups, and utilize peer educators and counsellors drawn from these groups.

1.1. General medical care services

1.1.1. Principles

Successful programmes delivering medical care, including HAART, to active IDUs have identified important principles of medical care:
- accessibility
- free-of-charge
- user-friendly with non-judgmental and unbiased staff
- tailoring to individual needs
- continuity of care through referral systems among health services, community organizations, injecting drug use networks and families.

1.1.2. Multidisciplinary approach

WHO favours a multidisciplinary approach for the provision of treatment and care for people living with HIV (PLHIV). The care team should have experience with drug-dependency issues and should meet on a regular basis to review the status of IDUs under treatment and provide case management. The formation of a care team typically includes:
- a clinician (a physician, infection disease specialist or other medical practitioner)
- a medical nurse
- a social worker
- a counsellor
- a substance dependence specialist.[3]

Psychiatrists and psychiatric services are not necessarily the most appropriate to provide substance dependence treatment. Many of the complications that need treatment are those best managed by physicians. There is the risk of additional stigmatization of drug users because of their association with psychiatric services, particularly if they do not have psychiatric comorbidity.

[3] This may be an addiction specialist, a psychiatrist or psychologist and/or (in eastern Europe) a narcologist.

1.1.3. Components

A major challenge in delivering care to IDUs is their need for concurrent services addressing both biomedical and psychosocial issues.

Medical care should be comprehensive and should provide:
- HIV/AIDS treatment
- substance dependence treatment, inclcuding opioid substitution therapy
- diagnosis and treatment of other comorbidities and injecting related health issues (see section II.2.1)
- prophylaxis/suppression for specific HIV opportunistic infections[4]
- vaccination for hepatitis B virus (HBV)[5]
- palliative care for patients with advanced disease.[6]

While providing medical care to IDUs it is essential in medical settings to also address:
- treatment adherence;
- reduction of drug use and sexual risk behaviours;
- information on injecting techniques to decrease the complications of injection;
- support for sexual partners;
- support social matters (through social services);
- reducing and avoiding stigmatization and discrimination through:
  - ensuring the human rights of IDUs are respected, and that they receive quality services addressing their health needs, including HAART;
  - ensuring that health care workers are aware of their own feelings and prejudices and of the effect these may have on their patients, their professional performance and the successful outcome of drug-dependence treatment and HAART;
  - guarantee confidentiality.

The ready availability of such services will enhance a programme's credibility, while their absence will signal a lack of concern for the immediate needs of IDUs *(43)*.

1.2. Harm reduction

Harm-reduction interventions reduce the adverse health, social and economic consequences of psychoactive substance use for individual drug users, their families and their communities, without necessarily reducing or eliminating drug use. Appropriate support, provided by accessible and non-judgemental health care teams and delivered through community-based programmes and outreach strategies, has proven highly effective. Comprehensive harm-reduction programmes reduce new HIV infections among IDUs *(16, 44–46)*.

The key components of an effective harm reduction package targeting drug users include:
- community outreach, with a focus on peer approaches;
- behavioural change communication, including risk-reduction information;
- needle and syringe access and disposal;
- drug dependence treatment, particularly OST;
- HIV testing and counselling;
- condoms and STI prevention and treatment;
- primary health care, including hepatitis B vaccination, vein and abscess/ulcer care, overdose management; and
- a supportive policy and legislative environment.

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[4] For example, *Pneumocystis jirovecii* pneumonia (PCP), candidiasis, cryptococcosis, toxoplasmosis, *Mycobacterium avium* complex and cytomegalovirus. Interactions between antifugals commonly used in the treatment of candidiasis and cryptococcosis and methadone should be considered.

[5] Please refer to Protocol 8, *Prevention of hepatitis A, B and C and other hepatotoxic factors in people living with HIV,* and Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection.*

[6] Please refer to Protocol 3, *Palliative care for people living with HIV.*

Harm-reduction services should be involved in:
- HIV/AIDS treatment delivery where feasible, including the provision of direct ART services;
- ART adherence support, including maintaining follow-up of IDUs who drop out of care;
- providing low-threshold (easy to access) entry points for both HIV/AIDS and drug-dependence treatment;
- providing information on:
  - safer drug use and HIV prevention
  - potential interactions between psychoactive drug use and HIV/AIDS treatment
  - ARV treatment, including how to manage side-effects;
- referrals to other harm-reduction services, including drug-dependence treatment programmes, community support services and other health care services;
- planning HIV treatment for IDUs; and
- conducting outreach to IDUs for HIV testing, counselling, treatment and care.

1.3. Drug-dependence treatment and OST

Management of drug-dependent individuals should also involve a multidisciplinary team, including physicians, nurses, counsellors, outreach workers, social workers and pharmacists *(47)*. Government agencies, nongovernmental organizations (NGOs) and community groups should assist in the delivery of services. Treatment of drug dependence, including drug substitution therapy, provides many benefits in the prevention and treatment of HIV/AIDS, by:
- improving access to HIV treatment and care and general health care
- retaining active drug users in treatment
- reducing the transmission of HIV, viral hepatitis and bacterial infections
- decreasing the need for hospitalization
- improving and facilitating adherence to and follow-up of HAART *(1, 3, 11, 45, 48–51)*.

It also assists in:
- reducing illicit opioid use
- reducing criminal activity
- decreasing deaths due to overdose
- cutting down on high risk behaviours for HIV transmission
- improving social integration.

The benefits of substitution therapy programmes can be maximized by:
- prescribing higher rather than lower doses of methadone or buprenorphine;
- orienting programmes towards maintenance rather than abstinence;
- offering assessment and treatment of psychiatric comorbidity and social problems;
- using contracts between patient and clinician or contingency management and counselling to reduce the use of additional drugs;
- ensuring ready access to services, e.g. by making location, opening hours and cost convenient; and
- providing a user-friendly environment *(52–54)*.

Where substitution therapy is available, consideration should be given to offering HIV/AIDS medical care and providing HAART at the same site from which drug substitution therapy is provided. This approach can:
- achieve maximal levels of treatment supervision
- enhance efficacy
- reduce the risk of developing ARV drug resistance
- facilitate the management of interactions between methadone and HIV/AIDS medications.

Other benefits of prescribing HAART in OST clinics include:
- the possibility of concurrent long-term treatment for drug dependence and HIV/AIDS;
- the opportunity to use directly observed treatment (DOT) in dispensing ART to patients who already visit the clinics daily to receive methadone;[7] and
- experience in treating medical conditions related to substance use *(1, 51)*.

There is evidence that DOT is an effective strategy in the provision of HAART with treatment for substance dependence. Using DOT to provide HAART in conjunction with methadone maintenance is recommended because it:
- results in significant numbers of patients achieving maximum viral suppression *(11)*;
- achieves higher levels of viral suppression than either standard care or treatment adherence support *(48)*; and
- minimizes the impact of HAART on the IDU's daily routine.

1.4. Psychosocial support

Services that can address both the biomedical needs and the psychosocial issues of IDUs concurrently are essential. There is a wide range of psychosocial support services that should be available in accordance with the patient needs of IDUs, including:
- support services for adherence to ART;
- psychological support, such as group therapy for IDUs and family members;
- peer support groups;
- educational programmes;
- psychiatric/psychological services for assessment and management of mental health disorders; and
- social services to deal with problems related to housing, employment, finances, legal matters, discrimination and other issues.

Former IDUs often have been uniquely successful in educating and motivating current IDUs to:
- access effective prevention, treatment and care services
- prepare for treatment, e.g. through advice on possible side-effects associated with ARVs
- adhere to HAART and other treatments.

2. Models of comprehensive HIV/AIDS care for IDUs

HIV/AIDS treatment and care, including HAART, should be delivered as part of a comprehensive care model. Combining or integrating HIV/AIDS and substance dependence services provides opportunities for HIV prevention, enhances adherence to both HIV/AIDS and substance dependence treatment and provides better overall care. A comprehensive service develops expertise in effectively treating substance dependence and providing HIV care. There are several models for effectively combining HIV prevention, treatment and care with substance dependence treatment, including:
- a single site for both HIV/AIDS care and substance dependence treatment:
  - on-site HIV/AIDS medical care in substance dependence treatment facilities or
  - substance dependence treatment in HIV/AIDS services;[8]
- separate HIV/AIDS and substance dependence treatment services in close proximity with good coordination and liaising, including referrals to other services; and
- primary care services for both drug dependence management and HIV/AIDS care through general practitioners or office-based practice.

[7] A second "take-home" dose of ARV drugs is also likely needed.
[8] A variation on the one-site model is a mobile health care service linked, for example, to a HIV/AIDS medical care centre, a substance dependence treatment facility or a harm-reduction service. Mobile services can provide HIV and STI screening, HIV/AIDS treatment, referrals for substance dependence treatment and mental health and other services.

The effectiveness of the models will depend on the infrastructure and organization of the health care system. Where specialized departments (for example, drug treatment centres and departments of internal medicine) exist, liaising and case management should be common practice.

3. Prisons

Reaching IDUs in prisons and other closed settings is crucial because prisons exacerbate the risks of both HIV infection and drug dependence. Incarcerated IDUs should receive the same package of services as those who are not incarcerated, including HAART. Treatment for HIV/AIDS and/or substance dependence may have begun prior to imprisonment, and HAART should continue in prison *(55)*.

Providing prevention, treatment and harm-reduction interventions to IDUs in prison benefits individual inmates as well as the community at large *(22, 56, 57)*. Comprehensive programmes in prisons should include:

- information, education and communications on HIV/AIDS
- voluntary testing and counselling
- condoms
- bleach or other disinfectants
- needle and syringe exchange
- substitution therapy
- clinical management of drug-dependent prisoners that meets local community standards
- HIV/AIDS services (including ART), as well as hepatitis and TB services
- follow-up care with links to community services
- treatment of other substance dependency problems.

Upon release, prisoners need to be guaranteed continuity of care *(58)*. There is a need to forge strong links between communities and drug dependence treatment centres, prisons, labour camps and other centres of detention, as many drug-dependent people move back and forth between the community and such closed settings. Closed settings should be seen as opportunities for HIV prevention, treatment and care and should be monitored and evaluated for a range of indicators that cover drug use, HIV and social issues.

Guidance on HIV prevention and treatment in prisons and other closed settings is available from WHO *(59, 60)*.

IV. Clinical management of HIV-infected IDUs

1. Initial evaluation

Care for HIV-positive IDUs must address substance use and substance dependence, psychological and social issues, and medical complications associated with injecting drug use and HIV/AIDS.

1.1. Evaluation of substance use and dependence

Standardized assessment tools should be used for screening and initially evaluating substance use and dependence. Preferred screening and assessment instruments are suggested below and in the annexes. In Europe, the preferred assessment instrument is the European version of the Addiction Severity Index (EuropASI; see Annex 1). Any screening or assessment must be voluntary and fully informed, with explanation of why the service needs to understand the individual's substance use and associated problems. Under-reporting use of illicit substances is common, so all patients should be screened for substance use and dependence (see Annex 2 for alcohol and drug listing).

Patients who admit to substance use should be examined further, as should those who do not but present the clinical signs or symptoms of drug use, including injections. It is crucial to assess drug dependency, as it has implications for patient management strategy. A simple and rapid initial assessment of drug dependence can be provided by non-specialized staff, based on 10 questions adapted from the "Symptom checklist for mental disorders" in the *International statistical classification of diseases and related health problems*, 10th revision (Annex 3).

Typically a substance use and dependence assessment includes a complete history of substance use and treatment and a physical examination. A substance use and treatment history will include:

- substances used, including alcohol and combinations of drugs, and age at first use
- modes of drug administration
- lifetime, recent and current use
- changes in drug effects over time
- history of tolerance, overdose and withdrawal
- periods of abstinence and attempts to quit
- complications of substance use (hepatitis, abscesses, etc.)
- current problems, including severity of dependence
- types and outcomes of previous treatment for drug dependence.

A physical examination may indicate substance dependence and/or complications associated with substance use. A checklist of physical symptoms such as the examination findings suggestive of addiction or its complications (see Annex 4) is useful. The physical complications of opioid or other drug dependence should be identified and addressed as part of the overall treatment plan.

Further evaluation of drug dependence severity and appropriate treatment strategy should be done by, or in close collaboration with, substance dependency treatment experts or other trained staff. In addition, risk-taking behaviour associated with bloodborne diseases can be documented using a standardized instrument such as the Bloodborne Virus Transmission Risk Assessment Questionnaire (see Annex 5).

1.2. Initial evaluation of HIV/AIDS status

Initial evaluation of IDUs' HIV/AIDS status is no different from that of non-users. Offering HIV testing, counselling and information should be routine procedure in health care settings dealing with IDUs. Health care providers should explain the reasons for offering the test and its importance for correct clinical management. However, a patient has the right to refuse the test. Initial assessment of HIV status should include the following:

- pretest HIV counselling and information;
- a serological test for HIV antibodies (typically ELISA and/or rapid tests), followed by a western blot confirmatory test; and
- post-test counselling, including information on reducing risk behaviours, whether the results are positive or negative.

1.3. Further clinical evaluation

Further evaluation is required for developing a strategy of clinical management of HIV-infected IDUs, including:

- presenting symptoms
- physical examination[9]
- mental health and social assessment[10]
- preparedness for treatment
- routine laboratory assessments
- CD4 lymphocyte count to determine the severity of immunodeficiency
- viral load testing, if available
- history of contraception use and pregnancy test if indicated
- assessment for hepatitis B and C[11]
- screening for TB[12]
- testing for STIs
- assessment for psychiatric disorders
- weight
- other tests based on the patient's condition.

For more detailed information refer to the Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

Since many IDUs present for care at an advanced stage of HIV infection, it is important to thoroughly evaluate new patients for active opportunistic infections. The initial history and physical examination will usually identify common complications, including:

- oral candidiasis and difficulty swallowing, suggesting oesophageal candidiasis
- non-healing genital or anal ulcers, indicating herpes simplex
- fever with cough and/or shortness of breath, suggesting bacterial pneumonia, TB or PCP.

These conditions should not be interpreted as exclusion criteria for HAART, but as cases requiring clinical judgement. Initial evaluation should be followed by treatment of opportunistic infections and other conditions as indicated. For further details, please refer to Protocol 2, *Management of opportunistic infections and general symptoms of HIV/AIDS.*

1.4. Psychosocial assessment

Mental health comorbidities are common among IDUs with HIV. Some estimates suggest that between 25% and 50% of drug users also have a comorbid mental health problem.

A thorough psychosocial assessment should be undertaken at initial evaluation, focusing on:

- any source of instability that might undermine adherence to treatment
- depression and other mood disorders[13]
- other psychiatric problems.

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[9] Particular attention should be given to possible indications of substance dependence and its complications (see the previous section, IV.1.2).
[10] See the next section, IV.1.4.
[11] For more details see Protocol 6, *Management of hepatitis C and HIV coinfection*, and Protocol 8, *Management of hepatitis B and HIV coinfection.*
[12] For more details see Protocol 4, on *Management of tuberculosis and HIV coinfection.*
[13] Adherence to HAART has been found to be higher for depressed patients who adhere to antidepressant treatment than for those who do not adhere to it or are not given it *(61)*.

The use of a standardized screening instrument, such as the Brief Psychiatric Rating Scale (BPRS) *(62)* for psychotic illnesses or the Montgomery Asberg Depression Rating Scale (MADRS) *(63)*, may be of benefit and improve detection of psychological illness. The latter scale may be particularly useful for physically ill individuals. Referral for a full mental health evaluation and/or formal psychiatric diagnosis might be indicated.

The severity of HIV-related medical problems must be considered throughout psychosocial assessment. Social factors to be assessed include:
- social stability, family and community support
- homelessness
- major life events and crises
- financial security
- nutrition.

2. Management of opioid dependence

The management of substance dependence is critical in the care of HIV-positive IDUs as HIV infection and drug dependence in the same person are not isolated problems; each influences the progression of the other. There are a variety of treatment modalities for drug dependence, ranging from drug-free residential to pharmacologically assisted outpatient treatment, including maintenance and detoxification regimens. Given the often chronic nature of substance dependence, detoxification alone is seldom effective in producing long-term and sustained change. Most treatment options focus on opioid dependence and much less on on other kinds of substance dependence. Although in Europe, HIV/AIDS most commonly occurs among people who inject opioids, effective treatment for dependence on cocaine and amphetamine-type stimulants (ATS) should also be provided.

A range of interventions for IDUs has evolved from total abstinence to the provision of safe injectable heroin *(64)*. Staff in substance-dependence services have to have regular ongoing contact with IDUs, whether or not they are on OST.

One of the most significant predictors of outcome in the management of drug dependence is retention in treatment. OST programmes retain patients in treatment, making it an ideal modality for the delivery of HAART to HIV-positive IDUs. All drug services should strive toward establishing methadone or buprenorphine maintenance in order to improve treatment outcomes. IDUs are three times as likely not to receive HAART if they are not enrolled in such a programme *(65)*.

2.1. Opioid substitution therapies

There are two main modalities for treatment of opioid dependence: pharmacotherapy and psychological therapy. Pharmacotherapies include:
- agonist maintenance with oral methadone and levo-alpha-acetyl-methadol (LAAM);
- partial-agonist maintenance with sublingual buprenorphine or combination sublingual buprenorphine and naloxone;
- antagonist maintenance with oral naltrexone; and
- anti-withdrawal/detoxification agents (methadone, buprenorphine and/or clonidine) for brief periods to facilitate entry into drug-free or antagonist treatment approaches.

The two main opioid substitution therapies available in Europe are methadone and buprenorphine. Both high-dose methadone (>60 mg) and buprenorphine substantially reduce the level of illicit opioid use in comparison with low-dose methadone *(66)*.

It is important to keep in mind that:
- Stabilization of opioid-dependent IDUs through OST is a key component to successful HIV/AIDS treatment, including HAART.

- OST is not universally available, and many HIV-positive IDUs presenting for treatment with ART may still be actively using heroin and other drugs.
- Lack of access to OST should not preclude drug users from having HAART.
- Active drug use should not preclude HAART.

2.1.1. Methadone

Methadone is one of the most effective and most frequently used types of pharmacological OST. Clinical trials have demonstrated the effectiveness of methadone maintenance for the treatment of opioid dependence and prevention of HIV. Such evidence is summarized in key WHO documents *(19, 67)*.

Dosages of methadone in different programmes range from 20 to 120 mg per day and sometimes higher. Doses above 60–80 mg per day are better at achieving retention in treatment and reducing illicit drug use.

As methadone is metabolized by the cytochrome P450 enzyme system, other medications that interact with this enzyme system should be used with caution (see also section IV.4.4.).

Patients on methadone treatment may increase alchohol use in place of illicit opioids. IDUs are at an increased risk of liver toxicity and impairment of the metabolism of certain ARV drugs.

2.1.2. Buprenorphine

The benefits of buprenorphine maintenance are similar to methadone maintenance and therefore for HIV-infected IDUs on buprenorphine the success of HAART will be increased. In France, where buprenorphine is widely used, studies have reported that for patients on HAART and buprenorphine, the CD4 count rises and the viral load decreases as expected *(68)*.

More recently buprenorphine, a partial opioid agonist, has been used for both detoxification and maintenance. A number of clinical trials have demonstrated the effectiveness of buprenorphine maintenance for the treatment of opioid dependence. Again, key WHO documents summarize the evidence *(19, 69)*.

The dosage used in maintenance can range between 12 mg and 34 mg, with an average dose of approximately 16 mg.

Due to its pharmacological functioning and partially antagonistic effect, buprenorphine may be safer in overdose than methadone; in addition, it appears to offer a slightly smoother withdrawal during detoxification. It is a sublingual preparation, so care must be taken during dispensing, as there have been reports of crushing and injecting the tablets *(70)*, which could lead to sharing of injecting equipment *(71)*.

2.2. Detoxification programmes (medically supervised withdrawal)

Detoxification from opioids is an initial component of some treatment programmes but should never in itself be considered a treatment for opioid dependence. It provides supervision to reduce the severity of symptoms and the medical complications of withdrawal, and it should be tailored to the patient. There are several important points to consider about detoxification.

- Detoxification programmes can provide entry points for HAART delivery.
- Reduction in methadone and buprenorphine doses should be negotiated with the drug user depending on the emergence of withdrawal symptoms.
- Access to psychological support should be available throughout the treatment.
- Detoxification for opioid dependants can be carried out using tapering doses of different medications including:

- methadone (stabilize on 40–60 mg once daily (OD) and reduce by 5 mg per week over 8–10 weeks);
- buprenorphine (stabilize on 8–10 mg OD and reduce over 5-6 weeks);
- clonidine;[14] and
- lofexidine (stabilize on 1.2–2.0 mg in divided doses (e.g. four times daily (QID)) and reduce over 2 to 3 weeks).

When used appropriately, the medications above can produce safe and less uncomfortable withdrawal, but the majority of patients will relapse into opioid use after withdrawal, regardless of the method or substance used. Relapse rates following detoxification can be reduced by offering after-care support with antagonist therapy, such as naltrexone at 50 mg per day, or 100 mg on day 1, 100 mg on day 3 and 150 mg on day 5. Given that one of the principal problems of naltrexone is compliance *(72)*, some services supervise ingestion in the after-care period.

2.3. Other treatment options

In addition to OST, treatment and management options include:

- self-help groups
- therapeutic communities[15]
- residential rehabilitation[16]
- psychological interventions such as:
  - cognitive behavioural therapy (CBT)[17]
  - motivational interviewing[18]
  - contingency management[19]
  - matrix model[20]
  - relapse prevention strategies, medical or psychological
- peer support programmes
- social skills training
- vocational training
- heroin replacement treatment (heroin, morphine).

Heroin-assisted treatment was recently shown to be of more benefit to long-time opiate injectors with unsuccessful abstinence-oriented and perhaps OST treatment histories who may have serious continuing medical problems *(77)*. However, heroin prescribing programmes remain highly controversial. Such an intervention might be considered when all other treatment services have been saturated, for example, where there is universal access to methadone and buprenorphine treatment.

2.4. Management of non-opioid dependence (including cocaine and ATS)

While it is estimated that there are now over 13 million injecting drug users worldwide, not all substance dependence is on opioids. It is also associated with sedatives, cocaine and ATS. It is vital that services respond to the needs of non-opioid users. HIV risk is also associated with non-opioid drugs, particularly where these drugs are injected. There are limited data on association between

[14] An alpha-adrenergic agonist that suppresses withdrawal signs and symptoms. The patient may require admission, given the associated risk of significant hypotension; consequently lofexidine may be preferable.
[15] Residential drug-free rehabilitation programmes of 3–15 months duration. Group or individual psychotherapy and vocational training may be available.
[16] Short-term residential programmes (6–8 weeks), often based on the 12-step Minnesota model.
[17] A time-limited, structured, goal-oriented psychological intervention focusing on the problems of the drug user entering treatment. The therapy identifies the determinants or high-risks of drug use and allows the user to relearn appropriate coping skills, leading to a healthier lifestyle; can be brief or extended *(73)*.
[18] Stimulates and enhances an individual's resolve to change behaviour.
[19] An intervention that reinforces or rewards appropriate behaviour. The reward may be in the form of vouchers for samples that test negative for drugs *(74, 75)*.
[20] Designed to integrate interventions into a comprehensive approach. Elements include: individual counselling, CBT, motivational interviewing, family education groups, urine testing and participation in 12-step programmes *(76)*.

ATS use and high-risk sexual behaviour. At present there is no proven effective substitution therapy for non-opioid drugs, although dexamphetamine has been prescribed for amphetamine users in Australia and the United Kingdom *(78)*. Bupropion and sustained-release methylphenidate are among a number of promising pharmacotherapies for the treatment of methamphetamine dependence.

With the exception of detoxification for opioids and heroin prescribing, the range of treatment options is similar to those shown above for services treating opioid IDUs not on OST. There are however, some further considerations in relation to medical management and psychological interventions:

- Acute medical detoxification from cocaine and ATS focuses on relief of psychiatric withdrawal symptoms.
- Acute withdrawal problems are typically dealt with in the first three to five days post-cessation; however, they can last up to two weeks, particularly in individuals with comorbid medical or psychiatric problems.
- Detoxification should only form one part of a broader drug-dependence treatment.
- ATS use in general (and methamphetamine use in particular) has been associated with poor treatment engagement and high rates of drop-out and relapse.

2.4.1. Symptoms and medications

- Agitation and acute depression often follow cessation of cocaine or ATS and may require a minor tranquillizer such as diazepam for a short period.
- Psychotic symptoms, such as paranoia, may require antipsychotic medication.
- Palpitations and restlessness may benefit from the use of propranalol (a beta blocker), which has been shown to improve treatment retention and decrease cocaine use among those with severe withdrawal symptoms *(79)*.
- Drugs that stimulate the dopamine system in the brain can help manage depressive symptoms and severe craving in heavy cocaine users. Amantadine, a Parkinson disease medication, may prove beneficial *(80)*, while desipramine, a tricyclic antidepressant, can increase the availability of dopamine *(81)*. Desipramine has been associated with cardiac rhythm disturbances and should be used cautiously in patients also using methadone.

2.4.2. Relapse prevention

Following detoxification, medications useful for relapse prevention include those that reduce euphoria and limit craving, such as topiramate, an anticonvulsant *(82)*, or that make the high less pleasant and produce anxiety, such as disulfiram *(83)*. Close monitoring of signs for possible drug interactions should be taken when prescribing these medications in conjunction with ARVs.

- Topiramate is cleared through renal elimination; therefore, caution should be exercised in cases of renal or hepatic insufficiency.
- Although there are no reports of significant interactions with ARVs, topiramate is susceptible to clinically relevant drug interactions due to induction of its metabolism *(84)*.
- Interactions can occur between disulfiram and compounds that utilize the cytochrome p450 enzyme system *(85)*.
- There are reported interactions between disulfiram and the liquid form (but not the capsule form) of lopinavir/ritonavir, which contains ethanol and thus precipitates a reaction *(86)*. The capsule form is thus the preferred option.

2.4.3. Other interventions

Although there is no proven substitution therapy available for stimulant injectors, drug dependency services have ongoing contact with these patients, which provide opportunities for adherence support, often through psychological interventions, and in some desipramine cases the possibility of dispensing medication. The psychological interventions mentioned above (section IV.2.3) also have proven benefits in the treatment of cocaine and ATS dependence. CBT, the community reinforcement approach, contingency management and 12-step programmes have all demonstrated efficacy in treatment of cocaine and ATS dependence.

3. Management of HAART in IDUs with HIV/AIDS

- Initiation of ART is rarely an emergency.
- Patients should be well informed and motivated, while potential barriers to adherence should be addressed.
- Health care providers should give written information (in appropriate language and consistent with literacy levels) about ART to all patients and their families prior to initiation of treatment.
- Preparations for receiving ART should include:
  - substance dependence treatment
  - stabilization of living conditions
  - treatment of psychiatric disorders
  - stabilization of serious medical conditions.

Initiation of ART for HIV-infected IDUs should follow the current recommendations for initiation of ART in other HIV-infected patients; see Table 1. (For further details, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*)

Table 1. Recommendations for initiating ART in PLHIV

WHO clinical stage	CD4 cell count	Recommendation
1	<200/mm^3	Treat
	200–350/mm^3	Consider treatment
2	<200/mm^3	Treat
	200–350/mm^3	Consider treatment
3	<350/mm^3	Treat
4	Regardless of CD4 count	Treat

While most clinicians regard CD4 counts as the more important indicator for initiation of treatment, viral load monitoring is useful, though not necessary, with >100 000 ribonucleic acid (RNA) copies/ml being the threshold level for ART.

A fundamental part of initiating treatment is ensuring that the patient is an active and a responsible participant in the plan. The key to effective HAART and treatment of any comorbidities is a careful assessment and education of the patient, leading to the development of an individualized treatment plan to maximize adherence. It is crucial that treatment plans be designed collaboratively by staff, patient and (where appropriate) family. All predictable potential barriers to successful treatment adherence should be addressed with this plan. The active participation of patients in their own treatment encourages closer cooperation with health care workers and better feedback on the effects of treatment.

3.1. Choice of HAART regimen

Selection of ARV drug regimens should include individual patient variables, such as comorbidities and other co-conditions. For IDUs, there are specific issues that should be identified during patient evaluation.

- IDUs may continue to actively use illicit drugs and may not be in OST.
- Comorbidities are very common, in particular mental health problems such as depression and alcohol dependence.
- Coinfections such as hepatitis C virus (HCV), HBV and TB are common.
- Drug interactions are more complex, for example, ARV interactions with illicit drugs or substitution treatments.
- IDUs may be homeless or otherwise difficult to contact.

- Adherence can be a more difficult issue with IDUs, particularly if they are receiving treatment for HCV or TB.

The above considerations have implications for the choice of treatment regimen. Issues of HAART for IDUs include the following *(4)*:

- Women who wish to become pregnant should not be prescribed efavirenz (EFV).
- Active hepatitis may be exacerbated more by nevirapine (NVP) than other drugs.
- Hepatoxicity may be due to direct drug toxicity or as a consequence of immune reconstitution syndrome (IRS) in patients with hepatotrophic viruses.
- For IDUs with hepatitis B coinfection, lamivudine (3TC) and tenofovir (TDF) are active against both infections.
- In alcohol users, the potential for pancreatitis is increased with didanosine (ddI).
- In alcohol users, the potential for peripheral neuropathy is increased with stavudine (d4T).
- In the presence of TB, EFV is preferable (abacavir (ABC) can be an option).
- Rifampacin for TB treatment should not be administered to patients receiving protease inhibitors (PI) (due to possible drug-induced hepatitis); however, rifabutin can be used (refer to Protocol 4, *Management of tuberculosis and HIV coinfection*).
- Intolerance of non-nucleoside reverse transcriptase inhibitor (NNRTIs) due to liver disease (HCV, HBV) or psychiatric disorders may require the use of a PI or ABC in first-line regimens.
- All possible drug interactions with other medications should be addressed.

3.2. Recommended HAART regimens for IDUs

Recommended regimens for IDUs are summarized in Table 2.

Table 2. HAART regimens for HIV-infected IDUs in different clinical situations

Treatment situation	First-line preferential	First-line alternatives[a]	Second-line preferred	Second-line alternatives
Injecting drug use without other significant clinical comorbidities or co-treatments, but needs ART	ZDV[b] + 3TC (or FTC)[c] + EFV[d]	TDF or d4T can replace ZDV. ABC or NVP or TDF can replace EFV.	ABC + ddI+ LPV/r[e] (or SQV/r)	NFV can replace LPV/r or SQV/r. ZDV or d4T can replace ABC if none were used in first line. EFV or NVP can replace ABC or ddI if none of either was used in first line.
Injecting drug use with HBV/HIV, with indications for treating HBV and using ART	ZDV+3TC (or FTC) + EFV	TDF or d4T can replace ZDV. ABC, NVP[f] or TDF can replace EFV.	ABC + ddI+ LPV/r (or SQV/r) and maintenance of 3TC and/or TDF	NFV can replace LPV/r or SQV/r. ZDV or d4T can replace ABC if they were not used in first line. EFV or NVP[f] can replace ABC or ddI if they were not used in first line.
Injecting drug use with TB/HIV using TB regimens with rifampicin (RMP) and needs ART	ZDV+3TC (or FTC) + EFV	TDF or d4T can replace ZDV. ABC or NVP[f] or TDF can replace EFV.	ABC + ddI+ LPV/r + RTV[g] (or SQV + RTV)	Maintain the PIs and substitute rifampicin for rifabituin in TB regimen, with adjustments in ARV dose if needed.
Injecting drug use with HCV/HIV using concomitant anti-HCV treatment and ART	ZDV+3TC (or FTC) + ABC[h, i]	d4T or TDF can replace ZDV. TDF can replace ABC.	Consult with a specialist with experience in the management of both diseases.	–

[a] Boosted PIs can be used as part of the first line ART in combination with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) when EFV is contraindicated.
[b] Methadone can significantly increase zidovudine (ZDV or AZT) concentrations. While the clinical significance is unclear, adverse events should be monitored.
[c] FTC (emtricitabine) is interchangeable with 3TC.
[d] EFV can significantly decrease methadone concentrations (60%) and methadone withdrawal is common. Significant methadone dose increase (e.g. 50%) is usually required.
[e] LPV/r (lopinavir/ritonavir) has been reported to cause methadone withdrawal and increased methadone dosage may be required.
[f] NVP can substitute for EFV in this situation, if no other options are available, but should be carefully monitored.
[g] LPV/r with extra dose of RTV (LPV/r + RTV). Refer to Protocol 4, *Management of tuberculosis and HIV coinfection.*
[h] ABC can mildly decrease methadone levels. Although risk of opioid withdrawal is low and dosage adjustments unlikely, some patients might require a methadone dose increase.
[i] Simplification strategy (start triple NRTIs and HCV therapy after the improvement of immunologic and virologic parameters with an induction phase with a NNRTI-based regimen). Refer to the Protocol 6, *Management of hepatitis C and HIV coinfection.*

Switching to second-line HAART should be done in case of treatment failure, which is measured clinically and immunologically. (Please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.) Treatment failure (occurrence of a new opportunistic infec-

tion or malignancy, recurrence of a previous opportunistic infection and the onset of WHO Stage III conditions) should be differentiated from immune reconstitution inflammatory syndrome (IRIS), which can occur in the first three months after initiation of HAART. The latter is an inflammatory response to previously subclinical opportunistic infections in advanced immunodeficiency. The opportunistic infection in IRIS should be treated as usual.

3.3. Hepatotoxicity of ARVs

- NRTI hepatotoxicity is not a frequent adverse effect but has been reported with ZDV, ddI and d4T in the form of liver enlargement, liver enzyme abnormalities and/or lactic acidosis. ABC and 3TC have also been implicated but to a lesser degree. Regimens containing ZDV/ddI and d4T/ddI combinations should be avoided.
- NNRTI hepatotoxicity has been associated mainly with NVP but has also been reported with EFV. NVP should be avoided if possible. Women and patients with high CD4 counts are at higher risk of these hepatic events (including NVP deaths).
- PI hepatotoxicity is often mild. However, high dose ritonavir (>1000 mg/day) appears more potentially hepatotoxic than other PIs. Unlike the hepatotoxicity associated with NNRTIs, which occurs in the first weeks of treatment, that associated with PIs can appear at any time during treatment. PI dosing is difficult in patients with decompensated liver disease and drug level monitoring may be helpful.
- Despite the common association of hepatotoxicity with HAART, almost 90% of HIV-infected patients, regardless of whether they are coinfected with hepatic viruses, will tolerate HAART without severe liver toxicity *(87)*.

3.4. Considerations for IDU patients with hepatitis C/HIV coinfection

All IDUs with hepatitis C should be considered for treatment with pegylated interferon and ribavarin. The sustained response rate for this treatment has been reported as 11–29% for genotype 1 and 43–73% for other genotypes *(88–90)*. Factors influencing response include CD4 count, HIV viral load and the presence of cirrhosis. Treatment is best provided at a high CD4 count before the need for HAART arises. If HAART intervention is required, the patient should be stabilized on therapy with a CD4 count of >200cells/mm^3 before anti-HCV treatment is initiated. (For further information please refer to Protocol 6 on *Management of hepatitis C and HIV coninfection*.)

The side-effects of hepatitis treatment have the potential to destabilize a successful HAART response. Consideration should be given to anti-HCV treatment at a substance dependency centre or HIV/AIDS centre where OST and HAART may be directly administered. A further advantage of this approach is that the patient can be monitored clinically, by the psychiatric/psychological support staff in the drug dependence service, especially since depression is one of the more serious side-effects of interferon *(91)*.

3.5. Considerations for IDU patients with TB/HIV coinfection

The treatment of TB and HIV coinfection in IDUs is complex; however, it can still be managed effectively *(92)*. Data supporting specific treatment recommendations are incomplete and research is urgently needed in this area. Please refer to Tables 2 (section IV.3.2. above) and 5 (see section IV.4.4.4.) for specific issues in HAART for IDUs with active TB.

Methadone dosage needs to be considered in the TB treatment of IDUs. As rifampicin is a potent inducer of cytochrome P450, it can lead to a reduction in circulating methadone levels, possibly requiring a substantially increased dosage. As buprenorphine is also metabolized by the cytochrome P450 pathway, it is suspected that rifampicin has a similar major impact on the buprenorphine level. Rifampacin also accelerates the metabolism of PIs. There are no reported interactions between methadone and rifabutin, so rifabutin may be an alternative in combination with PIs *(93)*. (See Table 5 in section IV.4.4.4.)

3.6. Adherence

Adherence is an important determinant of a successful response to HAART, since incomplete adherence has been associated with early emergence of ART resistance *(94, 95)*, virological failure and subsequent immunological and clinical failures *(96)*. Adherence rates over 95% are required to achieve optimal viral suppression *(97)*. If drug resistance develops, drug resistant viruses can be transmitted, necessitating revised treatment regimens *(96, 98)*.

The relationship between non-adherence and plasma HIV RNA levels is clear, but not proportionate: a small amount of non-adherence yields large losses of viral control. One study showed that a 10% decrease in adherence was associated with a doubling of the HIV RNA level *(99)*. In addition, CD4 count can decrease with adherence under 90% *(100)*.

The need for more than 95% compliance to treatment has allowed an incorrect view to develop that IDUs are poor candidates for HAART. IDUs are disproportionately and wrongly excluded from HIV/AIDS treatment, particularly HAART. Studies indicate that:

- the proportion of non-adherent individuals is similar in non-IDUs and IDUs on OST *(101, 102);* and
- rates of ARV resistance are no higher in IDUs than non-IDUs.

IDUs receiving stable care from experienced staff with adequate support can adhere to HAART and have clinical outcomes equivalent to those of HIV patients who do not use drugs *(9, 10, 94)*. In particular, consistent participation in methadone maintenance programmes has been shown to be associated with a higher probability of HAART use and better adherence to it *(1, 3, 11, 24, 44, 48–50, 103)*.

3.6.1. Factors influencing adherence

Adherence to HAART can be influenced by many types of factors.

Medical factors are:

- toxicity and side-effects of ARVs or interactions with other medications or substances
- hepatotoxicity, which is much higher among IDUs than non-IDUs[21]
- severe opportunistic infections
- comorbid psychiatric disorders, including depression *(39, 104)*.[22]

Personal factors are:

- continuing or relapsed drug use *(68)*
- concurrent problematic alcohol use or multiple drug dependence
- lack of prospects and motivation
- major life events and crises
- side-effects of ARVs or perception of same *(108, 109)*
- expectations of treatment success (by patients and providers).

Health-care-service-related factors are:

- stigmatization and discrimination in health care settings *(110)*
- perception of unfriendly and poor-quality health services *(102)*
- availability and accessibility of treatment services for drug dependence *(51, 111)*
- poor or non-existent links between services
- lack of continuity of care
- providers' belief that IDUs are unable to adhere to HAART *(110)*.

[21] Please see Protocols 6 and 7, *Management of hepatitis C and HIV coinfection* and *Management of hepatitis B and HIV coinfection*.

[22] Depression is also a determinant of clinical progression independent of adherence *(39, 105–107)*.

Social factors are:
- homelessness and lack of family or community support
- unemployment
- stigmatization and discrimination
- restrictive legislative and policies.

4. Monitoring of IDUs under treatment

4.1. Monitoring of substance dependence treatment

Monitoring the effectiveness of substance dependence treatment can be achieved through a number of means.
- Care planning is particularly informative; regular review by the case manager or physician is instrumental in achieving better outcomes.
- Care plans can set out short-, medium- and long-term goals; monitoring them indicates the degree of progress.
- Patient records are an essential element for documenting good practice and for informing evaluation and cover information on:
  - assessment results
  - treatment plans
  - daily dosages
  - side-effects of prescribed medicines
  - regimens used (including take-home doses)
  - medical care
  - psychological and psychiatric care
  - social care
  - laboratory findings
  - clinical observations
  - programme compliance observations
  - circumstances of leaving/terminating treatment
  - an agreement to terminate treatment
  - arrangements for after-care.
- The use of standardized instruments, such as the ASI (see Annex 1), allows progress to be monitored more formally.
- Screening for illicit drug use using urine, breath, saliva, blood or hair analysis can indicate the degree of response to the treatment.
- Drug screening is not a prerequisite; it should be undertaken with informed consent and should not be used to terminate treatment.

4.2. Monitoring of laboratory indicators with regards to HIV/AIDS

IDUs with HIV infection should be carefully monitored during the course of HIV infection to ensure continuum of care. Laboratory indicators, such as CD4 cell count and viral load should be monitored regularly whether or not a patient has started ART. For further information on patient monitoring please refer to Protocol 1 *Patient evaluation and antiretroviral treatment of adults and adolescents*.

4.3. Mangement of ARV toxicity and side-effects

Clinical side-effects of ARVs are relatively common, reported in nearly 50% of patients *(112)*, and are a leading cause of poor adherence to drug regimens *(113)*.

Management of possible side-effects is most effective when all staff are aware of the risk of side-effects in order to intervene early, and the patient understands the cause and nature of ARVs side-effects, and the importance of reporting them early in order to:

- organize adherence support
- adjust treatment regimens so they are safe, effective and acceptable
- minimize the risk of drug resistance because of poor adherence.

Early in the course of HAART, mild side-effects such as headache, nausea, diarrhoea and fatigue are common. They may often be managed simply with support, reassurance and symptomatic treatment such as analgesics or anti-diarrhoeal agents. These interventions are very useful in helping individuals to cope with side-effects without stopping or changing their HAART regimens.

Side-effects can vary from mild to very serious and can affect many organ systems. Major side-effects of ARVs by drug class and organ system *(114)* are shown in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*. Careful clinical assessment is required to exclude other possible causes of signs and symptoms that might be mistaken as ARV side-effects, for example opioid withdrawal syndrome is characterized by headaches, anxiety, diarrhoea and headaches.

In cases where the symptomatic measures are not sufficient or the toxicity is too severe it may be necessary to replace a side-effect-causing ARV drug with another ARV drug within the existing HAART regimen (please see Table 2 above). Please also see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

4.4 Drug-drug interactions in IDUs

Health care providers should counsel every patient on all possible interactions of ARVs with other drugs administered, including substitution therapy drugs (see Table 3), illicit/recreational drugs and medications for TB, HCV, HBV and other opportunistic infections. Awareness of interactions and reporting and management of symptoms is critical for the patient's well-being, treatment adherence and effectiveness, and management of drug interactions.

4.4.1. Methadone and ARVs

- Methadone is metabolized in the liver by several cytochrome P450 (CYP) enzymes (especially CYP3A4). Its level may drop when used in conjunction with drugs that induce cytochrome enzymes, and an increased dosage may be required. When used in conjunction with drugs that inhibit cytochrome enzymes, its level may increase and a dose reduction may be needed.
- Methadone itself inhibits the metabolism of ZDV, thus possibly elevating ZDV levels by as much as 43%; although no empiric dose reduction is currently recommended, signs of toxicity should be closely monitored *(115)*.
- Methadone can decrease ddI levels by up to 60%, leading to ddI underexposure, incomplete viral suppression and development of resistance.
- Nevirapine, efavirenz and ritonavir decrease methadone concentrations *(116, 117)* and produce withdrawal symptoms.
- NNRTIs are significantly more likely to interact with methadone than PIs, therefore IDUs on OST require careful monitoring.
- The PI LPV/r has also been shown to produce an increase of methadone metabolism necessitating dosage increases in some cases *(118)*.

Table 3. Interactions between ARV drugs and methadone[a]

Antiretroviral agent	Agent's effect on methadone	Methadone's effect on ARV agent	Comments
NRTIs			
Abacavir (ABC)	Methadone levels mildly decreased. Risk of opiate withdrawal low. Dosage adjustments unlikely but some patients might require methadone dose increase.	Peak concentration reduced (34%). Time to peak increased.	Data sparse – although one study showed an increase of 22% in oral methadone clearance. Risk of opiate withdrawal low. Methadone dose adjustment might be needed.
Didanosine (ddI) Buffered tablet Enteric coated capsule	None reported. No dosage adjustments necessary.	Concentrations decreased (60%) in buffered tablet but not in enteric coated (EC) capsule.	Only studied with twice-daily administration of buffered tablets. Hypothesized due to reduced bioavailability of didanosine in the setting of slower transit through the acidic environment of the stomach in patients taking methadone. Great inter-individual variability in didanosine pharmacokinetic data. No effect on enteric coated (EC) capsule Enteric coated (EC) capsule therefore preferred.
Empricintamin (FTC)	Not studied	Not studied	No known interactions
Lamivudine (3TC)	None reported	None reported	No known interactions
Stavudine (d4T)	None reported. No dosage adjustments necessary.	Concentrations decreased (18–27%). Clinical significance unclear.	Clinical significance of effect unclear.
Tenofovir (TDF)	None reported	None reported	No known interactions
Zidovudine (ZDV)	None reported No dosage adjustments necessary.	Concentrations significantly increased (43%). Clinical significance unclear. Adverse events possible.	Monitor for ZDV adverse events. Watch for anaemia, nausea, myalgia, vomiting, asthenia, headache and bone marrow suppression in recipients. If methadone trough levels are normal, suspect that problem is ZDV toxicity.
NNRTIs			
Efavirenz (EFV)	Methadone concentrations significantly decreased (60%). Methadone withdrawal common. Significant methadone dose increase (50%) usually required.	Unknown	Observe closely for signs of methadone withdrawal and increase dosage as necessary. Symptoms of withdrawal may be delayed for up to 2 or 3 weeks.

Antiretroviral agent	Agent's effect on methadone	Methadone's effect on ARV agent	Comments
Nevirapine (NVP)	Methadone concentrations significantly decreased (46%). Methadone withdrawal common. Methadone dose increase (16%) necessary in most patients.	None reported	In a case series of chronic methadone recipients initiating nevirapine, there was a need for 50% to 100% increases in the daily methadone doses to treat opioid withdrawal. Withdrawal symptoms generally occur between 4 and 8 days after starting nevirapine, although they may be delayed for up to 2 or 3 weeks.
PIs			
Lopinavir/ritonavir boost (LPV/r)	Methadone levels decreased (26–53%). Withdrawal might occur, requiring dosage increase. Side-effects may mimic withdrawal.	None reported	Methadone withdrawal reported. May require increased methadone dose.
Nelfinavir (NFV)	May decrease methadone levels (29–47%). Clinical withdrawal rarely reported. Methadone dosage may need to be increased.	Levels may be reduced but clinical significance unclear.	Clinical withdrawal was not reported in studies where decreased methadone concentrations were reported.
Ritonavir (RTV)	May decrease methadone levels (37%). Methadone dosage may need to be increased.	None reported	Studies limited Observe closely for signs of methadone withdrawal and increase dosage as necessary.
Ritonavir/tipranavir	May decrease methadone levels (50%). Methadone dosage may need to be increased.	None reported	
Saquinavir (SQV)	None reported	None reported	Studies limited, but no reported interactions.
Saquinavir 1600 mg, ritonavir 100 mg (SQV/r) Saquinavir 1400 mg, ritonavir 400 mg (SQV + RTV)	Methadone levels slightly reduced (SQV/r 1600/100 by 0–12%, SQV + RTV 1400/400 by 20%). No reported withdrawal. Methadone dosage adjustments may be necessary.	Unknown	Methadone dose adjustments may be necessary; requires ongoing monitoring.

[a] The methadone levels are based on trough levels measured in plasma 24 hours after ingestion of the last dose. For a useful evaluation of the methadone level, patients should have been on their doses for at least five days before testing.
Source: adapted from WHO. Leavitt et al. *(4,104).*

Opioid metabolization can be inhibited or induced by concomitant PIs, so patients should be monitored for signs of toxicity. The withdrawal symptoms generally occur within 4 to 10 days of ARV initiation. Withdrawal symptoms should be monitored clinically and dosage increases of 10 mg increments from days 8–10 should allow this problem to be managed. The required increase in methadone is not as great as expected from pharmacokinetic data.

Clinically, some of the potential interactions indicated above do not require a change in dose or medication. Practically, the use of NNRTIs does require an often significant dosage adjustment of methadone.

4.4.2. Methadone and other medications

Interactions between some medications used to treat comorbidities such as psychiatric disorders or TB associated with HIV in IDUs, and methadone or ARVs have also been reported and are indicated in Table 4. An up-to-date drug interaction database would doubtless prove useful to prescribing clinicians.

Table 4. Interactions among methadone, ARVs and other medications

Psychotropic medication	Use	Interaction with methadone	Interaction with ARV medications
Alprazolam (benzodiazepine)	Sedative	May result in an unpredictable interaction. Additive CNS depression and possible excessive sedation.	Alprazolam clearance decreased by 41%. Concurrent use of certain benzodiazepines (alprazolam, midazolam and triazolam) should be avoided with all PIs and EFV.
Desipramine	Tricyclic antidepressant	May result in unpredictable interaction. Possible increased TCA toxicity. Associated with cardiac rhythm disturbances and should be used cautiously with methadone.	Desipramine clearance decreased by 59%.
Fluoxetine (SSRI)	Treatment of depression and compulsive disorders	Decreased methadone levels in preclinical studies. Associated with cardiac rhythm disturbances and should be used cautiously with methadone	Ritonavir increased by 19%.
Fluvoxamine (SSRI)	Treatment of depression and compulsive disorders	Increased methadone levels reported.	No effect reported in preclinical study.
Sertraline (SSRI)	Treatment of depression and compulsive disorders	Increased methadone levels by 26%, without increase in side-effects. Associated with cardiac rhythm disturbances, caution should be used with methadone.	Not studied or reported.
St John's wort (*Hypericum perforatum*)	Antidepressant	Significant decrease in methadone levels reported.	Indinavir decreased by 57%. May lead to decreased response and resistance to NFV. Saquinavir (SQV) levels may be decreased.
Valproic acid	Anticonvulsant	None reported	ZDV increased in preclinical studies.
Other medications	**Use**	**Interaction with methadone**	**Interaction with ARV medications**
Carbamazepine	Anticonvulsant	Decreased methadone levels. May cause opioid withdrawal. A methadone dosage increase may be required. Consider using valporic acid as an alternative	Some interactions (refer to Protocol 1, *Patient evaluation and antiretroviral treatment in adults and adolescents*). Monitor for toxicities and dose adjustments.

Other medications	Use	Interaction with methadone	Interaction with ARV medications
Fluconazole	Antifungal	Increased methadone levels (35%). Clinical significance unknown, although cases requiring dose reduction reported. No signs of methadone toxicity reported. Other azole antifungal antibiotics may potentially influence opioid toxicity. e.g. itraconzale, ketoconazole, voriconazole.	Potential for bi-directional inhibition between some azole antifungal antibiotics and PIs. Monitor for toxicities and dose adjustments. Toxicity and anti-fugal outcomes observed with NNRTIs. Refer to Protocol 1, *Patient evaluation and antiretroviral treatment in adults and adolescents.*
Interferon-α + ribavirin	Anti hepatitis C treatment	Side-effects can mimic opioid withdrawal symptoms and methadone dose is often increased. In a study of HCV patients concomitantly receiving methadone and peginterferon-alfa 2a methadone levels increased 10-15%. Clinical significance unknown. Patients should be monitored for signs and symptoms for methadone toxicity.	Hepatitis C infection can aggravate the hepatotoxicity of several ARV regimens. (Refer to Protocol 6, *Management of hepatitis C and HIV coinfection*.)
Phenobarbital (barbiturate)	Anticonvulsant, sedative	Decreases methadone levels, often sharply. May cause withdrawal. A methadone dosage increase may be required.	Barbiturates such as phenobarbital are potent inducers of CYP3A4. Clinicians should consider avoiding concurrent administration of other potent inducers (e.g. EFV and NVP) in patients misusing barbiturates. May decrease NFV concentrations.
Phenytoin	Anticonvulsant	Decreases methadone levels, often sharply. May cause withdrawal. A methadone dosage increase may be required.	Some interactions (refer to Protocol 1, *Patient evaluation and antiretroviral treatment in adults and adolescents.*) Monitor for toxicities and dose adjustments.
Rifabutin	Anti-mycobacterial treatment of pulmonary TB	No change in methadone levels. Mild narcotic withdrawal symptoms.	Some interactions (refer to Protocol 1, *Patient evaluation and antiretroviral treatment in adults and adolescents*) but rifabutin may be a preferred option for the treatment of pulmonary TB as an alternative to rifampicin. Monitor for toxicities and dose adjustments.

Other medications	Use	Interaction with methadone	Interaction with ARV medications
Rifampicin (Rifampin) Rifampin/isoniazid	Treatment of pulmonary TB	Possibly severe decrease in methadone levels (33–68%). May induce methadone withdrawal. A methadone dose increase may be required.	PIs contraindicated. Rifampin should not be co-administered with LPV, NFV, SQV. Rifabutin may be a potential alternative, but not in combination with SQV.
Sildenafil	Erectile dysfunction agent	Not reported	No effect of sildenafil on PIs. Ritonavir increases sildenafil 10-fold. Saquinavir increases sildenafil 3-fold. Use cautiously and monitor for adverse effects.

Source: Leavitt et al., McCance-Katz et al. *(104,111)*.

4.4.3. Buprenorphine and ARVs

Buprenorphine and ARV interactions are less well researched than methadone interactions.

Morphine derivatives and opioid antagonists such as naltrexone should not be used with buprenorphine due to its partial antagonist effects. Elevations in liver enzymes (AST and ALT) have been reported in individuals receiving buprenorphine. There appears to be a mild elevation in liver enzymes in patients with hepatitis who receive buprenorphine long-term. As buprenorphine is metabolized by the cytochrome P450 3A4 enzyme system, other medications that interact with this system should be used with caution.

While in vitro evidence suggests that buprenorphine is metabolized by the cytochrome P450 enzyme (3A4 isomer) and would be affected in a similar way to methadone by enzyme inducers such as NVP, EFV and RTV, the evidence is not available from clinical trials to support this. To date, limited data exists on interactions between buprenorphine and ARVs; however, in examining both EFV and ZDV, the following observations have been made:

- Administering EFV with buprenorphine lowers buprenorphine levels but does not seem to produce clinical withdrawals *(119)*.
- ZDV with buprenorphine does not precipitate withdrawals, and ZDV levels do not decrease as they have been seen to do with methadone *(120)*.

Other potential interactions include those with:

- cytochrome P450 3A4 inhibitors such as fluconazole and macrolide antibiotics
- inducers such as phenobarbital, carbamazepine, phenytoin and rifampicin
- sedatives such as benzodiazepines.

Supervision of buprenorphine medication permits DOT with HAART, although in some cases, patients may only require buprenorphine doses every second or third day. Clinicians should remain aware of the potential for the sublingual buprenorphine to be crushed and injected, as this method has been linked with some cases of hepatitis in IDUs *(83)*.

4.4.4. Illicit/recreational drugs and ARVs

Interactions between ARVs and psychoactive substances used for non-medical purposes are possible and may have serious clinical consequences in terms of HAART efficacy or drug toxicity *(121)*. PIs and NNRTIs can inhibit or induce the cytochrome P450 system in the liver, which is responsible for the metabolism of benzodiazepines, amphetamines and opioids.

4.4.4.1 Benzodiazepines

- Benzodiazepines that are primarily dependent on CYP3A4 for metabolism – midazolam, triazolam, alprazolam and flunitrazepam – are likely to be affected by PIs and those ARVs that cause inhibition of CYP3A4, causing drowsiness, confusion and paradoxical aggression.
- NVP, which can induce CYP3A4, may lead to withdrawal symptoms and encourage dose escalation in benzodiazepines.
- The benzodiazepines where CYP3A4 metabolism plays a minor role include lorazepam, oxazepam, temazepam and diazepam, for which no interactions have been reported.

4.4.4.2 Cocaine

Cocaine may be used either by itself or in combination with other recreational drugs. Understanding the impact of cocaine use on HAART is important for successful treatment *(122)*.

- The metabolism of cocaine to norcocaine (an active hepatotoxic metabolite) occurs at CYP3A4.
- PIs and other drugs that inhibit CYP3A4 activity can lead to a fatal cocaine overdose.
- NVP, which induces this enzyme, can cause a build-up of a potentially hepatotoxic metabolite.

4.4.4.3 Amphetamine, methamphetamine and 3, 4 methylenedioxymethamphetamine (MDMA)

- These have similar metabolism mainly through the CYP2D6 pathway.
- Certain PIs, especially ritonavir may cause inhibition of CYP2D6 and therefore toxicity. A fatal MDMA/ritonavir interaction has been reported *(123)*.

4.4.4.4 Opioid-based drugs, such as heroin, codeine, morphine and other analgesics

Interactions with ARVs are similar to those described for methadone. Thus, NNRTIs and some PIs may result in opioid withdrawal and loss of analgesia.

4.4.4.5 Tetrahydrocannabinol (THC) (main active component of cannabis products)

- Information on potential interactions with ARVs is limited.
- A study looking at the effects of THC on HAART medication showed no clinically significant changes in the plasma levels of indiavir (IDV) or NFV *(124)*.
- Administration of potent CYP3A4 inhibitors (for example, PIs and EFV) might result in greater effect and longer duration of THC.

4.4.4.6 Other psychoactive drugs that may be used non-medically

- Gamma-hydroxybutyrate (GBH, liquid X) toxicity has been reported in conjunction with RTV and SQV *(125)*.
- Ketamine might inhibit CYP3A4 and increase side-effects of antiretroviral treatment.
- Phencyclidine[23] might be metabolized primarily by CYP3A4 and therefore PIs may increase the risk for phencyclidine toxicity.

Table 5 briefly summarizes available and postulated data on drug and ARV interactions. It also gives an indication of the primary site of metabolism within the liver; however, it must be recognized that there are significant numbers of other enzyme systems involved with each drug.

The lack of research in this area means that some of the interactions or effects are postulated on the basis of knowledge of enzyme substrates involved in metabolism of various drugs.

[23] Phencyclidine is commonly known as "PCP" or "angel dust", as the same acronym is also known as *Pneumocystis jirovecii* pneumonia and used in this and other protocols, in order to avoid confusion, phencyclidine is written out in this protocol.

Table 5. Interactions of illicit drugs and ARVs

Drug	Primary metabolism site	Interaction	Recommendation
Amphetamines	CYP2D6	RTV ↑ levels ⇒ toxicity.	Do not prescribe RTV or lopinavir/ritonavir even in low doses if patients report amphetamine use.
Barbiturates	CYP3A4	Barbiturates such as phenobarbital are potent inducers of CYP3A4.	Consider avoiding concurrent administration of other potent inducers (e.g. EFV and NVP) in patients misusing barbiturates.
Benzodiazepines	CYP3A4 involved with midazolam, triazolam, alprazolam & flunitrazepam	PIs ⇒ over-sedation. NVP ⇒ withdrawals.	Avoid concurrent use of alprazolam, midazolam and triazolam with all PIs and EFV.
Cocaine	CYP3A4	PIs and EFV ↑ levels ⇒ overdose. NVP⇒hepatotoxic metabolite.	Monitor for increased hepatotoxicity.
Codeine	UGT 2B7	PIs ↑ or ↓ metabolism ⇒ possible overdose ⇒ loss of analgesia.	Interactions with ARVs are similar to those described for methadone. Thus, NNRTIs and some PIs may result in opioid withdrawal and loss of analgesia. Should be monitored.
Heroin	Plasma	NFV, RTV ⇒ withdrawal.	No clinically significant interactions reported however interactions with ARVs are similar to those described for methadone. Thus, NNRTIs and some PIs may result in opioid withdrawal and loss of analgesia and clinicians should monitor.
MDMA (ecstasy) GHB (gamma-hydroxybutyrate)	CYP2D6	RTV ↑ levels ⇒ toxicity.	Do not prescribe PIs even in low doses if patients report MDMA or GHB use. MDMA–ritonavir interactions can be fatal.
Morphine	UGT 2B7	NFV, RTV ⇒ withdrawals, loss of analgesia.	Interactions with ARVs are similar to those described for methadone. Thus, NNRTIs and some PIs may result in opioid withdrawal and loss of analgesia. Clinicians should monitor.
Phencyclidine	CYP3A4	PIs, EFV ⇒ toxicity.	Monitor for phencyclidine toxicity.
THC	CYP3A4	PIs may ↑ concentration. NNRTIs may ↓ concentration.	No clinically significant interactions reported.

4.5. Adherence support and monitoring

Adherence support and monitoring should be part of the routine clinical care provided by all health professionals dealing with HIV-infected patients. Optimizing adherence in the first four to six months of treatment is crucial to ensure long-term immunovirological success *(110)*. Moderate deviations from high adherence (88–99%) during follow-up (the maintenance phase, after six months) have less severe impact. Several interventions for enhancing adherence are possible, but priority should be given to those aimed at the early months of HAART *(126–130)*.

When giving adherence counselling, health care providers have to make sure that every patient:
- has emotional and practical life support
- fits his/her drug regimen into a daily routine
- understands non-adherence leads to resistance and treatment failure
- recognizes that all doses must be taken
- feels comfortable taking drugs in front of others
- keeps clinical appointments
- understands the side-effects of ARVs and their interactions with OST and illicit drugs
- knows alarm signs and when to see a doctor about them *(51)*.

Other tactics for supporting adherence include:
- treating depression to enhance adherence *(61);*
- managing drug interactions and adjusting dosages;
- dispensing medication in small amounts[24] at frequent intervals to:
  - detect adherence problems before they lead to drug resistance;
  - limit treatment disruptions or misuse;
- directly observing ARV treatment, particularly when linked to drug dependence treatment.

4.6. Management of acute and chronic pain (including people on OST)

Pain management in opioid dependants is unnecessarily controversial. Clinicians are reluctant to prescribe adequate pain relief drugs because of:
- suspicion that patients are simply drug-seeking and are exaggerating the severity of their pain;
- misconceptions that methadone at its maintenance dosage is an adequate analgesic in itself for those IDUs stabilized on it;
- concern that prescribing a codeine-based drug will interfere with the drug testing carried out in methadone treatment clinics;
- complex interactions with ARVs, resulting in under-prescribing of analgesia; and
- inadequate access to appropriate analgesics in clinics.

Reluctance by clinicians can lead to the pain not being addressed adequately and patients sourcing their own drugs, perhaps illicitly.

4.6.1. Pain management in patients receiving methadone

Patients do not obtain adequate pain relief from their usual daily dose of methadone, to which they have become tolerant, from which several conclusions may be drawn.
- Additional analgesics should be prescribed to treat acute or chronic pain in HIV-infected IDUs who are on methadone maintenance treatment, starting with mild analgesia and progressing based on response.[25]
- Pethidine and piroxicam should not be administered with ritonavir or LPV/r.
- Alternative options (acupuncture, massage, etc.) for pain relief should be considered, particularly for chronic pain.

[24] Once-daily options, low pill burden and the use of fixed-dose combinations (FDCs) may be of benefit in the early stage of treatment. Please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

[25] Note that, as with methadone, NNRTIs and PIs will alter the metabolism of opioid based analgesics. Patients on long-term pain medication may require more of their opioid-based pain relief, just as they would require an increase of methadone.

- Careful monitoring of IDUs on ARVs and continuing pain medication is required, as dose adjustments or a change of timing may be necessary.
- Clinicians should treat IDUs on methadone for pain the same way they do non-methadone patients.[26]

4.6.2. Pain management in patients receiving buprenorphine

Further clinical studies are needed of patients treated for pain while on buprenorphine. Like methadone, buprenorphine has strong analgesic properties; however, the once-daily dosage for treatment of substance use is not sufficient to sustain pain relief. Therefore:

- Patients on buprenorphine needing pain relief should first be treated with a non-opioid analgesic when appropriate; a temporary increase in buprenorphine dosage may be sufficient.
- If acute pain is not relieved by non-opioid medications or an increase of buprenorphine, more aggressive pain management should be undertaken, including short-acting opioid pain relievers.
- When patients on buprenorphine require other opioid treatment for pain, the following should be borne in mind:
  - Morphine should not be prescribed.
  - Buprenorphine should be discontinued while other opioid pain medication is being taken.
  - Higher doses of short-acting opioid pain medication may be needed to achieve analgesia until the buprenorphine clears the body, when they should be decreased.
  - Buprenorphine should not be restarted until an appropriate period after the last dose of the opioid analgesic, given its half-life.
  - Non-combination opioid analgesics are preferable to avoid toxicity and other side-effects, and for easier dosage.
  - Patients with chronic pain who do not respond to increased buprenorphine and continually require additional analgesia may need to be transferred to methadone treatment *(131, 132).*

For further information on pain management, refer to Protocol 3, *Palliative care for people living with HIV*.

[26] For example, a woman on methadone who is in labour will require pain relief in exactly the same way as any other pregnant woman.

V. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected is important in the development of key indicators on access of IDUs to treatment and its success. Such indicators assist managers in decision making on ways to strengthen and expand these services to all those in need.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV patients ("seen for care" – this will be the denominator for the data below);
- number of IDUs among all HIV patients:
  - number of HIV-infected active IDUs (having injected in the past four weeks);
  - number of HIV-infected former IDUs (not having injected in past the four weeks);
- number of IDUs eligible for ART (CD4 <350 cells/mm^3):
  - number of active IDUs eligible for ART (having injected in the past 4 weeks);
  - number of former IDUs (not having injected in the past four weeks) eligible for ART;
- number of HIV-infected IDUs receiving HAART:
  - number of active IDUs receiving HAART;
  - number of former IDUs (not having injected in the past four weeks) receiving HAART;
- number of HIV-infected IDUs on OST:
  - number on methadone;
  - number on buprenorphine;
- number of IDUs on OST and HAART; and
- number of HIV-infected IDUs who have died including cause of death (e.g. HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

In addition, it may be useful to collect data on access of IDUs to other treatment (hepatitis C, hepatitis B and TB coinfections) for IDUs. Please refer to the following protocols for information on what data should be collected on these coinfections: Protocol 4 *Management of tuberculosis and HIV coinfection*, Protocol 6 *Management of hepatitis C and HIV coinfection*, and Protocol 7 *Management of hepatitis B and HIV coinfection*.

Annex 1. Addiction Severity Index (ASI), European version 6 (EuropASI6)[27]

A General Information - ***This is a standard interview that asks questions about several life areas – your health, employment, alcohol and drug use, etc. Some of the questions ask about the past 30 days or the past six months, while others are about your entire lifetime. All the information you give is confidential*** **(explain specifics)** ***and will be used to*** **(explain purpose).** ***Please answer the questions with your best estimates. If there are questions that you don't understand or prefer not to answer, please let me know. The interview will take about an hour to complete. Do you have any questions before we begin? First we'll start with some general background information.***

Patient Name: _____

A1. Patient ID: ☐☐☐☐

Interviewer Name:_____

A2. Interviewer ID: ☐☐☐

or

A3. Observer ID: ☐☐☐

A4. Date of Interview: ☐☐ / ☐☐ / ☐☐☐☐

A5. Date of Admission: ☐☐ / ☐☐ / ☐☐☐☐

A6. Time Frame of Interview: ☐
1 – Prior to Interview Date
2 – Prior to Admission Date
3 – Prior to Other Date: ☐☐ / ☐☐ / ☐☐☐☐

A7. Time Begun: ☐☐ : ☐☐

A8. Gender (1 – Male, 2 – Female): ☐

A9. Date of Birth: ☐☐ / ☐☐ / ☐☐☐☐
(Age:_____)

A10. Country of birth
a. Respondent ☐☐☐
b. Father ☐☐☐
c. Mother ☐☐☐

A11. Nationality ☐
1- National of this country 3-National of other country
2- EU national
Specify _____

A12. What is your current marital status? ☐
1 – Now married 4 – Divorced
2 – Living as married 5 – Separated 6 → A14
3 – Widowed 6 – Never Married

A13. How long have you been (A12 response)? ☐☐ Years ☐☐ Months

A14. How were you referred to treatment? ☐
-i.e. referred to this specific Tx program
1 – Self, family or friend
2 – Alcohol or drug use provider or agency
3 – Other healthcare provider or agency
4 – School
5 – Work or employee assistance program
6 – Community agency (unemployment office, shelter, church, etc.)
7 – Court or legal system

B Housing – ***The following questions ask whether you have lived in any kind of restricted or supervised setting during the past 6 months since _____ and the past 30 days since_____.***

[**NOTE:** 6 months = 180 days, inform client if necessary.]

B1. In the past **6 months**, about how many nights have you stayed in a hospital, inpatient alcohol, drug, or psychiatric unit, jail or prison, recovery or half-way house, or group home?

A. Past 6 months ☐☐☐ (000 → B8) **B.** 30 Days ☐☐

Of those nights, how many were in a(n):

	A. ☐☐☐	**B.** ☐☐
B2. inpatient unit for drug or alcohol treatment?		
B3. medical hospital?		
B4. psychiatric hospital?		
B5. jail or prison?		
B6. recovery / half-way house, or group home?		
B7. other kind of restricted or supervised living situation? What type of place? _____		

B8. How many nights have you spent in a homeless shelter? **A.** Past 6 months ☐☐☐ (000 → B9) **B.** 30 Days ☐☐

B9. How many nights have you lived on the street, or in places such as abandoned buildings, cars, or parks because you had nowhere else to stay? **A.** Past 6 months ☐☐☐ (000 → NOTE) **B.** 30 Days ☐☐

[**NOTE**: If B8A or B9A > 0 (i.e. if any time in a shelter or on the street in the past 6 months), skip to next NOTE.]

B10. Have you ever stayed in a homeless shelter or lived on the street (in places such as abandoned buildings, cars, or parks) because you had nowhere else to stay? ☐ 1-Yes, 0-No

[**NOTE**: If B1B + B8B = 30 (i.e. if all of the past 30 days were in a restricted living arrangement or shelter), skip to Medical.]

B11. In the past 30 days (when you were NOT in a restricted / supervised living situation or shelter), who have you lived with (. . . anyone else)? [Check all that apply]
___1. Alone
___2. Spouse/Partner
___3. Child(ren) < age 18
___4. Parents
___5. Other adult relatives
___6. Other adult non-relatives
___7. Not Answered

B12. In the past 30 days (when you were NOT in a restricted / supervised living situation or shelter), have you lived with anyone who has a current alcohol problem or uses drugs? ☐ 1-Yes, 0-No

[27] ***Source:*** adapted from Alterman AI et al. *(133)*. A manual will be available on the WHO website, http://www.euro.who.int/aids

C Medical - ***The following questions are about your physical health.***

C1. What kinds of health insurance do you have?
[Check all that apply]
___1. None
___2. Private insurance, private health plan
___3. Military health care
___4. Public health insurance (generally for senior citizens)
___5. Public health insurance (generally for the needy)
___6. Other (specify:_____)
___7. Not answered

[**NOTE:** If male, skip C2.]

C2. Are you currently pregnant? ☐
1-Yes, 0-No
2-Not Sure

Have you ever been told by a doctor or healthcare provider that you had any of the following physical or medical conditions?

	1-Yes, 0-No
C3. High Blood Pressure	☐
C4. Diabetes	☐
C5. Heart Disease	☐
C6. Stroke	☐
C7. Epilepsy or seizures	☐
C8. Cancer	☐
C9. HIV/AIDS	☐
C10. Tuberculosis or a positive test for TB (e.g. +PPD)	☐
C11. Hepatitis	☐
C12. Cirrhosis or other chronic liver disease	☐
C13. Chronic kidney disease	☐
C14. Chronic respiratory or breathing problem e.g. asthma, emphysema, COPD	☐
C15. Other chronic physical or medical conditions e.g. arthritis, chronic back pain, digestive probs (colitis, etc.) -if "Yes," specify:_____	☐
C16. Any type of physical disability that seriously impairs your vision, hearing, or movements? -if "Yes," specify:_____	☐

[**NOTE**: If C3 - C16 are all 0-No, Skip C17.]

C17. Have you ever been prescribed medication for any of these conditions? ☐
0 – No
1 – Yes, and still taking all necessary medications as prescribed
2 – Yes, and should be taking medications but am not
3 – Yes, but was told (by a Dr.) medication was no longer necessary

C18. Do you receive any kind of pension (or check) for a physical condition or disability? ☐
-Exclude psychiatric disability 1-Yes, 0-No

C19. In the past 30 days, would you say your physical health has been? ☐
0 - Excellent
1 - Very Good
2 - Good
3 - Fair
4 - Poor

(C20 – C23) ***In the past 30 days:***

[**NOTE**: Do NOT include problems that are completely due to being high, intoxicated, or in withdrawal from alcohol or drugs.]

C20. How many days have you had any physical or medical symptoms or problems? ☐☐ Days
e.g. illness, injury, pain, discomfort, disability
-include dental problems

C21. How many days have you been unable to carry out normal activities because of physical or medical symptoms or problems? ☐☐ Days

[**NOTE**: Introduce the Client Rating Scale.]

C22. How much have you experienced physical pain or discomfort? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

C23. How worried or concerned have you been about your physical health or any medical problems? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

C24. How important to you now is (ongoing or additional) treatment for any current physical or medical problems or conditions?
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

C25. How many times in your life have you been hospitalized (at least overnight) for physical or medical problems? ☐☐ Times
-Do not include alcohol/drug treatment, psychiatric hospitalizations, or non-complicated childbirth

	A. Past 6 months	**B.** 30 Days
C26. How many times have you used emergency room services for any type of problem?	☐☐☐ 000 → C27	☐☐
C27. How many days have you taken prescribed medication for a physical illness or condition? -Do not include medications for alcohol/drug/psych problems.	**A.** ☐☐☐ 000 → C28	**B.** ☐☐
C28. How many outpatient visits have you had with a doctor or healthcare provider? e.g. physical examination of any kind, or any other monitoring/care for a medical problem or condition. -Do not include alcohol/drug, or psych treatment.	**A.** ☐☐☐ 000 → **E/S**	**B.** ☐☐

D Employment/Support – ***The following questions are about your education, employment, and finances.***

D1. What is the highest educational degree that you received? ☐
1 – GED
2 – High School Diploma
3 – Associate's Degree
4 – Bachelor's Degree
5 – Master's Degree (or higher)
6 – None

D2. Do you have any other degrees, licenses, or certificates from a formal training program? ☐ 1-Yes, 0-No
(Specify)_____

D3. What is the last grade or year (Years) that you completed in school? ☐☐
(Specify)_____

D4. Have you ever served in the military? ☐ 1-Yes, 0-No

D5. Are you currently in a vocational training, or educational program? ☐
e.g. GED classes, skills training, college, etc.
0 - No, 1 - Part-time, 2 - Full-time

D6. Do you have a current and valid driver's license? ☐ 1-Yes, 0-No

D7. Do you own or have a car? ☐ 1-Yes, 0-No

D8. At this time, is it difficult to attend treatment, get to work/school, or find work because of transportation? ☐ 1-Yes, 0-No

[**NOTE:** Code D9. Ask question only if unable to code based on previous information.]

D9. Do you read/write (English) well enough to fill out a job application? ☐ 1-Yes, 0-No

---

D10. What is your current employment situation? [Check one]
___1. Full-time (35+ hrs/wk), → D12
___2. Part-time (< 35 hrs/wk), → D12
___3. Unemployed and actively looking for work (or on temporary lay-off), → D14
___4. Not in the labor force
-not working and not actively looking for work

D11. [If not in the labor force] What best describes your current situation?
[Check one, → D14]
___1. Homemaker
___2. Student
___3. Disabled
___4. Retired
___5. Not looking for work
___6. In an institution
___7. Other _____

D12. What kind of work do you do (primary job)? ☐☐
(Specify)_____

[**NOTE:** Code one category in D12 boxes.]
1 – Unskilled labour
2 – Skilled labour
3 – Low/level employees
4 – Small entreprenours
5 – Mid-level employees
6 – Professionals
7 – Other

D13. Is this job under the table ("off the books") work? ☐ 1-Yes, 0-No

D14. How long was your longest full-time job? ☐☐☐ Months
- With one employer/continuously self-employed
000 → D17

D15. How long ago did it end? ☐☐☐ Months
[**NOTE:** Enter 000 only if current FT job is longest.]

D16. What was your job/occupation then? ☐☐
(Specify)_____

[**NOTE:** Code one category from D12 NOTE.]

D17. In the past 6 months (since _____), how many weeks have you worked for pay? ☐☐ Weeks, Max = 26
-Include paid time off, sick days, vacation time, days self-employed, and under the table work
00 → D22

D18. In the past 6 months, how much money was your pay before taxes? € ☐☐☐☐☐

(D19 – D22) In the past 30 days:

D19. How many days have you worked for pay? ☐☐ Days
-Include paid time off, sick days, vacation time, days self-employed, and under the table work
00 → D22

D20. How much money was your pay before taxes?
€ ☐☐☐☐☐

D21. How many days have you had any work-related problems? ☐☐ Days
-e.g. Poor performance, arguments, being disciplined, missing time, etc.

D22. Have you applied for any jobs? ☐ 1-Yes, 0-No
e.g. submitted a resume, completed a job application, talked with a potential employer

---

D23. How important to you now is any kind of assistance (such as counseling, training, or education) to help you prepare for or find a job, or deal with work-related problems? ☐
--ongoing or additional assistance
0 - Not At all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

☐☐

The next series of questions* (D24 – D32) *ask about your sources of financial support and income.

D24.Do you live in government-subsidized housing or receive housing assistance? ☐ 1-Yes, 0-N

In the past 30 days, how much money have you received from:

D25.pension, social security, worker's or unemployment compensation? €☐☐☐☐☐

D25b. …*past 6 months?* €☐☐☐☐☐

D26.public assistance? €☐☐☐☐☐
e.g. welfare or TANF

D26b. …*past 6 months?* €☐☐☐☐☐

D27.other government assistance? €☐☐☐☐☐
e.g. food stamps, $ for heating/energy bills

D27b. …*past 6 months?* €☐☐☐☐☐

D28.child support or alimony payments? €☐☐☐☐☐
-from the child's parent, or an ex-spouse

D28b. …*past 6 months?* €☐☐☐☐☐

D29.illegal activities?
e.g. dealing/running drugs, prostitution, illegal gambling, selling stolen goods €☐☐☐☐☐

D29b. …*past 6 months?* €☐☐☐☐☐

D30.any other sources? €☐☐☐☐☐
e.g. borrowed/received $ from family or others, windfall income (inheritance, taxes, lottery, etc.)

D30b. …*past 6 months?* €☐☐☐☐☐

D31.What are your current sources of financial support for housing, food, and other living expenses?
[Check all that apply.]

___1. Employment
___2. Retirement
-e.g. pension, social security (SSI)
___3. Disability
-e.g. pension, social security (SSDI), worker's comp
___4. Unemployment compensation
___5. Government or public assistance
-e.g. welfare, TANF, food stamps, subsidized housing
___6. Child support or alimony
___7. Family, friends, or associates
___8. Illegal income
___9. Institution or supervised living situation
-e.g. hospital, rehab, half-way house, shelter, etc.
___10. Other, e.g. savings, etc:
Specify:_____
___11. None

D32.Have you ever legally declared bankruptcy? ☐ 1-Yes, 0-No

D33.Have you ever defaulted on a government loan? ☐ 1-Yes, 0-No
e.g. a federal education loan

D34.Are you more than a month behind in your payments for anything? ☐ 1-Yes, 0-No
e.g. housing, utilities, credit cards, child support, other loans/debt (medical bills, court costs, personal loans)

D35.How many people (not including yourself) currently depend on you for regular financial support? ☐☐
e.g. for housing, food, spending money, child support
-Include people the client supports as well as those he/she is obligated to support

D36.Do you have enough income to pay for necessities such as housing, food and clothing for yourself and your dependents? ☐ 1-Yes, 0-No
-Exclude money from illegal activity

E Drug / Alcohol - ***The following questions are about your alcohol and drug use, and any substance abuse treatment you may have received.***

Treatment History

E1. How many different times have you been treated for your alcohol or drug use? [ ][ ]
-Include in-person evaluations even if not followed by additional treatment. 00 → E6

E2. How many of these treatments were for Detox only? [ ][ ]
-Detox not followed by any additional treatment

E3. How old were you the first time you entered alcohol or drug abuse treatment? [ ][ ]

How many days have you:

	A. Past 6 months	**B.** 30 Days
E4. attended an outpatient program or office visits (for alcohol or drug treatment)?	[ ][ ][ ] 000 → E5	[ ][ ]
E5. taken medication prescribed to treat your alcohol or drug use? e.g. methadone, naltrexone, Revia, detox meds, etc. -Exclude Rx for nicotine dependence	[ ][ ][ ] 000 →E6	[ ][ ]
E6. attended self-help meetings like AA, NA, or CA?	[ ][ ][ ] 000 → E7	[ ][ ]

E7. What is the longest continuous period of time that you attended self help meetings at least 2 days a week?
[ ][ ] Years [ ][ ] Months

Alcohol Use

E8. How many years in your life have you drank alcohol on a regular basis, 3+ days per week? [ ][ ]
- Exclude clean time 00 → E10

E9. How many years in your life have you drank at least (5-men, 4-women) drinks per day on a regular basis, 3+ days per week? [ ][ ] >0 → E11

E10. Have you drank at least (5-men, 4-women) drinks in a day 50 or more days in your life? [ ] 1-Yes, 0-No

E11. How old were you when you first drank and felt the effects of alcohol? [if never, code 99] [ ][ ]

E12. In the past 6 months, during the month when you were drinking the most, how often were you drinking? [ ]
0 - No Use (→ E20)
1 - 1-3 times per month
2 - 1-2 times per week
3 - 3-6 times per week
4 - Daily

E13. In the past 30 days, how many days did you drink any alcohol? [ ][ ] 00 → E20

E14. When was your last drink? [ ][ ]
[00 if today, 01 if yesterday, 02 if 2 days ago, etc.]

E15. In the past 30 days, how many days did you have at least (5-men, 4-women) drinks in a day? [ ][ ]

E16. In the past 30 days, how much money have you spent on alcohol for yourself? € [ ][ ][ ][ ]

Alcohol Symptoms

In the past 30 days:

E17. Have you had any withdrawal sickness shortly after you cut down or quit drinking? [ ] 1-Yes, 0-No

E18. Have you had any trouble controlling, cutting back, or quitting drinking; or spent much of the day drinking? [ ] 1-Yes, 0-No

E19. Because of your drinking - have you had any medical or psychological problems; or messed up at work (school) or home, or got in arguments; or had trouble with the law? [ ] 1-Yes, 0-No

E20. Have you been bothered by cravings or urges to drink? [ ] 1-Yes, 0-No

E21. How many days did you have these or any other difficulties due to alcohol use? [ ][ ] 00 → E23

E22. In the past 30 days, how troubled or bothered have you been by these alcohol problems? [ ]
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

E23. How important to you now is (ongoing or additional) treatment for your alcohol use? [ ]
0 - Not at all
1 - Slightly
2 – Moderately
3 - Considerably
4 - Extremely

E24. How important to you is it to achieve/maintain total abstinence from alcohol (i.e., not drink at all)? [ ]
0 - Not at all
1 - Slightly
2 – Moderately
3 – Considerably
4 - Extremely

Drug Use Grid – Individual Substances

NOTE: Hand the client the Drug List, and then say: ***I'll be asking you about each group of drugs listed. We've already talked about alcohol. Let's start with Marijuana:***

Pre-A. Have you ever tried or taken any _____(even if it was only once or was prescribed)?
A. How old were you when you first tried _____?
B. How many years in your life have you used _____ 3 or more days per week? -Exclude clean time
C. Have you used _____ on 50 or more days in your life?
D. In the past 30 days, how many days did you use any _____?
E. In the past 30 days, did you use _____ ([0]-only as prescribed [Rx], or [1]-illegally or more than as prescribed [not as Rx])?

NOTE: If the client reports:
1. Never trying a specific drug (e.g. E25-A), **code "99" and skip to the next substance (E26-A)**.
2. Using 3 or more days per week for a year or more (e.g. E25-B), **skip the following item (E25-C), and continue**.
3. No usage in the past 30 days (e.g. E25-D = 00), **skip to the next substance (E26-A)**.

	A. Age of 1st Use? **[99 → next A]**	**B.** Yrs Regular Use (Lifetime)? **[>00 → D]**	**C.** Used 50+ Days (Lifetime)? **[1-Yes, 0-No]**	**D.** Past 30 Days Use? **[00 → next A]**	**E.** Used As Rx (Past 30 Days)? **[0-as Rx, 1-Not as Rx]**
E25. Marijuana	☐☐	☐☐	☐	☐☐	☐
E26. Sedatives	☐☐	☐☐	☐	☐☐	☐
E27. Cocaine	☐☐	☐☐	☐	☐☐	■
E28. Stimulants	☐☐	☐☐	☐	☐☐	☐
E29. Hallucinogens	☐☐	☐☐	☐	☐☐	■
E30. Heroin	☐☐	☐☐	☐	☐☐	■
E31. Methadone	☐☐	☐☐	☐	☐☐	☐
E32. Other Opiates	☐☐	☐☐	☐	☐☐	☐
E33. Inhalants	☐☐	☐☐	☐	☐☐	☐

Substance use – Problem Categories

01 – Alcohol	07 – Heroin
02 – Marijuana	08 – Methadone
03 – Sedatives	09 – Other Opiates
04 – Cocaine / Crack	10 – Inhalants
05 – Stimulants	11 – Other Substances
06 – Hallucinogens	12 – None

		Route(s) of Administration *In what ways have you used _____?*	
Primary Problem	**A.** Category	**B.** Lifetime [check all that apply]	**C.** Past 30 Days [check all that apply]
E34. Which substance listed (01-12) is causing you the **most** difficulty and may have led to your entering treatment?	☐☐ 12 → E37	__1. Swallowed __4. Injected __2. Snorted __5. Other __3. Smoked	__1. Swallowed __4. Injected __2. Snorted __5. Other __3. Smoked __6. No use
Indicate specific substance within the coded category:			
Secondary Problem	**A.** Category	**B.** Lifetime [check all that apply]	**C.** Past 30 Days [check all that apply]
E35. Which substance listed (01-12) is causing you the **2nd most** difficulty and may have led to your entering treatment?	☐☐ 12 → E37	__1. Swallowed __4. Injected __2. Snorted __5. Other __3. Smoked	__1. Swallowed __4. Injected __2. Snorted __5. Other __3. Smoked __6. No use
Indicate specific substance within the coded category:			
Tertiary Problem	**A.** Category	**B.** Lifetime [check all that apply]	**C.** Past 30 Days [check all that apply]
E36. Which substance listed (01-12) is causing you the **3rd most** difficulty and may have led to your entering treatment?	☐☐ 12 → E37	__1. Swallowed __4. Injected __2. Snorted __5. Other __3. Smoked	__1. Swallowed __4. Injected __2. Snorted __5. Other __3. Smoked __6. No use
Indicate specific substance within the coded category:			

[**NOTE**: 4. Injected = IV and non-IV injection; e.g. intramuscular, skin-popping, etc.]

Drug Use – Overall

E37. How many years in your life have you used any illegal or street drugs (excluding alcohol), or abused any prescription medication at least 3 or more days per week? ☐☐

E38. In the past 6 months, during the month when you were using illegal or street drugs (and/or abusing prescribed medications) the most, how often were you using any drugs? ☐
0 - No Use (→ E45)
1 - 1-3 times per month
2 - 1-2 times per week
3 - 3-6 times per week
4 - Daily

E39. In the past 30 days, on how many days did you use any drugs or abuse prescribed medications? ☐☐ 0 → E45

E40. When did you last use any drugs, or abuse any prescribed medications? ☐☐
-00 if today, 01 if yesterday, 02 if 2 days ago, etc.

E41. In the past 30 days, how much money did you spend on drugs? $☐☐☐☐
-Exclude money for medications that are part of drug treatment (e.g. methadone, detox meds, etc.)

Drug Symptoms

In the past 30 days:

E42. Have you had any withdrawal sickness shortly after you cut down or quit any drug? ☐ 1-Yes, 0-No

E43. Have you had any trouble controlling, cutting back, or quitting drugs; or spent much of the day using, being high, coming down from, or just trying to get drugs? ☐ 1-Yes, 0-No

E44. Because of your drug use - have you had any medical or psychological problems; or messed up at work (school) or home, got in arguments; or trouble with the law? ☐ 1-Yes, 0-No

E45. Have you been bothered by cravings or urges to use? ☐ 1-Yes, 0-No

E46. How many days did you have these or any other difficulties due to drug use? ☐☐ 00 → E48

E47. In the past 30 days, how troubled or bothered have you been by these drug problems? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

E48. How important to you now is (ongoing or additional) treatment for your drug use? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

E49. How important to you is it to achieve/maintain total abstinence from drugs (i.e., not drink at all)? ☐
0 - Not at all
1 - Slightly
2 – Moderately
3 – Considerably
4 - Extremely

E50. Since you started using, have you ever been completely abstinent (clean) from **drugs and alcohol** for at least 1 year? ☐ 1-Yes, 0-No 0 → E52
-Exclude prescribed and appropriately taken medications (i.e. methadone, psych meds)

E51. How long ago did this clean period end? ☐☐ Years ☐☐ Months
[If currently abstinent 1 year or more, code 00 00. Code most recent clean period of at least 1 year.]

Health Risks

[**NOTE**: If not already known, ask E52. Otherwise, fill in based on previous information.]

E52. Have you ever injected any drug? ☐ 1-Yes, 0-No 00 → E54
[Injected = IV and non-IV injection]

E53. When was the last time you shared syringes or injection equipment? ☐☐ Years ☐☐ Months Ago
-If never, code NN NN
-If within the past month, code 00 00

E54. In the past 6 months, with how many different people have you had sex, either oral, anal, or vaginal? ☐☐

E55. When was the last time you were tested for HIV/AIDS? ☐☐ Years ☐☐ Months Ago
-If never, code NN NN
-If within the past month, code 00 00

Tobacco – Cigarettes, etc.

E56. How old were you when you first smoked cigarettes or used tobacco in other forms? ☐☐ 99 → E59
e.g. chewed tobacco, cigars, pipes
-If never tried, code 99

E57. How many years in your life have you smoked cigarettes (or used tobacco in other forms) on a daily basis? ☐☐

E58. In the past 30 days, how many days did you smoke cigarettes (or use tobacco in other forms)? ☐☐

Gambling

E59. In your life, have you ever experienced any financial stress because of gambling? ☐ 1-Yes, 0-No

E60. In the past 30 days, how many days did you participate in any form of gambling, like the lottery, races/OTB, or casinos, or illegal gambling of any sort? ☐☐

F Legal – *The following questions are about your involvement with the criminal justice system and/or illegal activities.*

F1. In your entire life, have you ever been in jail or lock-up (even for a few hours)? ☐ 1-Yes, 0-No

F2. In your entire life, have you ever been arrested? ☐ 1-Yes, 0-No
0 → F18

F3. How old were you the first time? ☐☐
>17 → (F7-14)

F4. Before the age of 18, were you ever arrested for? [Check all that apply]
___1. Violent crimes or crimes against people
e.g. robbery, assault, rape
___2. Drug offenses
e.g. possession, dealing, manufacturing
___3. Crimes for profit or property crimes
e.g. shoplifting, burglary, auto theft, vandalism, arson
___4. Offenses that apply only to juveniles
e.g. running away, underage drinking, curfew violations, truancy
___5. Other offenses (Specify:_____)

F5. How many times were you convicted of a crime committed before the age of 18? ☐☐ Times

F6. Before the age of 18, how much total time had you spent in lock-up, a detention center, jail/prison, or a reform school? ☐☐ Months

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(F7 – F14) *Since the age of 18:*

Pre-A. Have you been arrested for _____?
[**NOTE:** If No, code 00 for **A.** and skip to next item]
A. How many times total?
B. How many times were in the **past 6 months**?

	A. Total	**B.** 6 months
F7. Possession of drugs? -or drug equipment (paraphernalia)	☐☐	☐☐
F8. Selling or manufacturing drugs? -selling includes dealing / distributing	☐☐	☐☐
F9. Robbery? -stealing with force, or threat of force	☐☐	☐☐
F10. Other crimes for profit? -shoplifting, theft, -fraud, selling stolen goods, vandalism, arson	☐☐	☐☐
F11. Violent crime? -assault, domestic violence, rape, murder	☐☐	☐☐
F12. Weapons, prostitution*, or gambling? -*include pimping, $ for sex, porn offenses	☐☐	☐☐
F13. Driving under the influence (DUI)? -of either alcohol or drugs	☐☐	☐☐
F14. Any other criminal offenses? -probation/parole violations, disorderly conduct, trespassing, violating a restraining order, neglect or desertion, non-support, etc.	☐☐	☐☐

F15. How long ago was the last time you were arrested for anything? [Code 00 if within the past month (30 days)] ☐☐ Years ☐☐ Months

F16. How many times have you been convicted of a crime committed since the age of 18? -e.g. probation, jail time, fines ☐☐ Times

F17. Since age 18, how much total time have you spent in jail or prison? ☐☐ Years ☐☐ Months

F18. Was your admission to treatment ordered by the legal system? -e.g. a judge required it ☐ 1-Yes, 0-No

Are you currently involved with the criminal justice system in any of the following ways? 1-Yes, 0-No

F19. On Probation? ☐
F20. On Parole? ☐
F21. Awaiting trial or charges? ☐
F22. Awaiting sentencing? ☐
F23. Involved in a drug court program or diversion program? ☐
F24. Other? -e.g. outstanding bench warrant, under restraining order, house arrest, electronic monitoring, pre-trial supervision ☐

F25. How serious do you feel your present problems are with the criminal justice system? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

(F26 – F30) *In the past 6 months:*

Pre-A. Have you _____?
[**NOTE:** If No, code 000 for **A.** and skip to next item]
A. # of days, past 6 months
B. # of days, past 30 days

	A. Past 6 Months	**B.** 30 Days
F26. sold or manufactured drugs? -dealt or distributed to make money, get sex, or profit in any other way	☐☐☐	☐☐
F27. robbed anyone?	☐☐☐	☐☐
F28. stolen anything, sold stolen goods, forged prescriptions or checks, destroyed property, or set fires (arson)?	☐☐☐	☐☐
F28c. …shoplifting	☐☐☐	
F28d. …burglary/B&E	☐☐☐	
F28e. …motor vehicle theft	☐☐☐	
F28f. …forgery	☐☐☐	
F28g. …fraud	☐☐☐	
F28h. …vandalism	☐☐☐	
F28i. …arson	☐☐☐	
F28j. …other theft/property offense	☐☐☐	
F29. threatened or assaulted anyone? -with or without a weapon; include domestic violence, rape, and murder -exclude robbery	☐☐☐	☐☐
F29c. … threaten without physical assault	☐☐☐	
F29d. …assault with a weapon	☐☐☐	
F29e. … assault without a weapon	☐☐☐	
F29f. … sexual assault	☐☐☐	
F29g. … murder	☐☐☐	
F29h. … other	☐☐☐	

F30. done anything else illegal? ☐☐☐ ☐☐
-carried unlicensed weapon, been involved with prostitution/pimping or illegal gambling, etc. [exclude personal drug use or possession, DUI]

F30c. …carry an unlicensed weapon ☐☐☐

F30d. …prostitution/pimping ☐☐☐

F30e. …illegal gambling ☐☐☐

F31. Overall in the past 30 days, how many days have you done any of the above activities / things? ☐☐

F32. How many days total have you driven under the influence of drugs or alcohol? **A.** Past 6 Months ☐☐☐ **B.** 30 Days ☐☐

G Family/Social: ***The following questions are about your family and social relationships.***

G1. Have you been in a relationship with a romantic or sexual partner during the past month? ☐ 1-Yes, 0-No
[**NOTE:** If No, skip G3A-G9A.]

G2. How many close friends do you have? ☐☐
-Exclude sexual partner/spouse, and any other adult family relatives
[**NOTE:** If 00, skip G3C-G9C.]

NOTE: For G3 – G9:
A. Refers to a wife/husband or partner
B. Refers to any other adult family members or relatives
e.g. parents, grandparents, siblings, grown children, aunts/uncles, cousins
C. Refers to any close friends

In the past 30 days, have you:

(1 – Yes, 0 – No)	A. Partner(s)	B. Adult Relatives	C. Close Friends
G3. spent time (in person) with (your / any):	☐	☐	☐
G4. had any contact such as phone calls, letters, or e-mail with (other): -If G3+G4 = 0, Skip to G9	☐	☐	☐
G5. talked to (A/B/C) about feelings or problems?	☐	☐	☐
G6. had trouble getting along with:	☐	☐	☐
G7. had any arguments with:	☐	☐	☐
G8. Do/does your (A/B/C) have a current problem with alcohol or use drugs? -Include only those people you have spent time or been in contact with in the past 30 days	☐	☐	☐
G9. If you need help, can you count on:	☐	☐	☐

G10. Do you currently have a restraining order against someone? ☐ 1-Yes, 0-No

G11. In the past 30 days, did any interactions with your partner, adult relatives or close friends result in pushing/hitting, or throwing things? ☐ 1-Yes, 0-No

G12. Aside from your partner, other adult relatives and close friends; are there any other people you keep in touch with that you can count on if you really need help? ☐ 1-Yes, 0-No
-e.g., minister, doctor, sponsor, counselor, lawyer

G13. Overall in the past 30 days, how satisfied have you been with your adult relationships? ☐
e.g. # of relationships, amount of contact, how well you communicate, get along, help each other out, etc.
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

G14. In the past 30 days, how troubled or bothered have you been by any problems with your adult relationships? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

G15. How important to you now is (ongoing or additional) treatment or counseling for any problems regarding adult relationships? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

G16. Do you find it hard to talk about your feelings or problems even with people you are close to? ☐ 1-Yes, 0-No

G17. Do you feel nervous or uncomfortable when you are with other people? ☐ 1-Yes, 0-No

G18. Is it important to you to have close relationships with anyone? ☐ 1-Yes, 0-No

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In the past 30 days (G19-G22):

G19. Have you attended religious services or activities sponsored by your house of worship? ☐ 1-Yes, 0-No
-Exclude self-help/AA meetings

G20. Have you done any volunteer work? ☐ 1-Yes, 0-No

G21. Have you often been bored or had difficulty just trying to pass the time? ☐ 1-Yes, 0-No

G22. How satisfied have you been with how you spent your free time? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

The following questions are about any abuse or trauma you may have suffered throughout your life.

G23. Have you ever been physically assulted/abused by someone you knew? ☐ 0 → G26
-Exclude sex abuse & code in G26

G24. How old were you when this first happened? ☐☐

G25. When did this last happen? ☐☐ Years Ago ☐☐ Months Ago
-If within past 30 days, code '00 00'

G26. Have you ever been sexually assaulted/abused by someone you knew? ☐ 0 → G29

G27. How old were you when this first happened? ☐☐

G28. When did this last happen? ☐☐ Years Ago ☐☐ Months Ago
-If within past 30 days, code '00 00'

G29. Have you ever been the victim of a violent crime like being mugged, assaulted? ☐ 0 → G32
-Exclude abuse as noted above, and combat experience

G30. How old were you when this first happened? ☐☐

G31. When did this last happen? ☐☐ Years Ago ☐☐ Months Ago
-If within past 30 days, code '00 00'

G32. Have you ever been in any other life-threatening situation? ☐ 0 → G35
-e.g. major disaster, serious accident/fire, military combat
-Exclude abuse, violent crimes as noted above

G33. How old were you when this first happened? ☐☐

G34. When did this last happen? ☐☐ Years Ago ☐☐ Months Ago
-If within past 30 days, code '00 00'

G35. Have you ever been in a situation where you saw someone being killed, mugged/assaulted, or badly injured? ☐ 0 → NOTE
-Exclude major disasters, serious accident/fire, and military combat as noted above

G36. How old were you when this first happened? ☐☐

G37. When did this last happen? ☐☐ Years Ago ☐☐ Months Ago
-If within past 30 days, code '00 00'

[**NOTE:** If no history of abuse or trauma (i.e., G23, G26, G29, G32, and G35 are all 0-No), skip to G40.]

G38. In the past 30 days, how troubled or bothered have you been by any feelings, thoughts, or other reactions related to these events? ☐
-Include nightmares/dreams, "flashbacks," etc.
0 - Not at all 3 - Considerably
1 - Slightly 4 - Extremely
2 - Moderately

G39. How important to you now is (ongoing or additional) treatment or counseling for any feelings, thoughts or other reactions related to these events? ☐
0 - Not at all 3 - Considerably
1 - Slightly 4 - Extremely
2 – Moderately

The following questions ask about your children or any other children living with you.

G40. How many children have you fathered / given birth to, or adopted? ☐☐ 00 → G45

G41. What are the ages of your living children, beginning with the oldest?

Child 1 ☐☐ Child 6 ☐☐
Child 2 ☐☐ Child 7 ☐☐
Child 3 ☐☐ Child 8 ☐☐
Child 4 ☐☐ Child 9 ☐☐
Child 5 ☐☐ Child 10 ☐☐

[**NOTE:** If all children are 18 or older, → G45]

G42. Is there an open custody case with the mother, father, or any other relative? ☐ 1-Yes, 0-No

G43. How many of your children are currently in court-ordered foster care? ☐☐ Children
-also include court-ordered foster care w/ relatives

G44. In the past 30 days, how many of your children (under the age of 18) have lived with you at least some of the time? ☐☐ Children

G45. In the past 30 days, have any other children (step/grandchildren, nieces, nephews, etc.) under age 18 lived with you at least some of the time? ☐ 1-Yes, 0-No
-Code children staying overnight with regularity, or who have stayed for extended periods

[**NOTE:** If G44 & G45 are 0, i.e. no children past 30 days, skip to G51]

G46. How many of the children (who have lived with you) have a serious medical, behavioral or learning problem requiring skilled care, treatment or services? ☐☐ Children

G47. At this time, how necessary are additional services to treat their problems? ☐
0 - Not at all 3 - Considerably
1 - Slightly 4 - Extremely
2 – Moderately

G48. In the past 30 days, how much trouble have you had getting along with those children (< 18) who have lived with you for at least some time? ☐
0 - Not at all 3 - Considerably
1 - Slightly 4 - Extremely
2 – Moderately

G49. How important to you now is counseling (e.g. parenting classes) to help you get along with those children (< 18) who have lived with you? ☐
- ongoing or addition to counseling
0 - Not at all 3 - Considerably
1 - Slightly 4 - Extremely
2 – Moderately

G50. At this time, do you need additional childcare services to attend treatment, go to work/school, or to find work? ☐ 1-Yes, 0-No

G51. Have you ever been investigated or under supervision by child protective services (CPS)? ☐ 1-Yes, 0-No 0 → Psych

G52. Have you ever had a child removed from the home by CPS? ☐ 1-Yes, 0-No

G53. Have you ever had parental rights terminated? ☐ 1-Yes, 0-No
-Permanently had your rights to be a parent ended by a court hearing

G54. Are you currently involved in a protective custody case or being investigated or supervised by child protective services? ☐ 1-Yes, 0-No

H Psychiatric: ***The following questions are about any treatment or evaluations you may have received for emotional or psychological problems.***

H1. In your life, how many times have you been inpatient for emotional/psychological problems? ☐☐ Times
e.g. in a hospital or residential unit

H2. In your life, have you ever been prescribed medication to treat emotional/psychological problems? ☐ 1-Yes, 0-No
0 → H4

H3. How many days have you taken medication to treat emotional or psychological problems? **A.** Past 6 months ☐☐☐ **B.** 30 Days ☐☐
000 → H4

H4. In your life, how many outpatient sessions have you had for emotional/psychological problems? ☐ 0 → NOTE
-Include in-person evaluations even if not followed through by additional treatment
-Also include OP units = primary/family Dr. for psych problems, and medication monitoring for psych problems
0 - None
1 - 1-5 sessions
2 - 6-25 sessions
3 - 26-50 sessions
4 - more than 50 sessions

H5. How many outpatient sessions have you had? **A.** Past 6 months ☐☐☐ **B.** 30 Days ☐☐
000 → NOTE

[**NOTE:** If H1, H2, H4 are all 0-No, i.e. no history of psych treatment, skip to H7]

H6. How old were you the first time you ever had treatment or an evaluation for emotional or psychological problems? ☐☐ Age

H7. Do you currently receive a pension (or check) for a psychological disability? ☐ 1-Yes, 0-No

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The following questions are about different ways you may have felt or acted. Some questions ask whether you ever felt or behaved in a certain way at any time in your life, and others focus on just the past 30 days.

Coding for A/B:
0 – No
1 – Yes
2 – Yes, but only when high or in withdrawal.

[NOTE: If client acknowleges a symptom, i.e., "Yes" ask: "Was this ONLY when high or in withdrawl?" and code 1 or 2 as appropriate.]

(H8 - H17):
A. ***In your lifetime***
B. ***During any of the past 30 days***
C. ***How many days ago did you last _____?***

Have you (ever):	A. Lifetime	B. 30 Days	C. Days Ago
H8. had trouble falling asleep, staying asleep*, or waking up too early? -*sleeping through the night	■	☐	■☐
H9. felt depressed or down most of the day (nearly every day for at least 2 weeks in a row)? -for past 30 days, code any days	☐	☐	■■
H10. felt anxious, nervous or worried most of the day (nearly every day for at least 2 weeks in a row)? -for past 30 days, code any days	☐	☐	■■
H11. had hallucinations? -heard or saw things that other people couldn't see or hear	☐ 0→H12	☐ 0→H12	☐☐
H12. had trouble thinking/concentrating, understanding, or remembering to the extent that it caused problems?	☐ 0→H13	☐	■■
H13. (since age 18) had difficulty controlling your temper, or urges to hit or harm someone?	☐ 0→H14	☐ 0→H14	☐☐
H14. (since age 18) pushed, hit, thrown things at, or used a weapon against someone?	☐ 0→H15	☐ 0→H15	☐☐
H15. had serious thoughts of suicide or killing yourself?	☐ 0→H16	☐ 0→H16	☐☐
H16. attempted suicide or tried to kill yourself?	☐ 0→H17	☐ 0→H17	☐☐
H17. experienced any other emotional or psychological problems not mentioned already? -e.g. eating disorder, mania, etc. Specify:_____	■	☐	■■

[**NOTE:** If all H9 – H17 are 0-No, i.e. no psychiatric symptoms or problems in the past 30 days, skip to H21]

(H18 – H20) ***In the past 30 days:***
-Exclude H8 (sleep problems) for H18 – H21

H18. How many days have you experienced these emotional or psychological problems? ☐☐ Days

H19. How many days have you been unable to carry out normal activities because of emotional / psychological symptoms or problems? ☐☐ Days

H20. How much have you been troubled or bothered by these emotional or psychological problems? ☐
0 - Not at all
1 - Slightly
2 - Moderately
3 - Considerably
4 - Extremely

H21. How important to you now is (ongoing or additional) treatment for psychological problems? ☐
0 - Not at all
1 - Slightly
2 – Moderately
3 - Considerably
4 - Extremely

A15. Time Ended: ☐☐:☐☐

Global Interviewer Confidence/Validity Rating:

Take into account the respondent's apparent ability and willingness to understand the questions, provide thoughtful, accurate estimates, and respond honestly. Overall, the respondent provided information that is:

1-Poor, 2-Fair, 3-Good ☐

Poor: Many items are likely grossly inaccurate, were refused, and/or the profile is contradictory or nonsensical.

Fair: Numerous apparent inaccuracies, refusals, and or inconsistencies but the overall profile seems reasonable with the exception of 1–2 problem areas.

Good: Some/few apparent inaccuracies, refusals, and or inconsistencies, but the general profile seems to be a good reflection of the respondent.

Annex 2. Alcohol and Drug Listing[28]

Alcohol – beer, wine, spirits; traditional or local brews, etc.

Cannabis – marijuana, hashish, etc.

Sedatives and hypnotics – benzodiazepines, barbiturates etc. (a separate category for *benzodiazepines* (tranquilisers) might be appropriate in those countries where their use is prevalent)

Cocaine – free-base cocaine etc. (a separate category for *"crack" cocaine* might be appropriate in those countries where this form of cocaine is prevalent)

Amphetamine-type stimulants (ATS) – amphetamine, methamphetamine, other amphetamine-type stimulants etc. (a separate category for *MDMA ("Ecstasy")* might be appropriate in those countries where this form of ATS is prevalent)

Hallucinogens – LSD, phencyclidine (PCP, ketamine), psilocybin, mushrooms etc.

Heroin

Methadone

Buprenorphine

Other opiate/opioid type drugs – morphine, opium, codeine, locally produced poppy straw, etc.

Inhalants – glues, butane, nitrous oxide (laughing gas), amyl nitrate, solvents, petrol, paint thinner, etc.

Other drugs – steroids, unknown, etc.

[28] There will be much local variation in the types of drugs used and in the local/colloquial (street/slang) names for the drugs. The main types of drugs used; local names, etc. should be established to construct a list of drugs appropriate to the local context. Certain drugs are also used in the treatment of drug related problems (most commonly methadone, buprenorphine and tranquilisers, but also other opioids and other drugs) and, where these drugs are commonly used in this way, should be dealt with separately. Prescribed drugs (such as methadone) should be defined in an understandable way; for example, "Methadone given (sold) to you by a doctor as part of your treatment". Some drugs are commonly used in combination with others. These combinations should be included (e.g. heroin and cocaine together).

Annex 3. ICD-10 symptom checklist for mental disorders: psychoactive substance use syndromes module[29]

The following questions ask about symptoms associated with your heroin or other opioid use, for which you are currently being treated. The questions apply to the time period immediately before you started your current treatment.

[For the following items, substitute the name of the opioid used for 'substance', where applicable]

1.[a]	Did you have a strong desire or sense of compulsion to use *substance*? ('craving')	*Yes*	*No*
2.	Did you find it difficult or impossible to control your use of *substance*?	*Yes*	*No*
3.	Did you experience withdrawal symptoms after going without *substance* for a while?	*Yes*	*No*
4.	Did you use substance to relieve or avoid withdrawal symptoms?	*Yes*	*No*
5.	Did you notice that you required more *substance* to achieve the same physical or mental effects? ('tolerance')	*Yes*	*No*
6.	Over time, did you tend not to vary your pattern of use of *substance*?	*Yes*	*No*
7.	Did you increasingly neglect other pleasures or interests in favour of using *substance*?	*Yes*	*No*
8.	Did you experience psychological or physical harm because of your *substance* use?	*Yes*	*No*
9.	Did you persist with using *substance*, despite clear evidence of harmful consequences?	*Yes*	*No*

10.	How long did you experience this pattern of problem drug use?		
	a. in years		
	b. in months		

Dependence indicated if **3 or more** of the symptoms 1, 2, 3, 5, 7 and 9 are present.

11.	**a. Record whether opioid dependence syndrome (F11.2) is present**	*Yes*	*No*
	b. If "Yes", record specific opioid: _____		

[29] ***Source:*** WHO (*134*).

Annex 4. Examination findings suggestive of addiction or its complications[30]

- General
  Odour of alcohol on breath
  Odour of marijuana on clothing
  Odour of nicotine or smoke on breath or clothing
  Poor nutritional status
  Poor personal hygiene

- Behaviour
  Intoxicated behaviour during exam
  Slurred speech
  Staggering gait
  Scratching

- Skin
  Signs of physical injury
  Bruises
  Lacerations
  Scratches
  Burns
  Needle marks
  Skin abscesses
  Cellulitis
  Jaundice
  Palmar erythema
  Hair loss
  Diaphoresis
  Rash
  Puffy hands

- Head, eyes, ears, nose, throat (HEENT)
  Conjunctival irritation or injection
  Inflamed nasal mucosa
  Perforated nasal septum
  Blanched nasal septum
  Sinus tenderness
  Gum disease, gingivitis
  Gingival ulceration
  Rhinitis
  Sinusitis
  Pale mucosae
  Burns in oral cavity

- Gastrointestinal
  Hepatomegaly
  Liver tenderness
  Positive stool hemoccult

- Immune
  Lymphadenopathy

[30] ***Source:*** adapted from Center for Substance Abuse Treatment *(135)*.

- Cardiovascular
  Hypertension
  Tachycardia
  Cardiac arrhythmia
  Heart murmurs, clicks
  Edema
  Swelling

- Pulmonary
  Wheezing, rales, rhonchi
  Cough
  Respiratory depression

- Female reproductive/endocrine
  Pelvic tenderness
  Vaginal discharge

- Male reproductive/endocrine
  Testicular atrophy
  Penile discharge
  Gynecomastia

- Neurologic
  Sensory impairment
  Memory impairment
  Motor impairment
  Ophthalmoplegia
  Myopathy
  Neuropathy
  Tremor
  Cognitive deficits
  Ataxia
  Pupillary dilation or constriction

Annex 5. Bloodborne Virus Transmission Risk Assessment Questionnaire (BBV-TRAQ)[31]

Instructions

- Please consider the following questions carefully and answer each one as accurately and truthfully as you can. All questions refer to your behaviour in the past MONTH / 4 week period (ie. **The month before current treatment commenced**).
- Try and remember that the only correct answer is an accurate and honest answer.
- Remember that the information you provide will remain completely confidential.

Part 1: INJECTING PRACTICES

Record your responses to each of the following questions by circling the answer option that you think is most relevant to you.

1.1 In the last month, how many times have you handled another person's used needle/syringe (eg. to dispose, to break-off needle) at a time when you had cuts, sores or lesions on your fingers and hands?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.2 In the last month, how many times have you sucked or licked left-over drugs from a spoon or other mixing container which had been used by another person?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.3 In the last month, how many times have you sucked or licked a filter which had been used by another person?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.4 In the last month, how many times have you sucked or licked a plunger after using it in a mix which has been used by another person?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.5 In the last month, how many times have you injected a drug that was filtered through another person's filter?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.6a In the last month, how many times have you injected a drug that was prepared in another person's used spoon or mixing container?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

↓

(Go to Question 1.7)

1.6b On those occasions how often did you clean the spoon or mixing container before using it?

Never Rarely Sometimes Often Every time

1.7 In the last month, how many times have you injected a drug prepared with water which had been used by another person?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.8 In the last month, how many times have you injected a drug which had come into contact with another person's used needle/syringe?

No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.9a In the last month, how many times have you injected a drug that you prepared immediately after 'assisting' another person with their injection (eg. injecting them, holding their arm, handling their

[31] ***Source:*** Fry et al. *(136).*

used needle/syringe; touching their injection site to feel for a vein, to wipe away blood, or to stop bleeding)?

No times *Once* *Twice* *3 - 5 times* *6 - 10 times* *More than 10 times*

↓

(Go to Question 1.10a)

1.9b ***On those occasions, how often did you wash your hands before preparing your mix?***

Never *Rarely* *Sometimes* *Often* *Every time*

1.10a ***In the last month, how many times have you injected a drug that was prepared by another person who had already injected or assisted in someone else's injection?***

No times *Once* *Twice* *3 - 5 times* *6 - 10 times* *More than 10 times*

↓

(Go to Question 1.11a)

1.10b ***On those occasions, how often did the person preparing the mix wash their hands before preparing the mix?***

Never *Rarely* *Sometimes* *Often* *Every time*

1.11a ***In the last month, how many times have you been injected by another person who had already injected or assisted in someone else's injection?***

No times *Once* *Twice* *3 - 5 times* *6 - 10 times* *More than 10 times*

↓

(Go to Question 1.12a)

1.11b ***On those occasions, how often did the person injecting you wash their hands before injecting you?***

Never *Rarely* *Sometimes* *Often* *Every time*

1.12a ***In the last month, how many times have you injected with a needle/syringe which had been handled or touched by another person who had already injected?***

No times *Once Twice* *3 - 5 times* *6 - 10 times* *More than 10 times*

↓

(Go to Question 1.13a)

1.12b ***On those occasions, how often did they wash their hands prior to handling the needle/syringe that you used?***

Never *Rarely* *Sometimes* *Often* *Every time*

1.13a ***In the last month, how many times have you injected with another person's used needle/syringe?***

No times *Once* *Twice* *3 - 5 times* *6 - 10 times* *More than 10 times*

↓

(Go to Question 1.14)

1.13b ***On those occasions, how often did you rinse it with a combination of full-strength bleach and water (ie. the '2x2x2' method) before you used it?***

Never *Rarely* *Sometimes* *Often* *Every time*

1.14 ***In the last month, how many times have you injected with a needle/syringe after another person has already injected some of its contents?***

No times *Once* *Twice* *3 - 5 times* *6 - 10 times* *More than 10 times*

1.15a ***In the last month, how many times have you touched your own injection site (eg. to feel for a vein, to wipe away blood, or to stop bleeding) soon after 'assisting' another person with their injection (eg. injecting them, holding their arm, handling their used needle/syringe; touching their injection site to feel for a vein, to wipe away blood, or to stop bleeding)?***

No times *Once* *Twice* *3 - 5 times* *6 - 10 times* *More than 10 times*

↓
(Go to Question 1.16a)

1.15b On those occasions, how often did you wash your hands before touching your own injection site?
Never Rarely Sometimes Often Every time

1.16a In the last month, how many times has another person touched your injection site (eg. to feel for a vein, to wipe away blood, or to stop bleeding)?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times
↓
(Go to Question 1.17)

1.16b On those occasions, how often did the person wash their hands before they touched your injection site?
Never Rarely Sometimes Often Every time

1.17 In the last month, how many times have you wiped your own injection site with an object (eg. swab, tissue, hanky, towel, etc) which had been used by another person
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.18 In the last month, how many times have you used a tourniquet (eg. medical tourniquet, belt, rope, tie, cord, etc) which had been used by another person?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.19 In the last month, how many times have you received an accidental needle-stick/prick from another person's used needle/syringe?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

1.20a In the last month, how many times have you re-used a needle/syringe taken out of a shared disposal/sharps container?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times
↓
(Go to PART 2)

1.20b On those occasions, how often did you rinse it with full-strength bleach before you re-used it?
Never Rarely Sometimes Often Every time

Part 2: SEXUAL PRACTICES

Record your responses to each of the following questions by circling the answer option that you think is most relevant to you. Please remember that "in the last month" refers to the month before you commenced current drug treatment.

2.1 In the last month, how many times have you engaged in unprotected vaginal sex with another person (ie. penetration of the vagina with the penis)?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

2.2 In the last month, how many times have you engaged in unprotected vaginal sex with another person (ie. penetration of the vagina with the penis) during menstruation?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

2.3 In the last month, how many times have you engaged in unprotected vaginal sex with another person (ie. penetration of the vagina with the penis) without lubrication?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

2.4 In the last month, how many times have you engaged in unprotected anal sex with another person (ie. penetration of the anus with the penis)?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

2.5 In the last month, how many times have you engaged in unprotected oral sex with another person (ie. lips and tongue come into contact with the vagina, penis and/or anus)?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

2.6 In the last month, how many times have you engaged in unprotected manual sex with another person (ie. fingers and hands come into contact with the vagina, penis and/or anus) during menstruation?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

2.7 In the last month, how many times have you engaged in unprotected manual sex with another person (ie. fingers and hands come into contact with the vagina, penis and/or anus) after injecting?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

2.8 In the last month, how many times have you engaged in unprotected manual sex with another person (ie. fingers and hands come into contact with the vagina, penis and / or anus) without lubrication?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

Part 3: OTHER SKIN PENETRATION PRACTICES

Record your responses to each of the following questions by circling the answer option that you think is most relevant to you. Please remember that "in the last month" refers to the month before you commenced current drug treatment.

3.1 In the last month, how many times have you come into contact with another person's blood (eg. through fights, slash-ups, self-mutilation, accidents, blood-sports, occupational, pimples, blood nose, etc)?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

3.2 In the last month, how many times have you been tattooed by someone who was not a professional tattooist?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

3.3 In the last month, how many times have you been pierced (eg. ear or body) by someone who was not a professional piercer?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

3.4 In the last month, how many times have you used another person's used razor (eg. disposable razors, razor-blades)?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

3.5 In the last month, how many times have you used another person's toothbrush?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

3.6 In the last month, how many times have you used another person's personal hygiene equipment (eg. nail file, nail scissors, nail clippers, tweezers, comb, brush)?
No times Once Twice 3 - 5 times 6 - 10 times More than 10 times

Please make sure that you have answered all relevant questions correctly.

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WORLD HEALTH ORGANIZATION
EUROPE

6 Management of Hepatitis C and HIV Coinfection

Clinical Protocol for the WHO European Region

Contents

I. Epidemiology and natural history of HCV in HIV infection

In Europe, the prevalence of hepatitis C virus (HCV) infection in HIV-infected patients is particularly high – and still rising, in contrast to the rest of the world. Yet only a minority of HCV/HIV-coinfected patients are treated for their hepatitis. The compounding effect of coinfection makes the care for these patients a major challenge.

In the pre-HAART era, the late consequences of HCV-related chronic liver disease in coinfected individuals were overshadowed by AIDS mortality connected with severe immune deficiency. With the development of HAART, morbidity and mortality among HIV-infected patients have decreased significantly. The consequences of liver-related disease associated with chronic HCV infection are now far more worrying. End-stage liver disease (ESLD) is now the predominant cause of death in patients coinfected by HCV and HIV, as well as in hepatitis B virus (HBV)/HIV-coinfected patients *(1)*, despite the availability of treatments with proven efficacy *(2–5)*. Most patients are, however, not treated, underscoring the need for treatment guidelines. Efforts must also be made, via multidisciplinary health-care services, to increase the applicability and availability of treatment, especially in more vulnerable populations, including but not limited to migrants, injecting drug users (IDUs), prisoners, people with psychiatric illnesses and people who consume too much alcohol.

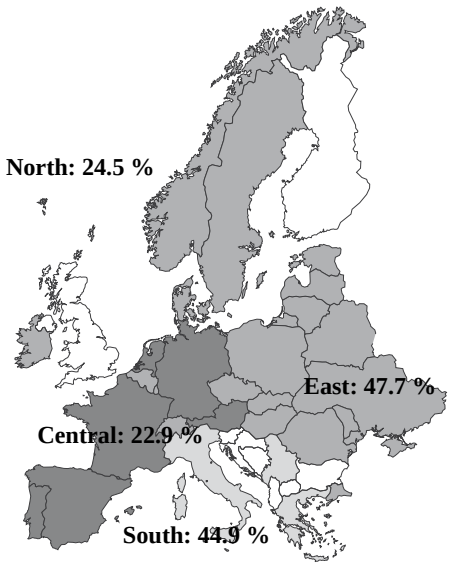
1. Prevalence, risk factors and transmission

Worldwide about 180 million people are chronic carriers of HCV. Overlapping routes of transmission for HCV and HIV result in a high frequency of coinfection in Europe.

1.1. Prevalence of HCV in HIV infection

The prevalence of HCV infection in individuals infected with HIV in the WHO European Region is very high, averaging 40% and reaching 50–90% in urban areas. Data from a EuroSIDA study (see Fig. 1) shows the prevalence is higher in the eastern (47.7%) and southern (44.9%) EuroSIDA regions than in the northern (24.5%) EuroSIDA region, due to the high rates of injecting drug use in the two former regions *(6)*.

Fig. 1. Prevalence of HCV in HIV-infected patients in Europe

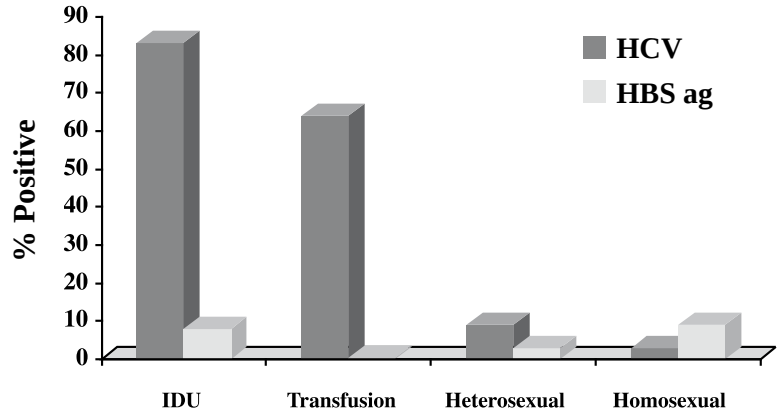


Source: Rockstroh et al. *(7)*.

The prevalence of HCV antibodies also varies widely among HIV transmission groups, ranging from 7–8% in men who have sex with men to 60–70% in haemophiliacs and 80–90% in IDUs, the most important group (see Fig. 2) *(8–12)*. HCV is easily transmitted among IDUs, which makes it difficult to prevent. IDU transmission occurs in several ways:

- sharing needles and syringes
- sharing auxiliary paraphernalia, such as cookers, straws, swabs, tourniquets and cotton
- sharing drug doses from a common syringe
- accidental needle-sticks.

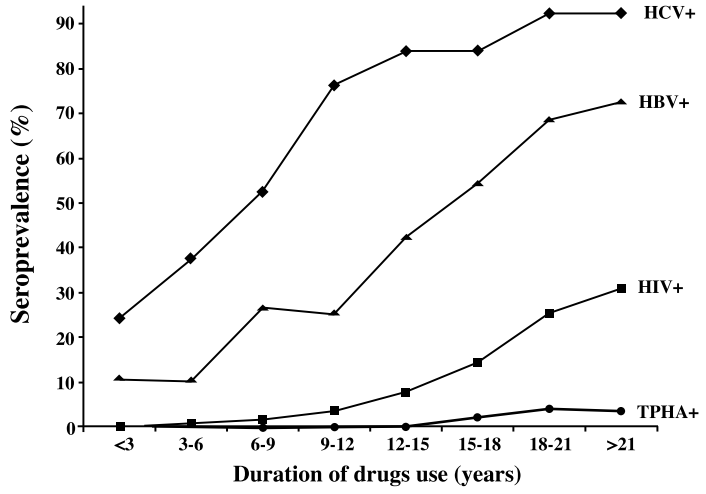
Fig. 2. Prevalence of HCV antibodies in different transmission groups



Source: Alter *(13)*.

The prevalence of HCV among IDUs increases with the duration of injection, as shown in Fig. 3.

Fig. 3. Prevalence of HCV among IDUs in relation to injecting history



Source: Quaglio et al. *(14)*.

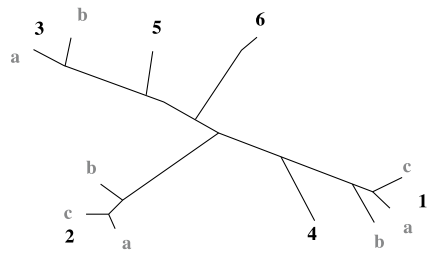
1.2. Primary modes of transmission

The primary modes of transmission for HCV are parenteral and vertical (from mother to child); it is rarely transmitted sexually. In Europe, the most common route of transmission occurs via injecting drug use. Although sexual transmission of HCV occurs in <1% *(15)* of monogamous couples, there have been increasing reports of sexual transmission between men who have sex with men (MSM) *(16)*. Household contact with an HCV-infected person has been associated with an average non-sexual transmission rate of 4% (0–11%) *(17)*. Other risk factors for transmission of HCV include tattooing and accidental needle-sticks in medical settings *(18)*.

1.3. Genotypes

HCV exhibits a high genetic heterogeneity around the world, with six different clades or genotypes being distinguished and differing as much as 30% in their genome (see Fig. 4). Furthermore, phylogenetic analyses can also distinguish subtypes and isolates within a particular type.

Fig. 4. Phylogenetic tree of HCV genotypes and subtypes

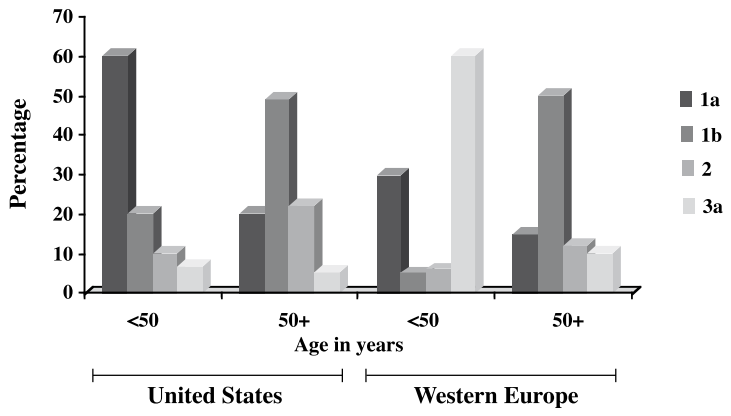


Source: Francisus *(19)*.

From an epidemiological point of view, infection with genotypes 3 and 4 is more prevalent in IDUs and HIV-coinfected patients than in monoinfected patients. Acute genotype 4 infection has recently been found among MSM *(16)*.

The distribution of genotypes may differ from one region of the world to another. As genotypes have differed in their sensitivity to the standard treatment since 2005 – pegylated interferon (PEG-IFN) and ribavirin (RBV) – it is important to know the genotype of each patient and the distribution of the genotypes in each country.

Fig. 5. Prevalence of genotypes 1–3 in the United States and western Europe



Source: Simmonds et al., Zeuzem S et al. *(20, 21)*.

2. Access of coinfected patients to hepatitis C treatment

Low percentages (0–23%) of coinfected patients have access to hepatitis C treatment *(22)*. There may be several reasons for this:

- The efficacy of PEG-IFN and RBV in treating coinfected patients was only published in 2004, and these drugs are not widely available.
- A great number of patients who continue active drug use do not have access to substitution treatment and/or ART.
- Many countries lack guidelines for diagnosis and treatment.
- Evaluation of the severity of HCV disease and treatment requires high technology and skills.
- Neuropsychological side-effects and toxicity are frequent during HCV treatment.
- Treatment is very costly.

3. Reciprocal influences of HIV and HCV

3.1. Impact of HIV infection on HCV disease progression

- Several studies have demonstrated that patients coinfected with HCV and HIV have more rapid fibrosis progression than monoinfected patients, even after taking into account age, sex and alcohol consumption *(23)*.
- People with HCV/HIV coinfection may have quantitative and/or qualitative deficiency in their immune responses to HCV. HIV accelerates the course of HCV-associated liver disease, particularly in patients who are more severely immune deficient, by increasing:
  - the HCV viraemia level from two- to eightfold, resulting in a significant decrease in spontaneous recovery from acute hepatitis *(24)*;
  - the risk of mother-to-child and sexual transmission (from averages of 6% to 20% and from 0% to 3%, respectively); and
  - rates of liver fibrosis (two- to fivefold), cirrhosis, decompensation, hepatocellular carcinoma (HCC) and liver-related mortality *(25)*.
- Liver disease is the leading cause of morbidity and mortality in HCV/HIV-coinfected patients in some parts of Europe, despite the suggestion that HAART, especially protease inhibitors, may decrease the severity of liver disease and the related mortality *(1)*.
- Comorbidities with hepatic consequences (drug hepatotoxicity, HBV, steatosis, alcohol or drug abuse) are frequent in coinfected patients and may increase the rate of complications associated with HCV-related liver disease. Patients with CD4 <200 cells/mm^3 are those most likely to progress to severe liver disease *(6, 23, 25, 26)*. For example, HIV-infected patients with CD4 <200 cells/mm^3 who drink more than 50 g of alcohol daily have a median expected time to cirrhosis of 16 years, versus 36 years for HIV-infected patients with CD4 >200 cells/mm^3 who drink 50 g or less of alcohol daily *(26)*.
- Spontaneous clearance of HCV is significantly lower in HIV-infected patients than in immunocompetent patients with acute hepatitis. As HCV ribonucleic acid (RNA) might become temporarily undetectable during the acute phase of HCV infection, clearance must be confirmed with a sensitive qualitative HCV RNA assay on at least two occasions six months apart *(27, 28)*.
- In profoundly immunosuppressed patients, HCV serology has occasionally been found to be falsely negative despite HCV chronic infection.[1] Such false negatives have become very rare due to the high sensitivity of third-generation serology *(27, 28)*.

[1] HCV RNA testing should, therefore, be performed in people at risk, such as IDUs and MSM, and in others who may be profoundly immunosuppressed and present unexplained ALT elevation despite negative HCV serology.

3.2. Impact of HCV infection on HIV disease progression

HCV has little or no effect on the response to ART or on immunological, virological or HIV-related clinical disease progression. Although HCV antibodies per se do not influence progression, infection with certain multiple genotypes might do so *(29)*.

Extended follow-up in various studies indicate that patients on HAART do not have any major differences in HIV-related mortality from HCV/HIV-coinfected patients or those infected with HIV alone, particularly if ART is given *(6)*. There is, however, an increased risk for liver disease-related morbidity and mortality in hepatitis-coinfected HIV, as well as more hepatotoxicity under ART regimens *(30)*.

II. Identification of HCV/HIV

1. Assessment of HCV risk and diagnosis of hepatitis C in HIV-infected patients

1.1. Initial laboratory assessment of HCV status

1.1.1. Step 1: All HIV-infected patients should be tested for HCV antibodies.

- For patients with acute HCV infection, it is important to bear in mind that antibodies may not be detectable for three to eight weeks following initial HCV infection. Retesting is not necessary if the infection was transmitted heterosexually and in the absence of other risky behaviour. For others who continue to run the risk of infection, such as active IDUs or MSM with multiple partners, testing is recommended every one to two years *(31)*.
- The presence of HCV antibodies is indicative of past or present infection. Antibodies persist indefinitely, in chronically infected patients but the antibody titres may decrease (and even disappear) in patients who clear HCV (either spontaneously or after antiviral treatment).
- HIV infection can impair antibody responses to HCV infection *(27)*, so a second- or third- generation enzyme immunoassay (EIA) for HCV antibodies should be used in coinfected individuals.
- In HCV antibody-negative HIV patients with profound immunosuppression, HCV RNA determination is recommended when there are liver test abnormalities or clinical suspicion of liver disease.

1.1.2. Step 2: When testing for HCV antibodies is positive, detection of HCV RNA should be performed to confirm or exclude active replication.

- HCV RNA can be detected as soon as a few days after infection.
- HCV RNA can be detected by PCR (polymerase chain reaction) or by TMA (transcription-mediated amplification).
- Persistence of HCV RNA more than six months after initial infection confirms chronic hepatitis C *(27, 31)*.
- Determination of HCV RNA can be done through qualitative or quantitative assays.
  - A qualitative assay is enough for diagnostic purposes.
  - A quantitative assay (viral load) is important for assessment of patients who will receive HCV treatment.
- High pretreatment HCV RNA levels are associated with lower rates of sustained virological response (SVR); the cut-off is generally 800 000 copies/ml (IU/ml) *(32)*. SVR rates may reach 60% in persons with either a genotype other than 1 or 4, or genotype 1 HCV infection with an HCV RNA level ≤800 000 IU/ml after 48 weeks of PEG-IFN and RBV treatment, as opposed to only 18% for those with genotype 1 and an HCV RNA level >800 000 IU/ml. *(2–5, 32)*.
- It is important to consider that viral load is higher (0.5–1 log on average) in HCV/HIV-coinfected individuals than in those who are monoinfected. This may also account for higher HCV transmission to children born to coinfected mothers. Therefore, assays with a wide dynamic range may represent an advantage.

1.1.3. Step 3: Use HCV genotype determination in predicting treatment response.

Distribution of genotypes differs between HCV-monoinfected and coinfected patients, as illustrated in Table 1.

Table 1.	Distribution of genotypes by monoinfection and coinfection, in %			
	Genotype 1	**Genotype 2**	**Genotype 3**	**Genotype 4**
Monoinfected	65	12	19	3
Coinfected	60	5	28	8

Source: Fried et al., Tottiani et al. *(33, 34)*.

- Infections with more than one HCV genotype appear to be more often (>5%) in patients coinfected with HCV and HIV, particularly IDUs and haemophiliacs *(29, 35)*.
- HCV genotype plays a predominant role as a predictor of SVR in HIV-infected patients, as it has been found in all studies of people without HIV infection.
  - For genotypes other than 1 or 4, SVR rates are generally high, ranging from 73% in the ACTG 5071 study *(4)* to 62% in the APRICOT study *(3)*, 53% in the Barcelona study *(5)* and 44% in the RIBAVIC study *(2)*.
  - For genotype 1, SVR rates range from 29% in APRICOT *(3)* to 17% in RIBAVIC *(2)* and 14% in ACTG 507 *(4)*, while Barcelona reported a 38% SVR rate for those with genotype 1 or 4 *(5)*.

For more information about laboratory assays for HCV, please see Annex 1.

1.2. Evaluation of HCV disease severity

- Evaluation of HCV disease severity should include attempting to define the duration of the infection. The date of infection is usually defined as the first date of risk exposure to HCV infection (first drug injection date, etc.).
- For decisions regarding treatment, the focus of the evaluation should be on chronic liver disease, comorbidities and co-conditions.

1.2.1. Clinical evaluation of liver disease

Clinical signs of cirrhosis are:
- stellar angiomas
- dysmorphic liver
- digital hippocratism (clubbing of the fingers)
- collateral abdominal circulation
- signs of hepatic decompensation (ascites, icterus, encephalopathy, etc.).

1.2.2. Biochemical parameters

Biochemical tests to be performed are:
- transaminases (ALT, AST)[2, 3]
- gamma glutamyl transpeptidase (GGT) (may increase in case of cirrhosis)
- alcalines phosphatases (to establish another possible cause of hepatic disease)
- bilirubine
- albumin
- prothrombin time.

[2] Alanine aminotransferase (ALT) levels do not necessarily reflect the stage of fibrosis, especially in HCV/HIV-coinfected patients. A normal ALT level alone should not be grounds to defer treatment. A biopsy in this situation can help to make a more informed decision. In the RIBAVIC study, baseline ALT >3 times the upper limit of normal was a predictor of higher SVR.
[3] Asparate aminotransferase (AST) levels should be controlled when performing the initial complete hepatic evaluation to eliminate other causes of hepatic disease; for example, in cases of alcoholic intoxication there may be an increase in AST and GGT.

1.2.3. Child-Pugzh score

The Child-Pugh Score, combining clinical symptoms and biological tests (Table 2), is useful for grading the severity of ESLD and should be performed in all patients with cirrhosis *(36)*.

Table 2. Child-Pugh classification

Clinical and biochemical parameters	Points		
	1	2	3
Bilirubin	<2 mg/dl (<34 μmol/l)	2–3 mg/dl (34–50 μmol/l)	>3 mg/dl (>50 μmol/l)
Albumin	>3.5 g/dl	2.8–3.5 g/dl	<2.8 g/dl
Ascites	Absent	Moderate[a]	Severe/ refractory[b]
Encephalopathy	Absent	Moderate (stage I–II)	Severe (stage III–IV)
Prothrombin time[c]	>60%	40–60%	<40%

[a] Controlled medically.
[b] poorly controlled.
[c] now replaced in some European countries by international normalized ratio (INR with the following Child-Pugh values: INR <1.70 = 1 point; 1.71–2.20 = 2 points; >2.20 = 3 points.
Source: Pugh et al. *(36)*.

Interpretation of the Child-Pugh classification:
- Class A (5–6 points) – compensated cirrhosis
- Class B (7–9 points) – compensated cirrhosis
- Class C (10–15 points) - decompensated cirrhosis

1.2.4. Ultrasound

Ultrasound (Doppler if possible) examination of the liver can reveal:
- cirrhosis: dysmorphy of the liver
- steatosis: hyperechogenic liver
- possibly early HCC: nodular unique or, rarely, multiple lesions.

1.2.5. Histological evaluation

Liver biopsy is the standard procedure for evaluation of the severity of liver disease (see Table 3 for indications). It is especially important for patients with a suspected low chance of SVR (genotype 1 with a high viral load) or excess risk of severe side-effects, and allows evaluating:
- the degree of fibrosis and necroinflammatory activity
- the presence of comorbidities (steatosis, drug toxicity, alcohol related lesions, HBV).

Table 3. Indications for liver biopsy in HCV/HIV-coinfected patients

Indications for biopsy	Biopsy not required
Genotype 1 or 4 with high HCV viral load (>800 000 IU/ml)	Genotype 2 and 3
Presence of comorbidities: - excessive alcohol consumption - coinfection with HBV and/or hepatitis delta virus - suspicion of medication-associated hepatotoxicity	Genotype 1 (and probably 4) with low HCV load (≤800 000 IU/ml) Clinical signs of cirrhosis

Biopsies must be performed by trained physicians, as significant complications may occur in 1/200 patients. They should be read by specialized anatomopathologists, as subtle differences may change

the classification of the severity of the disease. These limitations impede generalized biopsies for all HCV-infected patients (see section II.1.2.7 below for clinical situations not requiring liver biopsy). Activity and fibrosis are two major histological features of chronic hepatitis C that are included in proposed classifications, such as Ishak, Metavir and Knodell, that allow improved consistency in interpretation of hepatic fibrosis with a somewhat weaker reproducibility for hepatic inflammation grade *(37, 38)*. See Table 4.

Table 4. Metavir classification: activity and fibrosis scoring

Activity score (A)		Lobular necrosis		
		Absent (0)	**Moderate (1)**	**Severe (2)**
Parcellar necrosis	**Absent (0)**	A0	A1	A2
	Minimal (1)	A1	A1	A2
	Moderate (2)	A2	A2	A3
	Severe (3)	A3	A3	A3

A0 = no histological activity; A1 = minimal activity; A2 = moderate activity; A3 = severe activity.

Table 4a.

Fibrosis score (F)
F0: absence of portal fibrosis
F1: stellar portal fibrosis with no septa
F2: portal fibrosis with some septa
F3: many septa but no cirrhosis
F4: cirrhosis

Source: Simmonds et al. *(20)*.

This system assesses histological lesions in chronic hepatitis C using two separate scores, one for necroinflammatory grade (A for Activity) and another for the stage of fibrosis (F). The fibrosis stage and inflammatory grade are correlated, but for approximately one third of patients there is discordance. In lower grades of liver fibrosis (F0–F1), regardless of HCV genotype, treatment can be deferred. See Table 4a.

1.2.6. Non-invasive markers of liver fibrosis

Non-invasive tools for assessing liver fibrosis, such as those based on serum markers (for example, FibroTest™) or image technique (for example, FibroScan™) are available. Several non-invasive methods to evaluate inflammation and fibrosis have been developed for monoinfected patients and include serological tests combining serum fibrosis markers. They are used to distinguish Metavir fibrosis stages 0–2 from stages 3 and 4. The tests are quite reliable, are better accepted by patients than biopsies and could potentially save approximately 50% of patients from being biopsied.

Recently, alternatives to biopsies have become available for coinfected patients *(39)*, including a combination of biochemical tests indicating the degree of liver inflammation and fibrosis, such as the Forns index which has been recently validated for HIV/HCV-coinfected patients *(40)*, and an elastometric method reflecting the degree of fibrosis (see Annex 2) *(41, 42)*.

1.2.7. Clinical situations not requiring histological evaluation

The First European Consensus Conference on the Treatment of Hepatitis in HIV-Infected Patients did not mandate biopsy in cases where treatment is already indicated *(43)*. Treatment without biopsy or other liver assessment is recommended in the following situations:

- infection with HCV genotype 2 or 3;
- infection with HCV genotype 1 with a low viral load; and
- absence of major contraindications and patient willingness to undergo treatment, in which case the SVR will be on the order of 40–60% *(2–5)*.

Given the limitations of biopsy and the faster progression of fibrosis in HCV/HIV patients, treatment should still be offered when candidates for biopsy decline it or lack access to it.

1.3. Evaluation of comorbidities and co-conditions

1.3.1. Psychiatric disorders

- An initial evaluation of psychiatric disorders should be performed, as treatment with IFN can reveal and worsen depression. Treatment for hepatitis C should therefore be deferred in patients with moderate to severe depression until the condition improves. Prophylactic treatment with psychiatric drugs may be advisable and treatment may be feasible thereafter.
- In patients with mild psychiatric illness, treatment for hepatitis C should not be deferred and counselling and/or antidepressant medication should be offered along with HCV treatment.

1.3.2. Alcohol abuse

- Assessment of alcohol intake is an important part of evaluation (please see Annex 3).
- Heavy alcohol intake (50 g/day or more) contributes to fibrosis of the liver, which can be identified by biopsy in HCV patients independently of other predictors. This intake is equivalent to five or more drinks per day, in which a drink = 10 g of alcohol, for example 330 ml (12 oz) of beer, 150 ml (5 oz) of wine or 38 ml (1.25 oz) of hard alcohol.
- There is evidence of synergistic interaction between alcohol consumption ≥80 ml/day and chronic HBV or HCV infection *(44)*. Continued alcohol consumption increases HCV replication, accelerates fibrogenesis and liver disease progression in hepatitis B and C and diminishes the response and adherence to treatment (especially if consumption is >50 g/day).
- Active alcohol intake is considered a relative contraindication for IFN-based treatment, due to the documented non-compliance of heavy drinkers in medical therapies, combined with the side-effects that otherwise affect compliance *(45)*.
- Psychological, social and medical support should be offered to reduce alcohol intake to <10 g/day or stop it altogether.

1.3.3. Drug use

- Treatment of patients on opioid substitution therapy should not be deferred.
- Initiation of HCV treatment in active drug users should be considered on a case-by-case basis. (Please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users*.)
- Medical, psychological and social support from a multidisciplinary team should be provided for these patients.

1.3.4. Other comorbidities and co-conditions

Testing of comorbidities should include a comprehensive history with a particular focus on factors associated with more progressive liver injury. Analysis can include:

- testing for viral liver diseases[4]
- testing for tuberculosis (TB) and sexually transmitted infections (STIs) that need treatment before HCV treatment begins.[5]

When a treatment has been decided, other tests are needed:

- thyroid-stimulating hormone (TSH) dosage;
- dosage of antiperoxydase, antinuclear, anti-smooth muscle, anti-liver-kidney microsome antibody (LKM1);
- creatininaemia;
- proteinuria ;
- glycaemia;
- ferritinaemia;
- electrocardiogram (ECG, to detect coronary disease that could decompensate after treatment-induced anaemia);
- a pregnancy test.[6]

[4] For HBV and HAV please refer to Protocol 7, Management of hepatitis B and HIV coinfection.

[5] See Protocol 4, *Management of tuberculosis and HIV coinfection,* and the European STD Guidelines *(46).*

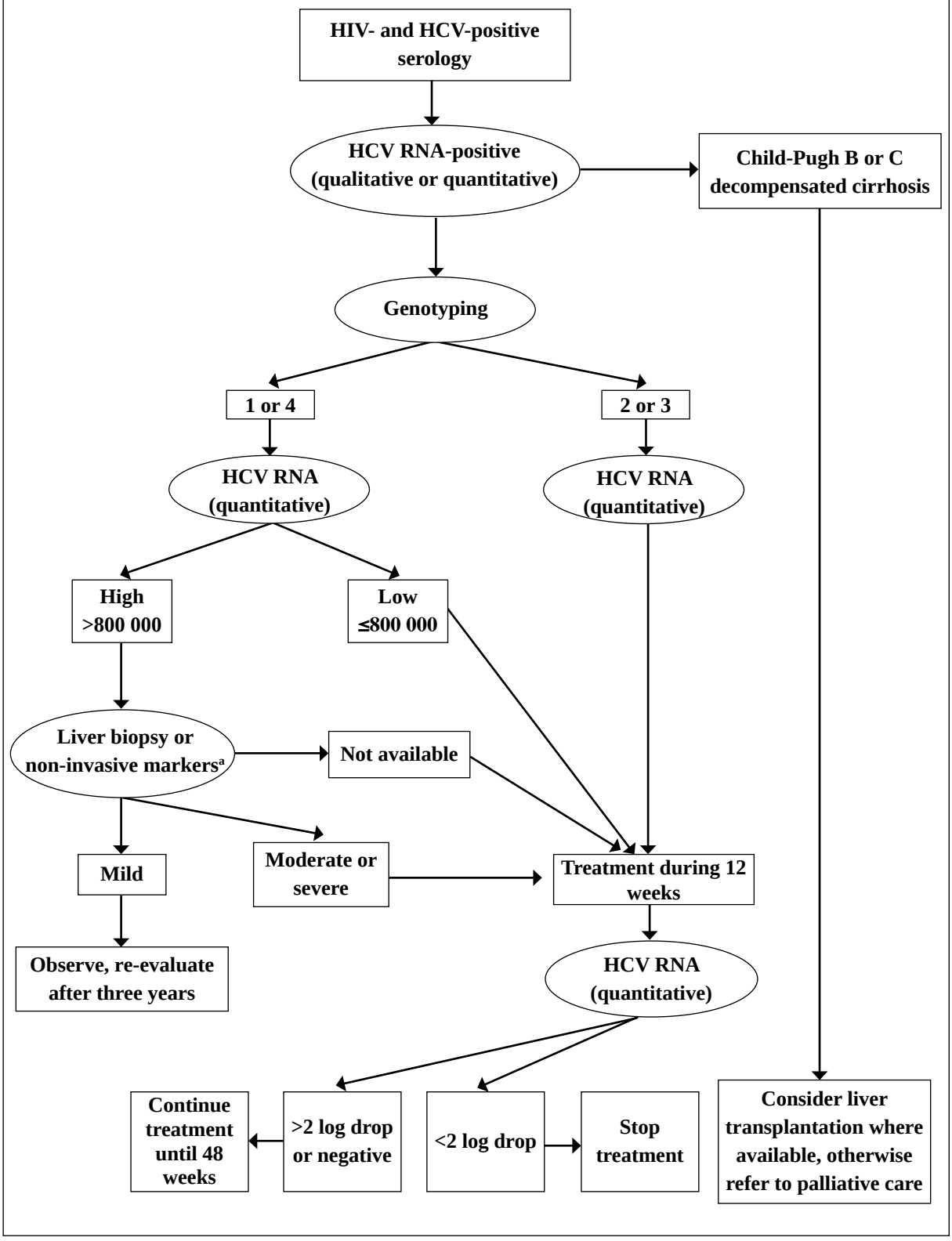
[6] It should be explained that because RBV is teratogenic and contraindicated during pregnancy, procreation should be avoided during treatment and six months after, and that due to higher levels of HCV viraemia in coinfected women, approximately 20% transmit HCV to their offspring, versus 7–8% in those monoinfected with hepatitis C (47).

1.4. Evaluation and treatment algorithms for hepatitis C

1.4.1. Algorithm 1

This algorithm is preferred and focuses on genotyping.

Fig. 6. Algorithm 1



[a] FibroScan (image technique), Fibro Test (serum fibromarkers)

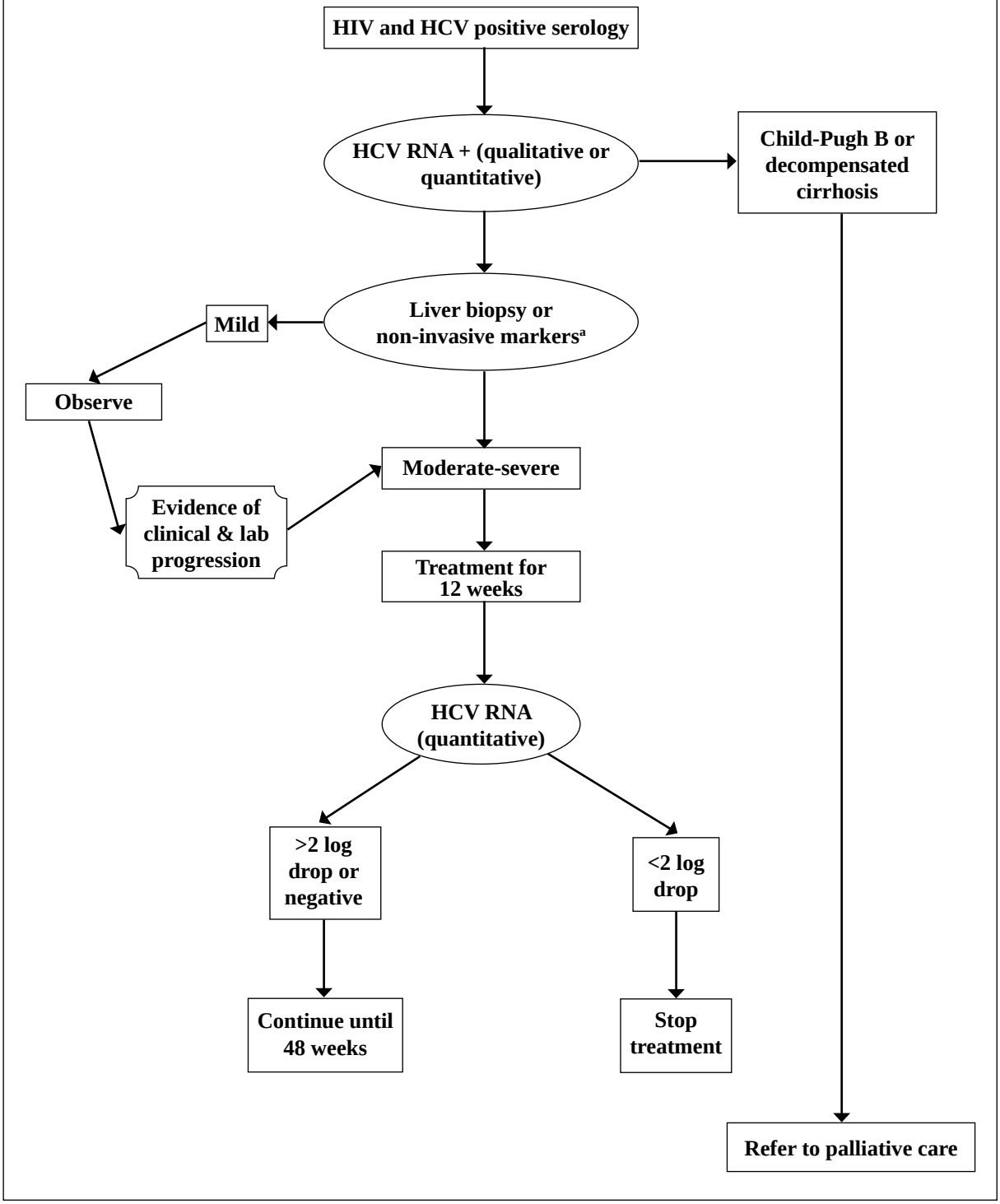
In Algorithm 1, the decision to treat lies mainly upon the HCV genotype determination and HCV quantification. Liver biopsy is limited to patients with genotype 1, high viral load and low response to PEG-IFN and RBV.

- Subsequent to an HCV/HIV positive serology, qualitative HCV RNA detection should be undertaken to confirm the chronicity of hepatitis.
- In case of positive HCV RNA, a genotyping should be performed.
- In case of genotype 2 or 3, more frequently found in IDUs, treatment should be proposed for all patients without liver biopsy where there is no contraindication (please see contraindications in section III.2.3).
- In case of genotype 1, the patient should have a quantification of HCV RNA, since responses are related to viral load. This test should be available everywhere HIV viral load is performed.
- In the absence of local testing possibilities, the patient should be referred to a specialist, or a sample should be collected at the district level and a genotyping test done centrally.
    - When viral load is low (≤800 000 IU/ml), treatment of genotype 1 is recommended without a liver biopsy.
    - When viral load is high (>800 000 IU/ml), an assessment of liver fibrosis by biopsy is recommended to differentiate patients with severe liver disease.
- A fibrosis score of F2–F4 indicates a need for *immediate* treatment.
- Mild liver disease (F0, F1) indicates that treatment should be delayed due to the low chances of SVR.
- Follow-up treatment should rely on HCV RNA quantification at week 12, and then HCV RNA qualitative detection at weeks 24 and 48.
    - At week 12, if the drop of viral load is less than 2 log, the treatment should be stopped because the chance of success does not exceed 1–2% regardless of genotype. Otherwise, the treatment should be continued.
    - Additional qualitative tests should be performed at week 24 and treatment should be stopped if HCV viral load is detectable; otherwise, treatment should be pursued until week 48 and treatment efficacy checked with a qualitative test at this time.
    - At week 72, HCV RNA detection should confirm or disprove a sustained virological response.
- Patients with cirrhosis should also be referred to a specialist for initial evaluation of their cirrhosis.

1.4.2. Algorithm 2

This algorithm is an alternative, focusing on liver biopsy and other tools in the absence of genotyping.

Fig. 7. Algorithm 2



[a] FibroScan (image technique), Fibro Test (serum fibromarkers).

2. Assessment of HIV risk and diagnosis of HIV/AIDS in HCV patients

All patients with HCV should be offered HIV testing and counselling because the two viruses share transmission routes and because HIV exacerbates the development of HCV. Health-care providers should explain the reasons for offering the test to patients and its importance in proper clinical management. However, patients have the right to opt out.

Initial assessment of HIV status should include:

- HIV pretest counselling;
- serological testing (typically enzyme-linked immunosorbent assay (ELISA) and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test if positive; and
- post-test counselling, including information on reducing risky behaviour, regardless of whether the HIV results were positive or negative.

Further clinical evaluation of HIV-infected patients is required to develop a strategy of clinical management. It should include:

- checking symptoms
- a physical examination
- evaluation of mental health and preparedness for treatment
- a routine laboratory assessment
- a CD4 lymphocyte count to determine the severity of immunodeficiency
- viral load testing if available
- pregnancy testing if indicated
- testing for comorbidities, including hepatitis B, TB and psychiatric disorders
- other tests as indicated by the patient's condition.

Table 5. Initial and pre-therapeutic evaluation for HCV/HIV-coinfected patients

	Tests	Initial evaluation	Pre-therapeutic evaluation
HCV disease	- qualitative HCV RNA	+	
	- transaminases (ALT, AST), GGT, alkaline phosphatases, bilirubin, albumin, prothrombintime	+	
	- HCV genotype		+
	- quantitative HCV RNA		+
	- ultrasound examination of the liver	+	
	- histological evaluation, non-invasive markers		+
HIV[a]	- CD4 cell count	+	
	- HIV RNA	+	
	- present antiretroviral regimen		+
Comorbidities and co-conditions	- HBV serology	+	
	- HAV serology	+	
	- TB diagnosis	+	
	- TSH dosage		+
	- auto-antibodies		+
	- creatininaemia, proteinuria		+
	- glycaemia		+
	- ferritinaemia		+
	- quantification of alcohol consumption	+	
	- drug consumption	+	
	- pregnancy test		+
	- ECG (if >50 years old or known cardiopathy)		+
	- psychiatric consultation if previous psychiatric history		+

[a] For more information refer to section on initial patient evaluation in Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

III. Clinical management of HCV/HIV patients

The key issue in the clinical management of HCV/HIV-coinfected patients is the treatment decision for each condition and when to initiate it. By the end of the laboratory and clinical assessment of patients with HCV/HIV coinfection, patients can be split into four categories:

1. patients not requiring hepatitis C or HIV/AIDS treatment
2. patients requiring only hepatitis C treatment
3. patients requiring only HIV/AIDS treatment
4. patients requiring both hepatitis C and HIV/AIDS treatment.

1. Coinfected patients not requiring any treatment

Coinfected patients not requiring any treatment meet the following criteria:

- CD4 count >350 cells/mm^3 and absence of HIV-related symptoms, and
- HCV antibodies, but absence of HCV RNA replication.[7]
- Coinfected patients *not* needing treatment should be monitored every six months (clinical follow-up, liver function tests) and every three years for histological liver lesions (using alternatives to liver biopsies).

2. Coinfected patients requiring only HCV treatment

Coinfected patients requiring only HCV treatment meet the following conditions:

- CD4 count >350 cells/mm^3 and absence of HIV-related symptoms, and
- active or chronic hepatitis C.[8]

HCV treatment offers the possibility of eradicating HCV within a defined treatment period. In the following situations, where the benefits outweigh the risks, there are two main reasons to consider all HCV/HIV-coinfected patients for HCV treatment:

- The liver disease progresses more rapidly to end-stage complications and at earlier ages than in HCV-monoinfected patients.
- Patients are at higher risk for developing hepatotoxicity following the initiation of ART than HIV-monoinfected patients. Efficient HCV treatment will hence facilitate the subsequent management of ART.

2.1. Indications for HCV treatment

- Genotype 2 or 3 regardless of HCV viral load or histology
- Genotype 1, viral load ≤800 000 IU/ml regardless of histology
- Genotype 1 or 4, viral load >800 000 IU/ml and moderate or severe fibrosis

2.2. Predictors of sustained virological response probability

Several baseline parameters can predict a greater likelihood of achieving an SVR *(32)*:

- infection with genotype 2 or 3
- viral load ≤800 000 IU/ml
- absence of cirrhosis
- age <40 years
- ALT levels >3 x upper limit of normal.

[7] Some patients may have HCV RNA but harbour genotype 1 or 4 and a mild disease. In such cases, treatment is not recommended; regular yearly monitoring is the recommended option, with an assessment for liver fibrosis after three years.
[8] For patients with evidence of advanced liver fibrosis, HCV treatment should be a priority.

2.3. Contraindications for hepatitis C treatment

The following contraindications for treatment of hepatitis C should be borne in mind:

- pregnancy, because of risk of IFN and RBV[9,10]
- cardiopathy, such as ischaemic disease and cardiac insufficiency
- psychiatric disorders or history of same
- active alcohol intake (>50 g/day)
- decompensated cirrhosis (Child-Pugh C).[11]

2.4. Treatment of acute hepatitis C

- Treatment of acute hepatitis C may reduce the risk of chronicity *(51)*. Therefore, if serum HCV RNA is not eliminated spontaneously within three months of the disease onset (clinically and/or laboratory documented), treatment with PEG-IFN is recommended for six months *(51)*.
- The use of combination treatment in this population remains a field of research.

2.5. Treatment of chronic hepatitis C (doses and schedules)

All patients should receive a combination of PEG-IFN α2a or α2b and RBV. The standard dose for PEG-IFN α2a is 180 μg once weekly (QW), and for PEG-IFN α2b it is 1.5 μg/kg body weight QW *(2–5)*.

The dose of RBV is critical. Although clinical trials in HIV/HCV-coinfected patients have used a fixed dose of 800 mg per day [400 mg twice daily (BID)] for all genotypes, studies from HCV-monoinfected patients support the use of 1000 mg to 1200 mg RBV per day (in 2 doses) for treatment of infections with genotypes 1 and 4, and 800 mg RBV per day (400 mg BID) for genotypes 2 and 3 *(49)*.

The current recommendations are as follows:

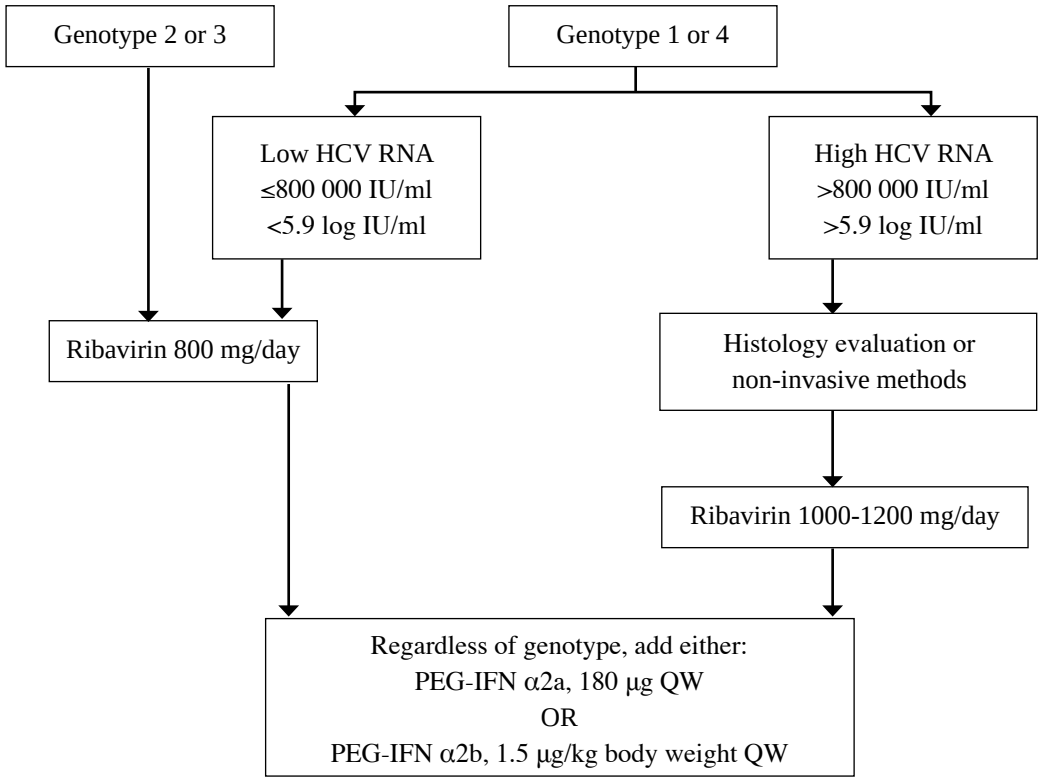
- for HCV/HIV-coinfected patients with genotype 1 or 4, an initial RBV dose of 1000–1200 mg once daily (OD);
- for HCV/HIV-coinfected patients with genotype 2 or 3, 800 mg OD *(43)*.

[9] Limited data suggest IFN does not have any effect on the embryo or foetus.

[10] RBV is teratogenic (causes birth defects) in multiple animal species and its use during pregnancy is contraindicated *(48)*. Since RBV may cause abnormalities in sperm, men taking it should wait six months after discontinuing use before attempting to impregnate a woman.

[11] IFN is very badly tolerated in these patients *(49)*; however, after regression of the decompensation, treatment may sometimes be initiated *(50)* and liver transplantation should be the primary treatment option for such patients.

Fig. 8. Therapeutic algorithm for HCV treatment in HIV-infected patients



Source: Alberti et al., Sulkowski *(43,52)*

2.6. Treatment duration

Regardless of genotype, the expected duration of treatment in coinfected patients should be 48 weeks. However, depending on HCV RNA levels at week 12, treatment may be interrupted earlier (refer to Algorithms 1 and 2 in section II.1.4 above) *(43)*.

Genotype 2 and 3 patients treated for six months have significantly higher relapse rates than those treated for one year *(5, 53)*. Therefore, all HCV/HIV-coinfected patients should be treated for one year. HCV genotype can be used as a predictor of response but not as a basis for modifying treatment duration, as with immunocompetent patients.

3. Coinfected patients requiring only HIV/AIDS treatment

Coinfected patients requiring only HIV/AIDS treatment satisfy at least one condition in each of the following bullet points

- CD4 count ≤350 cells/mm^3 in symptomatic patients or patients with viral load >100 000 copies/ml, *or* CD4 count ≤200 cells/mm^3 irrespective of symptoms;
  and
- HCV antibodies but no HCV RNA replication, or hepatitis C with contraindications to treatment (in the knowledge that they may be transient – see section III.2.3 on contraindictions).

3.1. Initiation of HAART

Initiation of ART in HCV/HIV-coinfected patients should follow the current recommendations for HIV-monoinfected patients *(54)*. (For further details, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*) (see Table 6)

Table 6. Recommendations for initiating HAART in HCV/HIV-coinfected patients

CD4 cell count	Recommendations
CD4 <200 cells/mm^3	Antiretroviral treatment
CD4 200–350 cells/ mm^3 or VL > 100 000 copies/ml	Antiretroviral treatment should be considered when there is a high viral load, a rapid decline in CD4 count or the presence of symptomatic HIV disease. It should be started before the CD4 count falls to <200 cells/mm^3.

3.2. Considerations in choosing a HAART regimen

In HCV/HIV-coinfected patients, the selection of an adequate first-line regimen should take into account major concerns and potential problems:

- adherence (a once-daily regimen should be favoured);
- hepatotoxicity of non-nucleoside reverse transcriptase inhibitors (NNRTIs) (acute, such as with nevirapine (NVP));
- drug interaction: didanosine (ddI) and zidovudine (ZDV) with RBV, efavirenz (EFV) and PEG-IFN (severe depression);
- use of opioid substitution therapy (OST): pharmacokinetic interaction between NNRTIs and methadone or buprenorphine (dose adjustments);
- coexistent medical/psychiatric conditions; and
- the same concerns as in monoinfection: potency, maintenance of future options, cost and availability.

3.3. First-line HAART regimens

Table 7. Treatment Regimens for first-line HAART in HCV/HIV-coinfected patients

	ARV drug classes	HAART regimens
Preferred first line	2 NRTIs + 1 NNRTI	ZDV[a] or d4T ↘ ↗ EFV[b] 3TC or FTC[c] ABC or TDF ↗ ↘ NVP[b]
Alternative first line	3 NRTIs	ZDV[a] ↘ ↗ ABC[d] 3TC or FTC[c] d4T ↗ ↘ TDF

[a] ZDV is not an absolute contraindication if a patient is on RBV, but haemoglobin (Hb) levels should be closely monitored.
[b] EFV has been considered the preferred NNRTI option, but NVP can be considered for patients without evidence of hepatic dysfunction, with close monitoring. However, it should be avoided in HIV-infected patients if CD4 is >400 cells/mm^3 (>250 mm^3 in women) *(55)*.
[c] Emtricitabine (FTC) is equivalent to 3TC. FTC is available together with TDF, and 3TC together with ABC as fixed-dose combination (FDCs).
[d] ZDV/3TC/ABC regimen is available as an FDC.

- In case of severe toxicity and side-effects in first-line antiretrivorals (ARVs), substituting another ARV with a different toxicity profile within the front-line regimens is recommended.
- Switching to second-line ARV regimens is recommended in the absence of immunological or virological response to ART, as measured by CD4 cell count and viral load. (Please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents* for further details).

3.4. Second-line HAART regimens

For second-line HAART, WHO recommends selecting three different drugs containing at least one new pharmacological class.

- The best options are regimens with a boosted protease inhibitor (PI) as the key drug, together with two nucleosides if a classical approach of 2 NRTIs + 1 NNRTI was the first-line treatment.
- In case of a simplified first choice with 3 NRTIs, the second-line should use a boosted PI + 1 NNRTI and/or 1 NRTI.

Among second-line NRTIs, those with better resistant profiles, such as ddI, ABC and TDF, should be given preference.

- The combination d4T+ddI has to be avoided due to the risk of mitochondrial toxity, leading to hepatic steatosis and potentially enhancing fibrosis *(56)*.
- TDF/ddi is also contraindicated due to negative pharmacological interactions.

Table 8. Treatment regimens for second-line HAART in HIV/HCV-coinfected patients

	ARV drug classes	HAART regimens
Preferred second line	2 NRTIs + 1 boosted PI	ABC + TDF or ABC + ddI[a] + LPV/r or SQV/r or ATZ/r[b]
Alternative second line	1 NNRTI +/- 1 NRTI + 1 boosted PI or double PI	ABC ↘ ↗ TDF EFV ➔ LPV/r SQV/r ATZ/r[b] or LPV/r + EFV or LPV/r + SQV

[a] A ddI dose in combination with TDF should be adjusted to less than 4.1 mg/kg per day so as not to compromise immune recovery. It is contraindicated in patients with cirrhosis and under RBV treatment, and should be used with caution in patients with less severe liver disease.
[b] Unboosted ATZ or NFV can be used in absence of a cold chain.

4. Coinfected patients requiring both HCV and HIV/AIDS treatment

Coinfected patients requiring both HCV and HIV/AIDS treatment meet the following criteria:

- CD4 count ≤350 cells/mm^3 in symptomatic patients or patients with viral load >100 000 copies/ml, or CD4 count ≤200 cells/mm^3 irrespective of symptoms; and
- acute or chronic hepatitis C.[12]

4.1. Strategy for initiation of treatment

See Table 9 below.

- If a coinfected patient has severe immunodeficiency (CD4 count <200 cells/mm^3), the CD4 count should be improved using HAART before commencing HCV treatment.
- If CD4 is between 200 and 350 cells/mm^3, HCV treatment should be offered first in order to avoid interactions between HAART and anti-HCV drugs and facilitate adherence. After HCV treatment is finished (12 months), HAART should be initiated.
- Patients, who need or are receiving HAART, should be in stable treatment (adherence to treatment, absence of side-effects, CD4 >200 cells/mm^3) for a few months before starting HCV treatment. HAART should be continued during HCV treatment but ddI, ZDV or d4T should be changed for other drugs (ABC, TDF, etc.) before initiating RBV.

[12] For patients with evidence of advanced liver fibrosis, HCV treatment should be a priority.

- In some cases (if CD4 nadir has never been <200 cells/mm^3), interruption of HAART during HCV treatment is feasible if the patient asks for it. In this case, the original regimen is usually reintroduced after the end of HCV treatment or in case the CD4 count drops <200 cells/mm^3 during the treatment.
- Patients with a low baseline CD4 count (<200 cells/mm^3) may tolerate HCV treatment less well and may be at higher risk for developing opportunistic infections, since IFN treatment is often associated with loss of CD4 cells in the bloodstream, although the CD4 percentage is conserved *(2–5)*.

Table 9. Algorithm for initiation of hepatitis C treatment and HAART in HCV/HIV-coinfected patients

Patients	HAART		HCV treatment
Untreated	**No indication for ARV** CD4 >350 cells/mm^3	⇨	Treat HCV first
	ARV initiation indicated CD4 200–350 cells/mm^3		Treat HCV first, then initiate HAART
	CD4 <200 cells/mm^3	⇨	Initiate HAART, wait until stable, and regimen is well tolerated, then treat HCV
ARV-treated	Replace ddI and ZDV if on alternative options. It is possible to interrupt HAART until the end of HCV treatment (if CD4 nadir was never <200 cells/mm^3, and patient asks for it).		Treat HCV if CD4 > 200 cells/mm^3.

4.2. Considerations of ARVs when treating both HCV and HIV infections

4.2.1 Zidovudine (ZDV)

ZDV, when taken concomitantly with RBV, is associated with an increased frequency of anaemia, but not severe neutropenia. When alternative options are available, ZDV should be replaced by another NRTI during HCV treatment.

4.2.2 Didanosine (ddI)

Didanosine used in association with RBV was shown to be associated with a markedly increased risk of lactic acidosis, pancreatitis (57, 58) and an unexpected number of hepatic decompensations in patients with cirrhosis (59). It is consequently contraindicated in patients with cirrhosis and should be used with caution in patients with less severe liver disease during PEG-IFN + RBV combination treatment.

4.2.3 Efavirenz (EFV)

EFV and PEG-IFN can be co-prescribed but must not be initiated simultaneously, as both drugs can induce psychiatric troubles. If EFV is well tolerated then IFN can be added.

4.2.4 Protease inhibitors (PIs)

A potential negative impact of PI use on SVR in patients with HCV/HIV coinfection treated with PEG-IFN + RBV has been suggested in a subgroup analysis of a single study (25). As there is no solid evidence regarding this possible negative impact of PI use on SVR, PIs cannot be excluded from recommended ARVs for HCV/HIV patients. However, more research is needed to obtain better evidence.

4.3. Hepatotoxicity of ARV drugs

HAART is associated with a higher risk of hepatotoxicity (defined as at least two fold ALT/AST increase above upper limit of normal (ULN)) in HCV/HIV-coinfected patients than in HIV-monoinfected patients *(30, 60–64)*. However, the incidence and risk factors for liver enzyme elevations in large cohorts of HCV/HIV-coinfected patients are not well defined. In several studies, however, independent risk factors for hepatotoxicity have been identified *(30, 60–64)*:

- previous liver transaminase elevations to a grade ≥ III
- higher baseline alanine amino-transferase values
- viral coinfection
- high plasma drug levels
- degree of immune damage *(64)*.

Hepatotoxicity has been associated with all currently used ARV drugs, but existing studies fail to demonstrate a consistent association between particular drugs or drug classes and the development of subsequent hepatotoxicity. Comparison of HAART regimens (single-PI, multiple-PI and NNRTI-based) has given inconsistent results for liver-tolerability in cohorts in which HCV/HIV-coinfected patients are underrepresented.

- Acute hepatotoxicity: in a single cohort study involving HCV positive and negative patients, the use of NVF within 12 weeks of initiating treatment and the use of full-dose ritonavir (RTV) (600 mg BID) have been implicated *(62)*. But most liver enzyme elevation events are sub-clinical and usually reverse spontaneously. NVP is not contraindicated in all HCV/HIV-coinfected subjects, but should be closely monitored when used in asymptomatic patients. A majority of experts recommend avoiding its use in patients with evidence of liver dysfunction.
- Chronic hepatotoxicity: the prolonged use of nucleoside analogue reverse transcriptase inhibitors (especially of those having a strong affinity for mitochondrial deoxyribonucleic acid (DNA) polymerase, such as ddI and d4T) exposes treated patients to a risk of chronic mitochondrial toxicity, whose target, among other organs, is the liver. This toxicity, possibly exacerbated in some patients by the specific chronic toxicity of PIs on the liver, may lead to hepatic steatosis and worsen pre-existing fibrosis.

4.4. ARV dose adjustment in patients with cirrhosis

- Like a majority of drugs metabolized in the liver, antiretroviral agents such as PIs and NNRTIs are metabolized with difficulty in patients with cirrhosis *(65, 66)*.
- Although the relationship between high plasma concentrations and toxicity is not constant for all antiretroviral agents, it has been clearly demonstrated for certain PIs, such as NFV, LPV and amprenavir (APV), and NNRTIs such as EFV *(67–70)*.
- Of the NRTIs, only ZDV and ABC are metabolized by liver enzymes other than cytochrome P450 (CYP) *(65, 66)*. Consequently, use of PIs, NNRTIs, ZDV or ABC in patients with liver-decompensated cirrhosis requires dosage adjustment in order to avoid a risk of drug accumulation. However, little specific guidance has been established to precisely adapt ARV dosages in patients with cirrhosis.

Table 10. Recommendations for antiretroviral dosage adjustment in patients with ESLD

ARV	Main metabolism pathway	Pharmacokinetic in ESLD	Adjustment recommendation
NRTI			
Zidovudine	80% liver glucuronidation and <5% renal elimination	Accumulation and increased risk of haematological toxicity	Dosage adjustment may be useful but no specific recommendations. Clinical monitoring and decreased daily dose in case of intolerance (anaemia).
Lamivudine	80% renal elimination	Not affected	No change
Emtricitabine	80% renal elimination	No data	No change
Stavudine	80% renal elimination	Not affected	Avoid due to high risk of hepatic steatosis.
Didanosine	50% renal elimination	No data	Avoid due to high risk of hepatic steatosis and pancreatitis.
Tenofovir	80% renal elimination	Not affected	No change
Abacavir	Liver glucuronidation; <5% renal elimination	Accumulation	Avoid.
NNRTI			
Nevirapine	Liver (CYP enzymes)	Reduced clearance	Avoid due to the risk of severe hepatotoxicity (grade 3 or 4).
Efavirenz	Liver (CYP enzymes)	Reduced clearance Little information	Careful monitoring of CNS side-effects if elevated transaminases. Drug monitoring if available.
PI			
Nelfinavir	Liver (CYP enzymes)	Reduced clearance	Drug monitoring
Indinavir	Liver (CYP enzymes)	Sparse data	Drug monitoring. If not available, dosage has to be reduced at least to: - 600 mg three times daily without RTV; or - 600 mg + 100 mg RTV BID.
Saquinavir	Liver (CYP enzymes)	No data	Drug monitoring
Lopinavir/r	Liver (CYP enzymes)	Altered	Drug monitoring
Atazanavir	Liver (CYP enzymes)	Altered	Decrease by 50%.
Amprenavir	Liver (CYP enzymes)	Altered	Decrease the dose: - to 450 mg BID if Child-Pugh A - to 300 mg BID if Child-Pugh B–C.
Fosamprenavir	Liver (CYP enzymes)	Altered	Contraindicated if severe liver disease

Source: Wyles & Gerber, Salmon & Taburet *(65, 66)*.

4.4.1 Recommendations

- In the absence of specific recommendations, the full dose of ARVs is usually prescribed in patients with compensated cirrhosis.
- If therapeutic drug monitoring is available, residual drug concentrations of ARVs should be measured at the first monitoring visit in order to adjust dosages.
- In cases of decompensated cirrhosis where drug monitoring is not available, one should:
  - avoid NNRTIs
  - reduce the daily dosage of ZDV and ABC
  - reduce the daily dose of most PIs (precise data are lacking).

5. Clinical monitoring

HCV/HIV coinfected patients should be carefully monitored during treatment. For monitoring of patients receiving ART please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

Patients treated for HCV should be followed monthly for clinical evaluation of treatment tolerance. The tests to be regularly performed are shown in Table 11.

Table 11. Monitoring during treatment

		Before treatment	W4	W8	W12	W16	W20	W24	W28	W32	W34	W36	W48	W72
Tolerance	Blood count and platelets*		W1 W2 W4	X	X	X	X	X	X	X	X	X	X	X
	CD4			X	X			X	X	X	X	X	X	X
	TSH				X			X			X			
Efficacy	Quantitative HCV viral load	X			X									
	Qualitative HCV RNA							X					X	X

Note: W=week
* Blood and platelets counts should also occur during weeks 1 and 2.

5.1. Virological response monitoring

See Table 11 above.

The virological response should be monitored by serum HCV RNA quantification before initiation of treatment and 12 weeks after starting treatment using the same sensitive test with a lower detection limit of 50 IU/ml:

- For patients with at least a 2 log reduction in viral load at week 12 – defined as an early virological response (EVR) – treatment should be continued.
- If a 2 log reduction in viral load is not achieved at week 12, treatment should be stopped, because the negative predictive value of achieving SVR is 99–100%. This rule is applicable to all genotypes.

The log rule at week 12 in coinfected patients is of great relevance to optimizing treatment. It encourages treatment of all candidates in the absence of contraindication, given that treatment can be stopped after 12 weeks if there is no chance of a cure.

After week 12, assessment should be made by a qualitative HCV RNA test, as follows:

- Week 24: for patients remaining positive for serum HCV RNA at week 24 (negative predictive value for achieving SVR is 100%), treatment should be discontinued.
- Week 48 marks the end of treatment response.
- Week 72: after six months off treatment, negative HCV RNA indicates an SVR. Recurrence of HCV infection thereafter is very rare.
- A new assessment might also be useful 12–24 months after the end of treatment.

5.2. Histological response monitoring

A new liver biopsy is not indicated except in patients with no SVR, for whom the result of liver biopsy could modify HCV treatment.

5.3. Tolerance monitoring

See Table 11 above.

A full blood count as well as transaminases and bilirubin tests should be performed in weeks 1, 2 and 4, and thereafter on a monthly basis. CD4 cell count should be monitored monthly. Additional laboratory tests can then be carried out at the physician's discretion and should include assessment of thyroid-stimulating hormone (TSH) at least every three months.

5.4. Management of toxicity and side-effects of PEG-IFN + RBV treatment

Side-effects of PEG-IFN and RBV occur in a majority of patients and may be severe *(2–5, 71)*. Effort should be made to keep patients on the optimal dose of PEG-IFN plus RBV and to proactively manage side-effects of treatment. It is important to maintain the optimal doses of RBV and PEG-IFN during treatment, especially during the first 12 weeks. The use of erytropoetin may make it possible to avoid decreasing RBV dosage *(72)*. However, if severe side-effects or laboratory abnormalities develop during treatment and no growth factor is available, the dosages of each product have to be modified until the reactions disappear, as described in section 5.4.2 below.

5.4.1. Anaemia and neutropenia

- Anaemia (<10 g/dl) is reported in up to 30% of patients receiving PEG-IFN + RBV and has been shown to impair quality of life *(2–5, 71)*.
- Anaemia increases with the concomitant use of ZDV and a lower baseline haemoglobin.
- ZDV should be replaced in patients with ART alternatives.
- Neutropenia (<1000 cells/mm^3) is observed in up to 50% of patients, but serious bacterial infections seem infrequent *(2–5, 71)*.

5.4.2. Dose adjustment of PEG-IFN and RBV

Table 12. Dose adjustment for side-effects and toxicity

	Reduce RBV to 600 mg	Withhold RBV	Reduce PEG-IFN by 70%, 50%, 25%	Withhold PEG-IFN	Discontinue combination
Absolute neutrophil count			<750/mm^3	<500/mm^3	
Platelet count			25 000–50 000/mm^3		<25 000/mm^3
Haemoglobin					
- no cardiac disease	8.5–10.0 g/dl	<8.5 g/dl			
- stable cardiac disease	decrease of ≥2 g/dl during any four weeks	<12 g/dl despite four weeks at reduced dose			

Source: European Medicine Agency *(73, 74)*.

- RBV should be reduced to 600 mg/daily (200 mg in the morning and 400 mg in the evening) if either of the following applies:
  - the haemoglobin of a patient without significant cardiovascular disease falls to <10 g/dl and ≥8.5 g/dl; or
  - the haemoglobin of a patient with stable cardiovascular disease fall by ≥2 g/dl during any four weeks of treatment (a return to the original dosage is not recommended).
- RBV should be discontinued if either of the following applies.
  - The haemoglobin of a patient without significant cardiovascular disease falls to <8.5 g/dl.
  - A patient with stable cardiovascular disease maintains a haemoglobin value <12 g/dl despite four weeks on a reduced dose.

If the abnormality is reversed, RBV may be restarted at 600 mg daily, and be increased to 800 mg daily at the discretion of the treating physician (a return to the original dosage is not recommended).

- In case of RBV intolerance, PEG-IFN monotreatment should be continued.
- Dose reduction of PEG-IFN is recommended if the neutrophil count is <750/mm^3 as described in Table 12 *(53)*. For patients with an absolute neutrophil count <500/mm^3 treatment should be suspended until values return to >1000/mm^3. Treatment should be reinstituted at 50% of the dose and the neutrophil count monitored.
- A 50% dose reduction is recommended if the platelet count is <50 000/mm^3. Cessation of treatment is recommended when platelet count decreases to levels <25 000/mm^3.

5.4.3. Influenza-like symptoms

- Paracetamol (possibly combined with non-steroidal anti-inflammatory drugs) should be used for influenza-like syndrome, particularly before injection of PEG-IFN.
- Low platelets are a relative contraindication for the use of acetylsalicylic acid, diclofenac or ibuprofen, because of the inhibition of platelet aggregation.
- Dose adjustment may be required in case of severe side-effects despite symptomatic treatment. An initial dose reduction to 75% or 50% of the dose is generally adequate.

5.4.4. Nausea

Nausea can be reduced with metoclopramide 10 mg three times daily (TID).

5.4.5. Depression

- Depressive mood changes are frequent and should be managed proactively with symptomatic treatment. In patients with a history of neurotic or minor depression, initiation of treatment with antidepressants before starting IFN-based treatment should be considered. Antidepressants are frequently needed for clinically-relevant depression. Use the following dosages:
  - selective serotonin reuptake inhibitors such as citaprolamin, paroxetin and tricyclic at initial dosages of 20 mg/day; and
  - antidepressants such as doxepine at an initial dosage of 50 mg/day.
- Consultation with an experienced psychiatrist for the establishment of a standardized treatment procedure is recommended.
- In patients with pre-existing depressive mood disorders or other profound neurotic disorders, initiation of specific psychiatric medication is recommended to reduce the destabilizing effect of IFN-based treatment.
- In patients with a history of hospitalization due to major depression or psychosis, IFN-based treatment is generally contraindicated. In large controlled studies the incidence of attempted or completed suicides, psychosis and major depression is <1% *(2–5, 71)*. The choice of treatment strategy should be made in consultation with a psychiatrist.
- In patients with a history of injecting drug use, benzodiazepines should be avoided because of their potential to induce addiction.

5.4.6. Dysthyroidism

IFN-induced dysthyroidism occurs in 7% of patients, but does not require treatment interruption.

- Thyroid hormone substitution is used in case of hypothyroidism.
- Beta-blockers are useful to relieve symptoms of hyperthyroidism *(75)*.

5.5. Management of treatment adherence

Even among patients who are appropriate candidates for treatment with IFN, acceptance of treatment is low in HCV/HIV-coinfected populations, predominantly due to treatment side-effects and toxicity. However, a proportion of patients who initially decline IFN treatment accept it after education and peer support programmes to facilitate successful treatment. Patients may continue to

work if necessary, with possible working time adjustments to accommodate for treatment and drug reactions.

Counselling is essential to increasing adherence. Physicians should:
- listen to patients' complaints
- teach them to recognize and manage side-effects
- discuss ways to improve compliance.

A team approach to patient care and management is an effective strategy for increasing adherence. The team should include physicians, nurses, psychiatrists where relevant and social workers or other care providers.

Initiatives that have proven effective include directly observed treatment, patient discussion groups, patient manuals, hotlines and psychological support. For further information on adherence please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users,* and Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

5.6. Management of non-responders

Non-response can be observed in any HCV treatment, ranging from "no viral decline during treatment" to "end-of-treatment virological response and subsequent virological relapse". The decision to treat patients again with PEG-IFN plus RBV should be based on:
- type of response
- toleration of the previous treatment
- extent of liver damage
- HCV genotype.

If the therapeutic aim in treating patients with biopsy-proven advanced fibrosis/cirrhosis is to delay or prevent disease progression in non-responders at week 12 and/or week 24, continuation with PEG-IFN monotreatment can be considered, since a histological response was observed in about 35% of non-responders who received PEG-IFN + RBV in four pivotal trials *(2–5)*. However, data on dose, duration and clinical benefits of such maintenance treatment are very scarce in HCV/HIV-coinfected patients, and further research is needed.

5.7. Management of end-stage liver disease (ESLD)[13]

5.7.1. Testing for hepatocellular carcinoma (HCC)

Cirrhotic patients should be screened for HCC at four-to-six-month intervals using ultrasonography and measurement of alfa-fetoprotein levels *(43)*. It has been found that HCC occurs more rapidly and is more aggressive in patients with HIV infection *(76)*. Patients whose test results are abnormal should be followed up at referral centres for diagnosis, staging and treatment, which is only available for early-stage HCC *(77)*.

5.7.2. Testing for oesophageal varices

Annual endoscopy, including the investigation of oesophageal varices in the gastric fundus, is recommended *(43)*. In the presence of significant oesophageal varices, a prevention of bleeding by non-cardioselective beta-blockers (associated with variceal ligation in case of > grade 2 varices) is recommended *(78)*. The most frequently prescribed drug is propanolol at a dosage varying from 40 to 160 mg/day in order to obtain a blocking effect (cardiac pulse reduction of 30%).

[13] For further details on ESLD, please see Annex 4.

5.8. Drug–drug interactions

5.8.1. Interactions between HIV drugs and HCV drugs

Interactions of ARV agents and anti-HCV drugs must be taken into account, as they partially explain the high rate of side-effects in HCV/HIV-coinfected patients treated for HCV.

- RBV competes for phosphorylation with thymidine and cytosine analogues such as ZDV and d4T *(79, 80)*. However, in controlled trials, no effect of RBV on the efficacy of the ARV combination treatment has been observed *(81)*.
- IFN has a moderate antiretroviral effect which may compensate for the effect of RBV on the efficacy of the ART regimen *(82)*.
- In contrast, the phosphorylation of ddI is increased by RBV *(83–87)*, which may explain some side-effects observed in co-administration *(56–58)*.

5.8.2. Interactions among recreational drugs, OST, anti-HCV drugs and ARVs

- No finding of interaction between opioids and anti-HCV drugs has been published.
- All PIs and NNRTIs are substrates and potent inhibitors or inducers of the cytochrome P450 system. Many classes of recreational drugs, including benzodiazepines, amphetamines and opioids, are also metabolized by the liver and can potentially interact with antiretrovirals. Overdoses as a secondary reaction to interactions between the amphetamine-type stimulants (MDMA) and PIs, particularly RTV, have been reported.
- ARVs that are CYP3A4 inducers (NVP, EFV and PIs) can decrease the level of methadone, causing withdrawal symptoms and increasing the risk of relapse into heroin abuse.
- An opiate metabolism can be inhibited or induced by concomitant PIs, so patients should be monitored for signs of toxicity. Withdrawal symptoms generally occur within 4–10 days of ART initiation. Withdrawals should be monitored clinically and dose increases of 10 mg increments from days 8–10 should manage the problem.

5.9. Hepatotoxicity of TB drugs in chronic HCV infection

- The rate of hepatotoxicity is significantly higher in TB patients with HCV or HBV coinfection (59%) than without coinfection (24%) *(88)*.
- Commonly used anti-TB drugs, such as isoniazid, rifampicin, pyrazinamide and ethambutol, are all hepatotoxic.
- Pyrazinamide is the most hepatotoxic and should be avoided in TB patients with severe chronic liver disease *(89)*.
- It is not necessary to adapt doses of anti-TB drugs in hepatic insufficiency.
- In decompensated liver disease, a regimen without pyrazinamide should be used.
- Streptomycin, ethambutol, and a reserve drug such as fluoroquinolone can be used if treatment is necessary in patients with fulminant liver disease. Consultation by a specialist is required.
- Alternative anti-TB drugs with lower hepatotoxicity (rifabutin, amikacin, ofloxacin, levofloxacin, etc.) might be used in cases of severe liver dysfunction, The treatment of these special cases should be decided in consultation with an acknowledged expert.
- Hepatotoxicity occurrence justifies a monthly monitoring of liver functions.

IV. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected is important in the development of key indicators on access to treatment and its success. Such indicators assist managers in decision-making on ways to strengthen and expand these services to all those in need.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV patients ("seen for care" – this will be the denominator for the data below);
- number of HIV patients coinfected with HCV;
- number of HCV/HIV-coinfected patients with chronic hepatitis C;
- number of HCV/HIV-coinfected patients with chronic hepatitis C receiving:
  - only HCV treatment
  - only ART
  - both treatments; and
- number of HCV/HIV-coinfected patients who have died (in a given period) including cause of death (e.g. liver-related deaths, HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

Annex 1. Laboratory assays for HCV *(31)*

Detection of HCV antibodies

Detection of HCV antibodies is the first step in screening patients for suspected HCV infection. Currently available assays are highly sensitive, and specific HCV antibodies are detected with enzyme immunoassays (EIA). These assays detect mixtures of antibodies directed against various HCV epitopes located in HCV proteins: core, NS3, NS4 and, in third-generation tests, NS5 *(1, 6)*. The specificity and sensitivity of currently available EIAs for HCV antibodies are greater than 99% in immunocompetent patients with active viral replication (presence of HCV RNA). For patients with acute HCV infection, it is important to bear in mind that antibodies may not be detectable for three to eight weeks following initial infection.

The presence of HCV antibodies is indicative of past or present infection. Antibodies persist indefinitely in chronically infected patients, but antibody titres may decrease or even disappear in patients who clear HCV either spontaneously or after ART.

Different types of assays and immunoblot tests, were used in the past to confirm positive EIAs results in low-risk populations, such as in healthy blood donors. The excellent performance of currently available EIAs and the general availability of HCV RNA testing make these assays outdated. In blood banks, nucleic acid testing (NAT) has recently been implemented. With NAT, the presence of HCV RNA is analyzed in small blood pools and, if a viral genome is detected, an individual analysis of the implicated blood samples is performed. With the addition of NAT, the risk of HCV transmission has been reduced to around 1/1 000 000 donations.

Qualitative detection of HCV RNA

HCV RNA can be detected as soon as a few days after infection. In general, qualitative assays to detect HCV RNA are more sensitive than most currently available quantitative assays. However, the latest quantitative methods are very sensitive and in the future could become the universally used methods.

The qualitative detection procedure begins with RNA extraction from clinical samples. In most centres RNA extraction has become fully automated, increasing its reproducibility. Thereafter, the target is amplified, either by PCR or TMA.

There are currently two commercially available qualitative assays to detect HCV RNA: one PCR-based assay (Cobas Amplicor HCV v. 2.0, Roche) with a sensitivity of 50 IU/ml and one TMA assay (Versant HCV RNA qualitative assay, Bayer) with a sensitivity of 5–10 IU/ml. The specificity of both assays is close to 100%.

Quantification of HCV RNA

In individuals who become chronically infected, HCV RNA levels are relatively stable over time *(90)*. HCV RNA quantification can be obtained by two techniques.

1. PCR assays
Quantification is based on amplification of the viral template with a known amount of synthetic RNA standard added to each reaction. The relative amounts of amplified viral template and standard amplicons are measured at the end of the PCR reaction. More recently, "real time" PCR has been developed, with many advantages such as simplicity, rapidity, wider linear range of HCV RNA concentrations and minor risk of contamination. Real-time PCR is already replacing conventional PCR assays.

2. DNA assay
Another approach to quantifying HCV RNA is signal amplification, in which viral genomes are released from the virions and hybridized in solution using target probes. The HCV RNA with target probes are

then captured onto microwell plates. Additional target probes bind the viral RNA to branched-DNA amplifier molecules. The signal is amplified by hybridization of oligonucleotide probes conjugated with alkaline phosphatase for detection and quantification of the HCV RNA.

Determination of HCV genotype *(91)*

Two methods can be used to determine HCV genotype:

1. RT-PCR assay, based on analysis of the 5' untranslated region of the HCV genome is the most commonly used method. Typing errors are rare but can occur between genotype 1 and some isolates of genotype 4; sub-typing errors might occur in 15–20% of cases. These errors can be explained by the high degree of nucleotide conservation within this region.

2. Serology: determination of HCV genotype can also be performed by detecting type-specific antibodies. Several antigenic determinants have been identified after epitope mapping of the NS4 and core proteins of HCV. These epitopes have been used to develop a competitive EIA (Murex HCV EIA) and an immunoblot assay (RIBA, Chiron Corp).

There are studies demonstrating a lower performance of tests aimed at detecting HCV antibodies in HIV-infected patients, as well as cases of HCV antibody seroconversion coinciding with the administration of HAART (probably due to immune restoration). However, latest generation HCV antibody EIAs have incorporated multiple HCV antigens and are very sensitive in HIV-infected patients. Recently, sera from 559 HIV-infected and 944 HIV-negative IDUs were tested both for HCV antibodies using a third-generation assay and for HCV RNA using a commercially available test. Of the HIV-infected individuals, 547 (97.8%) had detectable HCV antibodies, and only one HCV antibody-negative patient had detectable HCV RNA *(27, 28)*. The figure was similar for HIV-negative patients, indicating that HCV antibody screening using latest generation assays is reliable in coinfected patients.

Annex 2. Alternative biochemical tests to assess hepatic fibrosis

Table 13. Initial reports from all major serum assays

	No. of patients	Serum markers	Significant fibrosis	Auro (95% CI)	Cut-off	Sensitivity	Specificity	PPV[a]	NPV[b]	Comments
Indirect assays										
Wai et al. *(92)*	192	APRI (AST, platelets)	Ishak ≥3	0.88 (0.80–0.96)	≤ 1.5	41%	95%	88%	64%	Simple index; accurately predicts significant fibrosis and cirrhosis
Forns et al. *(93)*	476	Forns Index (age, GGT, cholesterol, platelet count)	Metavir ≥2	0.86	<4.2	94%	51%	40%	96%	Approx. half of those with insignificant fibrosis detected;. use of cholesterol a confounding variable
Ziol at el. *(94)*	327	FibroScan™ (hepatic elastography)	Metavir ≥2	0.79 (0.73–0.84)	>8.7	56%	91%	88%	56%	Excellent for the detection of cirrhosis; continuous variable strength
Imbert-Bismut et al. *(95)*	134	FibroTest™ (α2 macroglobulin, α2 globulin, .γglobulin, apolipoprotein A1, GGT and total bilirubin)	Metavir ≥2	0.87 (SD 0.34)	0.30	87%	59%	63%	85%	False positives with inflammation and haemolysis; large validated data reported
Castera et al. *(96)*	183	Combined FibroScan and FibroTest	Metavir ≥2	0.88 (0.82–0.92)		NA	NA	NA	NA	Combined score appears to enhance efficacy
Direct assays										
Patel et al. *(97)*	402	Fibrospect hyaluronic acid, tissue inhibitor of metalloproteinase 1 (TIMP-1) and alfa2-macro-globulin	Metavir ≥2	0.831	0.36	77%	73%	74%	76%	No indeterminate score across all stages
Kelleher et al. *(98)*	95	SHASTA (hyaluronic acid, AST & albumin)	Ishak ≥3	0.87	0.30	88%	72%	55%	94%	Detection of early fibrosis in HCV/HIV-coinfected patients
Rosenberg et al. *(99)*	1021	ELF (Propeptide III collagen, TIMP 1, HA)	Scheuer 3 or 4	0.80 (0.76–0.85)	0.102	90.5%	41%	99%	92%	Validated for multiple etiologies; high reproducibility and automated processing strength

[a] PPV: positive predictive value.
[b] NPV: negative predictive value.

Annex 3. Alcohol screening questionnaires

The following is an overview of the most used and well-established alcohol screening questionnaires.

CAGE Test

CAGE *(100)* is an acronym of the four questions:
1. Have you ever felt you ought to **C**ut down on your drinking? (yes/no)
2. Have people **A**nnoyed you by criticizing your drinking? (yes/no)
3. Have you ever felt bad or **G**uilty about your drinking? (yes/no)
4. Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover (**E**ye-opener)? (yes/no)

Item responses are scored 0 or 1, with a higher score an indication of alcohol problems. A total score of 2 or greater is considered clinically significant.

AUDIT Test

The AUDIT Test *(101)* was developed as a simple method of screening for excessive drinking, alcohol dependence and harmful drinking (see Table 14 below). It has the following advantages:
- cross-national standardization, the only screening test designed for international use;
- identifies hazardous and harmful alcohol use, as well as possible dependence;
- it is brief, rapid and flexible;
- designed for primary health-care workers; and
- focuses on recent alcohol use.

A score of 8 in men and 7 in women indicates a strong likelihood of hazardous or harmful alcohol consumption. A score of 13 or more is suggestive of alcohol-related harm.

Table 14. AUDIT TEST

1. How often do you have a drink containing alcohol?				
(0) Never	(1) Monthly or less	(2) 2–4 times a month	(3) 2–3 times a week	(4) 4 or more times a week
2. How many drinks containing alcohol do you have on a typical day when you are drinking?				
(0) 1 or 2	(1) 3 or 4	(2) 5 or 6	(3) 7 to 9	(4) 10 or more
3. How often do you have six or more drinks on one occasion?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
4. How often during the past year have you found that you were not able to stop drinking once you had started?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
5. How often during the past year have you failed to do what was normally expected of you because of drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
6. How often during the past year have you needed a first drink in the morning to get yourself going after a heavy drinking session?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
7. How often during the past year have you had a feeling of guilt or remorse after drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
8. How often during the past year have you been unable to remember what happened the night before because you had been drinking?				
(0) Never	(1) Less than monthly	(2) Monthly	(3) Weekly	(4) Daily or almost
9. Have you or has someone else been injured as a result of your drinking?				
(0) No	(2) Yes, but not in the past year		(4) Yes, during the past year	
10. Has a relative or friend or a doctor or other health worker been concerned about your drinking or suggested you cut down?				
(0) No	(2) Yes, but not in the past year		(4) Yes, during the past year	

Source: Baber et al. *(101)*.

Annex 4. Management of end-stage liver disease

Hepatocellular carcinoma

As HIV-infected patients live longer, especially in industrialized countries where they have access to HAART, HCC may begin to emerge in those who would have otherwise have succumbed to complications from their primary HIV disease. For this reason, HCC is projected to become an increasingly significant clinical problem in the HIV populations *(76, 102–104)*.

Early diagnosis of HCC is particularly important in patients coinfected with HCV and HIV, because it is more aggressive and, in its advanced stages, incurable *(59)*. Prevention, therefore, becomes key to controlling the health-care burden of this disease.

The recommendations for HCC management developed in 2000 by the European Association for the Study of the Liver (EASL) *(105)* are being updated. Such recommendations might be problematic in view of the wide geographical variations in disease epidemiology and treatment availability. Guidelines for managing HCC arising in connection with HIV coinfection are lacking.

Early diagnosis

The 2000 EASL guidelines describe patient selection and surveillance intervals *(105)*. Patients with cirrhosis should be screened, if liver transplantation is feasible. A screening interval of every six months has been established to allow detection of tumours <3 cm in diameter. Patients whose screening results are abnormal should be followed up at referral centres for diagnosis and staging.

Ultrasonography and measurement of alpha-fetoprotein (AFP) levels, at six-month intervals, are the most commonly used methods to screen patients with cirrhosis for HCC *(77, 106)*. AFP values >400 ng/ml are considered diagnostic of HCC.

Treatment

Treatment for HCC is usually classified as curative or palliative *(77, 105)*. Curative treatment includes:

- surgical resection
- liver transplantation
- arterial embolization
- percutaneous ethanol injection in patients with small tumours who are not candidates for resection; a modest survival advantage has been shown for chemoembolization in randomized, controlled trials and one meta-analysis.

Most patients cannot undergo resection or liver transplantation because of underlying cirrhosis or advanced disease at diagnosis.

Early-stage HCC

A solitary tumour <5 cm, or up to 3 tumours <3 cm, in a patient with well-preserved liver function, constitutes early-stage HCC *(4, 8)*. Monoinfected patients can be successfully treated with curative therapies, although response rates and survival benefits are variable. Surgical resection and transplantation yield 5-year survival rates ranging from 60% to 70%. Recurrence, however, can be as high as 50% at 3 years and 70% at 5 years.

Percutaneous ethanol injection induces a complete response in about 80% of patients whose tumours are ≤3 cm. Response rates are lower with large or multinodal tumours *(105)*.

Advanced HCC

Most patients with HCC (approximately 50%) have advanced disease at diagnosis *(77, 105)*. Patients with advanced disease are candidates for loco-regional or systemic treatments rather than curative approaches *(4)*. Transarterial chemoembolization is the only palliative therapy that has been shown to improve survival, with careful patient selection.

Prevention and recurrence

HIV patients are likely to have other risk factors predisposing them to HCC, such as alcohol abuse and concurrent HBV infection. Among HIV patients, vaccination against HBV is strongly recommended. HCV/HIV-coinfected patients should receive treatment for chronic HCV infection using combination IFN and RBV.

Orthotopic liver transplantation

Orthotopic liver transplantation (OLT), where available, is the only therapeutic option for patients with end-stage liver disease. Accumulated experience in North America and Europe in the last five years indicates that three-year survival in selected HIV-infected recipients of liver transplants was similar to that of HIV-negative recipients *(107–110)*. HIV infection by itself is not, therefore, a contraindication for liver transplantation.

As the survival of HIV-infected patients with ESLD is shorter than that of non-HIV-infected patients, the OLT evaluation should be done after the first liver decompensation. The current selection criteria for HIV-positive transplant candidates include:

- no history of opportunistic infections or HIV-related neoplasms, except infections that can be efficaciously treated and prevented, such as TB, candidiasis or *Pneumocystis jirovecii* pneumonia (PCP);
- CD4 cell count >100 cells/mm^3; and
- plasma HIV viral load suppressible with antiretroviral treatment.

For drug users, a two-year abstinence from heroin and cocaine is also required, although patients in a methadone programme can be accepted.

The main problems in the post-transplant period are pharmacokinetic and pharmacodynamic interactions between ARVs and immunosuppressors, and the management of HCV infection relapse, one of the main causes of post-transplant mortality. Experience with PEG-IFN and RBV is scarce in this population.

Table 15. Three-year survival of patients with and without HIV-infection who had a liver transplant before and during the HAART period

Survival	Before HAART (<1996)	During HAART period (1996–2004)	
	HIV-infected patients (n = 32)	HIV-infected patients (n = 24)	Non-HIV-infected patients (UNOS) (n = 5225)
One year	69%	87%	87%
Two years	56%	73%	82%
Three years	44%	73%	79%

Source: Tzakis et al., Miró et al., Ragni et al., *(108–110)*.

Annex 5. Research needs and alternative treatments

Epidemiology

Studies on the epidemiology and the social impact of HCV in patients infected with HIV should be actively investigated, with a special emphasis on vulnerable populations.

HIV management

Studies addressing the optimal time in the course of chronic HIV infection to commence ART in HCV-coinfected patients should be initiated.

HCV management and physiopathology

- Studies to validate the utility of non-invasive methods of liver disease progression should be performed.
- Long-term follow-up studies of patients with and without SVR are strongly encouraged to determine late relapses, the duration of histological improvement and the effect of clinically relevant outcomes such as decompensation, HCC and death.
- Studies on pathophysiology, including extrahepatic viral reservoirs and the specific immune response to HCV, should be conducted.

Future directions for treatment

Research should also investigate:

- optimizing the response to existing treatments, such as higher doses of RBV or PEG-IFN
- treatment durations
- the utility of maintenance treatment
- the optimal regimen for delaying disease progression.

Higher doses of RBV

The optimal RBV dose for treatment of HCV genotype 1 and the potential benefits of prolonged treatment should be investigated. The optimal dose of RBV remains unclear. It is possible that higher SVR rates can be achieved by higher doses of RBV. In most of the published literature on HIV/HCV-coinfected patients, the RBV dose was 800 mg, in order to avoid anaemia, which was considered a greater problem in HIV-infected patients, especially those taking ZDV. However, in HIV-negative patients with genotype 1 HCV infection, it is clear that higher SVR rates are achieved with 1.0/1.2 g RBV (≤75 kg/>75 kg) than with 800 mg *(49)*. Thus, alternative strategies for HIV-infected patients need also to consider higher RBV doses. It is important to note that higher RBV doses appeared to be well tolerated in the Barcelona study *(5)*, where RBV was given by body weight as follows (per day): 800 mg, <60 kg; 1 g, 60–75 kg; and 1.2 g, >75 kg.

Higher doses of IFN

It is possible that higher SVR rates can be achieved by higher doses of IFN but this has not been investigated in HIV-infected patients.

Treatment duration

A shorter duration of treatment for patients with HCV genotypes 2 and 3 should be investigated.

In HIV-negative patients, SVR rates are the same for genotype 2 and 3 HCV infections if they are treated for 24 weeks instead of 48. However, analogous studies have not been reported for PLHIV *(5)*. Thus, studies emphasizing alternative dosing intervals are also needed for genotype 2 and 3 HCV infection before shorter regimens can be recommended. On the other hand, it might be useful to evaluate the usefulness of longer treatment duration for genotype 1 HCV infections with high viral loads.

IFN maintenance treatment

Studies on the use of maintenance treatment in patients with no SVR and with advanced liver disease are strongly recommended, including evaluation of the optimal dose and duration of treatment. Maintenance treatment is aimed at decreasing the incidence of ESLD without effecting SVR. The histologic response results of the ACTG 5071 study *(4)* described above provide a rationale for this approach. There are studies designed to test this hypothesis in both HIV-infected (SLAM-C) and HIV-uninfected people (HALT-C), but it remains undecided.

Acute HCV infection

The optimal treatment for acute HCV infection in HIV-infected patients should be investigated.

New treatments

As the current therapies are suboptimal in efficacy, tolerability and quality of life, the development of new drugs to improve these issues should be actively pursued.

Phase II and III trials of new drugs should be performed in HIV/HCV-coinfected patients as a priority due to the accelerated course of hepatitis infections in these populations.

There are many compounds under development, and some have progressed into Phase II clinical studies *(111)*:

- Viramidine (Valeant) is a prodrug of RBV that causes substantially less anaemia. In phase II studies, it was associated with less anaemia than RBV and SVR rates that were not inferior. Phase III studies are underway.
- Albuferon-alfa™ (Human Genome Sciences), is a fusion of albumin and IFN that prolongs IFN half-life.
- Interleukine-2 (IL-2) treatment has also been examined as a method to boost HCV antibody immune responses and enhance treatment responses. However, an early study in HIV/HCV-coinfected patients was associated with significant toxicity and provided no evidence of effectiveness *(10)*.
- NM283 (Idenix) interferes with the HCV polymerase and, in Phase II studies; its use was associated with a modest reduction in HCV RNA levels.
- VX 950 (Vertex) is an HCV protease inhibitor that is being examined in clinical trials.

The development of direct antivirals that block essential viral enzymes represents a straightforward approach to developing new agents to target HCV. Although all HCV enzymes are, in theory, equally appropriate for therapeutic intervention, the NS3–4A serine protease and the NS5B RNA polymerase have emerged as the most popular targets. A number of competitive inhibitors of the NS3 protease as well as nucleoside and non-nucleoside inhibitors of the NS5B polymerase are being developed. The efficacy shown by NS3 serine protease and the NS5B RNA-dependent RNA polymerase inhibitors in recent proof-of-concept clinical trials has validated the effort of finding clinical candidates and triggered a renewed interest in this area *(112)*.

Table 16. A sample of the drug pipeline for hepatitis C

Compound	Company	Clinical phase	Target	Mechanism of action
BILN 2061 (Ciluprevir)	Boehringer-Ingelheim	Phase II[a]	NS3–4A protease	Product-derived serine protease inhibitor
VX-950	Vertex/Mitsubishi	Phase Ib	NS3–4A protease	Serine protease reversible covalent inhibitor
NM283 (Valopicitabine)	Idenix/Novartis	Phase II	NS5B polymerase	Nucleoside analogue (chain terminator)
JTK-103	Japan Tobacco	Phase II	NS5B polymerase	Non-nucleoside allosteric inhibitor
HCV-796	ViroPharma/Wyeth	Phase Ia	NS5B polymerase	Non-nucleoside allosteric inhibitor
Host targets/immunomodulators				
Actilon (CpG-10101)	Coley Pharmaceutical Group	Phase Ib	Toll-like receptor-9	Immunomodulator
ANA245 (Isatoribine)	Anadys Pharmaceuticals	Phase Ib	Toll-like receptor-7	Immunomodulator
ANA975	Anadys Pharmaceuticals	Phase Ia	Toll-like receptor-7	Immunomodulator (prodrug of ANA245)

[a] Development has been halted due to cardiotoxicity in monkeys.
Source: Nunes et al. *(42)*.

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WORLD HEALTH ORGANIZATION
EUROPE

7 Management of Hepatitis B and HIV Coinfection

Clinical Protocol for the WHO European Region

Contents

I. Epidemiology and natural course of HBV infection

1. Prevalence of chronic hepatitis B

Approximately 400 million people worldwide are chronically infected with the hepatitis B virus (HBV), and approximately 1 million die annually of HBV-related disease. The worldwide prevalence of hepatitis B virus ranges from 0.1% to 20% *(1)*. This wide range is largely due to differences in age at the time of infection. Following acute HBV infection, the risk of developing chronic infection varies inversely with age: 90% for perinatal infection, 25–50% for infection at age 1–5 years and 1–5% for all others *(2)*.

About 45% of the world population live in areas where chronic HBV is highly endemic (≥8% of the population have the hepatitis B surface antigen (HBsAg), 43% live in intermediate-endemicity areas (2–7% HBsAg-positive) and 12% live in low-endemicity areas (0.6% to <2% HBsAg-positive). Intermediately endemic areas include eastern and southern Europe and the Russian Federation, while northern and western Europe have low endemicity (see Table 1).

Table 1. Prevalence of hepatitis *(2)*

Areas of endemicity	Prevalence of HBV carriers	Predominant modes of transmission
Central Asian republics, parts of eastern Europe	High (≥8%)	Perinatal Childhood (horizontal)
Western and northern Europe	Low (<2%)	Sexual contact Injecting drug use
Other countries	Intermediate (2–7%)	Early childhood (horizontal)

2. Modes of transmission and risk factors

HBV is detected in blood and body fluids (semen, saliva, nasopharyngeal fluids), and it can be transmitted either sexually or by exposure to infected blood or fluids. There are four major modes of transmission:

- sexual contact
- mother-to-child transmission at birth
- parenteral (blood-to-blood)
- through other infected bodily fluids.

The world's predominant mode of HBV transmission is perinatal. If a pregnant woman is an HBV carrier and is also hepatitis B e antigen (HBeAg)-positive, her newborn baby has a 90% likelihood of being infected and becoming an HBV carrier. Of these children, 25% will die later from chronic liver disease or liver cancer *(2)*. Other risk factors favouring HBV transmission include:

- receiving blood and/or blood products
- drug-injecting, tattoos and other skin-piercing activities
- unprotected penetrative sex, in particular anal and vaginal sex
- organ transplants
- health care occupational risks
- haemodialysis.

In low-endemicity areas, the highest incidence of HBV infection is among teenagers and young adults. The most common modes of transmission among these two groups are sexual transmission and blood-to-blood transmission due to injecting practices *(2)*.

3. Genotypes

HBV is classified in seven major genotypes, A–G. Genotypes A and D are the most common types in Europe. The seroconversion rates of hepatitis B e antigen (HBeAg) and the rates of morbidity and mortality related to liver disease are similar in patients with genotypes A and D. However, sustained biochemical and virological remission are more common in patients with genotype A who have had HBeAg seroconversion than in the corresponding genotype D patients *(3)*. No correlation between HBV genotypes and response to lamivudine or adefovir treatment has been demonstrated, as it has been with interferon.

4. Epidemiology of HBV infection in HIV-infected patients

HBV and HIV have common routes of transmission and endemic areas, but HBV is about 100 times more infectious. Consequently, more than 70% of HIV-infected people have a blood marker of past or present HBV infection *(2, 4)*. Men who have sex with men (MSM) show higher rates of HBV/HIV coinfection than injecting drug users (IDUs) or heterosexuals *(5)*. The risk of chronic hepatitis B is greater in cases of HBV/HIV coinfection and congenital or acquired immunosuppression as a result of lymphoproliferative disease, immunosuppressant drugs or maintenance haemodialysis. HBV-related liver diseases (including cirrhosis and its complications) is more progressive in cases of HIV coinfection than in monoinfection *(6)*.

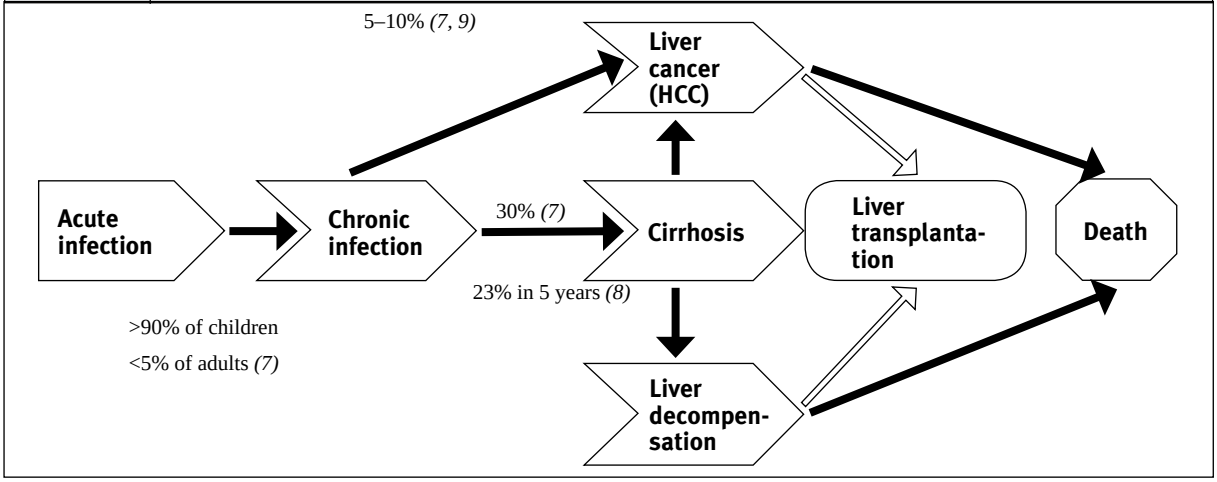
5. Natural course of HBV infection

After an acute HBV infection acquired in adulthood, 90–95% of adults develop a broad, multispecific cellular immune response that eliminates the virus and ultimately leads to the development of protective antibodies for hepatitis B surface antigen (HBsAg). Less than 1% of those who have had an acute infection develop a fulminant hepatitis, and the remaining 5–10% become chronically infected *(2)*.

5.1. Complications of chronic hepatitis B

After an average of 30 years, 30% of patients with chronic active hepatitis B will progress to cirrhosis. Liver failure decompensation occurs in about one quarter of cirrhotic patients with hepatitis B over a five-year period; another 5–10% will go on to develop liver cancer (see Fig. 1). Without treatment, approximately 15% of patients with cirrhosis will die within 5 years.

Fig. 1 . Natural course of chronic HBV infection



HCC: hepatocellular carcinoma.

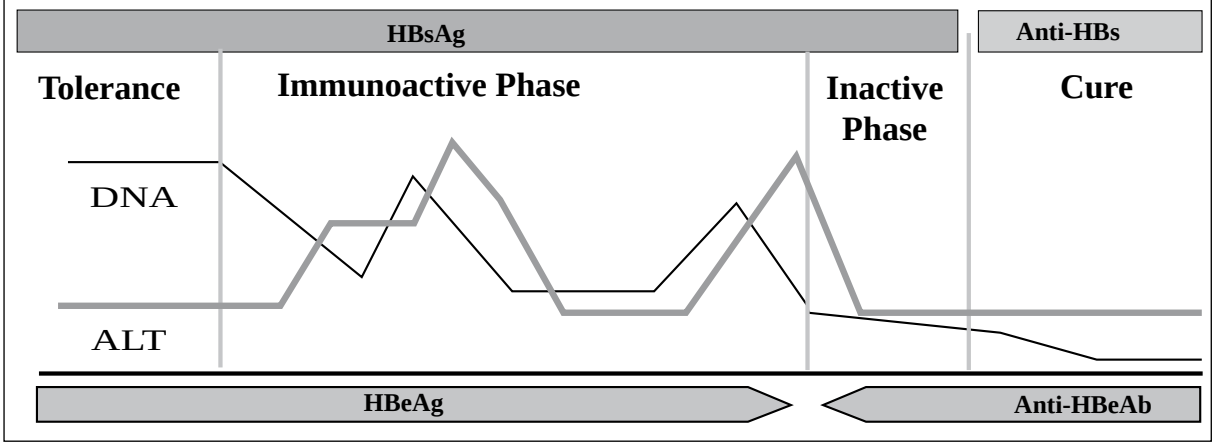
A number of patients with chronic hepatitis B will develop hepatocellular carcinoma (HCC). Those at increased risk for developing HCC include adult males with cirrhosis who contracted hepatitis B in early childhood. Between 60% and 90% of HCC patients have underlying cirrhosis, but only 5% with cirrhosis will develop HCC. Up to 80% of liver cancers in the world are due to HBV. The median survival frequency of HCC patients is <3 months without appropriate treatment, which includes surgery, percutaneous treatments, hepatic irradiation and chemotherapy *(2)*.

5.2. Evolutionary phases of chronic hepatitis B

Chronic hepatitis B generally develops over many years, during which time patients pass through a number of phases, as illustrated in Fig. 2 below *(2)*.

- The immunotolerant phase occurs in younger individuals who are HBeAg-positive, have a high HBV deoxyribonucleic acid (DNA) levels (2×10^4–2×10^8 IU/ml), and persistently normal alanine aminotransferase (ALT) levels.
- The immunoactive phase with HBeAg-positive or HBeAg-negative chronic hepatitis B, mild HBV DNA levels (2×10^3–2×10^7 IU/ml) and persistently elevated ALT levels; the patient is at times symptomatic.
- The non-replicative phase, corresponding to inactive HBsAg carriers. During HBeAg seroconversion, be it spontaneous or under pressure from treatment, there is an inactive HBsAg carrier state in which HBeAg is negative. During this period, HBV DNA is typically $<2 \times 10^3$ IU/ml (often undetectable), with a normal or mildly elevated ALT level. A small number of long-established chronic carriers apparently terminate their active infection and become HBsAg-negative (up to 1% per year) *(7)*.

Fig. 2. Evolutionary phases of chronic hepatitis B infection *(2)*



ALT: alanine aminotransferase; DNA: deoxyribonucleic acid; HBeAb: hepatitis B e antibody; HBeAg: hepatitis B e antigen; HBsAb: hepatitis B surface antibody; HBsAg: hepatitis B surface antigen.

HBV infection in adults generally consists of:

- an early replicative phase with active liver disease (HBeAg-positive chronic hepatitis B)
- a late low- or non-replicative phase with HBeAg seroconversion
- remission or inactivation of liver disease.

Seroconversion from HBeAg to hepatitis B e antibody (HBeAb), either spontaneously or with treatment, is typically accompanied by:

- a decline in HBV DNA levels (<19 IU/ml or <105 copies/ml)
- normalization of liver enzymes
- resolution of necroinflammatory activity on liver histology.

The rate of spontaneous resolution of active replication and seroconversion from HBeAg to HBeAb is 5–20% per year. During this process, some individuals develop an escape variant, a consequence of emerging mutations in the precore region that disrupts HBeAg production. These precore and core mutant viruses develop under selective immune pressure and are able to retain high levels of HBV replication *(8)*. Patients thus affected – HBeAg-negative chronic hepatitis B patients – are clinically identified by the absence of HBeAg and the presence of HBeAb and high HBV DNA levels. This particular pattern is most commonly seen in eastern Asia and southern Europe because of the higher prevalence of non-A genotypes there, which predisposes the population to this mutation.

6. Reciprocal impact of HIV and HBV

6.1. Impact of HIV infection on HBV disease progression

- HBV infection is more frequent and more severe in the HIV-infected *(6, 9)*.
- In HBV/HIV-coinfected patients, necroinflammatory activity in the liver tends to be milder, but higher HBV replication results in more severe liver fibrosis with increased risk (4.2 times greater) for cirrhosis with a more rapid progression to end-stage liver disease.
- In HBV/HIV-coinfected patients with cirrhosis, hepatocellular carcinoma (HCC) may appear more aggressive and at an earlier age than in those not HIV-infected. In addition, it presents with multifocal lesions more frequently *(10)*.
- HIV appears to be a risk factor for reactivation of hepatitis B in patients who have developed hepatitis B surface antibodies (HBsAb, which 60–70% of HIV-infected individuals have), especially in patients with severe immunodeficiency *(11)*.
- Patients coinfected with HIV 1 and HBV, especially those with low CD4+ nadir counts, are at increased risk for liver-related mortality.

6.2. Impact of HBV infection on HIV disease progression

- The majority of the clinical studies that have examined the influence of HBV on HIV disease progression and consider HBsAg a marker of chronic HBV infection have not been able to prove that HBV has any role in HIV disease progression *(6)*.
- There is, however, an increased risk for liver disease-related morbidity and mortality in hepatitis-coinfected HIV patients, as well as more hepatotoxicity under antiretroviral treatment regimens or when active treatment from both HIV and HBV is interrupted.

II. Identification of HBV/HIV

1. Assessment of HBV risk and diagnosis of hepatitis B in HIV-infected patients

1.1. Initial laboratory assessment of HBV status

All HIV-infected patients should be:

- tested for HBsAg (the presence of HBsAg for a minimum of 6 months indicates chronic hepatitis B);
- tested for hepatitis B core antibodies (HBcAb); and
- assessed for previous HBV vaccination (HBsAb).

HBcAb alone without HBsAg could be due to occult hepatitis. In this rare situation, HBV DNA is recommended (see below).

1.2. Evaluation of HBV disease severity

Further evaluation is essential for making a decision regarding treatment, focusing on in-depth laboratory diagnosis and clinical evaluation.

1.2.1. Clinical evaluation for signs and symptoms of advanced liver disease

Examination for signs and symptoms of liver disease is required. The presence or absence of clinical evidence for cirrhosis might be the key issue in defining treatment strategy in HBV/HIV-coinfected patients. The clinical signs of cirrhosis are:

- enlargement and dysmorphy of the liver;
- portal hypertension (hepatic encephalopathy, digestive haemorrhage due to oesophageal varices and splenomegaly);
- vascular spiders, palmar erythema and digital hippocratism (mostly in alcoholic liver cirrhosis rather than viral liver cirrhosis); and
- jaundice, ascites, oedema and a tendency to bleed.

The Child-Pugh classification is a simple, convenient prognostic measure in patients with liver cirrhosis (see Table 2). It may be used to predict patient survival rates and is interpreted thus:

- Class A (5–6 points) → compensated cirrhosis
- Class B (7–9 points) → compensated cirrhosis
- Class C (10–15 points) → decompensated cirrhosis.

Table 2. Child-Pugh classification

Clinical and biochemical parameters	POINTS		
	1	2	3
Bilirubin	<2 mg/dl (<34 µmol/l)	2–3 mg/dl (34–50 µmol/l)	>3 mg/dl (>50 µmol/l)
Albumin	>3.5 g/dl	2.8–3.5 g/dl	<2.8 g/dl
Ascites	Absent	Moderate[a]	Severe/ refractory[b]
Encephalopathy	Absent	Moderate (stage I–II)	Severe (stage III–IV)
Prothrombin time[c]	>60%	40–60%	<40%

[a] Controlled medically.
[b] poorly controlled.
[c] now replaced in some European countries by international normalized ratio (INR) with the following Child-Pugh values: INR <1.70 = 1 point; 1.71–2.20 = 2 points; >2.20 = 3 points.
Source: Pugh RNH et al. *(12).*

1.2.2. ALT level

- Serial measurements are preferred, as ALT may fluctuate significantly.
- Elevated ALT is a marker of liver inflammation.
- An ALT level three times the upper normal limit is correlated with a cirrhosis risk.
- Normal ALT levels can also be associated with liver disease progression, particularly in HBeAg-negative patients.
- Liver enzymes should be monitored on a regular basis, every six months for normal ALT levels. If liver enzymes become abnormal for a period of at least three months, HBV treatment is required.

1.2.3. Determination of HBeAg

- HBeAg-positive patients almost invariably have high HBV DNA levels independent of their ALT levels.
- HbeAg-negative patients may also have progressive liver disease.
- However, in both situations detection and measurement of HBV DNA should be performed, as combining serological test results with DNA levels can determine treatment strategy. In limited-access settings, HBV DNA determination should be privileged.

1.2.4. HBV DNA level

- Results should be expressed in international units (IU) per millilitre (1.0 IU = 5.4–5.8 copies/ml, depending on assay), the WHO standardized quantification unit for HBV DNA, and in decimal logarithm (log_{10}) IU/ml for precise assessment of baseline and significant HBV DNA changes upon treatment.
- If HBV DNA is initially found to be <2000 IU/ml, especially in patients with elevated ALT or other signs of liver disease, serial measurements should be undertaken at least semiannually, since such patients may exhibit wide fluctuations in HBV DNA.
- Different tests produce different absolute results; consequently, the thresholds given for therapeutic goals can only be indicative.
- A single type of HBV DNA assay should be used for monitoring a patient. If a change of assay is planned, both tests should be used in parallel for at least two subsequent samples.
- If only HBcAb is present at the initial assessment, it may be indicative of occult HBV infection (see Table 3). Occult HBV is usually assumed when HBV DNA is detected at low levels by highly sensitive techniques and in the absence of HBsAg. Occult HBV is found more frequently in HIV-positive patients than in HIV-negative patients, but its clinical relevance is uncertain. Currently, there is no evidence for the need to routinely detect or treat occult HBV.

Table 3. Classification of chronic hepatitis B virus infections based on laboratory determinants *(13)*

	HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBV DNA
Chronic active hepatitis B						
HBeAg-positive patients	+	–	+	+	–	+
HBeAg-negative patients[a]	+	–	+	–	+	+
Occult HBV infection	–	–	+	–	+	+[b]
Inactive HBV carrier state	+	–	+	–	+	–

[a] Precore mutant HBV strain;
[b] only detected by polymerase chain reaction (PCR) methods.

- Patients with HBeAg-negative chronic HBV are distinguished from inactive HBV carriers by the presence of $>10^4$ HBV DNA copies/ml (or >2000 IU/ml), elevated ALT and necroinflammatory liver disease. The literature suggests that HBeAg-negative chronic hepatitis B entails a particularly high risk of progressive hepatic fibrosis *(14, 15)*. In contrast, inactive HBV carriers usually have undetectable HBV DNA.

1.2.5. Ultrasound and other evaluations

Ultrasound examination of the liver (if possible Doppler ultrasound examination) can reveal:
- cirrhosis: dysmorphy of the liver
- steatosis: hyperechogenic liver
- possibly early HCC: nodular unique or rarely multiple lesions.

Where available, patients with liver cirrhosis should also have:
- serum alpha-fetoprotein (AFP) assessment to detect HCC; and
- upper gastrointestinal endoscopy for detecting the presence of oesophageal varices (with risk for gastrointestinal bleeding).

In the presence of significant oesophageal varices, prevention of bleeding by non-cardioselective beta blockers is recommended. The most frequently prescribed drug is propanolol at a dosage allowing a pulse reduction of at least 25–30% (40–160 mg daily may be necessary) *(16).*

1.2.6. Histological evaluation

There are a number of advantages of liver biopsy, including:
- wide availability;
- assessment of necrosis, inflammation and fibrosis;
- elimination of other causes of liver damage (opportunistic agents, drug toxicity, alcohol, steatosis, etc.);
- assessment of patients with consistently normal ALT levels who are HBV/HIV-coinfected and have liver cirrhosis.

Activity and fibrosis are two major histological features of chronic hepatitis included in proposed classifications. Interpretation of liver biopsies using the Metavir scoring system (see Table 4) improves consistency in the interpretation of hepatic fibrosis, with a somewhat weaker reproducibility for the hepatic inflammation grade. The fibrosis stage and inflammatory grade are correlated in two thirds of patients.

Table 4. Metavir classification: activity and fibrosis scoring *(17)*

Activity score (A)		Lobular necrosis		
		Absent (0)	**Moderate (1)**	**Severe (2)**
Parcellar necrosis	**Absent (0)**	A0	A1	A2
	Minimal (1)	A1	A1	A2
	Moderate (2)	A2	A2	A3
	Severe (3)	A3	A3	A3

A0 = no histological activity; A1 = minimal activity; A2 = moderate activity; A3 = severe activity.

Table 4a.

Fibrosis score (F)
F0: absence of portal fibrosis
F1: stellar portal fibrosis with no septa
F2: portal fibrosis with some septa
F3: many septa but no cirrhosis
F4: cirrhosis

Source: Simmonds et al. *(18).*

Noninvasive methods for measuring markers of fibrosis (such as FibroTest™) or liver stiffness (such as FibroScan™) have been shown to provide an adequate estimate of the extent of fibrosis. If these methods are available, they can substitute for performing a liver biopsy *(19-22)* (see Table 4a).

See section III below for two algorithms for HBV diagnosis in HIV-infected patients, as well as treatment options for coinfected patients.

1.2.7. Clinical situations not requiring histological evaluation

Decision to initiate HBV treatment does not require histological evaluation for every patient. In particular, HBV treatment may be considered without a liver biopsy when:

- there are clinical signs of cirrhosis;
- the CD4 count is <350 cells/mm^3 and antiretroviral treatment is indicated (see section III.3.1 below); or
- there are no clinical signs of cirrhosis and the CD4 count is >350 cells/mm^3, ALT is more than twice the normal upper limit and HBeAg is positive.

2. Evaluation of comorbidities and co-conditions

2.1. Psychiatric disorders

- Psychiatric disorders are not a contraindication for HBV treatment.
- Patients needing interferon (IFN) should be evaluated for psychiatric disorders. IFN should be avoided for patients with acute psychiatric disorders, and deferred for patients with moderate to severe depression until the condition improves.

2.2. Alcohol abuse

- Assessment of alcohol intake is an important part of evaluation (see Protocol 6, *Management of hepatitis C and HIV coinfection,* Annex 3).
- Heavy alcohol intake (≥50 g/day) contributes to fibrosis of the liver and can be identified by biopsy in patients with HBV independently of other predictors. This intake is equivalent to five or more drinks per day. One drink is defined as 330 ml (12 oz) of beer, 150 ml (5 oz) of wine, or 38 ml (1.25 oz) of hard liquor, containing approximately 10 grams of alcohol.
- There is evidence of a synergistic (more than additive) interaction between heavy alcohol consumption (≥80 ml/day) and chronic HBV or hepatitis C virus (HCV) infections *(23)*.
- Alcohol consumption increases HBV replication, accelerates fibrogenesis and liver disease progression in hepatitis B and C, as well as diminishing the response and adherence to anti-hepatitis treatment (especially if consumption is >50 g/day).
- Active alcohol intake is considered a relative contraindication for interferon-based treatment. This recommendation is based on the documented non-compliance of heavy drinkers with various medical therapies, and the fact that the side-effects of interferon treatment already make compliance extremely difficult *(24)*.
- Psychological, social and medical support should be offered to stop alcohol intake or reduce it to under 10 g/day.

2.3. Drug use

- Patients on opioid substitution therapy should not be excluded from treatment.
- Initiation of HBV treatment in active drug users should be considered on a case-by-case basis (see Protocol 5, *HIV/AIDS treatment and care for injecting drug users)*.
- Psychological and social support by a multidisciplinary team should be provided for such patients.

2.4. Other comorbidities and co-conditions

Testing for comorbidities should include a comprehensive medical history that focuses on cofactors associated with more progressive liver injury, and it should cover other viral liver diseases, tuberculosis (TB) (see Protocol 4, *Management of tuberculosis and HIV coinfection*) and pregnancy. Serological testing for hepatitis delta virus (HDV) might be suggested in chronically HBV-infected patients, especially IDUs. In case of persistent elevated ALT despite correct HBV treatment, pegylated interferon (PEG-IFN) can be added to antiretrovirals (ARVs), but efficacy and tolerability have not been assessed in HIV-coinfected cases *(25)*.

3. Assessment of HIV risk and diagnosis of HIV/AIDS in HBV patients

All patients with HBV should be offered HIV testing and counselling because the infections share routes of transmission, and because HIV accelerates HBV progression. Health care providers should explain to patients the reasons for offering the test and its importance for correct clinical management. However, a patient has a right to refuse an HIV test.

The initial assessment of HIV status should include:

- pretest counselling;
- serological tests (typically, enzyme-linked immunosorbent assay (ELISA) and/or rapid tests) for HIV antibodies, followed by a western blot confirmatory test; and
- post-test counselling irrespective of the result, including information on reducing risky behaviour.

Further clinical evaluation of HIV-infected patients is required to develop a clinical management strategy for HBV/HIV-coinfected patients. For detailed information, see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

III. Clinical management of HBV/HIV patients

By the end of the laboratory and clinical evaluation, patients can be put into one of three treatment categories:
1. not requiring hepatitis B or HIV treatment
2. requiring only hepatitis B treatment
3. requiring only HIV treatment or both hepatitis B and HIV treatment.

For clinical management of patients with HBV/HIV coinfection the key issue is the treatment of HBV and HIV and a strategy for its initiation. This decision should be based on analysis of the following parameters:
- HBV DNA levels
- severity of liver disease
- CD4 count and indications for antiretroviral treatment (ART)
- contraindications.

HBV treatment should be considered for any HBV/HIV-coinfected patient with evidence of active liver disease (high ALT level, significant serum HBV DNA level, necro-inflammation lesions or fibrosis in liver biopsy), irrespective of the CD4 count.

1. Coinfected patients not requiring treatment

These patients have the following status:
- CD4 count of ≥350 cells/mm^3; and
- mild or not progressing HBV disease (HBV DNA <20 000 in HBeAg-positive patients, or HBV DNA <2000 in HBeAg-negative patients; normal ALT; no severe liver disease if a biopsy has been performed).

Since there is no immediate need for treatment, the patient's health should be carefully monitored by:
- a CD4 count every three to six months;
- clinical monitoring of HIV-related symptoms every three to six months;
- ALT measurements every six months for patients with inactive HBV infection (since liver disease may reactivate even after many years of quiescence), and AFP or ultrasound for HCC.
- HBeAg-positive patients with elevated ALT levels and compensated liver disease should be observed for three to six months for spontaneous seroconversion from HBeAg to HBeAb prior to initiation of treatment.

2. Coinfected patients requiring only hepatitis B treatment

HBV/HIV-coinfected patients needing only hepatitis treatment have the following features:
- CD4 count of >350 cells/mm^3;
- HbeAg-positive and HBV DNA >20 000 IU/ml, or HbeAg-negative and HBV DNA >2000 IU/ml;
- clinical cirrhosis and detectable HBV DNA (>200 IU/ml); and
- histologically proven active disease (Metavir score ≥A2 or F2), or persistently elevated ALT levels in the absence of other causes of ALT elevation.

2.1. Anti-HBV drugs for treatment of hepatitis B in HIV-coinfected patients not requiring ART (doses and schedules)

Since no large-scale randomized controlled trials have been conducted to determine the efficacy of anti-HBV drugs in HBV/HIV-coinfected patients, recommendations for treatment and monitoring

need to be derived from what data are available plus what is already known about the treatment of HBV mono-infected patients.

Three antiviral drugs are recommended for use, PEG-IFN-α 2a, standard IFN-α 2a or 2b, and adefovir (ADF).

2.1.1. IFN and PEG-IFN

The highest effectiveness of interferon has been demonstrated in patients with HBeAg, ALT levels more than twice the upper limit of normal and low HBV DNA levels. PEG-IFN is becoming a standard treatment for HBV, and it is the preferred option in patients with these features and a CD4 count of >500/mm^3.

Dosage and administration of PEG-IFN-α 2a (26) are:
- 180 µg/week for 48 weeks, independent of HBeAg/HBeAb status.

Dosage of INF-α 2a or 2b (26) is:
- for HBeAg-positive cases, 10 million units (MU) subcutaneous 3 times weekly, or 5 MU daily for 4–6 months; and
- for HbeAg-negative cases, same dosage for 12 months.

2.1.1.1 Contraindications

Absolute contraindications are:
- pregnancy and breastfeeding;
- decompensated liver disease (due to an increased risk for thrombopenia, death from liver failure or sepsis);
- uncontrolled psychiatric disease;
- significant leukopenia or thrombocytopenia;
- unstable coronary artery disease, diabetes or hypertension; or
- uncontrolled seizure disorder.

Relative contraindications are:
- autoimmune diseases (e.g. psoriasis and rheumatoid arthritis)
- prior history of depression or psychiatric illness.

2.1.2. Adefovir (ADF)

With ADF, a nucleotide analogue, a progressive and efficient suppression of HBV DNA is observed. The rate of HBV-resistant strains is very low in the short term (3% after 2 years) but has recently been shown to be as high as 28% after five years of monotreatment *(27)*.

ADF dosage is 10 mg orally once daily *(28)*.
- The optimal duration of treatment is indefinite in the absence of other treatment.
- It is recommended to continue treatment with ADF for at least 12 months.
- ADF dosage should be adapted to creatinine clearance (CrCl):
  - if CrCl is 20–49 ml/min, 10 mg every 48 hours
  - if CrCl is 10–19 ml/min, 10 mg every 72 hours
  - if the patient is on haemodialysis, 10 mg every 7 days following dialysis.

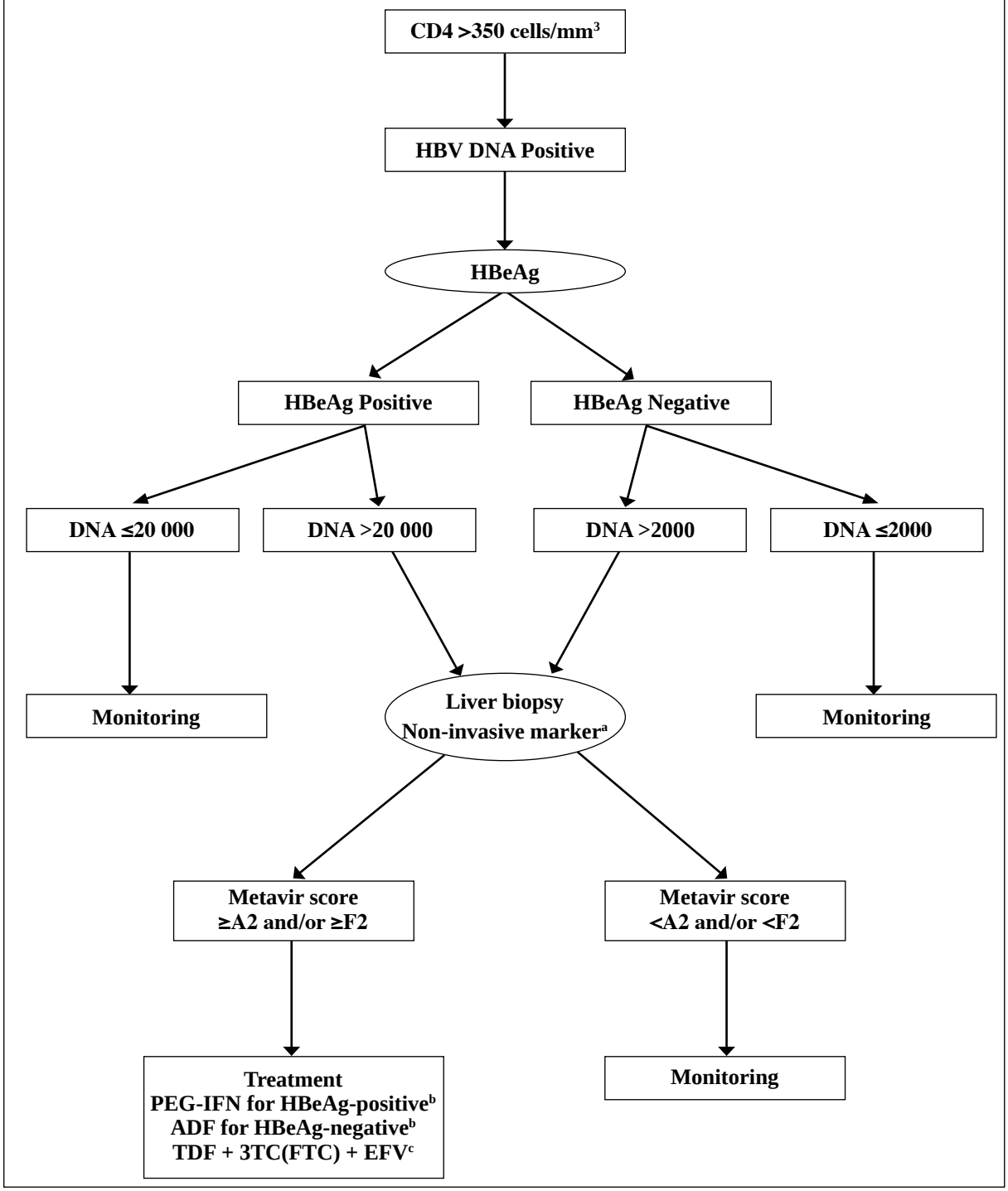
Contraindications are pregnancy and nephrotoxicity.

2.2. Evaluation and treatment algorithms for chronic hepatitis B in HIV-infected patients not requiring ART

2.2.1. Algorithm 1

The approach in this algorithm focuses on a determination of HBV DNA (in the absence of clinical cirrhosis). See Fig. 3.

Fig. 3. Algorithm 1

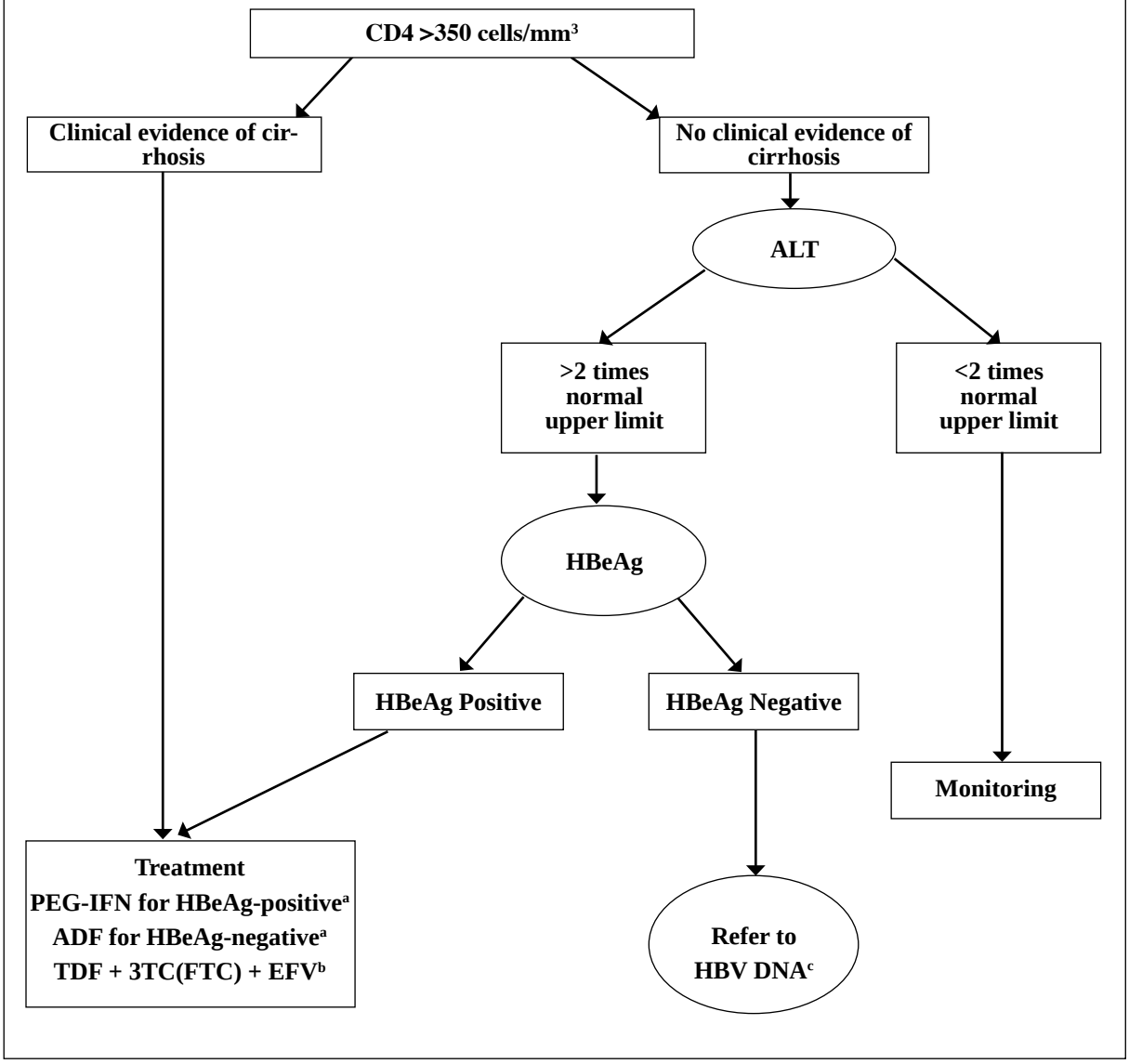


[a] Non-invasive markers: FibroTest -serum markers, FibroScan- image technique.
[b] Either PEG-IFN or ADF is the choice for HBV/HIV-coinfected patients who do not need ART. ART can be considered for patients with CD4 counts of 350–500 cells/mm3 if PEG-IFN, IFN or ADF are not available.
[c] Premature use of ART can expose patients to ART side-effects and a risk of developing HIV resistance to tenofovir (TDF) or lamivudine (3TC), which can compromise future ART.

2.2.2. Algorithm 2

The second algorithm's approach is focused on clinical evaluation, in particular for settings where HBV DNA is not available. This approach allows identifying those HBV/HIV-coinfected patients in need of hepatitis B treatment for whom a decision regarding treatment can be made without determining the HBV DNA level (i.e. patients with clinical cirrhosis, and patients with no clinical signs of cirrhosis, but with elevated ALT levels and positive HBeAg). However, patients with suspected chronic hepatitis B (HBeAg-negative with ALT more than twice the upper limit of normal) should be referred to a higher level of medical care for evaluation of HBV DNA and the appropriate course of treatment.

FIG. 4. ALGORITHM 2



[a] PEG-IFN or ADF is the best choice for HBV/HIV-coinfected patients who do not need ART. ART can be considered for patients with CD4 counts of 350–500 cells/mm^3 if IFN or ADF are not available.
[b] Premature use of ART can expose patients to ART side-effects and a risk of developing HIV resistance to TDF or 3TC, which can compromise future ART.
[c] In case of negative HBeAg, the further diagnostic algorithm is the same as shown in Algorithm 1.

2.2.3. Treatment options for HBV/HIV-coinfected patients with decompensated liver disease *(29)*

- Patients with decompensated liver disease require long-term, indefinite treatment, as virological relapse after discontinuation of treatment can be accompanied by a rapid clinical deterioration.
- ADF is safe in patients with decompensated liver disease, and is frequently associated with significant clinical improvement. Prolonged treatment is, however, associated with 28% drug resistance after five years in monoinfected patients. Thus, close monitoring for HBV DNA is recommended every six months in order to detect drug resistance in case of a viral load increase of more than 1 log, in which case genotyping should be performed. Interferon is contraindicated in patients with decompensated liver disease due to its very poor tolerability profile.

3. Coinfected patients requiring only HIV or both hepatitis B and HIV treatment

For these patients medication decisions are based on recognition of the dual effect of some antiretroviral drugs on HBV and HIV viruses, such as lamivudine (3TC) and tenofovir (TDF) *(30-32)*.

3.1. Considerations regarding treatment of hepatitis B

3.1.1. Symptomatic patients with a CD_4 count of 200 – 350 cells/mm^3

The decision to treat for HBV is mainly based on HBV DNA levels.

- In HBeAg-positive patients with HBV DNA >20 000 IU/ml and HBeAg-negative patients with HBV DNA >2000 IU/ml, the ART regimen must include two dual-activity drugs (anti-HBV and anti-HIV).
- In patients with low levels of HBV DNA, an ART regimen containing two dual-activity drugs is optional but highly recommended in anticipation of an early switch due to a reactivation of hepatitis.

3.1.2. Patients with CD_4 count < 200 cells/mm^3

When CD4 count is <200 cells/mm^3 and ART has been initiated there is a risk of a severe reactivation of hepatitis B during immune reconstitution, which may include a life-threatening hepatitis flare. Irrespective of indications for HBV treatment, the ART regimen for these patients must therefore include two dual-activity drugs in order to minimize the risk of HBV reactivation.

3.1.3. HIV-infected patients with clinical evidence of cirrhosis

- Clinical cirrhosis is an absolute indication for treatment.
- The HBV DNA threshold for initiation of HBV treatment is lower than in patients without cirrhosis (over 200 IU/ml, i.e. as soon as detectable).
- No medications are contraindicated for patients with compensated cirrhosis.
- Patients with decompensated cirrhosis should be referred for palliative care.
- Patients with cirrhosis require clinical observation, liver function monitoring and drug monitoring.
- It might be necessary to adjust the dose of ARV metabolized by the liver. If this is not feasible, then didanosine (ddI) and stavudine (d4T) have to be avoided and a regimen with a protease inhibitor (PI) should be closely monitored (see Protocol 6, *Management of hepatitis C and HIV coinfection* for recommendations on antiretroviral dosage adjustment in patients with end-stage liver disease (ESLD).

3.2. Considerations regarding treatment of HIV infection

3.2.1. Initiation of HAART

Initiation of ART in HBV/HIV-coinfected patients should follow the current recommendations for HIV-monoinfected patients (see Table 5). (For further details, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*)

Table 5.	Recommendations for initiating HAART in HBV/HIV-coinfected patients
CD4 count	**Recommendations**
≤200 cells/mm^3	Antiretroviral treatment is recommended. ART regimens should contain two dual-activity drugs (targeting both HBV and HIV).
200–350 cells/mm^3	Antiretroviral treatment should be considered with a high viral load or rapid decline in CD4 count, but should be started before the CD4 count falls to less than 200 cells/mm^3. If HBV treatment is indicated, ART regimens containing two dual-activity drugs are also indicated or highly recommended.

3.2.2. First line HAART regimens

Table 6.	First-line HAART for HBV/HIV-coinfected patients	
	ARV drug classes	**HAART regimens**
Preferred first line	2 NRTIs + 1 NNRTI	TDF[a] + (3TC or FTC[b]) + EFV[c]
Alternative first line	3 NRTIs	ZDV + (3TC or FTC[b]) + TDF

[a] If TDF is not available, 3TC should be a mandatory component of the regimen.
[b] FTC is equivalent to 3TC and is available together with TDF as a fixed-dose combination *(33, 34)*.
[c] Nevirapine (NVP) can be considered instead of efavirenz (EFV) for patients without hepatic dysfunction and with close monitoring. It should be avoided in women with CD4 count >250 cells/mm^3 or in men with CD4 count >400 cells/mm^3.

3.2.3. Second line HAART regimens

Table 7.	Second-line HAART for HBV/HIV-coinfected patients	
	ARV drug classes	**HAART regimens**
Note: TDF and 3TC or FTC should be utilized for hepatitis treatment in addition to the second-line HAART.	2 NRTIs + 1 boosted PI	ABC + (ddI or d4T[a]) + (LPV/r or SQV/r or NFV)
	1 NNRTI + 1 NRTI + 1 boosted PI[b]	EFV + (ABC or d4T[a]) + (LPV/r or SQV/r or NFV)
	2 PIs (1 boosted)	LPV/r + SQV

[a] If zidovudine (ZDV) was not used in the first line, d4T can be considered an option in second-line ART.
[b] An optional regimen supported by a recent study is LPV/r + EFV *(35)*.

3.3. HIV-infected patients with 3TC-resistant HBV strains

- 3TC (lamivudine) resistance develops more rapidly in HBV/HIV-coinfected patients, and even at the higher doses (300 mg daily), it appears in almost 50% and 90% of coinfected patients after two and four years, respectively, of 3TC treatment *(36, 37)*.
- In the presence of suspected lamivudine resistance, the first step is to confirm it, if resistance testing is available *(38, 39)*. Otherwise resistance may be suspected if the HBV viral load increases more than 1 log in a compliant patient taking 3TC, and the patient should be switched to TDF *(40–42)*.
- TDF is the essential ARV for the HAART regimen in 3TC-resistant patients.

4. Monitoring and evaluation of HBV/HIV-coinfected patients

4.1. Hepatitis B treatment response

Relevant response is defined as:

- durable normalization of ALT levels;
- sustained HBV DNA suppression (at least a 1 log decrease of HBV DNA after three months of treatment and an undetectable viral load <200 IU/ml in the long term) *(43)*;
- durable HBeAb seroconversion in initially HBeAg-positive patients, very rarely observed with nucleotide–nucleoside analogues and in HIV-positive patients.

4.1.1. Monitoring of HBV DNA

See Table 8. Note in addition the following:

- In HBeAg-positive patients with HBV DNA <20 000 IU/ml and in HBeAg-negative patients with HBV DNA <2000 IU/ml, DNA levels should be monitored every six months.
- In patients on treatment (including ARVs with anti-HBV activity), an initial response is defined as at least 1 log drop in HBV DNA levels within one to three months. HBV DNA should then be measured at least every six months and if possible every three months.
- Resistance should be suspected in compliant patients if HBV DNA levels increase by 1 log or more. If possible, resistance testing should be performed.

Table 8. Monitoring during treatment

		Before treatment	Month 1	Month 2	Month 3	Every three months	Every six months
Efficacy	**ALT**	X		X	X	X	
	HBV DNA	X			X	X (if available)	X

4.1.2. Monitoring of ALT

- If the ALT level was initially normal, it should be carefully monitored after one month, then every three months over the course of treatment, and every three to six months if no treatment is indicated.
- For patients receiving PIs and/or non-nucleoside reverse transcriptase inhibitors (NNRTIs), serum aminotransferase level follow-up is warranted every month during the first three months of starting any new ART; after this, a follow-up should be performed every three months to identify any drug-related hepatotoxicity.

4.2. Monitoring and evaluation of ART in HBV/HIV-coinfected patients

- CD4 cell count should be monitored every three to six months.
- HIV viral load (if available) should also be monitored every six months.

Please refer to the Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents* for further information.

4.3. Monitoring of adherence to treatment

- Patient counselling is important to avoid discontinuation of HBV drug regimens.
- Patients should be counselled about the side-effects and toxicity of HBV and ARV drugs and advised to consult a physician early for toxicity management.
- If patients do not understand the signs of side-effects, they may not report them to their physicians, jeopardizing adherence, limiting treatment efficacy and increasing the risk of developing resistance.

For more information on adherence monitoring and support refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents.*

4.4. Management of hepatotoxicity

All medical staff should be aware of the risk of side-effects to allow them to make early recommendations and interventions.

Hepatotoxicity is a significant side-effect of ARV use that may increase morbidity and mortality among treated HBV/HIV-coinfected patients. The management of liver toxicity is based mainly on its clinical impact, severity and pathogenic mechanism.

4.4.1. Immune reconstitution in HBV/HIV-coinfected patients

The liver damage induced by chronic HBV is mainly immune-mediated. The immunodeficiency caused by HIV infection is responsible for attenuating the inflammatory reaction in the liver of HBV/HIV-coinfected patients. The inhibition of HIV replication with ART leads to the syndrome of immune reconstitution, with clinical hepatitis following the first weeks after initiation of ART, typically in patients with very low CD4 count and/or very high levels of HIV ribonucleic acid (RNA) before ART *(44)*. These symptoms are usually prevented by including a dual-activity drug in the ARV regimen (see above).

4.4.2. Drug-related hepatotoxicity

- Liver toxicity may also occur in patients receiving nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), especially d4T and ddI, and may lead to severe microsteatosis with lactic acidosis (in exceptional cases). The condition is potentially severe, with a high mortality rate, and in case of symptomatic lactic acidosis requires immediately switching to another ARV with a different toxicity profile.
- The rate of severe hepatotoxicity (grade 3 or 4) associated with NNRTIs is relatively low but may be significantly higher in HBV- and HCV-coinfected patients *(45, 46)*.
- The major toxicities associated with nevirapine (NVP) are hepatotoxicity and hypersensibility reactions (rash); both may be severe and life-threatening. Symptomatic NVP-associated hepatic or serious rash toxicity, although uncommon, is three to seven times more frequent in women than in men *(47)*.
- If CD4 >250/mm^3, there is about 10 times greater risk of severe symptomatic hepatotoxicity than in patients with CD4 <250/mm^3.
- The risk of hepatotoxicity and rash are highest in the first six weeks of NVP treatment; starting NVP at half doses during the first six weeks minimizes the risk.
- Elevated serum aminotransferase levels are relatively common in HIV-infected patients receiving PI-based ART (2–8.5% of PI-treated patients) *(48, 49)*.
- HBV/HIV coinfection has been associated with a high risk of developing drug-induced liver injury, and with a greater risk of severe liver injury than in patients who have concurrent liver disease from other causes.
- If no other cofactors exist, the degree of hepatotoxicity is the main determinant of the clinical approach. (see Table 9).

Table 9. Standardized hepatotoxicity scale *(50)*

Toxicity grade	ALT and AST changes relative to the upper limit of normal	Increase from baseline
1	1.25–2.5 times	1.25–2.5 times
2	2.6–5.0 times	2.6–3.5 times
3	5.1–10.0 times	3.6–5.0 times
4	>10.0 times	>5.0 times

- If hepatotoxicity is severe, switching the ART regimen to one with lower potential hepatotoxicity is recommended.
- If hepatotoxicity is mild to moderate (grades 1 and 2), it is reasonable to continue the same ART regimen with a close follow-up of liver enzymes.

4.4.3. Hepatotoxicity of TB drugs in the context of chronic HBV infection *(51, 52)*

- The rate of hepatotoxicity is significantly higher in TB patients with HCV or HBV coinfection (59%) than in those without (24%) *(52)*.
- Commonly used anti-TB drugs, such as isoniazid, rifampicin, and pyrazinamid are hepatotoxic.
- Pyrazinamide and isoniazid are the most hepatotoxic and should be avoided in TB patients with known chronic liver disease.
- It is not necessary to adapt dosage of anti-TB drugs in cases of hepatic insufficiency.
- In decompensated liver disease, a regimen without rifampicin should be used.
- Streptomycin, ethambutol and a reserve drug such as fluoroquinolone can be used if treatment is necessary in patients with fulminant liver disease. Consultation with a specialist is required.
- Alternative anti-TB drugs with lower hepatotoxicity may be used in case of liver dysfunction, for example, rifabutin, amikacin, ofloxacin and levofloxacin. The treatment of these special cases should be decided in consultation with an acknowledged expert.
- Hepatotoxicity appears in the first two months of TB treatment, thus requiring close initial monitoring of liver functions.

IV. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to treatment and its success. Such indicators assist managers in decision-making on ways to strengthen and expand these services to all those in need.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV patients ("seen for care" – this will be the denominator for the data below);
- number of HIV patients coinfected with HBV (HbsAg-positive);
- number of HIV-positive patients with active hepatitis;
- number of HIV-positive patients with active hepatitis receiving:
  - HAART with 3TC and/or TDF;
  - ART without 3TC and/or TDF;
  - exclusively on hepatitis B treatment (e.g. IFN or ADF);
- number of HIV-infected patients vaccinated against HBV; and,
- number of HBV/HIV coinfected patients who have died (in a given time period) including cause of death (e.g. liver-related deaths, HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, overdose or suicide).

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EUROPE

8 Prevention of Hepatitis A, B and C and Other Hepatotoxic Factors in People Living with HIV

Clinical Protocol for the WHO European Region

Contents

I. Prevention strategies

The strategies for limiting the spread of hepatitis include:
- vaccination against hepatitis B and A;
- prevention of mother-to-child transmission of hepatitis B virus (HBV) and hepatitis C virus (HCV);
- reducing risk of infection through safer sexual behaviour and reducing harm related to injecting drug use;
- counselling to reduce liver-related harm;
- prevention through transfusion of blood and blood products; and
- prevention in health care settings.

1. Vaccination against hepatitis B and A

1.1. Hepatitis B

All HIV patients not coinfected with HBV should be vaccinated against it. (See also Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection.*)

The schedule for HBV vaccine in HIV-infected adult patients *(1, 2)* is as follows.
- HBV vaccination should start with the conventional dose (20 µg at months 0, 1 and a third time between months 6 and 12) for patients with a CD4 count >500 cells/mm^3.
- In individuals with CD4 cell counts between 200 cells/mm^3 and 500 cells/mm^3, an intensive vaccination schedule is recommended (20 µg at months 0, 1, 2 and 12). Patients who do not respond to this first cycle, measured by level of hepatitis B surface antibody (HBsAb) (<10 IU/litre) should receive booster doses or start a new vaccination cycle with 40 µg at months 0, 1, 2 and 6–12 *(3)*.
- It is generally accepted that an adequate response to hepatitis B vaccine is the production of serum HBsAb at levels >100 IU/litre (or at least 10 IU/litre). Studies on vaccination in HIV patients have used either the 0/1/6-month or the 0/1/2/12-month hepatitis B schedule *(3, 4)*.
- Patients with CD4 counts <200 cells/mm^3 should receive antiretroviral treatment (ART) first. Vaccination should be deferred until a clinically significant immune reconstitution has been achieved, preferably after the CD4 count has increased to >200 cells/mm^3.
- Compared to HIV-negative patients, those who are HIV-positive:
  - are less likely to respond to HBV vaccine;
  - have lower mean antibody titres (by a factor of about 30); and
  - lose "protective" antibody levels more quickly (40% loss in one year versus 5% loss in those who are HIV-negative).
- Routine or direct administration of booster doses is not recommended. Humoral response to HBV vaccine may decline progressively over time, and may put the patient at risk of acute infection in case of exposure. Yearly monitoring of HBsAb is recommended, and booster doses should be given when HBsAb <10 IU/litre. For further information on hepatitis B vaccine, please refer to Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection.*

Hepatitis B vaccine response correlates with CD4 count, as shown in Table 1.

Table 1. Hepatitis B vaccine response at differing CD4 counts *(3,5)*

CD4 count (cells/µl)	% of patients achieving HBsAb >10 IU/litre
>500	87
>350 with standard dose	39
>350 with doubled dose	64
<350	26[a]

[a] Physicians should weigh the risk of HBV infection against the benefit of vaccination in severely immunocompromised patients.

Other adult populations at risk for HBV who should be vaccinated include:
- sexual partners of HBV carriers
- men who have sex with men (MSM)
- sex workers (SWs)
- other people with multiple sexual partners
- patients with STIs
- IDUs
- prisoners, both male and female[1]
- patients on haemodialysis
- health care workers exposed to blood or blood products.

For HBV vaccination of children and use of hepatitis B immunoglobulin (HBIg), please refer to Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection.*

1.2. Hepatitis A

- All HCV/HIV- and HBV/HIV-coinfected patients who are not also coinfected with the hepatitis A virus (HAV) but are at risk for it should be vaccinated (see the risk of HAV infection and further strategies in Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection*).
- The response rate to vaccination is reduced and correlates to CD4 count.
- Mean HAV antibody titres in HIV-positive responders are about one tenth what they are in HIV-negative responders.
- Although the absolute lower limit of antibody level required to prevent HAV infection has not been established, a study using a HAV antibody (Ab) threshold of 33 mIU/litre showed the levels of response in Table 2.

Table 2. Hepatitis A vaccine response at differing CD4 counts *(6)*

CD4 count (cells/µl)	% of patients achieving HAV Ab >33 mIU/litre	
	Month 7	Month 9
≥500	73	67
200–499	53	69
<200	11	9[a]

[a] Physicians should weigh the risk of HAV infection against the benefit of vaccination in severely immunocompromised patients.

[1] Prisoners are at increased risk of HBV infection due to injecting drug use and unprotected sex.

- Though response to vaccination in immunocompromised patients is reduced, WHO policy is to administer vaccine regardless of CD4 level. Immunoglobulin should be administered concurrently for those with severe immunosuppression (CD4 cell count <200).
- Non-responders to HAV vaccine should be revaccinated once their CD4 count has risen in response to HAART, ideally ≥500 cells/mm^3.

For HAV vaccination of children and use of hepatitis A immunoglobulin, please refer to Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection.*

There are certain contraindications that need to be kept in mind even though hepatitis A vaccine is inactivated and no special precautions are needed when vaccinating immunocompromised people.

- HAV vaccine should not be administered to patients with a history of serious allergic reaction to it.
- Vaccination of patients with moderate or severe acute illnesses should be deferred until their conditions have improved.
- The safety of HAV vaccination during pregnancy has not been determined. However, because it is an inactivated vaccine, the theoretical risk to the fetus is low. The risk associated with vaccination should be weighed against the risk of HAV infection.

2. Prevention of mother-to-child transmission (PMTCT)

2.1. PMTCT of HBV

- All HIV-infected women should be screened for hepatitis B surface antigen (HBsAg) as a routine part of prenatal testing.
- In pregnant HBV/HIV-coinfected women who need or do not need ART for their own health, the antiretroviral (ARV) combination has to include 3TC, as it is effective against both viruses.
- The transmission rate of HBV is reduced by replication suppression; the doses and duration at which ARVs are administered should be the same as for HIV mono-infected women (see Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants*).
- In children born to chronically HBV-infected mothers, administration of vaccine within 12 hours after birth provides up to 95% protective efficacy *(7)*. Since the added value of administering HBIg concurrently with hepatitis B vaccine is quite low, its benefits and cost should be considered.
- In cases in which the mother is HBsAg-positive, the neonate should receive the single-antigen HBV vaccine along with 0.5 ml of HBIg within 12 hours of birth. These children can then receive the HBV vaccine series on a normal schedule of three doses (at 0, 1 and 6 months). In neonates weighing less than 2000 g, the initial vaccine following delivery is associated with a lower rate of immunogenicity. Therefore, these children should receive four doses of HBV vaccine (at birth and 1, 2–3 and 6–7 months) *(8)*.
- Children of HBsAg-positive mothers should undergo testing for HBsAg and HBsAb at 9 and 18 months. If the surface antibody level is less than 10 mIU/ml, the entire three-vaccine series should be repeated. Testing for hepatitis B core antibody (HBcAb) in these children is discouraged because passively acquired maternal antibodies may be detectable up to 24 months of age.
- When a woman's HBV status is still unknown at delivery but is later discovered to be positive, HBIg may be administered up to seven days after birth. In cases of unknown maternal hepatitis status among children weighing less than 2000 g at birth, physicians should administer both the HBV vaccine and immunoglobulin.
- Neonates born to HBV-negative mothers should receive their first HBV vaccination in the hospital. Neonates weighing less than 2000 g are a prominent exception to this rule. Because of the reduced immunogenicity of the HBV vaccine in this group, vaccination should be delayed until one month of age *(9)*.

2.2. PMTCT of HCV

- HCV mother-to-child transmission (MTCT) in HIV-infected women is high (between 5% and 20%) *(10)*. When possible, HCV treatment should be offered before pregnancy to women of childbearing age. Although several MTCT risk factors have been identified, there are currently no interventions available to prevent vertical transmission of HCV.
- Normally, elective caesarean section is advised for women who are HIV-infected as a means of preventing transmission to the infant. However, if the viral load is <1000 copies/ml, then vaginal delivery could be considered. Based on the current evidence, these same guidelines apply for women who are HCV/HIV-coinfected *(11, 12)*.
- Prevention of ribavirin embryopathy includes:
  - a pregnancy test before starting treatment and every month during treatment; and
  - counselling (of both the woman and her partner) to avoid pregnancy and use condoms while either partner is taking ribavirin and for at least six months afterwards.

3. Preventing and reducing risk of infection

3.1. Safer sexual behaviour

- All patients – those in the general population as well as those in vulnerable populations (SWs, IDUs, MSM, etc.) – should be counselled about safer sex and the use of condoms for any form of penetrative sex. Condoms are an effective means of preventing sexual transmission of HIV infection as well as hepatitis B and C infections.
- The sexual transmission of hepatitis A is mostly found in MSM, linked to oro-anal contact; preventive measures include using either a vertically cut condom or some plastic food wrap to cover the anal area before oral contact.

3.2. Reducing harm related to injecting drug use

- In addition to risks resulting from sexual behaviour, IDUs are vulnerable to bloodborne virus (HIV, HCV, HBV, HAV and HDV) as a result of collective use of injecting equipment. In some countries in Europe, over 70% of HIV infections are attributed to IDUs *(13)*.
- Effective evidence-based strategies to reduce risk of HBV and HCV transmission through injecting drug practices are:
  - linking to harm-reduction programmes, particularly needle exchange and opioid substitution therapy; and
  - counselling of patients with high-risk drug and sexual practices, especially those who are seropositive, on risk reduction.

For more details, please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users*

4. Counselling to reduce liver-related harm

All patients should be counselled on ways to reduce liver-related harm.

- Alcohol consumption should be stopped or reduced to no more than 10 g/day.
- Smoking should be stopped, as it has been associated with an increased risk of hepatitis cellular carcinoma (HCC) in some studies of patients with chronic HBV disease. The effects of smoking and alcohol may be synergistic *(14)*.
- The active component in cannabis – endocannabinoid (found in both marijuana and hashish) – has been found to have many physiological and patho-physiological functions. It has recently been implicated in the haemodynamic alterations occurring in cirrhosis *(15)*.
- No dietary factors have been linked specifically to HBV disease activity or severity. However, excess iron is associated with reduced responsiveness to interferon treatment and increased risk for HCC. Thus, iron supplements should be avoided unless iron deficiency is present *(16)*.
- Vitamin A in excessive amounts can be directly hepatotoxic; it is not recommended unless there is documented deficiency *(17)*.

- Herbal supplements should be used with caution, if at all. Many of these preparations can be severely hepatotoxic *(18)*, for example, chaparral, comfrey, germander, jin bu huan and kava kava. Due to a lack of regulation of supplements, formulations and doses can vary widely.
- Patients who have coexisting non-alcoholic fatty liver disease should be simultaneously counselled on:
  - optimizing body weight
  - achieving and maintaining normal triglyceride levels
  - controlling diabetes mellitus.

5. Prevention of transmission through transfusion of blood and blood products

Precautions to prevent infection through blood and blood products include:

- screening of all blood products for HBsAg and HCV Ab
- screening for HBcAb, and HCV RNA quantification[2]
- virus inactivation of plasma-derived products.

6. Prevention in health care settings

As it is not possible to identify all people infected with bloodborne pathogens, guidance to protect health care workers against HIV and hepatitis viruses is based on the concept that all patients should be assumed to be infectious. The application of universal precautions requires that all blood and body fluids be regarded as potentially infectious and that appropriate protective action be taken. Universal precautions include:

- infection-control practices, such as appropriate sterilization of medical and dental equipment;
- discouraging the excessive use of injections and promoting safe injection practices among health care workers; and
- strongly recommending vaccination against hepatitis B for all health care workers exposed to blood or blood products.

Prevention of hepatitis B and C transmission in health care settings is similar to prevention of HIV transmission there. For further information, please refer to Protocol 13, *Post-exposure prophylaxis for HIV infection.*

[2] Even when this screening is performed, there is still a minor risk of transmission.

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EUROPE

9 Support for Sexual and Reproductive Health in People Living with HIV

Clinical Protocol for the WHO European Region

Contents

I. Introduction

As the health and well-being of people living with HIV (PLHIV) improve due to antiviral treatment (ART), it has become necessary to reconsider many previous policies concerning their sexuality and reproduction. A rights-based approach to caring for their sexual and reproductive health (SRH) is needed to:

- empower them as individuals;
- ensure that they consider themselves capable of healthy and satisfying sexual lives through the effective management of their HIV infection; and
- address other SRH concerns effectively.

The purpose of this protocol is to assist health care providers at every level during consultations with PLHIV (whether or not on ART) on sexual and reproductive health. The present protocol includes steps that should be taken during such consultations, based on WHO documents and available evidence.

II. Background

Reproductive health (RH) is concerned with the reproductive system and its processes and functions at every stage of life. The term implies that people should be able to have a satisfying, responsible and safe sex life, and that they should be able to reproduce and freely decide whether, when and how often to do so *(1)*.

Reproductive health overlaps but is not synonymous *sexual health (2)*. Sexual health encompasses positive aspects of sexuality and sexual relationships, as well as problems with power dynamics in these relationships, including coercion, violence and discrimination. It concerns "the enhancement of life and personal relations, and not merely counselling and care related to reproduction and sexually transmitted diseases" *(1)*.

In order to attain and maintain SRH, people must be empowered to exercise control over their sexuality and reproduction and have access to related health services *(2)*. SRH services are offered by a variety of providers – from primary care physicians in western Europe to obstetricians, gynaecologists, urologists, dermatovenerologists and sexologists in eastern Europe – at venues that include family planning centres, youth-friendly health centres and sexually transmitted infection centres.

Reproductive health care providers should use any opportunity to promote voluntary testing and counselling for HIV infection and strive to improve access to care for PLHIV. HIV specialists should be informed of the reproductive rights and choices of PLHIV and refer them to appropriate RH services for quality assistance.

In Europe, reproductive health services for drug-using women are particularly important. Female injecting drug users (IDUs) are difficult to reach through the usual RH services and may mistakenly perceive themselves as infertile because of drug-related amenorrhea.

III. Principles of SRH Services for PLHIV

1. General principles

- Provision of RH services should follow the human rights principles of non-discrimination, participation and accountability.
- Services should be comprehensive and client-oriented, addressing all the needs of PLHIV during their lifetime.
- There should be no discrimination towards PLHIV, irrespective of any risk behaviours.
- Women should not be forced to have an abortion because of their HIV status.
- Confidentiality is to be a guiding principle in all services for PLHIV, including SRH services.

These principles are based on recognition of the needs of PLHIV:

- to obtain complete and correct information regarding their SRH choices
- to have or not have children and to make informed decisions about the choice
- to have access to the same full range of SRH services as HIV-negative people
- to be treated without stigmatization or discrimination in health care settings
- to expect confidentiality and respect for their human rights from health care providers
- to be involved in the formulation of policies and programmes that affect them.

2. Principles of HIV testing and counselling

HIV testing and counselling should be offered to clients and their partners during:

- testing for or treatment of reproductive tract infections (RTIs) and sexually transmitted infections (STIs);
- contraceptive counselling, with an emphasis on the benefits of knowing one's status when choosing a method of contraception;
- pre-conception, for planned pregnancy and childbirth to minimize mother-to-child transmission (MTCT);
- prenatal care, to maximize care for the mother and the prevention of MTCT (PMTCT);[1]
- newborn care, to facilitate safe choices regarding feeding options when HIV status is unknown;
- consultation regarding options for unwanted pregnancies;
- screening consultation for cervical cancer; and
- outreach work, especially among groups at high risk of infection (e.g. IDUs, men who have sex with men (MSM) or sex workers).

[1] For more information please refer to Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants.*

3. Patient counselling

Every HIV-infected patient attending SRH services should receive appropriate counselling on sexual and reproductive health issues, such as:

- reduction of risky sexual behaviour and safer sex negotiation, for both HIV-discordant and -concordant partners;
- the causes and management of sexual dysfunction;
- family planning and contraception;
- cervical cancer screening;
- STIs;
- hepatitis B vaccination;
- substance use;
- interactions between ARVs and other drugs; and
- interactions between contraceptives and illicit drugs.

Psychological support should be provided during counselling, with referrals for further assistance as required.

IV. Sexual health of PLHIV

Sexual health is affected by a variety of issues *(3)*, including:
- sexual well-being (satisfaction, pleasure and freedom from dysfunction)
- HIV, other STIs and RTIs
- mental health
- violence related to gender and sexuality
- physical disabilities and chronic illnesses
- unintended pregnancy and unsafe abortion
- infertility.

1. Taking a sexual health history

A sexual history should be included when obtaining the medical history of PLHIV. It will help equip the provider to discuss risk-reduction strategies for preventing further transmission, such as reducing the number of sexual partners or using condoms, and make appropriate referrals *(4, 5)*.

Health care providers should be non-judgemental of the range and diversity of their patients' sexual practices and backgrounds. A provider's attitude will affect the quality and effectiveness of care provided to PLHIV. Providers should:
- be open and able to discuss sex and other sensitive issues
- be prepared to take a comprehensive sexual history
- be able to manage debilitating SRH problems that patients face *(4)*
- be sensitive to the needs of PLHIV who may have suffered violence
- have current information and refer patients to appropriate support *(5, 6)*.

It is a fundamental duty of all health workers to use their professional skills ethically and be aware of the laws in their country. The main ethical principles of the health care profession are:
- do no harm
- respect the rights of the patient
- assure informed consent
- maintain the highest degree of patient confidentiality.

A list of recommended topics and suggested questions to use in obtaining a sexual history is provided in Annex 1.

2. Sexual well-being

While many of the sexual health issues faced by PLHIV are similar to those faced by their non-infected peers, some issues are particular to those living with HIV.

2.1. Sexual dysfunction among women

The limited evidence available suggests that sexual dysfunction is common in women following disclosure of HIV infection. It may be attributed to:
- psychological factors (including post-diagnosis depression, anxiety, irritability, loss of self esteem, altered/disturbed body image, change of roles in couple relationship, social isolation and fear of infecting others);
- medical factors (such as endocrinopathies and autonomic and peripheral neuropathies, gastrointestinal symptoms and headache);
- previous violence and associated fear and trauma;

- lipodystrophy, a side-effect of ART that can result in stigmatization and sexual isolation *(7–9)*; and/or
- infrequent sex, avoidance and non-communication *(10)*.

2.2. Sexual dysfunction among males

Among HIV-infected males, ART has been associated with low libido, erectile dysfunction and increased serum estradiol levels *(11)*.

Table 1. Clinical signs of male sexual dysfunction

Clinical signs	**Possible cause**
Historical	
Abrupt onset	Psychogenic impotence (HIV diagnosis, performance anxiety)
Absent nocturnal/early morning erections	Vascular or neurological disease
Loss of erection after penetration	Anxiety or vascular steal
Exam	
Reduced femoral or peripheral pulse	Vascular disease
Testicular atrophy/loss of muscle bulk/loss of facial or body hair	Hypogonadism
Laboratory	
Low serum-free testosterone, high prolactin or abnormal thyroid-stimulating hormone (TSH) levels	Endocrinologic dysfunction
Abnormal lipids	Atherosclerosis

Source: Colson & Sax *(12)*.

2.3. Interactions between erectile dysfunction drugs and ARVs

Sexual dysfunction, including a decrease in sexual interest, has been noted in both females and males receiving ART regimens with PIs *(13, 14)*. Switching HIV-infected patients to regimens that do not contain PIs may alleviate some symptoms associated with sexual dysfunction *(15)*, while among some male patients, sildenafil or apomorphine hydrochloride may improve erections *(16)*. Recreational use of Viagra (sildenafil) is common among some groups *(17, 18)*. Prescription of ARVs and erectile dysfunction agents should be based on possible side-effects and drug interactions.

Table 2. Interactions between erectile dysfunction agents and antiretroviral drugs

Erectile dysfunction agent	Agent dose	ARV	ARV dose	Agent effect on ARV levels	ARV effect on agent levels	Potential clinical effects	Management
Sildenafil (Viagra)	—	Amprenavir	—	—	Not studied; may increase sildenafil levels	Increased sildenafil effects (hypotension, priapism)	Initiate sildenafil at 25 mg QOD-OD and adjust dose as indicated; not recommended to exceed 25 mg in a 48-hour period.
	25 mg x 1 dose	Indinavir	800 mg TID	Indinavir AUC: increased 11%; Cmax: increased 48%	Sildenafil AUC: increased 340%; Cmax: increased 300% (levels exceeded those achieved by a 100 mg single dose)	Increased sildenafil effects (hypotension, priapism)	Initiate sildenafil 30–45 minutes before sex and adjust dose as indicated; not recommended to exceed 25 mg in a 48-hour period.
	—	Lopinavir/ ritonavir	—	—	Not studied; may increase sildenafil levels	Increased sildenafil effects (hypotension, priapism)	Initiate sildenafil 30–45 minutes before sex and adjust dose as indicated; not recommended to exceed 25 mg in a 48-hour period.
	—	Nelfinavir	—	—	Not studied; may increase sildenafil levels.	Increased sildenafil effects (hypotension, priapism)	Initiate sildenafil 30–45 minutes before sex and adjust dose as indicated; not recommended to exceed 25 mg in a 48-hour period.
	25 mg x 1 dose	Nelfinavir	1250 mg Q12H	Not studied	No significant change	—	No dose adjustment necessary.
	100 mg x 1 dose	Ritonavir	300 mg, 400 mg and 500 mg BID on Days 2, 3 and 4–8, respectively	—	Sildenafil AUC: increased 1000%; Cmax: increased 290%; Tmax: delayed 3 hours	Increased sildenafil effects (hypotension, priapism)	Initiate treatment at a 25 mg dose; do not exceed 25 mg in 48-hour period.
	—	Saquinavir	—	—	Sildenafil AUC: increased 200–1100%	Increased sildenafil effects (e.g. headache, flushing, priapism)	Initiate sildenafil 30–45 minutes before sex and adjust dose as indicated; not recommended to exceed 25 mg in a 48-hour period.

Erectile dysfunction agent	Agent dose	ARV	ARV dose	Agent effect on ARV levels	ARV effect on agent levels	Potential clinical effects	Management
Tadalafil (Cialis)	—	Lopinavir/ ritonavir	—	—	Not studied; may increase tadalafil levels.	Increased tadalafil effects (e.g. hypotension, priapism)	Do not coadminister. Suggested alterna-tive agents: sildenafil, vardenafil.
	20 mg x 1 dose	Ritonavir	200 mg BID	—	—	Increased tadalafil effects	Do not exceed 10 mg tadala-fil every 72 hours.
Vard enafil (Levitra)	10 mg x 1 dose	Indinavir	800 mg Q8H	Not studied	Vardena-fil AUC: increased 16-fold; Cmax: increased 7-fold; half-life: increased 2-fold	Increased vardena-fil effects (hypoten-sion, nausea, priapism, syncope)	Consider initiating vardenafil at lower dose and titrate to effect. Dose should not exceed 2.5 mg in any 24-hour period.
	—	Lopinavir/ ritonavir	—	—	Not studied; may increase vardenafil levels	Increased vardenafil effects (hy-potension, priapism, etc.)	Initiate vardenafil at 5 mg OD and adjust dose as indicated; not recommended to exceed 20 mg in a 48-hour period.

AUC: area under concentration-time curve; Cmax: maximum blood concentration; Tmax: time of peak concentration; OD: once daily; BID: twice daily; TID: three times daily; QOD: every other day; Q: every (Q8H= every 8 hours)
Source: adapted from HIV InSite *(19)*.

2.4. Substance use

When asking about sexual practice it is important to list all medications taken by a patient, including recreational, illicit and herbal/alternative drugs. Substance use by PLHIV may increase risky sexual behaviour and HIV transmission. If HIV-infected patients also receive ART or are about to initiate it, potential drug interactions should be considered and discussed with them. Table 3 summarizes some interactions between alcohol and ARVs and between marijuana and ARVs. (For more information about illicit drugs and ARV interactions please refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users.*)

Table 3. Interactions between ARVs and alcohol/marijuana

Substance	ARV	ARV dose	Substance dose	Substance effect on ARV levels	ARV effect on substance levels	Potential clinical effects	Management
Alcohol	Abacavir	600 mg OD	0.7 g/kg body weight	Abacavir AUC: increased 41%; half-life: increased 26%	No significant change	—	No dose adjustment necessary
	Amprenavir	—	—	—	—	Propylene glycol toxicity (acidosis, central nervous system (CNS) depression)	Use of alcoholic beverages is not recommended with amprenavir oral solution. Suggested alternative: amprenavir capsules.
Marijuana (THC – tetrahydrocannabinol)	Indinavir	800 mg Q8H x 21 days (pharmacokinetics measured at 14 days)	4% THC cigarettes	Indinavir AUC: no significant change; Cmax: no significant change; Cmin: decreased 34%	Not clinically significant	—	No dose adjustment necessary
	Nelfinavir	750 mg TID	4% THC cigarettes or 2.5 mg dronabinol TID	Nelfinavir AUC: no significant change; Cmax: decreased 17%; Cmin: no significant change	Not clinically significant	—	No dose adjustment necessary

AUC: area under concentration-time curve; Cmax: maximum blood concentration; Cmin: minimum blood concentration; THC: tetrahydrocannabinol.
Source: HIV InSite, New York State Department of Health AIDS Institute *(19, 20)*.

2.5. Aspects of mental health

Depression after HIV diagnosis may be a reason for sexual dysfunction in PLHIV. Appropriate psychological support should be an essential part of sexual dysfunction management, as not all PLHIV will need antidepressant therapy, and such support can facilitate a healthy sexual life. Some patients who have been referred for psychotherapy and prescribed antidepressants after their HIV diagnosis experience side-effects that include sexual dysfunction. More recently developed antidepressants with minimal drug interactions can be used when sexual dysfunction has been attributed to the older agents *(6)*.

Table 4. Antidepressant agents with sexual dysfunction side-effects (men and women)

Antidepressant	Therapeutic dosage	Potential clinical effects due to ARV interactions
Fluoxetine (Prozac)	10–40 mg/day	Increased delavirdine, ritonavir effects; possibly increased fluoxetine effects
Paroxetine (Paxil)	10–40 mg/day	Decreased paroxetine effect with fosamprenavir
Sertraline (Zoloft)	50–100 mg/day	Drug interactions unlikely with ARVs
Venlafaxine XR (Effexor XR)	75–375 mg/day	Increases in serum level of venlafaxine possible with RTV coadministration
Possible substitutions for individuals experiencing sexual dysfunction from other antidepressant agents		
Bupropion sustained release (Wellbutrin SR)	Not to exceed 400 mg/day (in divided doses) due to increased risk of seizures, particularly in individuals who have other risk factors for seizures	Clinically important drug interactions with PIs unlikely (preliminary in vitro data show weak inhibition by ritonavir)
Mirtazapine (Remeron)	15–45 mg/day	Increases in serum level of mirtazapine possible with ritonavir coadministration.

Source: HIV/AIDS Bureau, Colson & Sax, Anderson (6, 12, 21) .

3. STIs and RTIs

Management of STIs and RTIs should include the following components:
- medical and sexual history
- informed consent for testing and exam procedures
- physical examination
- testing for STIs and RTIs
- preventive measures (such as hepatitis B vaccination)
- treatment as needed, with consideration for potential ARV interactions
- for STIs, partner notification and fulfilment of any public health obligations
- counselling on risk reduction, and referral as appropriate
- scheduling of follow-up visits and consultations.

In general, the management of RTIs and non-HIV STIs for PLHIV is similar to that for other patients, with several differences.
- The clinical presentation of STIs may vary with HIV disease stage.
- Longer therapeutic courses may be needed.
- Potential drug interactions with ARV drugs should be evaluated.
- Enhanced surveillance is necessary due to the rapid progress and frequent recurrence of infections in PLHIV.

There are special considerations for the management of syphilis, vulvovaginal candidiasis and bacterial vaginosis in PLHIV; see Annexes 2–4.

Among HIV-infected women, higher rates and/or greater severity of the following STIs and RTIs and their complications have been noted than among HIV-negative women:
- pelvic inflammatory disease (PID)[2]
- human papillomavirus (HPV) infection, causing cervical dysplasia *(22–24)*
- cervical intraepithelial neoplasia (CIN)[3]
- vaginal yeast infections.

[2] PID is sometimes noted as a co-epidemic of HIV in some urban populations of reproductive age *(6)*.
[3] Rates are substantially higher among women in the advanced stages of HIV/AIDS *(25)*.

Among MSM, increased levels of rectal chlamydial infection, syphilis, gonorrhoea, herpes simplex virus (HSV), lymphogranuloma venereum (LGV), anal dysplasia and genital herpes are common regardless of HIV status *(26–32)*. In addition, anal cancer is strongly associated with HPV infection, and it is significantlsy more likely among MSM who are HIV-infected *(33, 34)*.

Testing procedures vary depending on resources and particular STI prevalence (see Table 5). Health care providers should accordingly consult local STI management guidelines for further advice.

Table 5. STI testing for PLHIV

Test	Rationale or risk group	Result	Recommended action
Venereal disease research laboratory slide test (VDRL) or rapid plasma reagin (RPR)	Syphilis screening	Negative Positive	Repeat every 3–6 months, counsel on prevention of STIs. Follow *European STD guidelines* (http://www.iusti.org/guidelines.pdf) for the management of syphilis *(35)*. See also Annex 2.
Pap smear	Detection of cell changes	See section VIII	Cf. section VIII and Annex 5 below.
Gonococci (GC) and *Chlamydia* testing	For all women with initial Pap smear, and for any symptomatic men	Negative Positive	Counsel on prevention of STIs; repeat if necessary. Treat patient; refer partner(s) of previous 60 days for evaluation and treatment.
GC and *Chlamydia* testing, urethral	MSM	Negative Positive	Retest annually, counsel on prevention of STIs. Treat patient; refer partners of previous 60 days.
GC and *Chlamydia* testing, pharyngeal	Men and women who have oral-genital sex	Negative Positive	Retest annually, counsel on prevention of STIs. Treat patient; refer partners of previous 60 days.
GC and *Chlamydia* testing, rectal	Women and men who have receptive anal sex	Negative Positive	Re-test annually, counsel on prevention of STIs Treat patient; refer partners of previous 60 days.
Lymphogranuloma venereum (LGV)	MSM	Positive	Treat patient; refer partners of previous 30 days.

GC: gonococci; RPR: rapid plasma reagin; VDRL: venereal disease research laboratory slide test.
Source: United States Department of Health and Human Services HIV/AIDS Bureau *(6)*.

3.1. Partner notification

It is essential that every effort be made to treat the partners of those HIV-infected people diagnosed with other STIs; otherwise, the likelihood of STI reinfection is high. Following a safety assessment to consider the implications of notifying sexual partners (i.e. a risk assessment for intimate partner violence), and in accordance with local protocols and regulations, patients should be encouraged to ensure that their sexual partners are evaluated and treated. Partner management strategies are based on the premise that the sexual partners of people with STIs are likely to be infected with the same STIs, but that they may be asymptomatic, and that they may not otherwise seek care. The various options for partner notification and treatment should be discussed with the patient. Depending on the resources of the provider and the individual situation of the patient, options include:

- the patient informing and accompanying a partner for testing;
- provider-assisted notification followed by testing and treatment; and
- in rare cases, expedited partner treatment in which the patient delivers medication to a partner without a clinical examination *(36–38)*.[4]

[4] This is not the preferred option due to the possibility of the partner's coinfection with multiple STIs including HIV, implications for drug interactions or allergies and medicolegal issues.

3.2. Interactions of STI/RTI drugs and ARVs

If PLHIV are on ART, possible drug interactions with other STI treatment drugs should be considered and discussed with them (see Table 6).

Table 6. Interactions between other STI/RTI drugs and ARVs

STI/RTI agent	STI/RTI agent dosage	ARV	ARV dosage	Agent effect on ARV levels	ARV effect on agent levels	Potential clinical effects	Management	Suggested alternative agent(s)
Azithromycin	600 mg x 1 dose	EFV	400 mg x 7 days	No significant change	Azithromycin AUC: no significant change; Cmax: ↑ 22%	—	No dose adjustment necessary	—
	1200 mg x 1 dose	IDV	800 mg TID	No significant change	—	—	No dose adjustment necessary	—
Ciprofloxacin	750 mg Q12H x 3 days	ddI	200 mg (buffered formulation) Q12H x 3 days	ddI AUC: ↓ 16%; Cmax: ↓ 28%	Ciprofloxacin AUC: ↓ 15-fold (with simultaneous ddI dosing); ↓ 26% when ciprofloxacin is dosed 2 hours before or 6 hours after ddI tablets.	↓ ciprofloxacin effects	Consider ddI enteric coated capsule or administer ddI tablets/ suspension 6 hours prior to or 2 hours after ciprofloxacin administration	—
	750 mg x 1 dose	ddI	400 mg (enteric coated capsule) x 1 dose	Not studied	No significant change	—	No dose adjustment necessary	—
Co-trimoxazole (TMP/SMX)	160/800 mg Q12H x 1 week	IDV	400 mg Q6H x 1 week	No significant change	TMP AUC: ↑ 19%; SMX AUC: no significant change	—	No dose adjustment necessary	—
Erythromycin base (E-Base, Ilosone, E-Mycin, Eryc, Ery-Tab)	—	APV	—	Not studied; may ↑ APV levels	Not studied; may increase erythromycin levels	—	Dose adjustment not established	Azithromycin, clarithromycin
	250 mg QID x 7 days	SQV	1200 mg TID	SQV AUC: ↑ 99%; Cmax: ↑ 106%	—	↑ SQV effects	Dose adjustment not established	—
Famciclovir (Famvir)	500 mg x 1 dose	FTC	200 mg x 1 dose	No significant change	—	No significant change	No dose adjustment necessary	—

STI/RTI agent	STI/RTI agent dosage	ARV	ARV dosage	Agent effect on ARV levels	ARV effect on agent levels	Potential clinical effects	Management	Suggested alternative agent(s)
Metronidazole (Flagyl)	—	APV	Oral solution (contains propylene glycol)	—	—	Propylene glycol toxicity (acidosis, CNS depression)	Do not coadminister with APV oral solution	Amprenavir capsules
	—	LPV/r	Oral solution (contains alcohol)	—	—	Disulfiram reaction (hypotension headache, nausea, vomiting)	Do not coadminister; consider LPV/r capsules	—
	—	RTV	Oral solution (contains alcohol) and capsules	—	—	Disulfiram-like reaction (headache, hypotension, flushing, vomiting)	Do not coadminister	—
Sufamethoxazole	1000 mg x 1 dose	ddI	200 mg (buffered formulation) x 1 dose	No significant change	No significant change	—	No dose adjustment necessary	—
Trimethoprim (Trimpex)	200 mg x 1 dose	ddI	200 mg (buffered formulation) x 1 dose	ddI AUC: no significant change; Cmax: ↑ 17%	TMP AUC: no significant change; Cmax: ↓ 22%	—	No dose adjustment necessary	—

↑: increase; ↓: decrease; QID: four times daily
Source: HIV InSite *(19)*.

4. Violence related to gender and sexuality

Gender- and sexuality-related violence has a detrimental effect on a victim's physical, emotional and social life. By understanding the range of complications he or she may be experiencing, health care providers are able to offer more effective HIV/AIDS treatment. In many cases the victim, who is most often female, will not only be infected with HIV by the perpetrator, but also, due to feelings of low self-worth, socioeconomic factors or oppressive tactics, she will not be diagnosed until a later stage of the disease *(39, 40)*.

Treating PLHIV who have been subjected to violence requires the provider to do the following things *(39, 41–44)*:

- Routinely evaluate the possibility of violence for all female (and male when indicated) HIV-infected patients.
- Keep the health and welfare of the patient as the first priority. "Safety first" and "do no harm" should be guiding principles.
- Avoid retraumatizing the patient with questions that are likely to provoke a strong or emotional reaction, cause distress or insinuate a negative judgement.
- Be prepared to respond to distress and highlight the patient's strengths.
- Be prepared to provide appropriate care, follow-up and support services (referrals).
- Maintain confidentiality.

- With respect to partner notification, take into account the harm that may occur if an abuser is notified. Where such notification is mandatory, the patient should be informed about the consequences of disclosure prior to identifying the partner.
- Agree with the person who has suffered violence upon any action that is to be taken with respect to the abuser or perpetrator. Respect the patient's wishes, as her or his consent is essential. In accordance with legal obligations, exceptions may need to be made for suspected abuse of minors.
- Be prepared for emergency intervention if a patient or a patient's dependants feel they are in imminent danger.
- Provide psychological support or refer the patient to a specialist for such support, as well as for legal counselling if appropriate.
- Counsel the patient on post-exposure prophylaxis (PEP) (for prevention of STIs, emergency contraception, etc.) (Please refer to Protocol 13, *Post-exposure prophylaxis for HIV infection* for further information.)

5. Impact of disabilities and chronic illnesses on sexual health

Compared to non-disabled people, individuals with a physical, sensory, intellectual or mental health disability are often at increased risk for contracting and transmitting HIV, for substance abuse and for restricted access to services and interventions *(45, 46)*. While PLHIV with physical disabilities and chronic illnesses contend with the same sexual health issues as their non-disabled peers, they often face additional barriers to care, such as:

- difficulty accessing treatment centres due to lack of mobility or independence;
- ineffective communication (lack of interpreters – including sign language – confused, complicated explanations, too technical language, etc.); and
- homophobia, HIV stigma and the misconception among professional health providers that the physically disabled do not have sex.

Disabled individuals, especially women, may also be at an increased risk for gender-based violence due to factors such as:

- increased physical vulnerability
- need for attendant care
- social isolation
- lack of economic independence
- decreased access to health care
- less education about safer sexual behaviours
- difficulty being believed *(47–49)*.

Health care providers should ensure that PLHIV with disabilities or chronic illnesses have the same support, treatment and access to care as the non-disabled population. The range of possible mental and physical disabilities and chronic illnesses is broad, as are the specific sexual health concerns that may need to be addressed. Providers should be prepared to:

- ensure patients have full access to information, care and treatment support;
- address substance use;
- address gender-based violence;
- provid referrals to disability support organizations, substance use centres, institutions for gender-based violence, etc.;
- determine the individual's knowledge of and negotiation skills for safer sex;
- determine the level of support available from other care providers and family members for contraception and safer sex practices;
- adapt safer sex messages for the use of the disabled;
- address contraindications for ART and other drugs needed to treat a patient's physical disability/chronic illness; and
- coordinate with other health care providers.

V. Contraception

The recommendations for contraceptive methods in this section are based on a comprehensive manual of recommendations on eligibility criteria for contraceptive use *(50)*. The manual includes HIV/AIDS as a factor in determining eligibility for each major contraceptive method.

1. Preliminary visit

In addition to medical eligibility criteria, the patient's social, cultural and behavioural context must also be considered. Contraceptive recommendations should be individualized for each woman and couple, based on disease stage and treatment as well as lifestyle and personal desires. Each woman is best placed to interpret the risks and benefits the available methods may have for her. It should be the patient who makes the final selection of contraceptive method. To make an informed choice, she requires information on:

- the method's effectiveness
- its correct use
- its risks and benefits
- common side-effects
- signs and symptoms that would necessitate a return to the clinic
- cost and convenience issues
- the method's effect on transmission of STIs, including HIV.

Counselling should help women living with HIV to make decisions about their fertility. It should therefore include information on:

- effective contraceptive methods to prevent pregnancy and STI transmission;
- the effects of HIV disease progression on health;
- the effectiveness and availability of ARVs;
- the services that provide ART;
- the interactions between ARVs and contraceptives;
- the risk of HIV transmission to an uninfected partner while trying to become pregnant;
- the possible impact of HIV on pregnancy, including adverse pregnancy outcomes;
- the risk of MTCT and the risks and benefits of strategies to reduce it, including ARV prophylaxis, caesarean section and bottle-feeding;[5] and
- the possible birth defects associated with the use of some ARVs.

2. Medical eligibility criteria for contraceptive use by women living with HIV

Most contraceptive methods are safe and effective for use by women with asymptomatic HIV infection as well as for women with developed HIV/AIDS disease *(50)*. However, transmission of HIV and other STIs (HIV/STIs) warrants special consideration during family planning counselling because preventing transmission is as important as preventing pregnancy. Since condoms are the only contraceptive method shown to protect against acquiring and transmitting HIV/STIs, family planning services should strongly encourage and facilitate their consistent and correct use *(51)*.

[5] For more information, please refer to Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants*.

3. General contraceptive methods

3.1. Barrier methods and spermicides

3.1.1. Dual protection

- Dual protection is defined as the simultaneous prevention of STI transmission and unwanted pregnancy. It can be achieved by the consistent use of latex condoms, either alone or in combination with another method.
- Dual protection is also achieved by avoidance of penetrative sex, particularly in situations of high risk.
- Dual protection may be indicated to compensate for a reduction in the effectiveness of hormonal contraceptives due to interactions between ART and hormonal contraception (see section V.4.1 below).
- Dual protection strategies should be part of the counselling and support provided by all reproductive health services *(52)*.

3.1.2. Male latex condoms

- When used consistently and correctly, male latex condoms[6] protect against female-to-male, male-to-male and male-to-female transmission of HIV, as shown in studies of HIV-discordant couples[7] *(53)*.
- In HIV-infected couples, condoms can offer individuals protection against new HIV strains. Limited evidence suggests that infection with more than one strain of HIV may accelerate the progression of HIV disease *(54)*.
- Laboratory studies have demonstrated the impermeability of latex condoms to infectious agents, including the smallest viruses, contained in genital secretions.
- Latex condoms may be less effective in protecting against those STIs not transmitted by semen or fluid (such as herpes, human papillomavirus and syphilis), since the infected areas may not be covered by the condom *(51)*.
- Clear instructions on correct condom use are essential. To provide optimum protection against infection, they must be of good quality and be used consistently and correctly.
- Emergency contraception can be offered as a backup in case a condom breaks or slips (see section V.3.6 below).
- For serodiscordant couples, information and access to post-exposure prophylaxis for uninfected partners should be offered if a condom breaks or slips.
- Despite the method's efficacy, low rates of condom use have been reported, even following disclosure of positive HIV status to sexual partners *(55)*.
- Use of condoms to prevent HIV/STI transmission should be emphasized in cases where prevention of pregnancy is not a concern, such as pregnancy or any kind of infertility, e.g. due to sterilization or menopause.

3.1.3. Female condoms

- Available data indicate that female condoms, used correctly and consistently, provide protection against STIs, including HIV *(56–58)*.
- The limited data available suggest they may be slightly less effective than male condoms for the prevention of pregnancy *(59)*. However, they offer several advantages, including:
  - the possibility of insertion prior to intercourse;
  - no necessity for removal immediately after ejaculation; and
  - greater female control, though some degree of negotiation and male cooperation is still required.

[6] Condoms made of animal membranes do not protect against HIV, as such when the term condom is used in this document, it refers to latex condoms unless otherwise stated.

[7] Couples with discordant serostatus – those in which one sexual partner is HIV-positive and the other HIV-negative – may require special support. Protected sex using a condom is the only way to ensure PLHIV that HIV-negative sexual partners can remain uninfected.

3.1.4. Other barrier methods (diaphragms, cervical caps)

Women for whom pregnancy is an unacceptable risk should be advised that other contraceptive barrier methods (diaphragms and cervical caps) may not be appropriate because of their relatively higher typical-use failure rates for those who cannot use them consistently and correctly. It should also be stressed that they do not protect against the transmission of HIV or other STIs.

3.1.5. Spermicides

- Since nonoxynol-9 may cause some side-effects, condoms lubricated with it should no longer be promoted; nevertheless, it is better to use a nonoxynol-9-lubricated condom than no condom *(60)*.
- The safety concerns with nonoxynol-9 also apply to other spermicidal products marketed for contraception. Spermicides should not to be used by women living with HIV, neither alone or with other barrier methods such as diaphragms or cervical caps.
- There is no evidence that nonoxynol-9-lubricated condoms provide any more protection against pregnancy or sexually transmitted infections than condoms lubricated with silicone.

3.2. Low-dose combined oral contraceptives (COC)

Table 7. Low-dose COC (≤35 µg of ethinylestradiol (EE)) for women living with HIV

Status	Category[a]	Comment
High risk of HIV	1	Overall, evidence is inconsistent regarding whether there is any increased risk of HIV acquisition among COC users.
HIV/AIDS without ART	1	Limited evidence suggests no association between COC use and changes in RNA levels or CD4 counts among HIV-infected women. There is also limited evidence showing no association between COC use and female-to-male HIV transmission, and mixed results regarding increased risk of HIV and HSV shedding among HIV-infected women using hormonal contraception.
HIV/AIDS + ART	2	For women on ART, refer to the section on drug interactions below (V.4.1). As there may be drug interactions between hormonal contraceptives and ARVs, such use is classified as Category 2.
Drug interactions		
ARVs	2	It is important to note that ARV drugs have the potential to decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. The limited data available suggest that interactions between many ARVs (particularly some NNRTIs and PIs) and hormonal contraceptives may alter the safety and effectiveness of both. For women initiating or continuing hormonal contraceptive use while on ART, the consistent use of condoms is recommended for preventing HIV transmission; it may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive. See section V.4 below.

[a] Category 1: no restrictions for use of contraceptive method; use in any circumstances. Category 2: advantages of using method generally outweigh theoretical or proven risks. Generally advisable to use the method.
Note: COCs do not protect against HIV/STIs. If there is risk of HIV/STIs, the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against HIV/STIs.
Source: WHO (50).

There are concerns that women may have a greater risk of acquiring STIs when using hormonal contraceptives, possibly due to decreased condom usage. Yet the evidence is inconsistent regarding whether hormonal contraceptive users have greater risk of acquiring HIV than non-users *(50)*.

3.3. Progestogen-only contraceptives (POCs)

Progestogen-only contraceptives include progestogen-only pills (POPs), injectable progestogens (depot medroxyprogesterone acetate (DMPA) and norethisterone-enantate (NET-EN)) and progestogen implants (levonorgestrel implants (Norplant and Jadelle) and etonogestrel implants (Implanon)) (see Table 8).

Table 8. Progestogen-only contraceptives for women living with HIV

Condition	Category[a]			Comment
	POP	D/NE	LN/ETG	
High risk of HIV	1	1	1	Overall, evidence is inconsistent as to any increased risk of HIV acquisition among POC users.
HIV/ AIDS without ART	1	1	1	Studies conflict over whether there is increased risk of HIV and HSV shedding among HIV-infected women using DMPA.
HIV/AIDS + ART	2	2	2	For women on ART, refer to the section on drug interactions (V.4.1 below). As there may be interactions between hormonal contraceptives and ARVs, it is classified as Category 2.
Drug interactions				
ARV	2	2	2	ARVs have the potential to decrease or increase the bioavailability of steroid hormones in hormonal contraceptives (see section V.4.1 below). It is not known whether the contraceptive effectiveness of injectable POCs (such as DMPA and NET-EN) would be compromised, as they provide higher blood hormone levels than other POCs and COCs. Studies are underway to evaluate potential interactions between DMPA and selected PI and NNRTI drugs. For women initiating or continuing hormonal contraceptive use while on ART, the consistent use of condoms is recommended for preventing HIV transmission; it may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

D/NE: depot medroxyprogesterone acetate (DMPA)/norethisterone enantate (NET-EN); LNG/ETG: levonorgestrel implants (Norplant and Jadelle) and etonogestrel implants (Implanon); POP: progestogen-only pill.

[a] Category 1: no restrictions for use of contraceptive method; use in any circumstances. Category 2: advantages of using method generally outweigh theoretical or proven risks. Generally advisable to use the method.

Note: POCs do not protect against HIV/STIs, though neither has the use of POCs been associated with HIV acquisition or transmission (61). If there is risk of HIV/STIs, the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against HIV/STIs.

Source: WHO *(50).*

3.4. Combined contraceptives in injectable, patch and ring form

For women living with HIV, there are no restrictions on the use of combined injectable contraceptives (CICs), combined contraceptive patches or combined contraceptive vaginal rings.

- CICs provide for the release of a natural estrogen plus a progestogen. Two CIC formulations, both given at four-week intervals, are considered here: Cyclofem (medroxyprogesterone acetate 25 mg plus estradiol cypionate 5 mg) and Mesigyna (norethisterone enantate 50 mg plus estradiol valerate 5 mg).
- The combined contraceptive patch is a 20 cm^2, three-layer patch applied to the buttocks, torso, abdomen or upper arm to release ethinylestradiol and a progestogen (norelgestromin) transdermally. The combined contraceptive patch currently available is Evra (17-deacetyl norgestimate (norelgestromin) 150 µg plus ethinylestradiol 20 µg). A new patch has to be applied once a week for three consecutive weeks each month.
- The combined contraceptive vaginal ring releases ethinylestradiol and a progestogen (etonogestrel) from a 54 mm ethylene vinyl acetate copolymer ring. The vaginal ring formulation currently available is NuvaRing (etonogestrel 120 µg plus ethinylestradiol 15 µg). It is inserted once a month, taken out after 21 days to allow the normal menstrual cycle, and a new ring is inserted after a 7-day break.

The contraceptive effect of CICs, patches and vaginal rings is achieved by inhibiting ovulation. These contraceptive methods are new, with little epidemiological data on their long-term effects (see Table 9).

TABLE 9. CICs AND COMBINED CONTRACEPTIVE PATCHES AND RINGS FOR WOMEN LIVING WITH HIV

Status	Category[a]			Comment
	CIC	Patch	Ring	
High risk of HIV	1	1	1	—
HIV/AIDS without ART	1	1	1	Relatively limited information is available on the safety of the combined contraceptive patch and vaginal ring. At present, there are no restrictions on the use of CICs, patches or vaginal rings for women living with HIV.
HIV/AIDS + ART	2	2	2	For women on ART, refer to the section on drug interactions (V.4.1 below). As there may be interactions between hormonal contraceptives and ARVs, this use is classified as Category 2.
Drug interactions				
ARVs	2	2	2	ARVs have the potential to decrease or increase the bioavailability of steroid hormones in hormonal contraceptives (see section V.4.1 below). The limited data available suggest that potential drug interactions between many ARVs, particularly some NNRTIs and PIs, and hormonal contraceptives may alter safety and effectiveness of both. For women initiating or continuing hormonal contraceptive use while on ART, the consistent use of condoms is recommended for preventing HIV transmission; it may also compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

[a] Category 1: no restrictions for use of contraceptive method; use in any circumstances. Category 2: advantages of using method generally outweigh theoretical or proven risks. Generally advisable to use the method.
Note: CICs, patches and rings do not protect against HIV/STIs. If there is risk of HIV/STIs, the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against HIV/STIs.
Source: WHO *(50)*.

3.5. Intrauterine devices (IUDs)

IUDs can be safely used by women living with HIV, whether asymptomatic, on ART or clinically well, but such users should be closely monitored for pelvic inflammatory disease (PID). IUDs are not usually recommended for women living with AIDS who are not on ART if more appropriate contraceptive methods like condoms or steroid hormonal contraceptives are available and acceptable.

While physicians should be wary of over-diagnosing PID, it is highly probable with IUD-wearers when one or more of the following symptoms are observed:
- lower genital tract infection
- cervical motion tenderness
- adnexal tenderness
- enlargement of one or both Fallopian tubes, a tender pelvic mass
- direct or rebound tenderness
- elevation of temperature (temperature may be normal in many cases of PID).

Hospitalization of patients with acute PID should be seriously considered when:
- the diagnosis is uncertain
- surgical emergencies such as appendicitis and ectopic pregnancy cannot be excluded
- a pelvic abscess is suspected
- severe illness precludes management on an outpatient basis
- the patient is pregnant
- the patient is unable to follow or tolerate an outpatient regimen
- the patient has failed to respond to outpatient treatment.

The levonorgestrel-releasing intrauterine device (LNG-IUD) releases 20 µg of levonorgestrel (LNG) daily, directly into the uterus. Because LNG suppresses endometrial growth, users can expect a marked reduction in the amount of menstrual blood. Many women experience little or no bleeding (amenorrhea) within a year of beginning use. In sexual relations where the recommended condoms are not used, a reduction of menstrual blood loss may be regarded as a means of decreasing the risk of female-to-male HIV transmission (see Table 10).

TABLE 10. IUDs FOR WOMEN LIVING WITH HIV

Condition	Category[a] (I: initiation, C: continuation)				Comment
	Cu-IUD		LNG-IUD		
	I	C	I	C	
High risk of HIV	2	2	2	2	Among women at risk of HIV, copper-releasing IUD (CU-IUD) use did not increase risk of HIV acquisition.
HIV/AIDS without ART	2	2	2	2	Limited evidence shows no increased risk of overall or infection-related complications among IUD users when comparing HIV-infected women with non-infected women. Furthermore, it shows no association between IUD use among HIV-infected women and increased risk of transmission to sexual partners. IUD users with AIDS should be closely monitored for PID.
HIV/AIDS + ART	3	2	3	2	IUD users with AIDS should be closely monitored for PID.
Clinically well on ART	2	2	2	2	—
Drug interactions					
ARVs	2/3	2	2/3	2	There are no known drug interactions between ARVs and IUDs. However, IUD use by AIDS patients is classified as Category 3 for insertion and Category 2 for continuation, unless the woman is clinically well on ART, in which case both insertion and continuation are classified as Category 2.

Cu-IUD = copper-releasing IUD; LNG-IUD = levonorgestrel-releasing IUD (20 µg/24 hours),

[a] Category 1: no restrictions for use of contraceptive method; use in any circumstances. Category 2: advantages of using method generally outweigh theoretical or proven risks. Generally advisable to use the method. Category 3: method not usually recommended unless other more appropriate methods are not available or not acceptable (theoretical or proven risks usually outweigh the advantages of using the method).

Note: IUDs do not protect against HIV/STIs. If there is risk of HIV/STIs, the correct and consistent use of condoms is recommended, either alone or with another contraceptive method. Male latex condoms are proven to protect against HIV/STIs.

Source: WHO *(50)*.

3.6. Emergency contraception

Emergency contraception can prevent pregnancy when:

- a contraceptive method fails
- no method was used
- sex was forced.

Emergency contraceptive pills inhibit or delay ovulation, and prevent implantation and fertilization or transport of sperm/ova by altering the endometrium.

When used within 72 hours after sex:

- the Yuzpe regimen (COC) prevents about 74% of expected pregnancies *(62)*;
- POPs prevent 85% of expected pregnancies under typical use and 89% under correct use *(63)*; and
- POPs produce fewer side-effects than COCs.

3.6.1. Emergency contraceptive pill regimens

- One of the best-studied progestogen-only regimes consists of 1.5 mg of levonorgestrel (two pills containing 0.75 mg taken either in a single dose or at a 12-hour interval). Ideally, the pills should be taken within 72 hours of unprotected intercourse.
- If low-dose pills containing 30 µg ethinylestradiol and 150 µg levonorgestrel are used, four pills should be taken in a first dose as soon as convenient, but no later than 72 hours after unprotected intercourse. These should be followed by a second dose of four pills 12 hours later.
- The standard regimen (the Yuzpe method) consists of the combined oral pills containing 50 µg ethinylestradiol and 250 µg levonorgestrel. Two pills should be taken in a first dose as soon as convenient, but no later than 72 hours after unprotected intercourse. These should be followed by a second dose of the same pills 12 hours later.

The most common side-effects of hormonal emergency contraception are nausea and vomiting. The Yuzpe regimen is associated with a 42% incidence of nausea and a 16% incidence of vomiting *(64)*. These problems were significantly less common among users of the levonorgestrel regimen, at 23% and 6%, respectively *(63)*. The Yuzpe regimen can be used if levonorgestrel or mifepristone are not available.

Several observations should be made about the management of side-effects:

- Taking the pills with food or at bedtime may help reduce nausea.
- If vomiting occurs within two hours of taking the pills, the dose should be repeated. In cases of severe vomiting, the repeat dose may be administered vaginally.
- The majority of women will have their menstrual period on time or slightly early. If there is a delay of more than one week, a pregnancy test should be performed.
- A single dose simplifies the use of levonorgestrel for emergency contraception without increasing side-effects.
- Breast tenderness, headache, dizziness and fatigue may occur.

Hormonal emergency contraception may have side-effects in women living with HIV.

- There are no studies of side-effects in women living with HIV, neither on ART or off. Nausea and vomiting are side-effects with some ARTs and may be intensified when taking emergency contraceptive pill regimens.
- The Yuzpe regimen should be avoided in women taking indinavir, atanazavir, amprenavir or efavirenz since it raises estradiol levels, which may increase the risk of thrombo-embolic disease (see section V.4.1 below).

3.6.2. IUDs as emergency contraceptives

- A copper-releasing IUD can also be used within five days of unprotected intercourse as an emergency contraceptive.
- When the time of ovulation can be estimated, the Cu-IUD may be inserted more than five days after intercourse if necessary, as long as the insertion does not also occur more than five days after the earliest estimated ovulation.

3.6.3. Mifepristone

- Orally administered mifepristone (10 mg), an antiprogestin, offers high efficacy with few side-effects when taken within 120 hours (five days) of unprotected intercourse *(65)*.
- Mifepristone can delay menstruation, which may in turn increase patient anxiety.
- There are no studies about the efficacy or side-effects of mifepristone in women living with HIV, either with or without ART.

3.7. Surgical sterilization procedures

Given that sterilization is a surgical procedure intended to be permanent, special care must be taken to ensure that every patient who chooses it is making a voluntary informed choice. All patients, irrespective of HIV status, must understand the permanence of sterilization and be informed of alternative contraceptive methods. The indications and contraindications for sterilization are the same as for HIV-negative patients.

As sterilization provides no protection against STI acquisition or HIV transmission, it is essential to stress the importance of condom use, particularly as sterilization has been associated with a decrease in condom use. The national laws and existing norms for sterilization procedures must also be considered in the decision process.

The general health of any PLHIV who opt for this procedure must be examined carefully before any elective surgery is undertaken. A decision to proceed depends on any existing AIDS-related illnesses that may compromise the patient.

3.8. Fertility-awareness methods and coitus interruptus

Fertility-awareness methods and coitus interruptus are characterized by higher typical-use failure rates than other methods and should not be routinely recommended for either HIV-positive or -negative women.

3.9. Lactational amenorrhea method

This method is not recommended due to the need to avoid HIV transmission in serodiscordant couples and breastfeeding infants. Replacement feeding is recommended where acceptable, feasible, affordable, sustainable and safe. Otherwise, exclusive breastfeeding is recommended during the first months of life and should then be discontinued as soon as feasible.

Mothers living with HIV should be helped to make the best choice for feeding their infants in accordance with their circumstances, and to carry out their decision. They should thus receive counselling that includes information about the risks and benefits of various infant feeding options (based on local assessments), and support to carry out their choice safely and appropriately.

3.10. Future prospects

Developmental work on microbicides, which could provide an invaluable method of dual protection, is underway. Such products are inserted into the vagina before sexual intercourse to prevent transmission of HIV/STIs and would be thus under the control of the woman. Although some microbicides aim to provide dual protection against unintended pregnancies and HIV/STIs, others are only intended to prevent the latter. So far, no microbicides have been shown to decrease MTCT effectively, nor are any microbicidal products on the market for the prevention of sexual transmission of HIV or other STIs. Until effectiveness trials demonstrate safety and efficacy, microbicide use should not be promoted.

4. Contraception for women on ARV

WHO recommends using highly active antiretroviral treatment (HAART) for PLHIV who are eligible for ART in accordance with the WHO clinical staging system (for more information please see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*).

ARV regimens recommended by the WHO Regional Office for Europe for first- and second-line therapy are shown in Table 11.

Table 11. Recommended first- and second-line HAART regimens for adults and adolescents

First-line regimens	Second-line regimens
ZDV + 3TC[a] + EFV[b] or NVP	LPV/r[c] + ddI + ABC LPV/r[c] + TDF + ABC LPV/r[c] + TDF + (ZDV + 3TC)[d]
TDF + FTC[a] + EFV or NVP	LPV/r[c] + ddI + ABC LPV/r[c] + ddI + ZDV
ABC + 3TC[a] + EFV or NVP	LPV/r[c] + ddI + ZDV LPV/r[c] + (ZDV + 3TC)[d]

[a] 3TC (lamivudine) and FTC are considered interchangeable agents, given their activity, tolerance and resistance profiles. They are both listed in this table as a reflection of the commonly available FDCs.
[b] For the purpose of this table, treatment failure on an NVP- or EFV (efavirenz)-based regimen is considered to result in NNRTI class cross-resistance.
[c] LPV/r is listed as the preferred RTV-boosted protease inhibitor (PI) in this table, but other boosted PIs can be substituted based on individual programme priorities. ATV/r, SQV/r, FPV/r and IDV/r are all possibilities. In the absence of a cold chain, NFV can be employed as the PI component, but it is considered less potent than a boosted PI.
[d] ZDV + 3TC is listed here for "strategic" use, as resistance to both drugs is predicted to be present following failure on the respective first-line regimen listed. ZDV may prevent or delay the emergence of the K65R mutation; 3TC will maintain the M184V mutation, which may decrease viral replicative capacity as well as induce some degree of viral resensitization to ZDV. It must be stressed that the clinical efficacy of this strategy in this situation has not been proven.

4.1. Interactions between ARVs and steroids in hormonal contraceptives

The limited data available suggest that several ARVs, especially NNRTIs and PIs, have the potential to either decrease or increase the bioavailability of steroid hormones in hormonal contraceptives. These drug interactions may alter the safety and effectiveness of both the hormonal contraceptives and the ARVs. The possible interactions betweem ARVs and COCs, as well as the suggested alternatives, should be taken into consideration and discussed with the patients.

Table 12 summarizes the most recent evidence regarding ARVs and steroids in COCs and provides management recommendations regarding use of the latter *(66)*.

Table 12. Interactions between ARVs and ethinylestradiol (EE)/ norethindrone (NE) acetate

ARVs	Effect of coadministration on EE, NE acetate and ARV levels	Recommendations
Protease inhibitors (PIs)		
Atazanavir (ATV)	EE ↑ 48%, NE ↑ 110%	Use the lowest effective dose or an alternative method.
Fosamprenavir (FPV)	EE and NE ↑, FPV↓20%	Do not coadminister, alternative contraceptive methods recommended.
Indinavir (IDV)	EE ↑24%, NE ↑26%	No dose adjustment required.
Lopinavir/ritonavir (LPV/r)	EE ↓ 42%	Use an alternative or additional method.
Nelfinavir (NFV)	EE ↓ 47%, NE ↓18%	Use an alternative or additional method.
Ritonavir (RTV)	EE ↓ 40%	Use an alternative or additional method.
Saquinavir (SQV)	No data	—
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz (EFV)	EE ↑ 37%	Use an alternative or additional method.
Nevirapine (NVP)	EE ↓ 20%	Use alternative contraceptive methods.

No data are available for interactions between ARVs and levonorgestrel. It is not known whether the contraceptive effectiveness of progestogen-only injectable contraceptives (such as DMPA and NET-EN) would be compromised – these methods provide higher blood hormone levels than other progestogen-only contraceptives or combined oral contraceptives.

4.2. Interactions between ARVs and IUDs

There are no known interactions between ARVs and either the copper- or the levonorgestrel-releasing IUDs.

4.3. Teratogenicity of EFV

- EFV is considered potentially teratogenic and should be avoided for women trying to conceive or not using effective contraception.
- It is recommended that women have a pregnancy test prior to initiating treatment with EFV.
- For women using effective contraception, EFV is a viable option for the NNRTI component of an ARV treatment regimen.

4.4. Adherence to contraception and HIV/AIDS treatment

HIV-positive women may need to take several pills each day for ART, prophylaxis or treatment of opportunistic infections, symptomatic relief or treatment of concurrent illnesses. In addition to potential drug interactions, the impact of pill burden on adherence to contraception and HIV-related therapies should be considered. A hormonal contraceptive method that requires daily administration will increase pill burden. Women need to be aware of these considerations when they select a contraceptive method.

5. Contraceptive methods for women on both ART and TB treatment

- For women receiving ART and tuberculosis (TB) treatment, drug interactions with certain hormonal contraceptives can reduce the effectiveness of hormonal contraception.
- Due to drug interactions, a non-hormonal method of contraception is preferable for women receiving both ART and TB treatment.

- If hormonal contraception is the only option, low-dose (<35 µg) estrogen COC is usually not recommended for women receiving rifampicin. Although evidence is limited, use of an oral contraceptive pill containing a higher dose of estrogen (50 µg) may be considered unless the patient is taking EFV, IDV, APV or ATV.
- DMPA can generally be used with rifampicin.
- The effectiveness of LNG-IUDs is unlikely to be reduced.

6. Considerations for the most vulnerable populations

Sexual and reproductive health services should strive to create a supportive and non-discriminatory environment for specific vulnerable populations. Due to the stigma attached to these populations, they often do not seek health care through conventional channels. It is therefore important for outreach to be part of the strategy for all SRH programmes in order to improve access for these groups.

6.1. Sex workers (male and female)

- Consistent condom use should be recommended to sex workers for use with clients and their regular partners to prevent HIV transmission to the uninfected partner.
- Pending evidence on the reuse of female condoms, it is recommended that they be used only once.

6.2. MSM

- MSM should be advised to use water-based or silicone-based lubricants during anal sex to maintain condom integrity.

6.3. IDUs

- Drug-related amenorrhea is not an indication of infertility. It is thus important to advise women who are injecting drug users on regular use of contraception to prevent unintended pregnancy.
- Links should be reinforced between RH and harm reduction (HR) services.

7. Recommendations for contraceptive methods

- Discussion of family planning should be initiated during post-test HIV counselling and continued in follow-up sessions and at regular intervals throughout care.
- All staff should understand that they have a professional responsibility to maintain HIV confidentiality.
- In addition to medical eligibility criteria, the social, cultural and behavioural context should also be considered, and recommendations for contraceptive methods should be tailored to the individual, based on disease stage, treatment, lifestyle and personal wishes.
- Transmission of HIV and other STIs warrants special consideration during family planning counselling. Family planning services should strongly encourage and facilitate the consistent and correct use of condoms as the only contraceptive method that protects against HIV and other STIs. Furthermore, all reproductive health services should provide support for dual protection.
- Links between harm-reduction services for IDUs and HIV/AIDS treatment and care services should be established and strengthened to provide better continuity of care.

VI. Safe abortion

Preventing unintended pregnancies and unsafe abortions is essential for improving the reproductive health of all women, including those living with HIV. Even where contraceptive services are available, unintended pregnancies still happen for a variety of reasons – contraceptives may fail, male partners may oppose using condoms or other forms of contraception, people may not use contraceptives for fear of side-effects, unprotected sex may be coerced or forced, etc. – and many women will seek termination of these pregnancies.

In case HIV infection is diagnosed during pregnancy, the woman may seek termination of pregnancy even if the pregnancy was planned or wanted. For whatever reason women living with HIV want to terminate a pregnancy, they should have access to safe abortion.

When induced abortion is performed by qualified people using correct techniques in sanitary conditions, it is a safe procedure. Restrictive abortion legislation is associated with a high incidence of unsafe abortion, performed by unskilled providers and/or in unhygienic conditions. On the other hand, abortion should not be presented as a method of family planning. Every woman has the right to – and should have the opportunity to make – informed choice regarding her pregnancy and should not be coerced, either into terminating the pregnancy or carrying it to term.

1. Abortion counselling

If a woman's HIV status is unknown, HIV testing and counselling should be offered during counselling on unwanted pregnancy; however, a HIV test should not be mandatory, and refusal to be tested should not affect her access to safe abortion services. Neither should HIV testing be requested in order to protect staff, as universal infection control precautions should be taken for every abortion.

Non-directive, non-judgemental, confidential counselling should be provided by a professional trained in pregnancy termination and well informed on the subject of HIV infection in pregnancy. Complete and accurate information, given respectfully in understandable language, will assist women in making the best decisions about their pregnancies. In cases of minors or people mentally incapable of informed consent, assistance should be provided according to national regulations. If drug use is involved, additional expertise may be required.

If sexual intercourse between an HIV-negative woman and an HIV-positive man results in pregnancy, HIV infection is unlikely to have occurred in the woman if the HIV antibody screening test is negative one month after exposure and can be excluded if negative six months after exposure. If an early diagnosis is needed, HIV infection should be highly suspected if there is:

- a positive detection of HIV RNA, starting 15 days post-exposure;
- p24 antigenaemia, starting 18 days post-exposure; or
- a positive HIV-antibody screening test, starting three weeks post-exposure (subject to confirmation and expert advice).

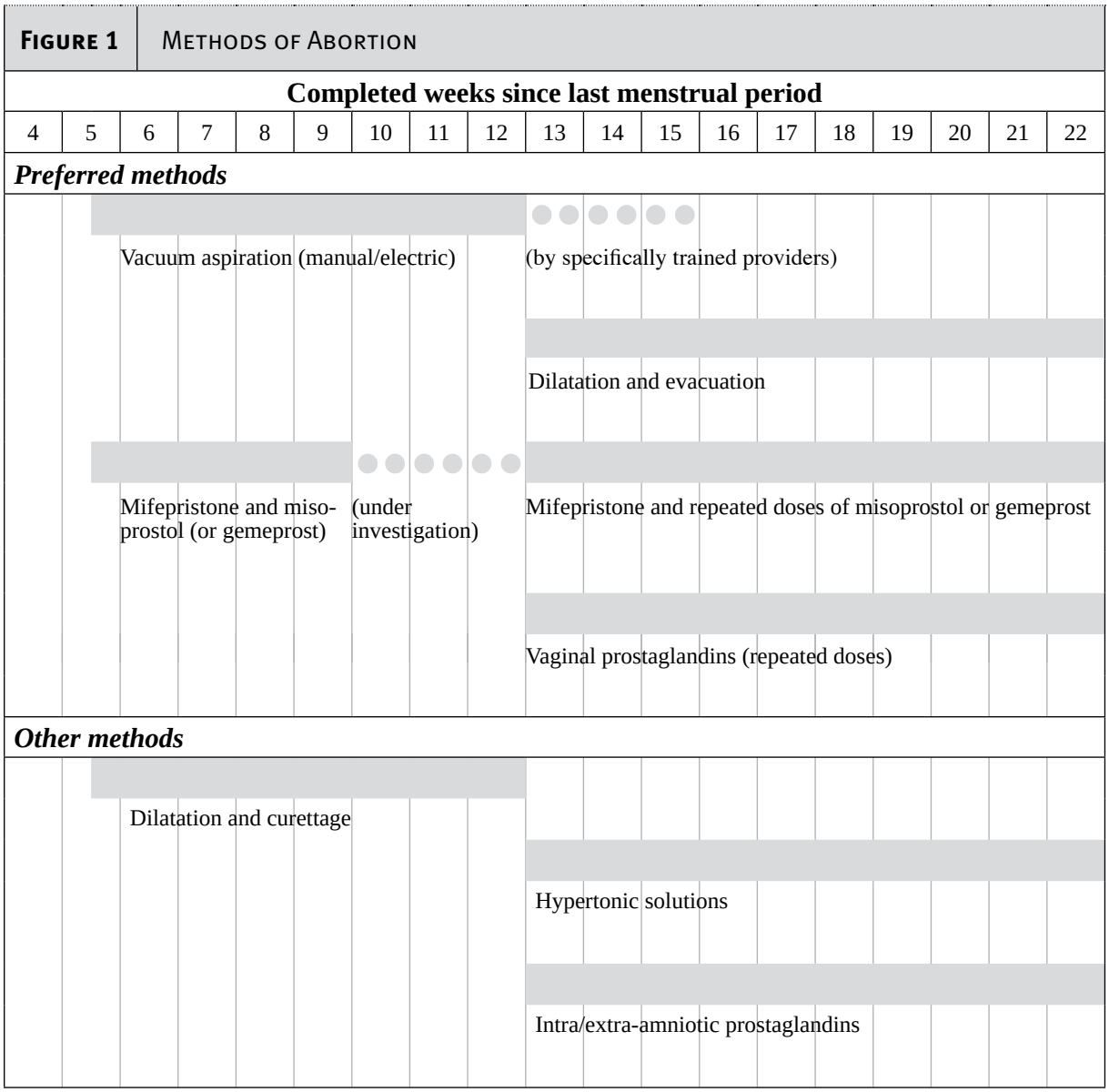
Counselling for HIV-infected women should include:

- the risks of pregnancy to her own health
- the risks of transmission to the newborn
- the effectiveness of ARVs and other interventions in reducing MTCT
- the potential side-effects of such interventions, including ARV toxicity.

2. Surgical and medical methods of abortion

Abortion methods used for women living with HIV do not differ from those used for HIV-negative women. Both surgical and medical methods of abortion are safe. See Fig. 1 for the recommended methods at various stages of gestation.

Figure 1 Methods of Abortion



Source: WHO *(67)*.

- The complication rate is low for abortions that meet international standards *(67)*.
- Haemoglobin should be measured and anaemia treatment initiated in accordance with etiology.
- The presence of infection in the lower reproductive tract at the time of abortion is a risk factor for post-procedural RTIs.
- The routine use of antibiotics at the time of abortion has been reported to reduce the post-procedural risk of infection by half. However, safe abortion can still be performed when antibiotics are not available for prophylactic use *(67)*.
- There is currently no data available about the effectiveness of the recommended dosages of mifepristone, misoprostole and gemeprost in women living with HIV, so the recommended dosages of these drugs for medical abortion *(67)* does not differ from those for HIV-negative women.
- There are currently no data available about potential interactions between mifepristone, misoprostole and ARVs in HIV-positive women.

3. Post-abortion care and family planning

Ensuring confidentiality is a key issue in post-abortion care. Post-abortion care for HIV-infected women should include:

- evaluation and treatment of any complications;
- minimizing transmission of HIV and other STIs in the post-abortion period, including from uterine bleeding;
- family planning counselling and services; and
- referrals for continuing HIV/AIDS treatment, care and support.

In settings where HIV and/or abortion are stigmatized, women living with HIV may need additional counselling and psychosocial support. Otherwise, post-abortion and family planning counselling should be the same, regardless of HIV status.

Most contraceptive methods can be started immediately post-abortion.

4. Recommendations

- Non-directive, non-judgemental, unbiased and confidential counselling about termination of pregnancy should be provided by a trained person (to the extent allowed by law).
- In countries where abortion is not against the law, safe termination of pregnancy should be available and accessible to women living with HIV.
- Family planning counselling and services should be essential components of post-abortion care, as they assist women in avoiding unintended pregnancies and reducing repeat abortions.

VII. Natural or medically assisted reproduction

Most PLHIV are of childbearing age and may desire to have children. They should have access to the same SRH counselling and services as other people. Nor is there, in cases of couple infertility, any reason to exclude couples with HIV from accessing reproduction technology.

1. Reproductive counselling for couples with HIV

The aims of reproductive counselling for couples with HIV include:

- reducing the risk of transmission to both the uninfected partner in HIV serodiscordant couples and their offspring;
- enabling informed reproductive choices;
- informing couples about the risks of HIV transmission and chances of pregnancy in both natural and medically assisted conception;
- preparing couples for the psychological impact of assisted conception, addressing the issues of:
  - availability
  - duration of treatment
  - failure
  - logistics;
- discussing the possibility of foster or adoptive parenting where available to couples with HIV; and
- informing and advising couples about hepatitis B (HBV) and C (HCV), including the risks of sexual transmission (HBV) and vertical transmission (HBV and HCV).

2. Fertility

2.1. Women

- Most women living with HIV menstruate about every 25–35 days, suggesting monthly ovulation *(68)*.
- So far, the impact of ART on fertility has not been explored in women living with HIV.
- Drugs, including methadone and psychotherapeutic medications, may contribute to menstrual disorders in women living with HIV *(69)*.
- HIV may not affect a woman's reproductive potential, unless she is highly immunosuppressed and presents with opportunistic infection. Nevertheless, fertility is lower in HIV-infected women than in the general population *(70)*.

2.2. Men

- HIV can be identified in the semen of men living with HIV regardless of the viral load in the blood.
- Many men living with HIV have normal semen analyses for fertility *(71)*.
- Healthy men living with HIV have semen fertility analyses similar to those of HIV-negative men, while AIDS patients have grossly abnormal semen *(72)*.
- Some ARV drugs may have an effect on spermatogenesis *(73)*.
- Men infected with HIV may experience sexual dysfunction including erectile dysfunction.

3. Pregnancy duration and outcome

- Women living with HIV have a greater risk of certain adverse pregnancy outcomes (intrauterine growth retardation, pre-term delivery, low-birth-weight infants, etc.) than HIV-negative women *(74)*.

- Although data are limited, several studies have suggested there is an increased risk of spontaneous abortion and stillbirth among women living with HIV *(74)*.
- The effects of HIV infection on pregnancy outcomes are likely to be more pronounced among women with symptomatic HIV infection *(75)*.
- Pregnancy does not have an effect on HIV disease progression or mortality *(76, 77)*.
- The risk of opportunistic infections among women with HIV does not appear to be altered by pregnancy.

4. Counselling before conception

Assisting people living with HIV in decisions about childbearing requires counselling on:

- the risk of HIV transmission to the partner, and interventions that can reduce it (see the next section);
- effects of HIV on pregnancy, including increased risk of certain adverse outcomes;
- the safety of ARVs during pregnancy, and their possible side-effects;
- the risk of birth defects while receiving particular ARVs; and
- the effectiveness of ARV prophylaxis, caesarean section and bottle-only feeding in reducing the risk of MTCT.

5. Reducing the risk for sexual transmission of HIV during conception

Special support should be considered for couples with discordant serostatus wishing to conceive:

- They need reproductive counselling and assistance to limit the risk of HIV transmission to the uninfected partner in unprotected sexual intercourse.
- Even though some serodiscordant couples have started pregnancies through timed unprotected intercourse without infecting the negative partner, this practice is unsafe and is not recommended.
- Specific methods of sperm preparation and testing can substantially reduce the chance of HIV transmission to the female partner *(78, 79)*. Male-positive discordant couples who want to have a child should be informed of risk-reduction techniques and encouraged to seek assistance at institutions that can provide the most effective methods of sperm preparation.

5.1. Sperm-washing and virological determination of HIV in semen

Sperm washing can be carried out in any laboratory providing assisted reproduction services to infertile couples. It is a three-step semen processing method consisting of:

1. gradient centrifugation to isolate motile spermatozoa and reduce the number of potentially infected non-spermatozoa cells;
2. repeated washing of the cell preparation to eliminate cell-free virus; and
3. spontaneous migration to obtain an aliquot of motile virus-free spermatozoa *(80, 81)*.

It is recommended that all processed samples be tested for HIV prior to insemination using polymerase chain reaction techniques *(82)*. HIV genome detection in semen requires special technical equipment and skills. The use of universal infection control procedures and specific training should be provided to laboratory staff to avoid HIV infection when handling potentially infectious semen.

6. Assisted reproductive technology in case of HIV infection

Fertility screening and STI diagnosis and treatment of both partners are needed before assisted reproductive technology can be considered. A history of fertility, HIV-related parameters (including CD4 count and viral load) and ART should be established.

Basic fertility assessment includes a clinical evaluation of ovulation, hormonal parameters (follicle-stimulating hormone (FSH), luteinizing hormone (LH) and prolactin) and tubal patency for women and a sperm analysis (count, motility, progression and morphology) for men.

6.1. Fertile couples

In serodiscordant fertile couples with an HIV-positive woman, the use of artificial insemination should be encouraged. Home artificial insemination – introducing sperm collected in a condom into the vagina after intercourse using a simple syringe or other clean receptacle, after advice on recognizing and identifying the fertile period – can provide a means of conception that prevents the male partner from becoming infected.

A number of serodiscordant couples with HIV-positive men wish to have children. There is no risk-free method for ensuring safe conception in this situation. However, the use of sperm-washing (see section VII.5.1 above) to reduce levels of HIV in semen has allowed many men living with HIV to father seronegative children *(83)*. In fact, with washed sperm of undetectable viral load, there is minimal risk of transmission of HIV to the female partner and children *(84)*.

If both the man and woman are HIV-positive, sperm washing can also be used to limit the woman's risk of HIV superinfection.

6.2. Infertile couples

After one year of repeated attempts at home artificial insemination without pregnancy, couples may be referred to infertility counselling and treatment. Artificial insemination and assisted reproductive technology are available in some places. Foster or adoptive parenting should also be considered.

For issues related to pregnancy in HIV-infected people and prevention of MTCT, please refer to Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants*.

VIII. Cervical intraepithelial lesions and cervical cancer

Cervical cancer is one of the most common types of cancer, causing deaths among women worldwide. The estimated number of new cases per year is 500 000 *(85)*. Human papillomavirus infection with oncogenic genotypes is the etiologic agent in the development of premalignant and malignant lower genital tract disease, including cervical cancer. The development of cancer from precursor lesions is a long process and may take up to 20 years, a process that has been the basis for the development of cytological screening programmes to detect pre-invasive disease (see Annex 5) *(86)*.

The relative risk for cervical intraepithelial neoplasia (CIN) is 5–10 times higher for women living with HIV than for other women *(87, 88)*.

1. Initial and follow-up evaluation

- Women should have a complete gynaecological examination, including a Pap test and pelvic examination, as part of their initial HIV evaluation.
- HIV-positive women are more likely to have genital warts and squamous intraepithelial neoplasia of the external genitalia than those who are HIV-negative *(89)*; careful physical examination of the external genitalia of women living with HIV is crucial.
- Cytology screening is effective in women living with HIV.
- Cervical cancer screening should be offered to women living with HIV at least once a year, using the same test offered to uninfected women (see Annexes 5–7).
- If an HIV-positive woman has been treated for precancerous lesions, she should have Pap smears every 4–6 months until at least three negative results have been be obtained *(89)*.
- A high-risk HPV deoxyribonucleic acid (DNA) detection test can be performed in case of a Pap smear with either atypical squamous cells of undetermined significance (ASC-US) or atypical squamous cells where a high-grade squamous intraepithelial lesion (HSIL) cannot be ruled out (ASC-H) *(89)*.
- Examination of the entire lower genital tract, including vagina, vulvae and perianal areas, colposcopy and biopsy of cervix, to confirm cytological and visual abnormalities is recommended in case of:
    - abnormal cytology (persistent low-grade squamous intraepithelial lesions (LSILs), ASC-US or HSILs);
    - an oncogenic HPV type; or
    - a history of untreated abnormal Pap smear *(89)*.

2. General management of patients with CIN

The general management of CIN among women living with HIV should not differ from that for the general population. Despite a modest effect of ART on spontaneous regression of CIN, follow-up of women on ART should be the same as follow-up of women not receiving ART.

Observation without specific intervention is recommended for biopsy-proven CIN 1 unless one of the following condition obtains:

- lesions persist over an 18–24 month period
- lesions evolve to CIN 2 or worse
- there is poor adherence to routine monitoring *(89, 90)*.

3. Treatment of cervical intraepithelial lesions

- HIV-infected women should be counselled before pre-cancer treatment to ensure that they understand the need for close follow-up and the possibility for repeated treatments.
- Cone biopsy can be done under local anaesthesia on an outpatient basis using a cold knife technique or a loop electrosurgical excision procedure (LEEP).
- CIN 2 and 3 require excisional or ablative treatment.
- Women living with HIV have a high rate of recurrence/persistence (40–60%) and progression of CIN 2 and 3 after treatment, and should therefore be monitored every six months after treatment. Prompt re-treatment should be provided when persistent, recurrent or progressive high-grade lesions are detected *(90)*.
- Hysterectomy is contraindicated as a pre-cancer treatment in the absence of other indications *(90)*.
- Treatment for CIN should not be modified for patients receiving ART.
- ART should not be instituted or modified for the purpose of treating CIN.
- Abstinence from sexual intercourse is recommended following treatment; if this is not possible, condoms should be used consistently and correctly.

4. Management of invasive cancer

- The International Federation of Gynecology and Obstetrics (FIGO) classification system is recommended for determining the cancer stage (*91*).
- For women with a CD4 count <200 cells/mm^3, surgery is the preferred option when appropriate, or attenuated treatment with radiation or chemotherapy *(90)*.
- Women with advanced HIV disease have a poor prognosis with all treatment modalities. For women with a CD4 count >200 cells/mm^3, standard treatment modalities may be used.
- Comprehensive palliative care programmes are essential for improving the quality of life for women with cervical cancer (see Protocol 3, *Palliative care for people living with HIV*).

5. Anal screening

There is no medical consensus about the use of anal Pap smear screening at this time.

IX. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to services and their success. Such indicators assist managers in decision- making on ways to strengthen and expand these services to all who need them.

The following data should be collected at the clinical level on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of HIV-infected women of reproductive age having sexual intercourse during the last six months;
- number of HIV-infected women (cumulative) using modern contraceptive methods;
- number of pregnant HIV-infected women;
- number of terminated pregnancies in HIV-infected women;
- number of HIV-infected people tested for STIs;
- number of HIV-infected people diagnosed with STIs;
- number of HIV-infected people who have received STI treatment;
- number of HIV-infected women tested for cervical cancer within the past three years;
- number of deliveries to couples with at least one HIV-positive partner; and
- number of deliveries after medically assisted conception in couples with at least one HIV-positive partner.

Data collection methods should follow the principles of confidentiality and should not lead to the disclosure of identifiable patient information inside or outside the clinical setting.

Annex 1. Suggested topics and questions for taking a sexual history

Begin the sexual history component by stating:
"Since sex is an important part of overall health, we ask everyone the following questions. Please give only answers that you feel comfortable with me knowing."

Sexual orientation/identity

1. Do you have sex with men, women or both?

2. Do you consider yourself heterosexual, homosexual, bisexual or other?

3. If applicable: do you consider yourself male or female?
   a. Have you ever had hormone therapy?
   b. Have you had or considered having a sex change?
   c. Have you had or considered having any sex-change surgery?

Sexual practices and sexual well-being

1. What kind of sex do you have:
   a. oral sex?
   b. vaginal sex?
   c. anal sex?
   d. other?

2. How do you protect yourself from HIV/STIs?

3. Do you ever use condoms or other barrier methods?

4. If yes, for what kind of sex?

5. If MSM:
   a. Are you more often the receptive or insertive partner?
   b. What protection do you use for each role?

6. When was the last time you had unprotected sex?

7. Do you use alcohol or drugs before or during sex?

8. How do you think alcohol or drugs affects your decisions and abilities to have safer sex?

9. Are you satisfied with your sexual life?

10. Do you have any kind of problem when having sex (sexual dysfunction)?

11. If so, what kind?

12. Do you now or have you in the past suffered from depression?

Prevention

1. Have you made any changes in your sexual behaviour because of HIV/STIs?

2. How do you protect your sex partner(s) from HIV?

3. What percentage of the time do you and your partner(s) use condoms (or other barriers such as diaphragms or cervical caps)?

Sex trading

1. Have you ever exchanged sex for food, shelter, drugs or money?

2. Are you earning an income by sex work?

Contraception

1. For heterosexual/bisexual patients:
   a. What method of birth control do you use?
   b. How long have you been using it?
   c. Do you use any additional barriers?

2. Are you interested in becoming pregnant?

3. If yes, do you have any plans for when? Are you interested in birth control?

Sexually transmitted infections (STIs)

1. Have you ever been treated for:
   a. syphilis
   b. gonorrhoea
   c. proctitis
   d. vaginitis
   e. genital herpes
   f. *Chlamydia*
   g. non-gonococcal urethritis (NGU)
   h. pelvic inflammatory disease
   i. genital warts

2. Note site, date, treatment and compliance

3. Have you ever had a Pap smear?
   a. When was the last time?
   b. To your knowledge, have any been abnormal?

Substance use

1. Do you smoke or chew tobacco?
   a. How many cigarettes/how much smokeless tobacco (chewing or snuff) do you consume per day?
   b. How long have you used tobacco?

2. How often do you drink alcohol? How many drinks per week on average?
   a. Have you ever drunk so much that the next day you didn't remember what you did ("blackouts")?
   b. Have you ever experienced withdrawal symptoms (cravings, "the shakes", "the DTs" (delirium tremens))?
   c. Are you ever worried about your alcohol use?

3. Do you use drugs for fun?
   a. What kinds of drugs?
   b. How often do you take these drugs (daily, weekly, monthly, occasionally)?
   c. For how long have you been taking them?
   d. Have you ever taken so much that the next day you didn't remember what you did?
   e. Are you ever worried about your drug use?

4. Are you on any medicine to help you sleep or relax? If so, what?

5. Are you on any pain relievers? If so, which ones?

6. Have you ever injected drugs and medications (including steroids or vitamins)?

7. If so, have you ever shared needles or works, even just once?

8. Have any of your current or past sex partners ever injected drugs?

Intimate partner or gender-based violence
(Read section IV.4. of this protocol first to help avoid causing unnecessary stress for the patient.)

1. Have you ever been sexually abused, assaulted or raped?

2. In your adult life, have you ever lived in a situation with physical violence or intimidation?

3. If yes to either of the above, when did they occur?

4. Are you currently encountering discrimination, humiliation or physical or sexual violence?

5. Are you afraid for your safety now? For example, are you physically forced to have sexual intercourse against your will? Do you have sexual intercourse because you are afraid of what your partner may do?

6. Have you been forced to do something sexual that you found degrading or humiliating?

Annex 2. Management of syphilis in PLHIV

- Cell-mediated and humoral immunity may modify the natural course of syphilis infection in HIV-coinfected individuals.
- The diagnostic and treatment of syphilis-coinfected PLHIV may be different due to a rapid clinical course with unusual manifestations, including increased risk of neurological manifestations and increased treatment failure rates *(6)*.
- The recommended treatment for early syphilis does not change for PLHIV. When possible, the cerebrospinal fluid (CSF) should be examined and a more intensive treatment be administered, regardless of the clinical stage of syphilis *(92)*.
- Clinical and serological evaluations of syphilis-coinfected patients should occur at 3, 6, 9, 12 and 24 months.
- In case of treatment failure, re-treatment should be undertaken as appropriate *(6)*.

Annex 3. Management of vulvovaginal candidiasis in women living with HIV

The controversy over whether vulvovaginal candidiasis (VVC), particularly recurrent VVC, is more common in women living with HIV than in matched control HIV-negative women remains largely unresolved *(93)*. Thus, it may be inappropriate to propose HIV testing in women with recurrent VVC.

In women living with HIV, candidiasis frequently involves several sites, including the vulva and vagina. It is often severe and frequently relapses.

The microbiological spectrum of VVC appears similar in HIV-positive and HIV-negative women *(93)*. Treatment involves topical application of a wide variety of imidazoles (miconazole, clotrimazole, econazole, butoconazole, terconazole, etc.) or nystatin. Although more expensive, imidazoles require shorter courses of treatment and appear to be more effective than nystatin *(94)*.

Treatment principles are identical to those for HIV-negative women. There is no evidence of refractory VVC responding to conventional antifungal treatment. Repeated treatment may be required for women living with HIV. It is recommended that any predisposing factors such as antibiotic use, the use of antiseptic/antibiotic vaginal preparations or vaginal douching be reduced or eliminated. Simultaneous treatment of rectal focuses with oral nystatin or fluconazole is useful in preventing recurrences. Although treatment of sexual partners is not recommended, it may be considered for women who have recurrent infection.

Table 13. Vaginal candidiasis

Antifungal agent	Dose	Frequency	Route	Duration
First-line treatment				
Fluconazole	100 mg	Single dose	PO	Once
Clotrimazole	500 mg	Single dose	Vaginal	Once
Second-line treatment				
Ketoconazole	200 mg	BID	PO	3 days
Ketoconazole	200 mg	OD	PO	7 days
Maintenance therapy				
Nystatin	2–4 million IU	BID	PO	10 days
or:				
Fluconazole	50–200 mg	OD	PO	Every day
Third-line treatment				
Ketoconazole	200 mg	OD	PO	Depends on response, usually 7–10 days
Itraconazole	100 mg	OD	PO	Depends on response, usually 7–10 days

PO: per os (orally)

Annex 4. Management of bacterial vaginosis in women living with HIV

Bacterial vaginosis (BV) is a clinical syndrome resulting from replacement of the normal hydrogen peroxide-producing *Lactobacillus sp.* in the vagina by high concentrations of anaerobic bacteria, such as *Gardnerella vaginalis* or *Mycoplasma hominis*. Additional studies are needed to confirm the relationship between altered vaginal microflora and the acquisition of HIV.

- Treatment of sexual partners has not been demonstrated to be beneficial.
- It is recommended that predisposing factors, such as the use of antiseptic/antibiotic vaginal preparations or vaginal douching, be reduced or eliminated.
- The recommended regimen for BV is metronidazole 400 mg or 500 mg PO BID for seven days. Patients taking metronidazole should be cautioned not to consume alcohol while they are taking the drug and within 24 hours of taking the last dose.
- Alternative regimens are:
    - metronidazole 2 g PO as a single dose
    - clindamycin 2% vaginal cream 5 g intravaginally at bedtime for seven days
    - metronidazole 0.75% gel 5 g intravaginally BID for five days
    - clindamycin 300 mg PO BID for seven days *(93)*.

Annex 5. Cervical cancer screening methods

1. The classic screening test for cervical cancer is the Pap smear. A single Pap test may have a false negative rate of 10–25% *(90)*. Accuracy is significantly improved with regular periodic screening. Controlled studies have not demonstrated a decrease in Pap test sensitivity or specificity in HIV-positive women. To use Pap tests as a screening method, basic infrastructure to perform cervical cytology screening should be available at all health care levels. The Bethesda system of classification is recommended for both HIV-positive and HIV-negative patients *(95)*. (See Annex 6 below.)
2. Alternative methods include visual inspection of the cervix (VIA) after application of 3–4% acetic acid, to differentiate normal cervical appearance from cervical lesions. This test is not recommended in settings where Pap smear is available.
3. Newer cervical screening techniques using liquid-based cytology increase sensitivity, albeit at greater cost, and offer the possibility of direct HPV DNA testing. The utility of this test in women living with HIV has not been assessed.
4. HPV testing using a high-risk HPV DNA test allows for the detection of oncogenic/non-oncogenic types and is recommended in case of borderline Pap results (ASC-US or ASC-H).

Annex 6. PAP smear report, in accordance with the 2001 Bethesda system

The Bethesda system of Pap smear classification is recommended for both HIV-negative and HIV-positive women *(95)* (see Table 14).

Table 14. Pap smear report (in accordance with the 2001 Bethesda system)

Specimen adequacy	Satisfactory for evaluation Unsatisfactory for evaluation
General categorization	Negative for intraepithelial lesion or malignancy Epithelial cell abnormality Other
Interpretation	Negative for intraepithelial lesion or malignancy Epithelial cell abnormalities *Squamous cell* Atypical squamous cells of undetermined significance (ASC-US) Low-grade squamous intraepithelial lesion (LSIL), including HPV changes and mild dysplasia/CIN 1 High-grade squamous intraepithelial lesions (HSIL), including moderate and severe dysplasia, CIN 2, CIN 3, carcinoma in situ Squamous cell carcinoma *Glandular cell* Glandular cell abnormalities

Source: Solomon et al. *(95)*.

Annex 7. Recommended management for abnormal Pap smears

Table 15. Recommended management for abnormal Pap smears

Pap smear result	Management (based on histology)
Unsatisfactory for evaluation	Repeat smear, correct the reason for unsatisfactory evaluation.
LSIL or ASC-US	Repeat smear in six months to one year: • if normal, continue with screening schedule as per national policy • if LSIL, ASC-US, refer for colposcopy.
HSIL or ASC-H	Refer for colposcopy.
Invasive carcinoma	Refer to hospital for further investigation and management.

Source: WHO (90).

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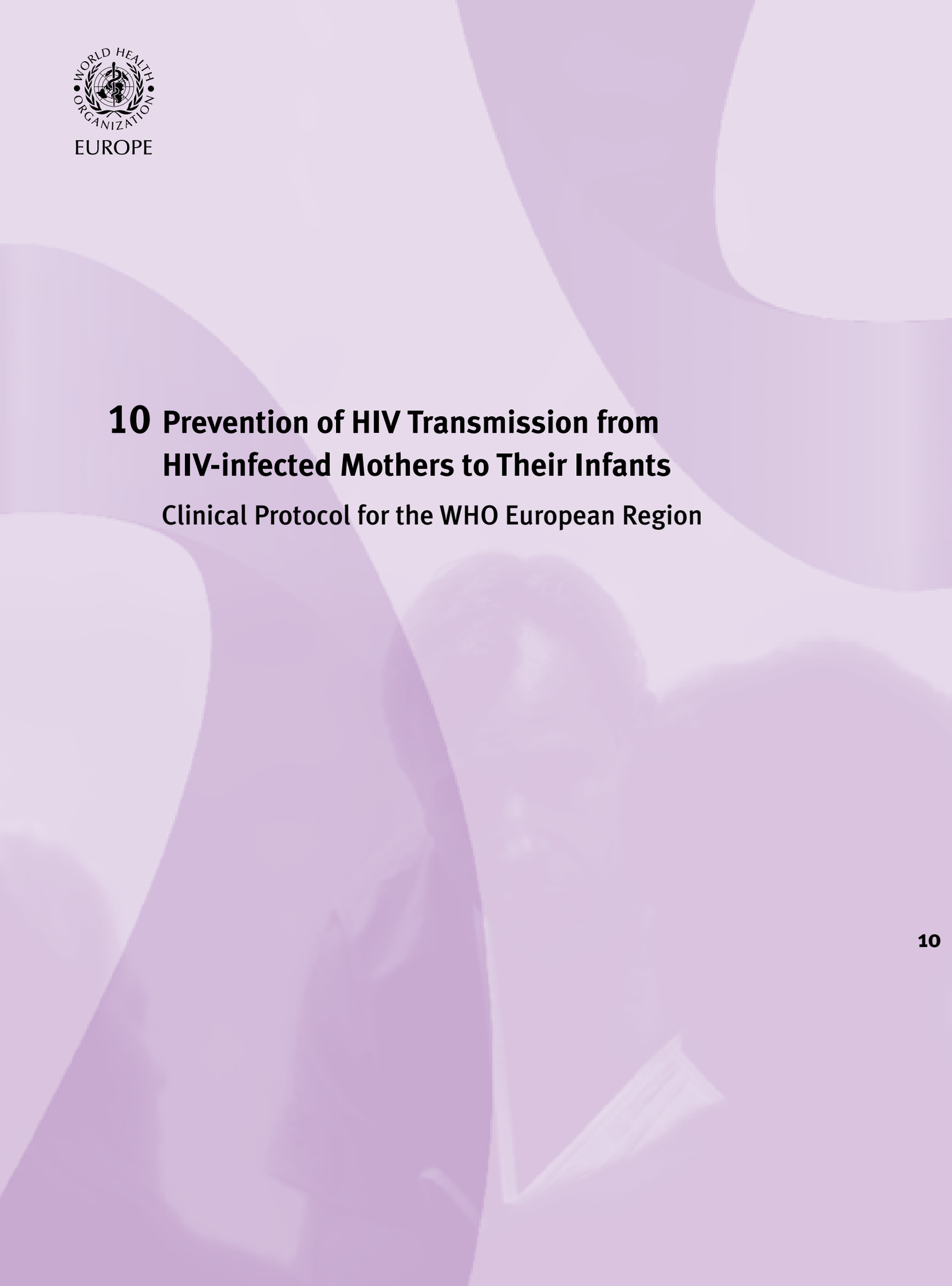
WORLD HEALTH ORGANIZATION
EUROPE

10 Prevention of HIV Transmission from HIV-infected Mothers to Their Infants

Clinical Protocol for the WHO European Region



Contents

I. Policy issues

- Clinical prevention of mother-to-child transmission of HIV (PMTCT) should be a part of the continuum of care for HIV-infected women and their children. Services providing PMTCT should be linked to other relevant governmental and nongovernmental services, such as HIV treatment and care, reproductive health, paediatric services, drug-dependence treatment, harm-reduction services, psychosocial support, child protection services, etc.
- Pregnant injecting drug users (IDU) should have the same non-discriminatory access to health care services – including antiretroviral treatment (ART), reproductive choices, PMTCT and maternity care – as pregnant women who do not use drugs.
- All medical records, whether or not they involve HIV-related information, should be treated according to appropriate standards of confidentiality. Only health care professionals with a direct role in the management of patients or clients should have access to such records, and only on a "need-to-know" basis.

II. Background

Increasing numbers of women living with HIV are becoming pregnant, and their infants will be at high risk for acquiring HIV infection in utero, during labour or through breastfeeding. In the absence of interventions, the risk of mother-to-child transmission (MTCT) of HIV is 15–30% in non-breastfeeding populations; breastfeeding increases the risk to 20–45% *(1)*.

Effective interventions for the prevention of MTCT (PMTCT) of HIV infection do now exist. Where these interventions are freely available and utilized, MTCT rates of 1% or 2% have been achieved *(1–3)*. They include:

- antiretroviral (ARV) prophylaxis during pregnancy, labour and the first weeks of life;
- obstetrical interventions, including pre-labour caesarean section (PLCS); and
- avoidance of breastfeeding *(4–6)*.

The challenge is to achieve similar rates throughout the WHO European Region, particularly in countries where the HIV epidemic is fuelled by injecting drug use and health systems are adversely affected by economies in transition. Several factors – high-level coverage of antenatal care (ANC), the availability of an extensive health care infrastructure, high literacy levels, a relatively low number of infections and the existence of effective interventions to reduce MTCT – offer an opportunity to eliminate infant HIV infection in the Region and thus provide a model for the rest of the world.

WHO promotes a four-pronged comprehensive strategic approach to the prevention of HIV infection in infants and young children:

1. primary prevention of HIV infection
2. prevention of unintended pregnancies among HIV-infected women[1]
3. prevention of HIV transmission from mothers to their infants
4. treatment, care and support for HIV-infected mothers and their families *(7)*.

This protocol focuses on the third prong of the strategy, prevention of HIV transmission from mothers to their children. It is consistent with the Region's goal of preventing HIV in infants in Europe *(8)*, specifically to eliminate HIV infection in infants by 2010 as indicated by reducing the infection rate among infants to less than 1 per 100 000 live births and the infection rate among infants born to HIV-infected women to less than 2%.

The European goal is congruent with the global goal set at the 2001 United Nations General Assembly Special Session (UNGASS) on HIV/AIDS of reducing the proportion of infants infected with HIV by 50% by 2010 *(9)*.

[1] Please see Protocol 9, *Support for sexual and reproductive health of people living with HIV.*

III. Initial evaluation

1. Initial evaluation of pregnant women in antenatal care settings

Antenatal HIV counselling and testing of pregnant women is an effective medical intervention that contributes to lowering rates of MTCT of HIV. In addition, it is an important entry point for the treatment and care of HIV-positive women and their children.

The intend of HIV testing is to capture every HIV infected pregnant woman as early as possible in order to introduce a package of PMTCT interventions and minimize risk of HIV transmission to her baby during pregnancy, labour and postpartum.

HIV testing should be voluntary and not forced. Women should provide written consent to the test and be able to refuse it. Testing should include obligatory counselling.

An initial assessment for determining HIV status should include:
- pretest counselling;
- serological testing for HIV antibodies (typically ELISA and/or rapid tests[2]), followed by a western blot confirmatory test if positive; and
- post-test counselling, including information on reducing risky behaviour, irrespective of the results.

For women infected with HIV, further evaluation is needed in collaboration with an HIV specialist to determine the clinical stage and to develop a PMTCT management strategy.[3]

Among the key aspects of pretest HIV counselling is identifying any drug use (including injecting drug use) and evaluating the risks of the woman's exposure to HIV from sexual partners. Drug use and especially drug dependence can have a large impact on pregnancy and fetal development, and they require special medical assistance during pregnancy, labour and the postpartum period for both mother and fetus/infant.

For more about the assessment of drug dependence and withdrawal symptoms in pregnant women, see section IV.2.3 below.

2. Patient counselling

After the initial evaluation, HIV-infected pregnant women should be counselled on the following, where relevant to their condition:
- condom use for prevention of sexual transmission of HIV and other STIs;
- the risk of HIV transmission to the fetus/neonate and how to prevent it;
- the risks and benefits of ARV prophylaxis as part of PMTCT strategy;
- the risks of hepatitis B and C virus (HBV and HCV) perinatal transmission and how to reduce them;
- the risks of perinatal syphilis transmission, and the need for treatment of syphilis, gonorrhoea and chlamydia to reduce the risk of HIV transmission;
- the impact of drug use on fetal development, including drug withdrawal syndrome and drug interactions (see section IV.4.2 below);
- referral to harm-reduction and drug-dependence treatment programmes, including substitution therapy where appropriate;

[2] Rapid HIV serological testing should be available in maternities for those women only presenting in health care service during labour

[3] For clinical and laboratory evaluation please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

- the implications of different modes of delivery in reducing the risk of HIV transmission, including the benefits and adverse effects of caesarean section (CS); and
- instruction on infant feeding (see also section IV.3.1 below).

With complete and accurate information about possible risks and management options, an HIV-positive woman can make an informed decision on whether to deliver or to terminate her pregnancy. Under no circumstance should she be coerced to terminate a pregnancy.

IV. PMTCT management in antenatal care settings and maternity wards

Randomized controlled trials (RCTs), open-label trials and observational studies have provided evidence of the effectiveness of ARV prophylaxis *(4, 10–24)* and caesarean section in PMTCT.

- Zidovudine (ZDV) administered early in pregnancy, during labour and delivery and postpartum to mother and infant has been shown to reduce vertical transmission from 25.5% to 8.3% in a non-breastfeeding population *(25–27)*.
- In mother–infant pairs receiving triple combination therapy including a protease inhibitor (PI), the MTCT rate can decrease to 0.9–1.3% *(5, 28)*.
- The protective role of caesarean section was demonstrated in both a meta-analysis *(28)* and a randomized clinical trial (RCT) *(29)* prior to the widespread use of combination therapy in pregnancy. However, mounting observational data demonstrating very low levels of transmission in women on therapy with undetectable viral loads who deliver vaginally have led to changes in the advice on their method of delivery *(30)*.
- If the decision is made to perform pre-labour caesarean delivery to prevent HIV transmission, it should be done at 38 weeks' gestation, as determined by the best clinical estimate, and amniocentesis should be avoided *(31)*.

Administration of ARV regimen for PMTCT should be considered in close collaboration with health providers of ANC services and HIV specialists. The package of prevention interventions for pregnant women should be based on:

- the need for ART
- the gestation stage at presentation
- the level of the clinical setting (primary health care, specialist referrals)
- the history of previous ARV use
- the presence of concomitant diseases or conditions
- the availability of ARVs.

For HIV-infected pregnant women, PMTCT rates are those same for those who use drugs as for those who do not.

The decision on when to start ART for pregnant women should be based on the WHO HIV/AIDS clinical staging system in combination with immunological criteria (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents,* Table 6 and Annex 2).

1. Possible scenarios for PMTCT management in ANC services and maternity wards

The vast majority of HIV-positive pregnant women fit in one of the following categories:

1. those who do not presently need ART for the sake of their personal health (see Table 1)
2. those who do need or might need ART for the sake of their health (see Table 2)
3. those who started ART before pregnancy (see Table 3)
4. those who do not present until around labour (see Table 4).

1.1. Pregnant women who do not yet need ART for their own health

Table 1. Pregnant HIV-positive women who do not yet need ART for their own health

Gestational age and CD4 count	ARVs during pregnancy	ARVs during labour	Postpartum ARVs		Mode of delivery
From 24–28 weeks CD4 >350 cells/mm^3	***If viral load (VL) is available and ≤10 000 copies/ml and patient is ZDV-naive***				
	ZDV (300 mg) per os, twice daily (PO, BID) *(32)* Monitor haemoglobin level.	*If PLCS:* Continue ZDV[a] only. *If spontaneous labour before CS date:* ZDV (300 mg)[a] every 3 hours until delivery + 3TC (150 mg), PO, BID + single-dose NVP (200 mg) at onset of labour	With NVP during labour (preferred)	*Mother:* ZDV (300 mg) + 3TC (150 mg) PO, BID x 7 days after delivery[b] *Infant:* ZDV syrup (4 mg/kg body weight) + 3TC (2 mg/kg body weight) PO, BID x 7 days[c] + single-dose NVP (2 mg/kg body weight) after birth	PLCS at 38 weeks of pregnancy or spontaneous delivery[d]
			Without NVP during labour	*Mother:* Stop ZDV. *Infant:* ZDV syrup (4 mg/kg body weight) PO, BID x 7 days[c]. Start within first 8 hours.	
	If VL is unavailable or >10 000 copies/ml, or if there is a known history of ZDV exposure[e]				
	ZDV (300 mg) + 3TC (150 mg) + SQV/r[f] (800 mg /100 mg) BID, PO[g]	Continue the same regimen until delivered	*Mother:* Stop all three drugs after delivery. *Infant:* ZDV syrup (4 mg/kg body weight), PO, BID for 7 days[c]. Start within first 8 hours.		If VL <1000 copies/ml at 36–38 weeks, wait for spontaneous labour.[h] If VL >1000 copies/ml at 36–38 weeks. opt for PLCS at 38 weeks. If VL is unavailable and adherence to HAART <95%, opt for PLCS at 38 weeks. If VL is unavailable and adherence to HAART >95%, opt for spontaneous labour.[h]

[a] If intravenous (IV) ZDV is available, start continuous IV infusion four hours before PLCS (2 mg/kg for first hour and 1 mg/kg/hour until cord is clamped).
[b] ZDV + 3TC during labour and for seven days postpartum is administered to reduce risk of nevirapine (NVP) resistance in mother and infant. If mother hasn't received NVP, stop ART after PLCS.
[c] If mother received ARV prophylaxis for less than four weeks during pregnancy, the infant should receive ZDV for up to four weeks. In preterm infants the dose of ZDV should be 1.5 mg/kg IV or 2.0 mg/kg PO.
[d] The woman should make the final decision of delivery method after knowing risks and benefits. In vaginal delivery, avoid invasive obstetrical procedures, such as fetal scalp monitoring and episiotomy.
[e] If mother has been exposed to ART or is at risk for having a resistant virus, baseline resistance can help guide ART choice.
[f] Lopinavir boosted with low dose ritonavir (LPV/r) (400 mg/100 mg) or nelfinavir (NFV) (1250 mg) BID, PO could be used as an alternative.
[g] Adherence could be problematic due to pregnancy-associated complications.
[h] Avoid invasive obstetrical procedures, such as fetal scalp monitoring and episiotomy. Episiotomy must not be performed routinely, but reserved for cases where there is a clear obstetric indication for the procedure *(33)*.

1.2. Pregnant women who need ART for their own health

Pregnant women who need ART for their own health but have not yet received it should be given a first-line highly active antiretroviral treatment (HAART) regimen. ARV regimens containing ZDV, 3TC and NVP are recommended as first-line treatment options and for preventing MTCT *(19, 34, 35)*. ART should be continued in such women after delivery for the benefit of their own health.

Table 2. Pregnant HIV-positive women who need or might need ART for their own health

Gestational age and CD4 count	ARVs during pregnancy and labour	Postpartum ARVs	Mode of delivery
Any gestational age CD4 <200 cells/mm^3	ZDV (300 mg)[a] + 3TC (150 mg) + NVP (200 mg)[b] BID, PO *Comments:* Start NVP with 200 mg once daily (OD) for the first 2 weeks, and then continue with 200 mg BID. Monitor liver enzymes at baseline, 2 weeks of treatment, 4 weeks, and every 4 weeks thereafter.	*Mother:* Continue the same regimen *Infant:* ZDV syrup (4 mg/kg body weight) PO, BID for 7 days.[c] Start within first 8 hours.	If VL <1000 copies/ml at 36–38 weeks, it is reasonable to await spontaneous labour.[d] If VL >1000 copies/ml at 36–38 weeks, opt for PLCS at 38 weeks. If VL unavailable and adherence to HAART<95%, opt for PLCS at 38 weeks. If VL unavailable and adherence to HAART >95%, opt for vaginal delivery.
Any gestational age CD4 is 200–350 cells/mm^3	ZDV (300 mg)[a]+ 3TC (150 mg) + SQV/r (800/100 mg)[e] BID, PO	*Mother:* Decision to continue treatment postpartum should be based on clinical and immunological indicators, as normal physiologic changes, i.e. increase of circulating plasma volume (haemodilution) during pregnancy reduces the CD4 cell level, which then restores during postpartum. *Infant:* ZDV syrup (4 mg/kg body weight) PO, BID for 7 days.[c] Start within first 8 hours.	

[a] Close monitoring of haemoglobin is required. ZDV can be replaced by TDF or ABC in anaemic symptomatic women and women who are ZDV-intolerant.
[b] The risk of NVP-associated hepatotoxicity substantially increases if CD4 >250 cells/mm^3 *(36)*.
[c] If the mother received ARV prophylaxis for less than four weeks during pregnancy, the infant should receive ZDV up to four weeks. In preterm infants, the dose of ZDV should be 1.5 mg/kg IV or 2.0 mg/kg PO.
[d] Risks and benefits should be discussed with the woman, who should make the final decision. In case of vaginal delivery, avoid invasive obstetrical procedures such as fetal scalp monitoring and episiotomy. Episiotomy must not be performed routinely, but reserved for cases with a clear obstetric indication *(33)*.
[e] LPV/r (400/100 mg BID) or NFV (1250 mg BID, PO) can be used instead of SQV/r. If PIs are not available, efavirenz (EFV) can be administered, but not earlier than the second or third trimester, due to risk of teratogenicity associated with its use in the first trimester.

1.3. Pregnant women who initiated ART before pregnancy

Table 3. Pregnant HIV-positive women who initiated ART before pregnancy

Gestational age	ARVs during pregnancy and labour	Postpartum ARVs	Mode of delivery
Any age	Continue current ARV regimen if it does not contain EFV. If a woman is on a regimen that contains EFV[a] and is in her first trimester, consider substituting SQV/r 800 mg/100 mg[b] or ABC; where CD4 count <250, NVP[c] can be used. The benefits of a second-line regimen outweigh the risks. Keep on current regimen during pregnancy, labour and afterwards.	*Mother* Continue same maternal ARV treatment after delivery. *Infant* Oral ZDV syrup (4 mg/kg body weight) BID for 7 days. Start within first 8 hours. In preterm infants the ZDV dose is 1.5 mg/kg IV or 2.0 mg/kg PO.	If VL <1000 copies/ml at 36–38 weeks, await spontaneous labour.[d] If VL >1000 copies/ml at 36–38 weeks opt for PLCS at 38 weeks. If VL is unavailable and adherence to HAART <95%, opt for PLCS at 38 weeks. If VL is unavailable and adherence to HAART >95%, opt for spontaneous labour.[d]

[a] Anecdotal cases of neural tube defects have been reported with EFV use in the first trimester. While it is important to discontinue EFV in the pre-conception period, the decision to replace EFV with another ARV should be carefully considered. Switching to another drug has the potential of viral rebound, while the fetus's neural tube formation should be finished by six weeks of gestation. In many western European hospitals, experienced HIV physicians continue an EFV-based regimen if the woman first presents to ANC providers at eight weeks of pregnancy or later. If a decision is made to stop EFV, do not discontinue the EFV-containing regimen without switching to another ARV compound in order to avoid the risk of non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance.

[b] LPV/r (400 mg/100 mg) or NFV (1250 mg) BID, PO can be used instead of SQV/r.

[c] The risk of NVP-associated hepatotoxicity substantially increases if CD4 >250 cells/mm^3 *(36)*; for dosage refer to Table 2 above.

[d] Risks and benefits should be discussed with the woman, who should make the final decision regarding the delivery method. In case of vaginal delivery, avoid invasive obstetrical procedures such as fetal scalp monitoring and episiotomy. Episiotomy must not be performed routinely, but reserved for cases with a clear obstetric indication *(33)*.

1.4. Pregnant women who first present around labour

Women presenting in labour without any antenatal assistance are often from vulnerable populations, such as IDUs or sex workers. It is important to assess their HIV status, as they may be at high risk for being infected. Offer a rapid test, and provide ARV prophylaxis for PMTCT if the woman is found to be HIV-positive after confirmation by western blot.

Table 4. Pregnant HIV-positive women who first present in labour (no ARVs during pregnancy)

Time of admission to hospital	ARVs during labour and delivery	Postpartum ARVs	Mode of delivery
During labour and delivery	ZDV (300 mg) every 3 hours until delivery + 3TC (150 mg) at onset of labour and then every 12 hours until delivery + NVP (200 mg once) at onset of labour	*Mother* ZDV (300 mg) + 3TC (150 mg) BID x 7 days after delivery[a] *Infant* [b] ZDV[c] 4 mg/kg body weight BID for 4 weeks + 3TC 2 mg/kg body weight BID for 4 weeks + single-dose NVP 2 mg/kg at 48–72 hours after birth[d]	Spontaneous vaginal delivery.[e] Avoid invasive obstetrical procedures such as fetal scalp monitoring and episiotomy.

[a] Further strategy for the ART and case management of a woman identified as HIV-infected during labour should be based on CD4 count, VL and clinical examination as soon as possible after delivery.
[b] Postpartum AZT and 3TC for infants should be initiated between 8 and 12 hours after birth if the mother received AZT and 3TC prophylaxis during labour and as soon as possible after birth if the mother did not receive ARV prophylaxis during labour.
[c] In preterm infants, the dose of ZDV should be 1.5 mg/kg IV or 2.0 mg/kg PO.
[d] If the mother misses a NVP dose, or takes NVP less than two hours before delivery, then the infant should be given an NVP dose immediately after delivery and a second dose at age 72 hours.
[e] For women not in active labour and with intact fetal membranes, PLCS can be suggested.

1.5. PMTCT in pregnant HIV-infected women with active tuberculosis

For HIV-infected pregnant women with active tuberculosis (TB), the first priority should be to treat the TB. For more information about TB treatment, refer to Protocol 4, *Management of tuberculosis and HIV coinfection*.

- Most first-line anti-TB drugs are safe for use during pregnancy except streptomycin, which is ototoxic to the fetus.
- If the length of the TB treatment jeopardizes ARV prophylaxis of MTCT, then ARV prophylaxis has to be prescribed concomitantly with the TB treatment.
- ARV regimens containing NVP or unboosted PIs should not be used concomitantly with rifampicin due to drug interactions *(37–41)*.
- The recommended ARV regimen for PMTCT in HIV-infected pregnant women receiving rifampicin is ZDV + 3TC + SQV/r (for dosage, refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*). Close monitoring of liver enzymes is required. In the absence of SQV/r, ABC may also be considered. However, further research on use of ABC in pregnant women is needed.
- ZDV/3TC/ABC is available as a fixed-dose combination (three drugs in one tablet). Triple-nucleoside or nucleotide reverse transcriptase inhibitor (NRTI) regimens appear to be less potent than NNRTI and boosted PI regimens *(42)*.
- If rifabutin is used instead of rifampicin, ARV regimens for the purpose of PMTCT remain as described above. Rifabutin levels may increase when coadministered with LPV/r; consequently, the rifabutin dosage may have to be reduced *(37)*.

2. Management of HIV-infected active IDUs during pregnancy

Pregnant women using drugs have a greater than normal risk of medical complications. They should be managed according to the possible impact their dependency has on their pregnancy, their fetus and their own health (see Table 6 below) *(43)*.The key issue for the management of drug-using pregnant women is therefore stabilization of illicit drug use or its reduction to the lowest possible level.

2.1. Organization of services

To manage pregnant HIV-positive IDUs effectively, they need to be persuaded to utilize health care services as early in pregnancy as possible, and the relevant services need to be accessible during the entire pregnancy. A key strategy is a team approach centred around antenatal, intrapartum and postpartum services that are linked to:

- harm-reduction services that refer pregnant IDUs to ANC
- drug-dependency treatment experts (throughout the pregnancy)
- HIV/AIDS services
- psychological and social services.

2.2. Assessment of drug dependence and withdrawal symptoms in pregnant women

Underreporting of illicit drug use is common. Women who admit substance use, as well as those who do not but have injection marks or other signs suggesting such use (see Table 5), should be examined further.

Drug-using women are often dependent on more than one psychoactive substance (nicotine, alcohol, cannabis, opiates, cocaine, ecstasy, other amphetamines, benzodiazepines) *(44)*, and clinical signs and symptoms of use and withdrawal can be difficult to identify. It is also important to differentiate clinical signs of pregnancy and symptoms of pregnancy complications from signs and symptoms of drug intake or withdrawal.

Table 5. Signs and symptoms of withdrawal from specific substances during pregnancy

Substance	Signs/symptoms
Alcohol	Agitation, tremors, sleep disturbance, tachycardia, hypertension, nausea, dilated pupils, seizures
Delta-9-tetrahydrocannabinol (in cannabis, marijuana, hashish)	Restlessness, irritability, mild agitation, insomnia, nausea, cramping
Tobacco (e.g. cigarettes)	Irritability, restlessness, difficulty concentrating, impaired task performance, anxiety, hunger, weight gain, sleep disturbance, cravings, drowsiness
Central nervous system (CNS) sedative hypnotics: alprazolam, barbiturates, chlordiazepoxide, diazepam, flurazepam, gluthethimide, meprobamate, methaqualone, etc.	Tremulousness, insomnia, chronic blink reflex, agitation, toxic psychosis, seizure, anxiety, agitation, muscle cramps, sleep disturbance, hypertension, fever, anorexia
CNS stimulants: methamphetamines, cocaine, methylphemidate, phenmetrazine, dimethyltryptamine, phencyclidine (PCP)	Muscle aches, abdominal pain, hunger, prolonged sleep, suicidal ideas, bradycardia, craving, depression
Opiates: codeine/oxycodone, heroin, hydromorphone, tripelenamine	Flu-like syndrome, agitation, dilated pupils, abdominal cramps, insomnia, anxiety, craving, tachycardia, hypertension

Source: adapted from Rayburn & Bogenschutz *(45)*.

Women who use drugs may or may not be drug dependent. As drug dependency has implications for patient management strategy, it is crucial to assess it. A simple and rapid initial assessment can be done by ANC staff, based on 10 questions adapted from *ICD-10 symptom checklist for mental disorders* (see Annex 3 in Protocol 5, *HIV/AIDS treatment and care for injecting drug users*). Several other validated and standardized drug-dependence screening and assessment instruments are available, including the Addiction Severity Index (ASI) (see Annex 1 of the same protocol for European version 6 (EuropASI6)) *(44)*. However, further evaluation of drug-dependence severity and appropriate treatment strategy should be done by or in close collaboration with a drug dependency treatment expert.

2.3. Impact of psychoactive substances during pregnancy and withdrawal

The effects of psychoactive substances during pregnancy are divided into the effects of drug use on the fetus and neonate (Table 6) and withdrawal symptoms (Table 5 above).

Table 6. The effects of psychoactive substances on the fetus, neonate and pregnancy outcome

Substance	Effects
Alcohol	Spontaneous abortion, microcephaly, growth deficiency, CNS dysfunction including mental retardation and behavioural abnormalities, craniofacial abnormalities (short palpebral fissures, hypoplastic philtrum, flattened maxilla), behavioural abnormalities.
Tobacco (e.g. cigarettes)	No congenital anomalies, intrauterine growth restriction (200 g lighter), preterm birth, placenta previa, placental abruption.
Delta-9- tetrhydrocannabinol (in cannabis, hashish)	No congenital anomalies, reduction of 0.8 weeks in the length of gestation, corresponding decrease in birth weight, subtle behavioural alterations.
CNS stimulants: antiobesity drugs, methamphetamines, cocaine, methylphemidate, phenmetrazine	Spontaneous abortion, hyperactivity in utero, congenital anomalies (heart, biliary atresia), depression of interactive behaviour, urinary tract defects, symmetric growth restriction, placental abruption, cerebral infarction, brain lesions, fetal death, neonatal necrotizing enterocolitis.
Narcotics: codeine, heroine, hydromorphone, meperidine, morphine, opium, pentazocine, triplennamine	Fetal growth restriction, no anomalies, intrauterine withdrawal with increased fetal activity, depressed breathing movements, preterm rupture of membranes, preterm delivery, meconium-stained amniotic fluid, perinatal death.

Source: adapted from Rayburn & Bogenschutz *(45)*.

2.4. Counselling on drug dependency and its treatment

Counselling is an essential component in managing treatment of drug-dependent HIV-infected pregnant women. It should cover all the issues mentioned in section IV.1, with emphasis on the following:

- the risks to the fetus and neonate from drugs;
- the benefits of opioid substitution therapy (OST) for the health of both mother and fetus;
- the risk of fetal stress due to uncontrolled withdrawal attempts without medical and psychological support;[4]
- the effects of pregnancy on OST dose maintenance and the possible need to increase it;[5]
- interactions between opioid substitutes and ARVs as part of PMTCT; and
- adherence to OST and ART.

[4] It is important that mothers understand that the fetus will also experience withdrawal symptoms.
[5] To avoid resistance to a dosage increase, the patient should be reassured that it has no relationship to drug dependency in the newborn child.

2.5. Opioid substitution therapy during pregnancy

If opioid-using pregnant women meet the criteria for dependency (see Annex 4 in Protocol 5, *HIV/AIDS treatment and care for injecting drug users*) they should be counselled about the risks and benefits of OST, and an agreement should be reached for a treatment programme and adherence to it *(44, 46, 47)*. Medications for the treatment of drug dependency (both opioid and non-opioid) in pregnant women are shown in Annex 1 of the present protocol.

2.5.1. Methadone substitution therapy *(46)*

Methadone substitution treatment is the currently recommended standard of OST for dependent pregnant women. OST prevents resumption of illicit drug use, withdrawal symptoms and craving, and it also reduces pregnancy-related complications *(44, 46)*. It should be combined with prenatal care and psychosocial counselling, such as support groups, community reinforcement, contingency treatment, cognitive behavioural skills training, motivational therapy and marital behavioural therapy.

Data show that medical withdrawal of opioid-using pregnant women (including those on methadone) during pregnancy carries an increased risk to the fetus of intrauterine death, even under the most optimal conditions *(46)*. There is evidence that methadone maintenance treatment, combined with prenatal services, promotes fetal growth, while continued use of heroin during pregnancy may result in infant morbidity *(46)*.

Table 7. Advantages and disadvantages of methadone treatment for pregnant women

Advantages	Disadvantages
Avoids contaminants that may harm the unborn child. No known fetal abnormalities are associated with pure heroin or methadone. Involves a known, regular dose. Avoids periods of drug withdrawal that may be associated with miscarriage early in the pregnancy, or fetal growth retardation and stillbirth late in pregnancy. Reduces the incidence of premature birth. Reduces the risk of intra-uterine growth retardation. Increases use of ANC services.	Increases the severity and duration of neonatal withdrawal compared to that of infants of untreated opioid-dependent mothers. Involves longer hospitalization and treatment of newborn infants. Leads to greater neonatal weight loss. Reduces demand of infant to feed.

Source: Brown et al. *(46)*.

Methadone is a long-acting substance which, if prescribed in adequate dosage, provides a relatively non-stressful environment in which the fetus can develop throughout pregnancy. Methadone provision should begin as early in pregnancy as possible; starting in the first trimester of pregnancy is optimal for both fetus and mother, and is associated with higher birth weights.

2.5.1.1. Dosage

Methadone dose should always be individually determined by the absence of subjective and objective abstinence symptoms and reduction of drug craving. The lowest effective dose should be used. Doses below 60 mg/day are not effective, and low-dose policies for pregnant patients often result in increased illicit drug use as well as reduced programme retention *(46)*. A small number of methadone patients are aberrant metabolizers, and some medications may speed liver metabolism. Such cases may require doses in excess of 120 mg/day.

2.5.1.2. Dosage reduction (detoxification)

Once a patient is stabilized on methadone, it should be decided in consultation with her whether a slow reduction, finishing sometime before the birth, is realistic, or whether methadone maintenance

must continue. Dose reduction is only possible to consider if the pregnancy is stable and has reached the second trimester. Dose reductions of 2.5–5.0 mg per week are considered safe (*46*). Withdrawal symptoms should be avoided as much as possible, as they cause the fetus considerable distress.

2.5.1.3. Dosage increase

During the later stages of pregnancy, methadone dosage may have to be increased or split (half each in the morning and evening) to produce a beneficial effect since greater plasma volume, an increase in plasma proteins that bind methadone and renal blood flow during pregnancy can contribute to a reduced plasma blood level of methadone. It may therefore be necessary to increase the methadone dosage by 5–10 mg to avoid withdrawal symptoms and prevent concurrent drug use. Note that the administration of NVP or EFV as part of a PMTCT regimen requires an increase of methadone.

2.5.1.4. Interactions between methadone and ARVs

Interactions between methadone and ARVs are the same in pregnant women as in other patients (cf. Protocol 5, *HIV/AIDS treatment and care for injecting drug users*, section on Drug-drug interactions and IDUs). If a pregnant woman receives an NNRTI (NVP or EFV) as part of a PMTCT regimen, the dose of methadone has to be increased, as NNRTIs significantly decrease concentration of methadone and generate withdrawal symptoms.

In a case series of chronic methadone recipients initiating NVP, 50–100% increases in the daily methadone doses were required to treat opiate withdrawal. Withdrawal symptoms generally occurred between four and eight days after starting NVP *(46)*.

Methadone significantly increases ZDV concentration (up to 43%), which may increase the risk for adverse effects; consequently, close monitoring is required.

SQV/r slightly reduces levels of methadone; no dosage adjustment is necessary, but continual monitoring is required.

2.5.2. Buprenorphine substitution therapy

As a Category C drug,[6] buprenorphine has implications for pregnancy *(49–51)*. While studies have not shown that buprenorphine is harmful to the fetus, it cannot be recommended for pregnant or lactating women. Its use can be considered if potential benefits justify the risks to the fetus *(52)*, for example, if methadone is not available or the patient cannot tolerate it. Women should be informed about the risks of buprenorphine use, and its use for patients who are or may become pregnant should be made carefully and on a case-by-case basis. Limited case reports from Europe and Australia indicate that doses can range from 0.4 to 24 mg/day, with pregnancies generally progressing normally *(50)*.

2.6. Management of HIV-infected drug-dependent women presenting in labour

The majority of drug-using women do not attend ANC and only arrive at the maternity ward around the time of labour. In such cases, maternity wards should be prepared to:

- assess drug use dependence (see Protocol 5, *HIV/AIDS treatment and care for injecting drug users*, Annex 1) and inform the neonatologist;
- offer rapid HIV testing if status is unknown or was negative during pregnancy;
- provide relevant treatment for withdrawal symptoms;
- initiate OST as necessary; and
- counsel about the effects of drugs on pregnancy outcome, on the newborn infant and on treatment approaches.

[6] According to the United States Food and Drug Administration, a Class C rating for use during pregnancy means that studies in animals have revealed adverse effects on the fetus (teratogenic, embryocidal or other) and that there are no controlled studies in women or studies in animals *(48)*.

See Table 4 above for a PMTCT regimen for HIV-infected women who have not received ARV prophylaxis during pregnancy, irrespective of their drug-dependence status. For opioid-dependent women presenting in the maternity ward who receive ARVs at the onset of labour, methadone should be sufficient to prevent withdrawal symptoms.

2.6.1. Pain relief[7]

Pain relief requires special attention during labour and the postpartum period, especially after CS. Pain management for opioid dependent pregnant women should be addressed in the same way as for other pregnant woman. A higher dose of analgesia may be needed to relieve pain *(53)*.

Epidural anaesthesia should be used as early in delivery as possible, and can be continued in the early postpartum period, especially after CS.

3. Postpartum management

PMTCT postpartum pharmacological management is described in Tables 1–4 above. All women with HIV infection should also be counselled on infant feeding options and contraception while in the maternity ward.

3.1. Counselling on infant feeding

Even when peripartum ARV prophylaxis is used, infants remain at substantial risk of acquiring infection during breastfeeding, which has been shown to result in HIV transmission to 14% of at-risk infants *(54–56)*. WHO recommends that HIV-infected mothers do not breastfeed at all when replacement feeding is acceptable, feasible, affordable, sustainable and safe (for definitions of these terms, see Annex 2). Otherwise, exclusive breastfeeding is recommended during the first months of life and should be discontinued as soon as these conditions for replacement feeding are met. Evidence suggests that exclusive breastfeeding in the first three months carries a lower risk of transmission than mixed feeding, which is therefore not recommended *(57, 58)*.

Counselling on infant feeding should stress the risks of transmission through breastfeeding and recommendations for replacement feeding, the importance of not breastfeeding during replacement feeding and how to safely prepare and administer the food. Mothers should have a follow-up visit to the paediatric outpatient clinics within two weeks after birth to check and ensure that there are no feeding problems.

3.2. Counselling postpartum contraception

Condoms remain the preferred option for reducing the risk of unintended pregnancy and HIV transmission. Lactational amenorrhoea (LAM) cannot be recommended as a contraceptive method, since breastfeeding is not recommended. (For more information, refer to Protocol 9, *Support for sexual and reproductive health of people living with HIV*, section on Lactational amenorrhea method.)

4. Neonate management in the maternity ward

4.1. Laboratory diagnosis of HIV in neonates

The first deoxyribonucleic acid polymerase chain reaction (DNA PCR) test for HIV should be performed within 48 hours of birth. Testing of the umbilical cord blood should not be done due to possible risk of contamination with maternal blood. A positive test will provisionally mean that the newborn infant is infected. A second HIV DNA test at six to eight weeks from birth should be performed regardless of the outcome of the first test. If PCR is not available, an HIV antibody test is recommended at 15–18 months, with a confirmatory western blot test.

HIV diagnostic testing for infants should be accompanied with counselling for caregivers, explaining the results and the need for additional testing to definitively determine the child's infection status.

[7] For further information regarding pain management for IDUs, refer to Protocol 5, *HIV/AIDS treatment and care for injecting drug users*, section on Management af acute and chronic pain.

Please see the algorithm 1 for HIV diagnosis in infants in Protocol 11, *Paediatric HIV/AIDS treatment and care*, section on laboratory diagnosis of HIV.

4.2. Management of dependence and withdrawal syndrome in neonates

4.2.1. Clinical examination

Neonatal withdrawal or abstinence syndrome (NAS) occurs in 50–80% of infants exposed to opioids in utero, usually within the first 24–72 hours after birth. However, only 5–20% of these infants have severe symptoms and need pharmacotherapy *(59)*. NAS from buprenorphine peaks within three or four days and lasts for five to seven days. NAS from methadone generally lasts up to four days *(60)*.

Clinical symptoms of NAS vary in severity and duration and include:
- tremors, increased muscle tone, restlessness, sleeping problems, protracted crying and hyperactive reflexes;
- regurgitation, vomiting and diarrhoea;
- tachypnea; and
- minor symptoms, such as fever, sneezing, sweating, nasal stuffiness and yawning.

Infants of mothers known or suspected to be drug users who are showing signs of withdrawal should be scored every four hours. The scoring should be applied in a consistent manner. Please see the scoring system for the signs and symptoms of NAS in Annex 3, which provides a basis for deciding treatment dosages (see Table 8 in the next below).

4.2.2. Treatment of NAS *(51)*

The aim of NAS treatment is to give the infant the chance to rest, get enough sleep and eat enough food; it will not eliminate all symptoms. The treatment should be carried out as follows.

- First stage is: supportive therapy. Provide a low-stress environment (quiet room, reduced illumination, swaddling, holding, hammock, pacifier), frequent small feedings (on demand) and no abrupt changes. If symptoms worsen, proceed to the second stage.

- Second stage is: pharmacological therapy. Phenobarbital solution is the agent of choice. If it is not successful or if convulsions occur, switch to morphine solution. Therapeutic doses for NAS treatment vary depending on NAS score; see Table 8 below, and Annex 3 for scoring. Occasionally, vomiting may be very serious, in which case replace the pharmacological agent temporarily with chlorpromazine (2–3 mg/kg/day in 3 or 4 doses intramuscularly (IM)).

Table 8. Therapeutic doses for NAS

Abstinence score		
	Phenobarbital solution	**Morphine solution**
8–10	6 mg/kg/day in 3 doses	0.32 mg/kg/day in 4 doses
11–13	8 mg/kg/day in 3 doses	0.48 mg/kg/day in 4 doses
14–16	10 mg/kg/day in 3 doses	0.64 mg/kg/day in 4 doses
17+	12 mg/kg/day in 3 doses	0.80 mg/kg/day in 4 doses

Source: adapted from Finnegan et al. *(51)*

Interactions between ARV drugs for neonates as part of PMTCT and the severity of the NAS treatment have not yet been studied.

4.3. Immunization

In countries with an incidence of more than 20 TB cases per 100 000 population *(61)*, all HIV-exposed asymptomatic children should be immunized with bacille Calmette-Guérin (BCG) in the maternity ward on the same schedule as infants who have not been exposed to HIV.

In countries with low TB incidence, BCG vaccine should not be administered to HIV-infected children, regardless of their clinical stage or immunodeficiency status. Other vaccinations should be considered, taking into account the national vaccination programmes. For further recommendations concerning immunization, please refer to Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection.*

5. Referrals

The continuum of care for HIV-infected women, their neonates and their families requires a team approach that should ensure provision of:

- paediatric care for the neonate, including HAART and prevention of opportunistic infections in the first year of life, if indicated;
- postpartum contraception for the mother;
- treatment and care of HIV/AIDS; and
- treatment for drug dependency and harm reduction.

To ensure proper follow-up, detailed reports on the ART received by the mother and neonate in the maternity ward should be sent to the mother's and child's physicians. For further information on treatment and care please refer to protocols 1, *Patient evaluation and antiretroviral treatment for adults and adolescents* and 11, *Support for sexual and reproductive health in people living with HIV.*

V. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected are important in the development of key indicators on access to PMTCT services and its success. Such indicators assist managers in decision making on ways to strengthen and expand these services to all women who need them.

The following data should be collected at the clinical level on a regular basis (e.g. monthly, quarterly or semi-annually):

Antenantenal care services should collect data on the:

- number of pregnant women
- number of pregnant women who were tested for HIV
- number of pregnant women who tested positive for HIV
- number of HIV-infected pregnant women who had an abortion
- number of HIV-infected pregnant women who received ARV prophylaxis during pregnancy
- number of HIV-infected pregnant women who are opioid-dependent injecting drug users
- number of HIV-infected pregnant women receiving OST
- number of HIV-infected pregnant women receiving OST and ARV prophylaxis.

Maternity services should collect data on the:

- number of HIV-infected pregnant women who presented in the maternity services;
- number of pregnant women who presented in the maternity services without prior HIV testing during pregnancy:
  - among these how many received a rapid HIV test:
    - among these how many tested HIV positive;
- number of HIV-infected pregnant women who presented in the maternity services without receiving ARV prophylaxis during pregnancy;
- number of HIV-infected pregnant women who received ARV prophylaxis during labour;
- number of HIV-infected opioid-dependent injecting drug users in the maternity services:
  - among these how many received OST treatment during labour;
- number of HIV-infected pregnant women who had a vaginal delivery;
- number of HIV-infected pregnant women who had a planned caesarean section;
- number of neonates born to HIV-infected women:
  - among these number who received ARV prophylaxis;
  - among these how many received milk formula feeding;
  - among these how many received exclusive breastfeeding;
- number of HIV-infected neonates, born to HIV -infected mothers, diagnosed by PCR;
- number of neonates born to opioid dependent women;
- number of neonates who received NAS treatment.

Annex 1. Currently available medications for substance-dependence treatment during pregnancy

Table 9. Medications available for treating substance dependence during pregnancy

Medication	Dosage	Side-effects	Clinical considerations
Opioid dependence			
Clonidine	0.1–0.2 mg every 4–6 hours, monitoring of withdrawal syndromes	Hypotension and sedation	More effective for somatic than psychological symptoms; will require adjunct drugs
Naltrexone	50 mg/d, or 100 mg Monday and Wednesday and 150 mg Friday	Abdominal pain, elevated liver enzymes in patients older than 40	Maintenance and withdrawal; do not administer if opioids have been used within one week
Buprenorphine	2–4 mg for induction a max. of 8 mg on first day; second day dosages up to 16 mg/d, depending on symptoms; may be given every other day at 8 mg dosage; 60+ mg usually more effective	Mild withdrawal syndromes, constipation, sedation	Maintenance and withdrawal; only office-based treatment; do not use within 24 hours of opioid use
Methadone	Dosage over 60 mg usually more effective	Sedation, constipation, decreased libido, ankle oedema	Maintenance of opioid dependence; restricted to licensed narcotics treatment programmes
Smoking cessation			
Nicotine patch	4 weeks of 21 mg/24 h then 2 weeks of 14 mg/24 h, then 2 weeks of 7 mg/24 h (Nicoderm CQ); or 15 mg/16 h (Nicotrol) 8 weeks	Local skin irritation, insomnia	Lower patch dose in those smoking <10 cigarettes/day; place new patch on different site daily
Nicotine gum	2 mg for those who smoke <25 cigarettes/day and 4 mg for those who smoke 25 or more/day	Jaw and mouth soreness, hiccups, dyspepsia	Schedule doses 1 piece every 1–2 hours rather than as needed; do not eat or drink 15 minutes before chewing or during chewing;
Bupropion sustained release	Start with 150 mg each morning for 3 days one week before quitting smoking; then 150 mg BID for 7–12 weeks; may be used up to 6 months	Insomnia and dry mouth; contraindicated with a history of seizures, eating disorders, head injury or in those who have used monoamine oxidase inhibitor within 14 days; pregnancy class B[a]	Prescription; alternative for those who do not want nicotine replacement

Medication	Dosage	Side-effects	Clinical considerations
Alcohol withdrawal			
Chlordiazepoxide	25–100 mg per dose	Sedation, dizziness, ataxia, confusion	Long half-life; may be given as a loading dose to reduce symptoms, then discontinued
Diazepam	15–60 mg per dose	Same as chlordiazepoxide	Shorter half-life, no active metabolites and not dependent on hepatic metabolism; generally requires dosing every 4–6 hours
Carbamazepine	400 mg loading dose, then 200 mg three times daily (TID), tapering over 5 days	Sedation, dizziness, ataxia, confusion, nausea and vomiting, bone marrow suppression	Effective for moderate-to-severe withdrawal, not well studied for severe withdrawal
Alcohol dependence			
Disulfiram	250–500 mg every day or two	Hepatitis, neuritis, peripheral neuropathy, disulfiram alcohol reaction (if alcohol is consumed)	Efficacy is enhanced by monitoring compliance; may also have efficacy for cocaine dependence
Naltrexone	Same as for opioid dependence	Same as for opioid dependence	Screen carefully for covert opioid dependence to avoid precipitating withdrawal; contraindicated in those anticipating surgery or needing narcotics for pain management

[a] According to the United States Food and Drug Administration *(48)*, Class B use in pregnancy rating means that either animal studies have revealed no evidence of harm to the fetus, with no adequate and well-controlled studies in pregnant women; or that animal studies have shown an adverse effect, while adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
Source: adapted from Rayburn & Bogenschutz *(45)*.

Annex 2. Definitions of acceptable, feasible, affordable, sustainable and safe replacement feeding

The following terms can serve as a starting point that should be adapted in the light of local conditions and unfolding research.

Acceptable. The mother perceives no barrier to replacement feeding, whether due to cultural or social causes or to fear of stigmatization or discrimination. If replacement feeding is acceptable to the mother, either she is under no social or cultural pressure to breastfeed and is supported by family and community in opting for replacement feeding, or she will be able to cope with pressure to breastfeed and deal with any stigma attached to replacement feeding.

Feasible. The mother (and family) has the time, knowledge, skills and other resources needed to prepare the replacement food and feed the infant up to 12 times every 24 hours. The mother can understand and follow the instructions for preparing infant formula, and with family support where available she can prepare sufficient replacement food every day, and at night, despite any disruptions it might cause in preparation of other family food or other work.

Affordable. The mother (and family), with community or health-system support if necessary, can pay the cost of purchasing/producing, preparing and using replacement food, including all ingredients, fuel, clean water, soap and equipment, without compromising the health and nutrition of the family. The concept of affordability also extends to access to medical care for diarrhoea if necessary and the cost of such care.

Sustainable. A continuous and uninterrupted supply and dependable system of distribution for all ingredients and products needed for safe replacement feeding should be available for as long as the infant needs it, up to one year of age or longer. If replacement feeding is sustainable, there should be little risk that formula will ever be unavailable or inaccessible, and another person will always be available to prepare the food and feed the child in the mother's absence.

Safe. Replacement foods should be correctly and hygienically prepared and stored, and fed in nutritionally adequate quantities with clean hands and utensils, preferably using a cup. Safety means that the mother or caregiver is able to:

- access a reliable supply of safe water (from a piped or protected-well source);
- prepare replacement food that is nutritionally sound and free of pathogens;
- wash hands and utensils thoroughly with soap and regularly sterilize the utensils;
- boil water to prepare each of the baby's feedings; and
- store unprepared food in clean, covered containers protected from rodents, insects and other animals.

Source: adapted from WHO *(57)*.

If the above criteria are not met, exclusive breastfeeding is recommended during the first months of life and should then be discontinued as soon as feasible. HIV-positive mothers should be helped to make the best choice according to their circumstances and to carry out their decision. They should thus receive counselling that includes information about the risks and benefits of various infant feeding options, based on local conditions, and guidance in selecting the most suitable option for their situation. Whichever infant feeding option is chosen, mothers should be supported in carrying it out safely and appropriately. While commercial infant formula will be acceptable, feasible, affordable, sustainable and safe for many HIV-positive women in the European Region, some women will choose other options in accordance with their personal circumstances.

Annex 3. Neonatal abstinence syndrome scores

Table 10. Neonatal abstinence syndrome scores

Sign or symptom	Score
Central nervous system disturbances	
High-pitched cry	2
Continuous high-pitched cry	3
Sleeps <1 hour after feeding	3
Sleeps <2 hours after feeding	2
Sleeps <3 hours after feeding	1
Hyperactive Moro reflex	2
Markedly hyperactive Moro reflex	3
Mild tremors when disturbed	1
Moderate–severe tremors when disturbed	2
Mild tremors when undisturbed	3
Moderate–severe tremors when undisturbed	4
Increased muscle tone	2
Excoriation (specify areas)	1
Myoclonic jerks	3
Generalized convulsions	5
Metabolic/vasomotor/respiratory disturbances	
Sweating	1
Fever <101 ºF (99–100.8 ºF, or 37.2–38.2 ºC)	1
Fever >101 ºF (38.4 ºC and higher)	2
Frequent yawning (>3–4 times)	1
Mottling	1
Nasal stuffiness	1
Sneezing (>3–4 times)	1
Nasal flaming	2
Respiratory rate >60/min	1
Respiratory rate >60/min with retractions	2
Gastrointestinal disturbances	
Excessive sucking	1
Poor feeding	2
Regurgitation	2
Projectile vomiting	3
Loose stools	2
Watery stools	3

Source: Finnegan et al. *(51)*.

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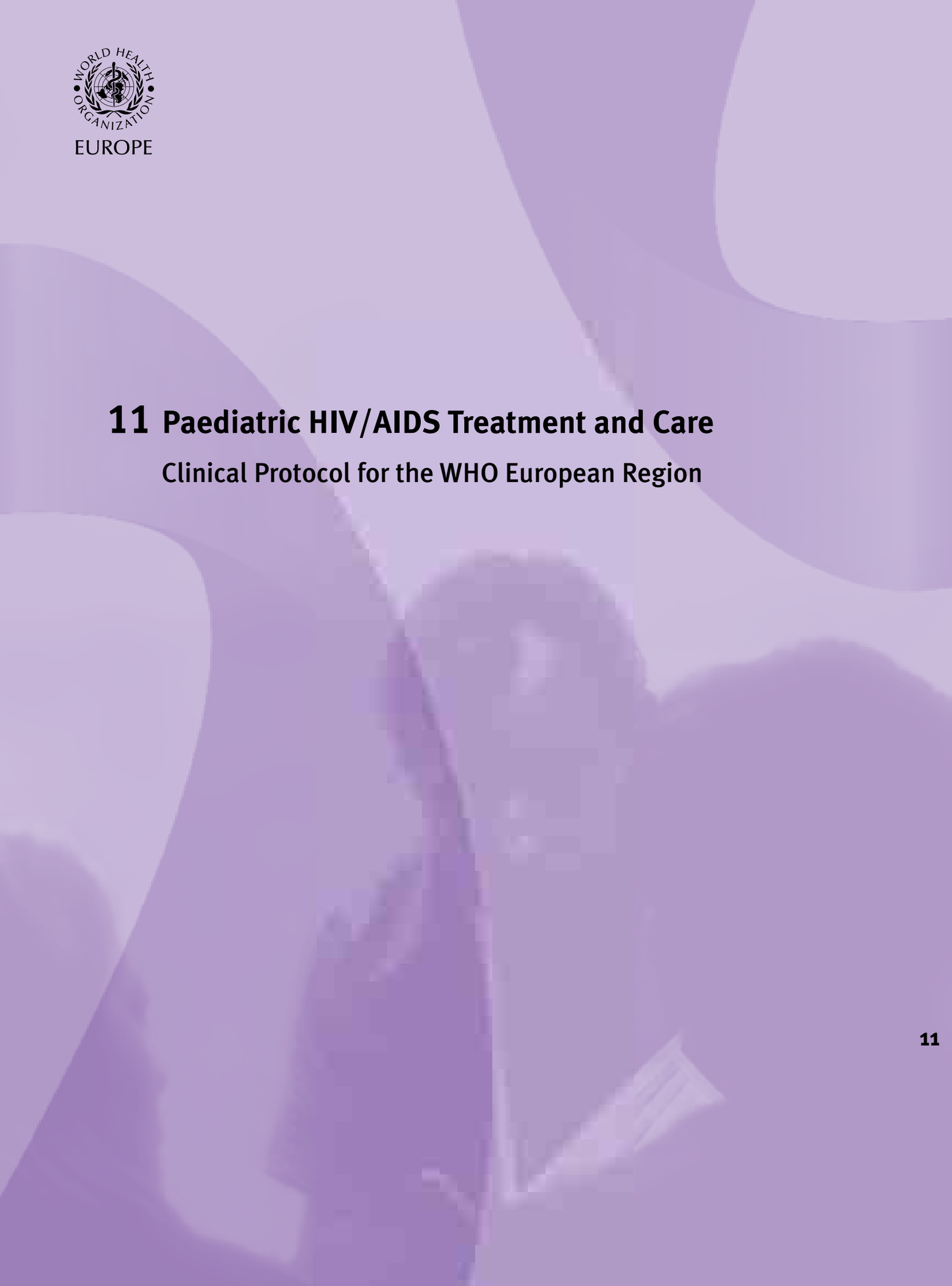
EUROPE

11 Paediatric HIV/AIDS Treatment and Care

Clinical Protocol for the WHO European Region



Contents

I. Introduction

The increasing number of reported paediatric AIDS cases in European countries *(1)* demands urgent action to improve survival and quality of life for the affected children.

The core component of treatment and care of infants and children infected with HIV is provision of antiretroviral treatment (ART). Optimal ART increases the length and quality of their lives.

The goals of paediatric ART are the same as for adults and adolescents, the prolongation of life and improvement of its quality (see Protocol 1 *Patient evaluation and antiretroviral treatment for adults and adolescents)*.

Policy for ART in paediatric HIV/AIDS cases should be based on the following principles.

- Antiretroviral (ARV) treatment should be available as part of a comprehensive package of paediatric HIV care.
- It should be consistent with Protocol 10 *Prevention of HIV transmission from HIV-infected mothers to their infants.*
- Paediatricians should provide routine care and collaborate closely with paediatric HIV specialists to monitor HIV progression and the need for ART.
- A continuum of care should be assured during childhood, during transition to adolescence and adulthood and in line with future treatment and care for adolescents and adults (see Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents).*

II. Laboratory diagnosis of HIV

1. Diagnosis of children ‹18 months of age

In children <18 months, virological assays are recommended for detecting plasma HIV DNA *(2)*, plasma HIV RNA *(3–7)* and immune complex-dissociated (ICD) p24 antigen *(8–10)*. Virological tests have recently become technically easier, less expensive and more reliable.

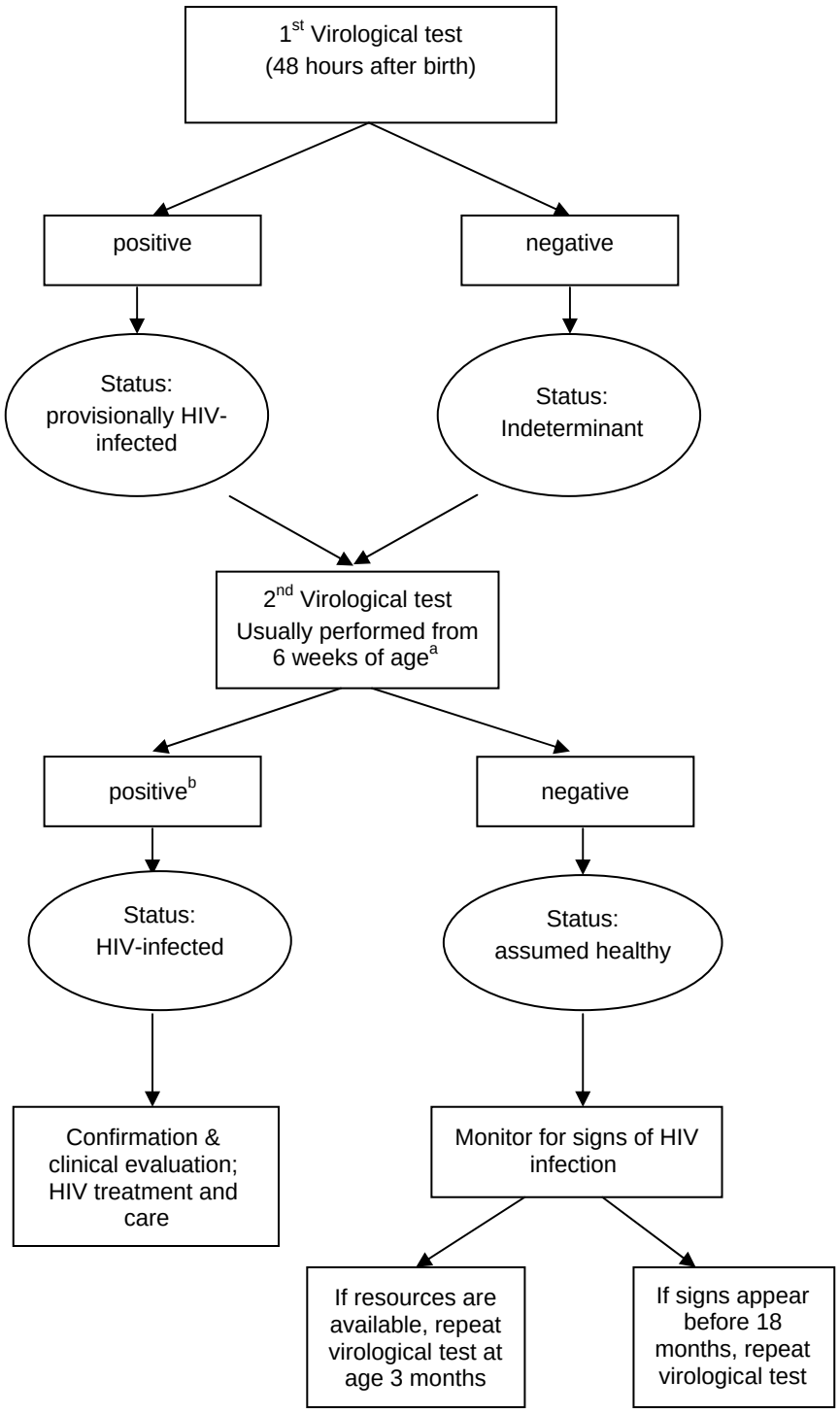
1.1. Diagnosis in non-breastfeeding infants

See the algorithm in Fig. 1 below.

- The probability of HIV diagnosis by DNA assay increases with age; 38% of infected children have positive DNA PCR tests by the age of 48 hours. By age 28 days, DNA PCR has 98% sensitivity *(11)* and 99% specificity in identifying HIV pro-viral DNA *(12)*.
- Infants with a positive virological test at age 48 hours may have an intrauterine infection.
- Infants with a negative virological test during the first week of life and subsequent positive tests have an intrapartum infection *(13)*.
- HIV infection can be diagnosed by HIV DNA or RNA detection in most infected non-breastfeeding infants by age 1 month and in virtually all infected infants by age 6 months.
- Blood samples from the umbilical cord should not be used for diagnostic evaluations because of potential contamination from maternal blood.
- A first virological test should be performed on infants about 48 hours after delivery, before mother and infant are discharged.[1] A positive virological test (usually DNA) means that the infant is "provisionally HIV-infected"; a negative result at this stage suggests an indeterminant status.
- The second virological test should be done at around 6 weeks of age. This is the key test for infants who tested negative with the first virological test. If this test is now positive, usually testing algorithms require confirmation by a repeat test on a separate specimen for confirmation.
- A second positive virological result indicates that the infant is HIV-infected and should be clinically evaluated to develop a management strategy, see section III below.
- If a second virological test is negative the infant is assumed to be uninfected, however, regular monthly monitoring for signs of HIV infection should be conducted and if resources are available, a third virological test may be offered at age of 3 months.

[1] In settings with limited resources or access to virological tests it may be more efficient and cost effective to conduct initial virological testing at 6 weeks or age, as HIV infection status can be reliably determined in almost all children at this stage (follow algorithm 1 from where 2nd test begins).

Fig 1. HIV virological diagnosis in non-breastfed infants born to HIV-infected mothers



[a] This may be the first diagnostic algorithm if testing at the age of 48 hours is not available.
[b] Usual confirmatory test should be followed on a new specimen.

1.2. Diagnosis in breastfeeding infants

- WHO EURO does not recommend breastfeeding for infants born to HIV-infected mothers.
- If alternative feeding is not available and an infant is breastfeeding, virological assays can be performed any time. If the result is negative then it should be conducted at least six weeks after complete cessation of breastfeeding, to confirm that the infant is not HIV-infected.

1.3. Diagnosis in infants exposed to ARV prophylaxis

- ARV prophylaxis to avoid mother-to-child transmission (MTCT) does not affect HIV DNA test results. HIV DNA remains detectable in the peripheral blood mononuclear cells of an HIV-infected child.
- The sensitivity of HIV RNA may be affected by ARV prophylaxis. Therefore, if the HIV RNA assay was negative while the infant was receiving prophylaxis, it should be repeated at least two weeks after prophylaxis has been completed.

1.4. Diagnosis in infants born to mothers on ART

- Infants of mothers who are on ART or have a low or undetectable viral load at delivery and do not breastfeed can be considered at low risk for acquiring infection *(14)*.
- Given the relatively high ARV levels found in breastfeeding infants, it is not known whether maternal ART during breastfeeding affects RNA detection in the infant.
- DNA detection is unaffected by maternal ART.

2. Diagnosis in children ≥ 18 months old

- By the age of 12 months, most uninfected HIV-exposed children will have lost maternal antibodies. HIV antibody testing with a positive result in a child at this age usually indicates HIV infection (96% specificity) *(15)*.
- Definitive HIV diagnosis in children ≥18 months old (whether HIV exposure is known or unknown) can be performed with antibody tests (ELISA or rapid test), while Western Blot has been used in the past, confirmation of HIV status is more reliably established with virological testing.
- Some clinical conditions are very unusual in the absence of HIV infection (*Pneumocystis* pneumonia, oesophageal candidiasis, lymphocytic interstitial pneumonitis (LIP), Kaposi sarcoma and cryptococcal meningitis). Diagnosis of such conditions and other stage 3 and 4 clinical (see Annex 1) diagnoses suggests HIV infection and indicates the need for an HIV antibody test.

III. Clinical management of HIV-infected children

1. Clinical and laboratory evaluations of HIV-infected children

All infants and children who are diagnosed with HIV infection should undergo clinical and laboratory evaluations to determine the stage of HIV clinical disease and immunodeficiency, eligibility for ART and other morbidities or issues to be addressed. This baseline assessment will also provide an opportunity to initiate cotrimoxazole preventive therapy and should serve as an opening to offer counselling and support to infected children and their parents/caregivers.

Clinical and laboratory evaluation of children with HIV should include the following:

- current clinical signs and symptoms to establish clinical stage (see Annex 1);
- exposure to and risk for coinfections (tuberculosis (TB), hepatitis B, hepatitis C);
- identification of comorbidities and medications taken to treat them;
- history of previous exposure to ARVs, including drugs used for prevention of mother-to-child transmission (PMTCT); and
- laboratory tests:
  - complete blood count;
  - CD4 cell count (absolute and percentage for children <6 years old);
  - liver enzymes (ALT and AST);
  - additional tests: bilirubin, creatinine, urinalysis, glucose;
  - testing for TB, hepatitis B and C (if at risk);
  - pregnancy tests for adolescent girls.

Other evaluations to be undertaken during the visit:

- anthropometrical measurements: weight, height/length and head circumference;
- nutritional assessment, including:
  - types of foods consumed and estimated amounts;
  - appetite and length of eating time;
  - problems associated with food intake;
  - identification of caregiver who feeds the child.
- social assessment:
  - general household hygiene and access to safe water;
  - availability of a secure refrigerator for medication storage;
  - the ability of family members and other caregivers to monitor adherence;

  and
- psychological status of both caregiver and child and a cognitive assessment of the child.

2. Nutritional support

Nutritional support should include early efforts to ensure adequate nutrient intake, based on locally available and affordable foods and the provision of micronutrients equivalent to the recommended daily allowance (RDA) *(16, 17)*.

- Increasing the energy intake of asymptomatic infants and children by 10% of the RDA for their age and sex is recommended.
- The energy intake of infants and children who are symptomatic or recovering from acute infections should be increased by 20–30% of the RDA *(18)*.
- Such requirements are minimal and may need to be augmented for children with nutritional deficiencies *(19)*.

- It is not necessary to increase protein intake beyond that required for a normally balanced diet (12–15% of the total energy intake) *(18)*.
- Vitamin A supplements should be given according to the WHO recommended high-dose prevention schedule for children at high risk[2] for deficiency *(20–22)*.
- Clinical observations indicated that infants with AIDS defining clinical disease commonly have temporary lactose intolerance and cow's milk protein (CMP) intolerance. Experts usually recommend that if the child presents with severe diarrhoea, special milk formulae and lactose CMP free milk, if available, can alleviate the problem.

3. Counselling caregivers

Parents and/or other caregivers of HIV-infected children should be counselled on several matters prior to starting children on ART. Adherence to ART is the key to successful treatment. It predicts and influences the virological and clinical response to treatment *(23)*, and its importance must be communicated to caregivers. The aims of such counselling should include:

- establishing trust with the caregiver and setting mutually acceptable goals for care;
- obtaining explicit agreement of the child's need for treatment and treatment adherence;
- identifying and addressing any of the caregiver's psychological issues that may decrease adherence;
- identifying a back-up caregiver who can help with adherence support;
- educating the patient and/or caregiver about the critical importance of maintaining at least 95% adherence, the link between partial adherence and resistance, and the way that temporary non-adherence can permanently limit choices;
- providing information about possible side-effects of ARVs and their management;
- emphasizing the need for follow-up visits and scheduling them; and,
- psychological and social issues should be discussed with caregivers and appropriate referrals should be offered, including:
    - social and rights based services;
    - peer support groups for parents/caregivers and for children.

Proper nutrition is also a prime counselling issue, including the optimal use of local foods, appropriate nutrition supplements and the nutritional management of HIV-related conditions affecting the appetite and the ability to eat (see section III.2 above).

Parents should be aware of developmental milestones and stages of growth that infants and young children should be reaching and the importance for these to be observed and discussed with the physician (see sections III.5.6 and III.5.7).

Prevention of infections should also be addressed, including *Pneumocystis jirovecii* pneumonia (PCP) prophylaxis (see section IV.3 below) and routine immunizations (see Protocol 12, *Immunization of people living with HIV and people at risk for HIV infection*).

3.1. Considerations of adolescent needs

Once a child reaches adolescence there are other considerations that need to be taken into account and addressed during counselling to ensure that appropriate treatment and care continue to be provided. During this time they pass through physical, psychological and sexual maturation, all which have implications in the continuum of their treatment and care. The following issues now need to be dscussed with and understood by the adolescent:

- disclosure of the HIV status to the adolescent if it had not already been done, this should include basic information related to HIV/AIDS;
- prevention strategies in light of impending sexual activity and fertility, including information on sexual and reproductive health and PMTCT (refer to protocols 9, *Support for sexual and*

[2] Children with severe infections or severe protien-energy malnutrition.

reproductive health in people living with HIV, and 10, *Prevention of HIV transmission from HIV infected mothers to their infants*;
- prevention of opportunistic infections and the need to treat them in an expedient manner;
- transition from paediatric to adult care, and that there may now be a change in health care providers as well as in ARV regimens;
- the importance of continuing to adhere to treatment and consequences of non-adherence;
- toxicity and signs of it; and
- ways to address possible stigma and discrimination.

4. ART in infants and children

The critical issue in clinically managing HIV-infected children is when to initiate lifelong ART. The effectiveness of HAART in reducing HIV-related morbidity and mortality in infants and children is comparable to that observed in adults *(24)*. However, there are unique considerations for HIV-infected infants and children, including:
- exposure to ZDV and NVP *(25–27)* and other ARVs taken during pregnancy, which may result in ARV resistance;
- age-dependent differences in immunological markers (e.g. CD4 percentage is used for children, not CD4 count);
- age-dependent pharmacokinetical differences;
- difficulties adhering to long-term combination treatment;
- difficulties taking medication during sleeping hours or at school; and
- unwillingness of children and adolescents to take medication.

Children should be started on ART when they have either an AIDS-defining illness or severe immunological failure (see Table 1). The decision to start ART should be made according to both CD4 percentage and age. It is now possible to determine the exact risk of progression to AIDS or death over the next calendar year based on these factors (a risk calculator is available from the HIV Paediatric Prognostic Markers Collaborative Study *(28)*). Infants who are at high risk for clinical progression, particularly for HIV encephalopathy, should start ART with a higher CD4 percentage than older children. Initiation of ART in children with a confirmed HIV diagnosis should be based on the WHO guidelines for clinical staging of paediatric HIV/AIDS (see Annex 1), immunological criteria and the Paediatric European Network for Treatment of AIDS (PENTA) guidelines[3] *(29)*.

Table 1. Criteria for initiation of ART in infants and children

WHO clinical paediatric stage	Age-specific treatment recommendations	
	<12 months[a]	≥12 months
1	Treat all	CD4-guided treatment[b]
2	Treat all	CD4-guided treatment[b]
3	Treat all	CD4-guided treatment[b]
4[c]	Treat all	

[a] The recommendation to treat all children <12 months differs from WHO global guidelines. European paediatric HIV experts generally believe that all infants diagnosed with HIV infection in the first year life should be treated, however, additional research is in need to confirm this recommendation.
[b] For CD4 guidance, refer to Table 2.
[c] Stabilize any opportunistic infection prior to initiating of ARV treatment.
Source: adapted from global guidelines, WHO *(30)*.

[3] Wherever possible, children with HIV in Europe should be cared for in collaboration with a member of the PENTA network. Full contact details are at http://www.ctu.mrc.ac.uk/penta.

4.1. Immunological, age-specific criteria for initiation of ART

- Immunological markers supplement clinical assessment and should therefore be used in combination with clinical staging.
- The threshold CD4 levels for severe immunodeficiency, as indicated in Table 2 below, are derived from longitudinal data on HIV-infected infants and children and indicate the levels at which ART is required. In general CD4 percentage is a more accurate marker in children aged under 5 years and CD4 count is the better guide for children aged over 5 years.
- Where the CD4 percentage is not available, absolute CD4 count thresholds may be used
- For children over the age of 5, the same cut-off value as in adults – i.e. 200–350 cells/mm^3 – can be used. There is a marked increase in risk of AIDS when the CD4 count drops below 200, so this should be avoided.
- A drop below threshold values should be avoided, as it significantly increases the risk of disease progression and mortality. ART should be initiated by these cut-off levels, regardless of clinical stage.
- For children with pulmonary TB, the result of CD4 measurement and clinical status should guide whether ART is urgently required or can be delayed (refer to Protocol 4, *Management of tuberculosis and HIV coinfection)*. See Annex 2 for an overview of the proposed revision to the immunological classification.

Table 2. CD4 criteria for initiation of ART

Immunological marker	Recommended threshold levels for initiating ART			
	≤11 months	**12–35 months**	**36–59 months**	**≥5 years[a]**
CD4 % and/or CD4 count	≤25% (≤1500 cells/mm^3)	≤20% (≤750 cells/mm^3)	≤15% (≤350 cells/mm^3)	≤200 cells/mm^3 (≤15%)

[a] Starting at 5 years of age CD4 cell count is a more accurate indication for initiation of treatment.
Source: adapted from WHO *(30)*.

HIV progression is more rapid in children than in adults. The predictive value of specific HIV RNA levels for disease progression is difficult to interpret, particularly for infants, so an assessment of viral load (VL) is not considered necessary before starting treatment. However, VL remains a useful measurement of treatment response and should be performed before starting ART and at one month and three months of treatment, if possible. The aim of treatment is to achieve an undetectable VL level (now usually defined as <50 copies HIV/ml plasma), which stops viral replication and reduces the chances of resistance to the ART combination being used.

The risk of progression to AIDS or death within 12 months based on age, CD4% or CD4 count or viral load may be a useful as complementary information to clinical and laboratory indicators when making a decision to initiate treatment. This may be calculated by using the risk calculator that can be accessed at http://www.ctu.mrc.ac.uk/penta/hppmcs *(31)*.

4.2. First-line HAART regimens

The choice of first-line ARV regimens for infants and children follows the same principles as for adults, with several additional considerations:

- the patient's age
- the suitability of drug formulations
- the side-effect profile
- the possibility of maintaining future treatment options
- anticipated patient adherence
- coexisting conditions (coinfections, malnutrition, metabolic abnormalities)
- risk of pregnancy in adolescent girls
- potential drug interactions.

In the absence of resistance assays, children who receive ARV prophylaxis should follow the standard first line ART regimens indicated in Table 3.

Table 3. First-line ART for infants and children

Age	ARV drug classes	ART regimens
<3 years (or <10 kg)	2 NRTIs + 1 NNRTI	ABC (or ZDV) + 3TC[a] + NVP[b]
≥3 years	2 NRTIs + 1 NNRTI	ABC (or ZDV) + 3TC[a] + EFV[b, c]

[a] The ABC + 3TC combination is very effective for ART-naive children. PENTA 5 follow up data clearly confirms the superiority of this regimen (http://www.ctu.mrc.ac.uk/penta/trials.htm *(32, 33)*. d4T should be avoided due to the increased risk of lipodystrophy *(34, 35)*.

[b] EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to post-pubertal girls who are either in the first trimester of pregnancy or are sexually active and not receiving adequate contraception. EFV is preferred over NVP in children older than three years.

[c] NVP should be avoided in post-pubertal girls (considered adults for treatment purposes) with baseline CD4 absolute cell counts >250 cells/mm^3.

4.3. HAART regimens in special circumstances

The triple-NRTI regimen can be considered an alternative option that simplifies initial treatment in special circumstances. The potency of this regimen with high viral load, which is common in infants infected in utero is a matter of concern, as has been demonstrated in adult studies *(36–38)*, and therefore its use is currently recommended to be considered for specific situations including to:

- pregnant adolescents with CD4 counts >250 cells/mm^3, for whom NVP and EFV are contraindicated; and
- adolescents with anticipated or documented poor adherence (if regimen is available as a fixed-dose combination (FDC)).

Table 4. Alternative ART

ARV drug class	ART regimen
3 NRTIs	ZDV + 3TC + ABC

4.4. ART in infants exposed to ARVs

There is a possibility of infants and children developing resistance to certain ARVs in utero, intrapartum or postpartum (during breastfeeding).

A resistant virus can be transmitted by:

- ARV-naive mothers who were infected with resistant HIV viruses;
- mothers exposed to ARVs before becoming pregnant; or
- mothers exposed to ARVs during pregnancy, whether for their own health or for MTCT prophylaxis.

The frequency of such transmission has not been well documented; consequently, the recommended ART regimens remain the same as for infants not exposed to ARVs.

4.4.1. Exposure through PMTCT

- If NVP or 3TC has been used for PMTCT, either alone or in a two-drug regimen, a single point mutation can result that may be associated with resistance to these ARVs *(39, 40)*. Further research is needed.
- Children who have previously received single-dose NVP or 3TC as part of PMTCT or other ARVs should not be denied access to life-sustaining ART.
- It is not yet clear whether triple-NRTI regimens offer benefits in such situations.
- The standard 2 NRTIs + 1 NNRTI first-line regimen is recommended *(30)*.

4.4.2. Continuing exposure due to maternal ART during breastfeeding

- Although some ARVs (NVP, ZDV and 3TC) are known to be present in breast milk, the concentration and quantity ingested by infants is less than therapeutic levels *(41, 42)*.
- If a breastfeeding infant is ill enough to require ART, the administration of ARVs at standard paediatric doses should be initiated, regardless of whether the mother is receiving ART.
- The standard 2 NRTIs + 1 NNRTI first-line regimen is recommended.

4.5. ARV dosage and age-dose adjustment

Every three months, the ARV drug dosage should be checked and adjusted according to the child's weight; otherwise, there is a risk of underdosing and developing resistance. Doses are calculated either on a milligram per kilogram body weight or milligram per square meter body surface basis. Standardization is important, so that non-expert personnel can safely dispense and/or check correct dosages for children. It is sensible clinical practice to round up doses into easier doses for the parents. It is better to overdose by up to 10% as the child rapidly grows. For ARV dosages please refer to Annex 3 *(30)*.

4.6. Adherence

Adherence is the key to achieving an effective clinical, immunological and virological response to ART, and it should be no less than 95% of the prescribed dosage *(23, 43, 44)*. An initial intervention strategy to improve adherence is described in section III.3 above on counselling of caregivers, and adherence monitoring is described in section III.5.5 below.

Medication strategies to improve adherence include:

- choosing the simplest regimen, with a lower dosing frequency and number of pills;
- prescribing carefully to avoid drug interactions;
- simplifying food requirements for administration of medication;
- informing patients and caregivers of possible side-effects, and anticipating and treating side-effects; and
- using the best-tasting liquid medication if possible, and introducing tablets as soon as feasible or if liquid medication is not available.

4.7. ART failure

Poor adherence, inadequate ARV dosage or potency *(23, 43, 45, 46)* and pharmacokinetic problems *(47)* can all contribute to treatment failure. Children should have been taking their first-line regimen for at least 24 weeks and adherence deemed adequate before treatment failure is suspected. The clinical criteria for treatment failure should be supported with immunological (CD4) criteria.

4.7.1. Immunological failure

In treatment failure, children on ART persist at or below the age-related CD4 threshold for initiating treatment (see Table 2 above). Failure is characterized by an initial immune recovery after initiation of ART, followed by a drop in CD4 measurements to values at or below their age-related threshold for initiation of treatment. Previous CD4 values are thus needed to define treatment failure using immunological criteria.

4.7.2. Virological failure

The definition of virological treatment failure is more complex, and consensus on it has not yet been reached. The overall aim of treatment is to reduce VL to levels below the lowest detection threshold (<50 copies/ml) and to maintain it as long as possible. A large number of children on treatment, however, have a detectable VL between 1000 and 50,000 copies/ml, but continue to have excellent clinical response and maintain high CD4% values. Since no clear single virological threshold can be recognized to prompt switching to second-line ART, the final decision should be taken based upon consideration of the clinical and immunological status of the child.

4.7.3. Clinical failure

The following are considered indicative of treatment failure:

- development of new or recurring Stage 3 or 4 events (see Annex 1) at least 24 weeks after initiation of a first-line regimen;
- lack of or decline in growth rate in children who show an initial response to treatment, despite adequate nutritional support and without other explanation;
- loss of neuro-developmental milestones (presence of two or more of the following: impairment in brain growth, decline in cognitive function and clinical motor dysfunction *(48)*); and
- new opportunistic infections, new malignancies, recurrence of refractory oral candidiasis or recurrence of oesophageal candidiasis.

Clinical disease progression should be differentiated from immune reconstitution inflammatory syndrome (IRIS), please see section III.5.3.

4.8. Second-line ART regimens

The entire regimen should be changed from a first-line to a second-line combination only in the event of immunological or clinical failure after 24 weeks of treatment. The new second-line regimen should include at least three new drugs, one or more of them from a new class, in order to increase the likelihood of treatment success and minimize the risk of cross- resistance, and it should be based upon drugs that retain activity against the patient's viral strain (see Table 5).

The advantages of PI-based regimens include proven clinical efficacy and well-described toxicities. Because of the diminished potential of almost any second-line nucleoside component, a low-dosed RTV-enhanced PI (PI/r) component is recommended.

TABLE 5. SECOND-LINE ART FOR INFANTS AND CHILDREN

First-line ART regimen at failure	Preferred second-line ART regimen		
	NRTI/NNRTI components		PI component[a]
2 NRTIs[a] + 1 NNRTI Containing ABC + 3TC + (+NVP or EFV)	ZDV + ddI[b]	+	LPV/r[d] or SQV/r[e] or NFV[f]
ABC + 3TC	ZDV + ddI[b]		
Triple NRTI (ZDV + 3TC + ABC)	ddI[b] + EFV[c] or NVP		

[a]Continuation of 3TC in the second line may be considered.
[b]Should not be taken on an empty stomach.
[c]EFV is not recommended for children <3 years of age or <10 kg, nor should it be given to sexually active girls who are not using adequate contraception.
[d]LPV/r is available as solid or liquid.
[e]SQV/r should not be used in children weighing <25 kg.
[f]Unboosted NFV may be used where no cold chain is in place, and should be taken with food (if other PIs are not available).

4.9. Strategies in the event of second-line treatment failure

Multidrug resistance in children who have received multiple antiretroviral regimens is an increasing problem in paediatric treatment in developed countries. Limited data are available for making recommendations about treatment options in these cases. Such decisions are complex and require consultation with an HIV specialist; refer the child and the caregiver to the tertiary-level hospital as indicated.

Possible strategies include:

- addition or substitution of new drugs (such as enfurvirtide/T20)
- strategic recycling of drugs
- structured treatment interruptions
- continuation of current treatment until additional drugs become available.

5. Monitoring children with HIV

Children with HIV should be monitored regularly in order to adjust case management strategy and treatment plans. Such monitoring should cover the health conditions of those not eligible for ART as well as those who are under treatment.

5.1. Routine monitoring of patients before ART

The main reasons for monitoring HIV-infected children are to identify the proper time for initiation of ART, to prepare the patient and caregiver for ART and to prevent, detect and treat common HIV complications.

- Clinical evaluation of infants and children not yet eligible for ART should be performed every 3–6 months.
- The same parameters that were used in the baseline evaluation should continue to be monitored. All children should be plotted on a growth chart, as growth failure is one of the commonest AIDS-defining symptoms in paediatric HIV.
- Clinical evaluation and CD4 measurements can be performed more frequently as the clinical or immunological threshold for initiating ART approaches (see Table 2).
- Evaluation and nutritional support should be provided during each contact with children and caregivers, preferably every month.

5.2. Routine monitoring of patients on HAART

Children's responses to ART should be monitored regularly, including clinical, laboratory and adherence monitoring.

5.2.1. Clinical monitoring

Clinical monitoring should be performed every three months, focusing on important signs of ART response, including:

- growth, especially in children who have been failing to grow;
- neurological symptoms and development in children who have encephalopathy or have been late in reaching developmental milestones; and
- type and frequency of opportunistic infections (bacterial infections, thrush, etc.).

5.2.2. Laboratory monitoring

- CD4 values should be measured every three months, or more often if clinically indicated.
- Laboratory monitoring of ARV toxicity and comorbidities should largely be directed by clinical symptoms.

5.3. Immune reconstitution inflammatory syndrome

IRIS has been observed in adults and less frequently in children starting ART, particularly those with very low CD4 values *(49–54)*. Symptoms are similar to those seen in opportunistic infections. They usually occur within the first three months after the start of potent ART *(55)*, concurrent with a rapid rise in CD4 values. It is also possible that immunological reconstitution may lead to the development of atypical presentations of some opportunistic infections.

5.4. Monitoring ARV toxicity

Distinguishing complications of HIV disease from toxicity secondary to ARVs is sometimes difficult. Alternative explanations for apparent ARV toxicity can include a concurrent infection (such as viral hepatitis infection in a child with hepatitis symptoms), or a reaction to a concurrent non-

ARV drug (such as isoniazid-induced hepatitis in a child on TB treatment or cotrimoxazole-induced rash in a child receiving preventive therapy). Such non-ARV-related adverse events do not necessitate a change in ARVs. Drug-related adverse events may be acute (occurring soon after the drug is administered), subacute (occurring within one or two days) or late (occurring after prolonged administration).[4]

Most toxicities are less common in children than in adults (for example, NVP-related symptomatic hepatotoxicity is rare in children). Adverse events can vary in severity from mild to severe and life-threatening. Take the following steps when managing ARV toxicity:

- Determine the seriousness of the toxicity.
- Establish whether toxicity is due to an ARV or a concurrent non-ARV medication.
- Consider other disease processes (for example, viral hepatitis in ARV patients with jaundice), since not all problems that arise during treatment are due to ARVs.
- Manage the adverse event according to its severity.
    - In case of severe life-threatening reactions, immediately discontinue *all* ARVs, manage the medical event and then reintroduce the same ARVs in a modified regimen, substituting for the offending drug when the patient stabilized. Such reactions are very rare and are usually only seen with fulminant hyperlactaemia.
    - In case of severe reactions, substitute for the offending drug without stopping ART. Severe reactions are also rare, and they most commonly occur when a child develops lipoatrophy or neuropathy from prolonged d4T use.
    - In case of moderate reactions, consider continuation of ART as long as feasible; if the patient does not improve on symptomatic treatment, consider single drug substitutions.
    - Mild reactions may be bothersome but do not require changes in treatment.
- For mild and moderate reactions, stress the importance of maintaining adherence despite toxicity.
- To reiterate, if life-threatening toxicity develops, *all* ARVs should be stopped until the patient's condition is stabilized.

Several distinct types of adverse effects common with certain ARVs or drug classes have been identified, including:

- adverse haematological events (anaemia, neutropenia and, more rarely, thrombocytopenia) from drug-induced bone-marrow suppression, most commonly due to ZDV treatment;
- mitochondrial dysfunction, primarily seen with the NRTI drugs, including lactic acidosis, hepatic toxicity, pancreatitis and peripheral neuropathy;[5]
- lipodystrophy and metabolic abnormalities, primarily seen with d4T and ritonavir-boosted PIs, as well as with certain other NRTIs;[6] and
- allergic reactions such as skin rashes and hypersensitivity reactions, more common with the NNRTIs but also seen with certain NRTIs, such as ABC.

[4] Brief details of toxicity for specific drugs can be found on the Children's HIV Association web site (http://www.bhiva.org/chiva) under the relevant name.
[5] NRTIs differ in their ability to affect mitochondrial function, with d4T having greater toxicity than ZDV, and 3TC or ABC having less.
[6] Abnormalities include fat maldistribution, particularly peripheral lipoatrophy associated with d4T and ZDV, and body habitus changes; hyperlipidaemia; hyperglycaemia, insulin resistance and diabetes mellitus; and osteopenia, osteoporosis and osteonecrosis.

5.4.1. Clinical signs of ARV toxicity and its management

Table 6. Signs of ARV toxicity and its management

Clinical manifestations	Laboratory abnormalities	Toxicity management
Acute serious adverse reactions		
Acute symptomatic hepatitis (NNRTIs – particularly NVP, more rarely EFV – NRTIs and PIs)		
Jaundice Liver enlargement Gastrointestinal symptoms Fatigue, anorexia Hypersensitivity (rash, fever, systemic symptoms), usually within 6–8 weeks Lactic acidosis (see below) if secondary to an NRTI	Elevated aminotransferase levels Elevated bilirubin	Discontinue all ARVs until symptoms resolve. Monitor aminotransferase and bilirubin levels. If the patient is on NVP, it should be discontinued and not re-administered. Once symptoms resolve, either: • change to an alternative ARV (required for NVP regimens); or • restart the ART regimen with close observation; if symptoms recur, substitute an alternative ARV (see Table 7).
Acute pancreatitis (NRTIs, particularly d4T and ddI, more rarely 3TC)		
Severe nausea and vomiting Severe abdominal pain Lactic acidosis (see below)	Elevated pancreatic amylase Elevated lipase	Discontinue all ARVs until symptoms resolve. Monitor serum pancreatic amylase and lipase. Once symptoms resolve, restart ART with an alternative NRTI, preferably without pancreatic toxicity (see Table 7).
Hypersensitivity reaction (ABC, NVP)		
ABC: acute onset of respiratory and gastrointestinal symptoms, including fever, fatigue, myalgia, nausea, vomiting, diarrhoea, abdominal pain, pharyngitis, cough, dyspnoea; rash (usually mild); progressive worsening of symptoms soon after receiving ABC dose, usually within 6–8 weeks NVP: systemic symptoms of fever, myalgia, arthralgia, hepatitis, with or without rash[c]	Elevated aminotransferase levels Elevated eosinophil count	Immediately discontinue all ARVs until symptoms resolve. NVP and ABC should *not* be re-administered to the patient in future. Once symptoms resolve, restart ART with an alternative ARV for ABC or NVP (see Table 7).
Lactic acidosis (NRTIs, particularly d4T)		
Generalized fatigue and weakness Gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia and/or sudden unexplained weight loss) Hepatitis or pancreatitis (see above) Respiratory features (tachypnoea and dyspnoea) Neurological symptoms (including motor weakness)	Increased anion gap Lactic acidosis (symptoms may continue or worsen despite discontinuing ART) Elevated aminotransferase levels Elevated CPK Elevated LDH	Discontinue all ARVs until symptoms resolve. Once symptoms resolve, restart ART with an alternative NRTI that has lower mitochondrial toxicity risk (e.g. ABC or ZDV) (see Table 7).

Clinical manifestations	Laboratory abnormalities	Toxicity management
Severe rash/Stevens–Johnson syndrome (NNRTIs, particularly NVP, less commonly EFV)		
Rash during first 6–8 weeks *Mild-to-moderate rash*: erythematous, maculopapular, confluent, most often on the body and arms; no systemic symptoms *Severe rash*: extensive rash with moist desquamation, angio-oedema or serum sickness-like reaction; or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema, conjunctivitis Life-threatening Stevens–Johnson syndrome or toxic epidermal necrolysis	Elevated aminotransferase levels	For mild or moderate rash, continue ART without interruption but under close observation. For severe or life-threatening rash, discontinue all ARVs until symptoms resolve. NVP should *not* be readministered to the patient. Once symptoms resolve, restart ART with an alternative ARV for NVP (see Table 7 below). (Note: most experts would not change to another NNRTI if the patient experienced severe or life-threatening Stevens–Johnson syndrome from NVP.)
Severe life-threatening anaemia (ZDV)		
Severe pallor, tachycardia Significant fatigue Congestive heart failure	Low haemoglobin	If refractory to symptomatic treatment (e.g. transfusion), discontinue ZDV only and substitute another NRTI (see Table 7 below).
Severe neutropenia (ZDV)		
Sepsis/infection	Low neutrophil count	If refractory to symptomatic treatment (e.g. transfusion), discontinue ZDV only and substitute another NRTI (see Table 7 below).
Chronic late serious adverse reactions		
Lipodystrophy/metabolic syndrome (d4T, PIs)		
Fat accumulation and/or loss in distinct regions of the body: • increased fat around the abdomen, buffalo hump, breast hypertrophy; and • fat loss from limbs, buttocks and face Insulin resistance, including diabetes mellitus Potential risk for later coronary artery disease	Hypertriglyceridaemia Hypercholesterolaemia Low HDL levels Hyperglycaemia	Do not prescribe d4T. Substitution of an NNRTI for a PI may decrease serum lipid abnormalities.
Severe peripheral neuropathy (d4T, ddI; more rarely 3TC)		
Pain, tingling, numbness of hands or feet; refusal to walk Distal sensory loss Mild muscle weakness and areflexia	None	Stop only the suspected NRTI and substitute an NRTI not associated with neurotoxicity (see Table 7). Symptoms may take several weeks to resolve.

Source: WHO *(30)*

5.4.2. ARV substitution in first-line regimens due to toxicity

Given the limited number of ARV options, drug substitutions should be limited to situations where toxicity is severe or life-threatening (see Table 6). Substitution with PIs because of toxicity should be avoided if possible.

Table 7. ARV substitution options in first-line ART

First-line ARV	Most frequent significant toxicities	Suggested first-line ARV drug substitution
ABC	Hypersensitivity reaction	ZDV
ZDV	Severe anaemia or neutropenia[a]	ABC
	Lactic acidosis	ABC
	Severe gastrointestinal intolerance[b]	ABC
EFV	Persistent and severe central nervous system toxicity[c]	NVP
	Teratogenicity (avoid in adolescent girls in first-trimester pregnancy or who have childbearing potential but do not receive adequate contraception)	
NVP	Acute symptomatic hepatitis[d]	EFV[e]
	Hypersensitivity reaction	NRTI substitution preferred, giving a triple NRTI (*Note*: may be less potent); or PI substitution (*Note*: premature start of second-line ARV)
	Severe or life-thr eatening rash (Stevens–Johnson syndrome)[f]	

[a] Defined as a severe, possibly life-threatening haematological abnormality that is refractory to supportive therapy.
[b] Defined as a severe, refractory gastrointestinal intolerance that prevents ingestion of the ARV regimen.
[c] Defined as severe central nervous system toxicity such as persistent hallucinations or psychosis.
[d] Symptomatic NVP-associated hepatic toxicity is very rare in HIV-infected children prior to adolescence.
[e] EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to post-pubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active without adequate contraception.
[f] Severe rash is defined either as an extensive rash with desquamation, angio-oedema or serum sickness-like reactions, or a rash with constitutional findings such as fever, oral lesions, blistering, facial oedema or conjunctivitis. Stevens–Johnson syndrome can be life-threatening. For life-threatening rash, most clinicians would not substitute EFV due to the possibility of NNRTI-class toxicity.

5.5. Monitoring adherence

As there is evidence that adherence to HAART predicts the virological and clinical response to treatment *(23, 43, 44)*, monitoring it is essential. Monitoring adherence should be seen as a team responsibility of the patient, caregiver and health care workers. Intervention strategies include:

- It is important to monitor and assess adherence at each visit, for example by using a simple questionnaire, and between visits by telephone or letter as needed
- using pill boxes, reminders, alarms, pagers or timers
- using patient education aids, including pictures and calendars
- patient support groups or one-on-one counselling
- directly observed treatment (DOT)
- adherence checklist for caregivers
- discussing potential adherence constraints with caregivers

When children are 8–10 years old at diagnosis, adherence may improve in contrast to younger children. The age, maturity and social circumstances of the children should be taken into consideration, and communication should occur in a language and at a level they can understand.

Children's support groups can be helpful, in which children come to the hospital and play (educational) games together. They learn they are not the only ones with HIV, while their caregivers also have the opportunity to talk with each other.

5.6. Nutritional and growth monitoring

Systematic evaluation of nutritional status and related symptoms is critical to early identification of malnutrition and poor growth, and it should be part of routine clinical monitoring of HIV-infected infants and children.

- For infants, nutritional evaluation should occur monthly and other children every three months, and includes:
  - mode of feeding[7]
  - frequency, duration or quantity taken
  - adequacy of supply
  - bowel and urine habits
  - reported problems *(56).*
- Children should be measured and weighed at each visit assessment:
  - use the same scale at each visit
  - measure length of babies supine
  - measure length of children >2 years standing
  - measure head circumference to obtain greatest
  - gender and age specificity should be taken into consideration
  - plot growth parameters on chart.
- If the child requires particular attention due to growth problems or special nutritional require ments it should be performed more often *(56).*

5.7. Developmental assessment

It is important to assess and continue to monitor the development of cognitive, motor, language and social skills of infants and young children as a significant proportion of them show early and marked delays in these areas that may be important early indicators of HIV disease progression *(57, 58).*

- A developmental assessment should be conducted at each visit.
- The assessment should include cognitive, motor, language and social skills.
- Discuss the infant's milestones and verify that the child is developing appropriately for age.
- Use the developmental chick list or observe the infant during the examination (see Annex 4) *(56).*

The primary aim is early detection of developmental weaknesses in order to facilitate intervention to prevent and/or reduce the impact of severe problems.

[7] The WHO Regional Office for Europe recommends infant formulae feeding; when this is not available exclusive breast-feeding is an alternative.

IV. Prevention and management of major opportunistic infections

The optimal management of children with HIV infection requires attending to more than just ART. Children with very low CD4 counts for their age are the most at risk for OIs. When considering prophylactic treatment in a newly presenting and severely immunosuppressed child, the first priority is to start effective ART to restore the immune response. For children who have failed multiple ART regimes and have very low CD4 counts, whether or not they are currently on ART, appropriate OI prophylaxis is extremely important.[8]

1. Tuberculosis

Tuberculosis (TB) represents a significant threat to child health, and HIV infection increases susceptibility to infection with *M. tuberculosis* and the risk of rapid progression to TB disease. Please refer to Protocol 4, *Management of tuberculosis and HIV coinfection*, for recommendations regarding identification of TB/HIV in infants and children, and clinical management of TB/HIV in children.

2. Disseminated mycobaceteriosis other than TB (DMOT)

DMOT is associated with severe immunosuppression and a CD4 count <50 cells/mm^3. Ninety per cent of cases are due to *Mycobacterium avium* complex (MAC). Median survival for children is six months from diagnosis. Such cases should be discussed with an HIV paediatrician.

2.1. Prophylaxis

DMOT can be prevented by giving all children with a CD4 count <50 azithromycin 20 mg/kg as a single weekly dose (to a maximum of 600 mg).

2.2. Diagnosis

Clinical features usually include prolonged fever, bone marrow suppression, weight loss and chronic gastrointestinal symptoms. In patients with DMOT, MAC may be isolated from the lungs, or acid-fast bacilli (AFB) may be detected in the stools or bone marrow. Radiological presentation can occur as enlarged hilar lymph nodes.

2.3. Treatment

Treatment involves a complex multidrug regime of ciprofloxacin, rifabutin and clarithromycin and is valid for all ages. Rifabutin is not available in a liquid formulation, but a suspension (10 mg/ml in cherry or simple syrup) can be formulated from the contents of capsules (60).

If the clinical presentation is suspected then mycobacterial blood cultures should be taken using the special bottles available from microbiology. Mycobacterial stool cultures should also be taken. Treatment for DMOT is shown in Table 8.

Table 8. Treatment of DMOT

Antimicrobial Agent	Dose	Frequency	Route	Duration
ciprofloxacin	30 mg/kg	BID (twice daily) (max dose 750 mg)	PO (orally)	6 months
+				
rifabutin	10–20 mg/kg	OD (once daily) (max dose 300 mg/day)	PO	
+				
clarithromycin*	7.5 mg/kg	BID (max dose 500 mg)	PO	

* If clarithromycin is not available, it can be substituted with ethambutol, 15 mg/kg OD, PO.

[8] Much of this section is based on or taken directly from *Treating Opportunistic Infections In HIV-Infected Children Guidelines for the Children's HIV Association* (CHIVA) *(59)*, with the permission of the authors and CHIVA. More details of the prevention and management of opportunistic infections in infants and children can be found on the Children's HIV Association website (http://www.bhiva.org/chiva/protocols/supportdocs/CHIVA-presubmissionAug06.pdf).

Be aware of possible complex drug interactions, especially with rifabutin. For possible drug interactions and management strategies please refer to www.druginteraction.org.

3. *Pneumocystis jirovecii* pneumonia

PCP is one of the most common categories of HIV-associated OIs, occurring in about 40–50% of children reported to have HIV infection. It has also been identified as the leading cause of death in infants with HIV infection and accounts for 50–60% of AIDS diagnoses in infants *(61, 62)*. PCP is most common in children under one year old (72% of children presenting with PCP) *(63)*, for whom chemoprophylaxis of PCP is recommended.

3.1. Prophylaxis

Prophylaxis with cotrimoxazole (trimethoprim-sulfamethoxazole, or TMP-SMZ) (see Table 9) is recommended for:

- all HIV-exposed infants, starting at 4–6 weeks of age and continuing until HIV infection can be excluded by virological testing (younger than 18 months of age in non-breastfeeding infants) or serological testing (18 months and older); and
- all children under one year old with documented HIV infection, regardless of symptoms or CD4 percentage.

Once initiated, prophylaxis should be continued until age 5, when discontinuing may be considered in accordance with the recommendations for adults and adolescents.

Table 9. Cotrimoxazole (TMP-SMZ) formulations and dosage for HIV-infected

Recommended once-daily dosage[a]	**Suspension** (5 ml syrup, 40/200 mg)	**Paediatric tablet** (20/100 mg)	**Single-strength adult tablet** (80/400 mg)	**Double-strength adult tablet** (160/800 mg)
<6 months 20/100 mg	2.5 ml	1 tablet	¼ tablet, possibly mixed with feeding[b]	–
6 months–5 years 40/200 mg	5 ml[c]	2 tablets	½ tablet	–
6–14 years 80/400 mg	10 ml[c]	4 tablets	1 tablet	½ tablet
>14 years 160/800 mg	–	–	2 tablets	1 tablet

[a] Some countries may use weight bands to determine dosage. The following table is from the CHAP trial:

Age	**Weight**
<6 months	<5 kg
6 months–5 years	5–15 kg
6–14 years	15–30 kg
>14 years	>30 kg

[b] Splitting tablets into quarters is not considered best practice. It should be done only if syrups are not available.
[c] Children of these ages (6 months–14 years) may be able to swallow crushed tablets.
Source: adapted from WHO *(64, 65)*.

After successfully treating an acute episode of PCP, it is necessary to continue secondary prophylaxis with cotrimoxazole on a long-term basis to prevent recurrence. It may be discontinued when the patient's CD4 count remains stable for at least three months.

3.2. Diagnosis

The clinical features of PCP are tachypnoea, dyspnoea, cough, hypoxia and low-grade fever. The onset may be insidious over one or two weeks with slowly increasing tachypnoea. Coughing is not usually prominent until the full clinical picture develops with severe dyspnoea. Physical findings are usually limited to fine crepitations. Fever is often low grade. A rapidly progressive course of disease leading to respiratory failure in a few days has also been described. The classic chest X-ray may be normal or hyperinflated early in the disease, but there is usually rapid development of complete opacification with air bronchograms. The alveolar infiltrates progress peripherally with late apical sparing and small pleural effusions reported. Occasionally bullae, cysts or pneumothorax may be seen.

In infants, bronchoscopy with bronchoalveolar lavage (BAL) is now the optimal method for diagnosing PCP. BAL can be done using an 8F nasogastric feeding tube in intubated children who may not tolerate bronchoscopy. If BAL cannot be performed immediately, then start cotrimoxazole treatment first (positive results can be obtained up to 48 hours after starting treatment). The microbiology laboratory should be informed prior to BAL, as it is very important to make a definitive diagnosis even after commencing treatment.

3.3. Treatment

See Table 9 above for the recommended initial treatment of PCP.

- After the acute pneumonitis has resolved, children with mild-to-moderate disease who do not have malabsorption or diarrhoea can receive treatment with the dose of TMP-SMZ 60 mg/kg every 12 hours, IV, once the child is on oral feeding (around the second week of treatment) administer treatment PO for a total of a 21-day course.
- If there is failure to respond to cotrimoxazole, or an allergic reaction, second-line treatment should be undertaken (see Table 10).
- In case of failure to respond to cotrimoxazole, repeated BAL or lung biopsy should be considered.
- Cytomegalovirus (CMV) is frequently found in BAL with PCP infection, but ganciclovir should only be used for children with PCP and CMV if they are not responding to standard PCP therapy.
- In case of a moderate and severe PCP, oral prednisolone might be an option: 2mg/kg 1 week, 1 mg/kg 1 week, 0.5mg/kg 1 week.

TABLE 10. SECOND-LINE TREATMENT

Antimicrobial agent[a]	Dose	Frequency	Route	Duration
pentamidine isethionate	4 mg/kg/day	OD	Pentamidine isethionate slow infusion IV for 14–21 days	14–21 days
or:				
dapsone	2 mg/kg (max. 100 mg)	OD	PO	21 days

[a] Atovoquone or clindamycin might also be a choice, however only limited data exists regarding its use in children.

4. Bacterial infections (non-mycobacterial)

Serious bacterial infections are very common among HIV-positive children. The frequency of bacterial infection increases with HIV disease progression and immunosuppression. The commonest organisms are *encapsulated Streptococcus pneumoniae and Haemophilus influenzae. Staphylococcus* aureus and gram-negative infections, especially *Pseudomonas aeruginosa*, are seen more commonly in children with severe HIV infection *(63)*.

4.1. Diagnosis

The clinical presentation of acute bacterial pneumonia in children with early HIV infection is similar to that in non-infected children: the commonest clinically diagnosed infection is acute pneumonia and primary septicaemia. The clinical signs may be less obvious in children with HIV. It is always important to obtain blood cultures. Ear infections and throat infections are very common. Sinusitis should be particularly sought for, either by clinical signs or sinus X-rays.

4.2. Treatment

A child with clinical evidence of an acute lower respiratory tract infection (fever, cough, raised respiratory rate, chest signs or CXR changes) should be treated promptly and empirically with broad-spectrum antibiotics (oral co-amoxiclav or IV ceftriaxone). The choice of oral or intravenous antibiotics depends on the patient's clinical condition. If there is a poor response to treatment add azithromycin (10 mg/kg OD for 5 days) and consider BAL. Generally, treatment regimes should be long (10–14 days).

5. Toxoplasmosis

Toxoplasma encephalitis should be considered in all HIV-infected children with new neurologic findings. Although focal findings are more typical, the initial presentation can be variable and reflect diffuse central nervous system (CNS) disease.

5.1. Prophylaxis

PCP prophylaxis also provides prophylaxis against toxoplasmosis. Atovoquone may also provide protection. Severely immunosuppressed children (with CD4 cell count <100/mm^3) who are not receiving TMP-SMZ or atovoquone and are found to be seropositive for *Toxoplasma* should be administered prophylaxis for both PCP and toxoplasmosis (i.e. dapsone plus pyrimethamine) (see Table 11).

Indication for prophylaxis prevention in Table 11 is IgG antibody-positive for *Toxoplasma* and severe immunosuppression (CD4 <15%).

Table 11. Prophylaxis to prevent first episode of toxoplasmosis

Antimicrobial agent	Dose	Frequency	Route	Duration
First line treatment				
cotrimoxazole	960 mg/m^2	OD	PO	Until CD4 >200 mm^3
Alternative				
dapsone	2 mg/kg (max 25 mg)	OD	PO	Until CD4 >200 mm^3
+				
pyrimethamine	1 mg/kg	OD	PO	
+				
folic acid	5 mg	Every 3 days	PO	
Or				
atovoquone	age 1–3 months 30 mg/kg	OD	PO	Until CD4 >200 mm^3
	age 4–24 months 45 mg/kg	OD	PO	
	age >24 months 30 mg/kg	OD	PO	

5.2. Diagnosis

A presumptive diagnosis of *Toxoplasma* encephalitis is based on clinical symptoms, serologic evidence of infection, and the presence of a space-occupying lesion on imaging studies. Clinical symptoms include motor and speech disturbances, often accompanied by headache, altered mental status, and fever. Children can also present with seizures, cranial nerve abnormalities, visual field defects, sensory disturbances, cerebellar dysfunction, meningismus and movement disorders *(66)*. Manifestations of extracerebral toxoplasmosis in HIV-infected children include ocular toxoplasmosis, which occurs most often in association with *Toxoplasma* encephalitis necessitating neurologic examination. Patients with chorioretinitis present with blurred vision, pain or photophobia *(67)*.

Children who are infected latently with *Toxoplasma gondii* have variable IgG titres and rarely possess IgM antibody. Although seroconversion and fourfold increase in IgG antibody titers may occur, the ability to diagnose active disease is commonly impaired by immunosuppression. IgM antibodies typically disappear a few months after infection but can remain elevated for more than 1 year confounding the differentiation of acute and remote infection *(68)*.

Additional investigations to support the diagnosis of *Toxoplasma* encephalitis include (where available) CT scanning of the brain that might indicate multiple, bilateral, hypodense, focal ring-enhancing lesions especially in the basal ganglia and cerebral corticomedullary junction in 70-80% of patients *(69)*. Magnetic resonance imaging is more sensitive and will confirm basal ganglia lesions in most patients *(70)*. Although toxoplasmic encephalitis can occasionally cause a single brain lesion on MRI, such a finding suggests an alternative diagnosis (primarily CNS lymphoma and tuberculoma) *(71)*.

Definitive diagnosis of *Toxoplasma* encephalitis requires histologic confirmation by brain biopsy, and can be considered when early neurologic deterioration is present despite empiric treatment or in children who fail to respond to anti-*Toxoplasma* therapy after 10–14 days. If lumbar puncture is not contraindicated, PCR of CSF should also be considered. Ocular toxoplasmosis is diagnosed on the basis of observation of characteristic retinal lesions in conjunction with serum specific antibodies.

5.3. Treatment

Acute induction therapy should be followed by chronic suppressive therapy (see Table 12).

Table 12. Treatment of acquired toxoplasmosis: acute induction therapy

Antimicrobial agenta	Dose	Frequency	Route	Duration
pyrimethamine *then*	2 mg/kg/day (max: 50 mg)	OD	PO	3 days
pyrimethamine +	1 mg/kg (max: 25 mg)	OD	PO	At least 6 weeks
sulphadiazine +	25-50 mg/kg (max:1.0-1.5 g/dose)	QID (four times daily)	PO	
Folic acid	10-25 mg	OD	PO	

6. Fungal infections

6.1. Candidiasis

6.1.0.1. Prophylaxis

Immune reconstitution with ART accompanied by a reduction in plasma HIV viraemia is the best intervention to reduce the rate of candida colonization and clinical disease *(72, 73)*. Other useful interventions include good oral hygiene, avoidance of unnecessary antibiotics and steroids, and specific antifungal medications. Continuous prophylactic anticandida therapy is rarely indicated, and may result in the emergence of resistant and refractory infections *(74)*. Universal primary antifungal prophylaxis is therefore not currently recommended and the indications for secondary prophylaxis should be individualized.

6.1.1. Oropharyngeal candidiasis (OPC)

6.1.1.1. Diagnosis

OPC has variable clinical manifestations: pseudomembranous (thrush), erythematous (atrophic), hyperplastic (hypertrophic) and angular cheilitis. Thrush is the most classic form of oral candidiasis, appearing as creamy white curd-like patches with inflamed underlying mucosae that are exposed after removal of the exudates. It can be found on the oropharyngeal mucosae, palate and tonsils. Erythematous OPC manifests as flat erythematous lesions on the mucosal surface. Hyperplastic candidiasis is composed of raised white plaques appearing on the lower surface of the tongue, palate and buccal mucosa and cannot be removed. Angular cheilitis occurs as red, fissured lesions in the corners of the mouth.

Diagnosis of oral candidiasis can be made by a KOH preparation and culture with microscopic demonstration of budding yeast cells in wet mounts or biopsy specimens. For recurrent or refractory OPC, cultures with in vitro susceptibility testing can be used to guide antifungal treatment *(75)*.

6.1.1.2. Treatment

Table 13. Treatment options for children with oropharyngeal candidiasis

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Fluconazole	3–6 mg/kg (max: 400 mg/day)	OD	PO	7–14 days
Alternative				
Itraconazole cyclodextrin oral solution *Or* Amphotericin B oral suspension	2.5 mg/kg (max: 200 mg/day) 1 ml (100 mg/ml)	BID QID	PO PO	7–14 days 14 days

6.1.2. Oesophageal candidiasis

6.1.2.1. Diagnosis

This condition can present with odynophagia, dysphagia or retrosternal pain, which can be severe enough to cause dehydration and weight loss in children. Although oropharyngeal candidiasis is common, evidence of it may be absent among children with oesophageal candidiasis, particularly those receiving HAART. Unlike infected adults, a substantial number of children with the condition may experience nausea and vomiting.

Oesophageal candidiasis has a classic cobblestone appearance on barium swallow. In refractory symptomatic cases, endoscopy should be performed to rule out other causes of refractory oesophagitis (HSV, CMV, MAC and azole-resistant *Candida* species). Endoscopies may show anything from a few small white raised plaques to elevated confluent plaques with hyperaemia and extensive ulceration.

6.1.2.2. Treatment

Table 14. Treatment options for children with oesophageal candidiasis

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Fluconazole *then* Fluconazole	6 mg/kg/day 3–6 mg/kg/day (max: 400 mg/day)	OD	PO PO	Day 1 14– 21 days
Alternative				
Itraconazole cyclodextrin oral solution *Or* Amphotericin B	paediatric dosage: 2.5 mg/kg or 5.0 mg/kg 0.3–0.5 mg/kg/day	BID OD OD	PO PO IV	At least 14–21 days At least 7 days

6.1.3. Candidaemia

6.1.3.1. Diagnosis

A new-onset fever in an HIV-infected child with advanced disease and a central venous catheter is the most common clinical manifestation of candidaemia. Systemic fungaemia can lead to endogenous endophthalmitis, and ocular examination by an ophthalmologist may be warranted among children with candidaemia. Diagnosis is best made with blood cultures using lysis-centrifugation techniques *(76)* or automated broth-based systems *(77)*. When fungaemia is present, retinal examination for endophthalmitis, abdominal CAT or ultrasound for hepatic or renal involvement, and bone scans for clinically suspected osteomyelitis may be appropriate.

6.1.3.2. Treatment

Primary prophylaxis of candidiasis in HIV-infected infants/children is not indicated.

Table 15. Treatment options for children with invasive candidiasis

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Fluconazole If failure to respond: Amphotericin B	10 mg/kg/day 250 mcg increased by 250 mcg to 1 mg/kg	OD OD or alternate day	IV IV	21 days 14 days
Alternative				
Amphotericin B lipid complex (Abelcet)	3 mg/kg	OD given over two hours	IV	2–3 weeks

7. Viral infections

7.1. Cytomegalovirus (CMV)

7.1.1. Prophylaxis

Severely immunocompromised children with HIV/CMV coinfection should have a dilated retinal examination performed every 4–6 months. Prophylaxis for children has not been well established and used.

Prophylaxis with oral ganciclovir or valganciclovir can be considered for HIV-infected adolescents who are CMV-seropositive with CD4 cells count of <50 cells/mm3 (see Table 16) but must be balanced with the risks of (val)ganciclovir-induced neutropenia, anaemia, conflicting reports of efficacy, lack of proven survival benefit, risk for emergence of ganciclovir-resistant CMV, and cost. Neither aciclovir nor valaciclovir should be used for CMV infection.

Table 16. Prophylaxis for severely immunosuppressed adolescents *(78)*

Antimicrobial agent	Dose[a]	Frequency	Route	Duration
Valganciclovir	900 mg	BID	PO	21 days
Maintenance phase Ganciclovir	900 mg	OD	PO	3–6 months

[a] There are presently no paediatric doses available

There are no data to guide decisions concerning discontinuation of secondary prophylaxis (chronic maintenance therapy) in children with treated CMV disease, but it is reasonable to consider stopping when there are sustained T-cell responses to ART.

7.1.2. Diagnosis

In HIV-infected children, CMV infection may be difficult to differentiate from active CMV disease. Because of transplacental transfer of antibodies from mother to child, a positive CMV antibody assay in an infant under 12 months old is indicative of maternal infection but not necessarily infection of the infant. In a child older than 12 months, a positive CMV antibody assay indicates previous infection with CMV but not necessarily active disease. At any age, a positive CMV culture is indicative of infection, but not necessarily of disease. CMV disease is rare in HIV-infected children, but it does occur in children with severe immunosuppression, in whom the common clinical manifestations include CMV retinitis (with white fluffy exudates), hepatitis and colitis.

CMV can be isolated in cell cultures from peripheral blood leukocytes, body fluids and body tissues. Using centrifuge-assisted shell vial culture amplification techniques, CMV can be detected within 16–40 hours of culture inoculation. A positive blood buffy-coat culture establishes a diagnosis of CMV viraemia and increases the likelihood that CMV disease or symptoms are caused by CMV, because children with positive blood cultures are at higher risk for developing end-organ disease.

Different methods have been used to detect CMV antigen or DNA directly and identify patients at risk for development of CMV disease, including detection of pp65 antigenaemia, qualitative and quantitative PCR and DNA hybridization. The DNA assays are more sensitive than buffy-coat or urine cultures for detecting CMV and can be used to identify patients at higher risk for developing clinically recognizable disease. CMV DNA detection in CSF by DNA PCR is highly sensitive for CMV disease. Quantitative DNA PCR can be used as a marker of risk for disease and to monitor response to therapy *(77)*.

7.1.3. Treatment

Table 17. Treatment of CMV infection

Antimicrobial agenta	Dose	Frequency	Route	Duration
First line treatment				
Induction phase Ganciclovir	5 mg/kg	every 12 hours	IV	7 days
Maintenance phase Ganciclovir	5 mg/kg	OD	IV	2–3 weeks

7.2. Varicella-zoster virus

7.2.1. Prophylaxis

Immunosuppressed HIV-infected children who are susceptible to varicella-zoster virus[9] (VZV) should avoid exposure to people with chicken pox or shingles. For the prophylaxis of chicken pox, HIV-infected patients susceptible to VZV should be administered varicella-zoster immunoglobulin (VZIg) as soon as possible, ideally within 96 hours after any close contact with chicken pox or shingles.

There are no data on the effectiveness of aciclovir for preventing chicken pox in HIV-infected children or adults.

7.2.2. Diagnosis

The diagnosis of VZV infection is often suspected from the clinical presentation A generalized severe pruritic vesicular rash and fever is diagnostic. Lesions appear first and are most numerous on the trunk, neck, and face. The vesicles contain fluid, rest on an erythematous base and ulcerate and dry to form crusts and scabs. Lesions during chronic VZV infection are varicelliform at onset but may evolve into non-healing, necrotic and crusted ulcers that become hyperkeratotic *(79)*.

The classical clinical presentation of zoster (a painful localized cutaneous vesicular eruption along one or more contiguous dermatomes) is diagnostic. Lesions evolve over 1 to 2 days to form vesicles, pustules, and crusts. In HIV-infected patients, zoster may be bullous, haemorrhagic, necrotic, and particularly painful. Blisters and crusts usually last 2–3 weeks, although necrotic lesions may last up to 6 weeks and heal with severe scarring. Zoster in HIV-infected children may also present as an atypical rash that extends beyond dermatomal boundaries or is bilaterally distributed or generalized or as multiple episodes of a disseminated rash more similar in appearance to chickenpox than zoster *(80)*.

Varicella pneumonitis in HIV-infected children is associated with severe pulmonary manifestations resulting in hypoxaemia and diffuse reticulo-nodular densities on radiography. Encephalitis occurs more frequently with zoster in the ophthalmic distribution, and cerebellar findings are typical; prominent symptoms include ataxia, tremors, and dizziness. Cerebral involvement results in fever, headache, vomiting and lethargy *(81)*.

Direct immunofluorescence expressed on the surface of infected cells from scrapings obtained from the base of skin, conjunctiva, or mucosal lesions allow VZV antigen detection, and is the diagnostic procedure of choice. Direct and indirect immunofluorescence or immunoperoxidase methods can also detect antigen in VZV-infected cells in tissue sections of lung, liver, brain, or other organs.

[9] Susceptible patients are those who have no history of chicken pox or shingles or who have no detectable VZV antibody.

7.2.3. Treatment

Table 18. Treatment of varicella-zoster infection

Infection	Antimicrobial agent[a]	Dose	Frequency	Route	Duration
Varicella	*Children with moderate or sever immune suppression, high fever or necrotic lesions*				
	Acyclovir	10–20 mg/kg	TID (three times daily)	IV	7 days after no new lesions
	Children with mild immune suppression and mild oral disease:				
	Acyclovir	20 mg/kg (max: 200 mg/dose)	QID	PO	7 days after no new lesions
Zoster	***Children with severe immune suppression, trigeminal nerve involvement or extensive multidermatomal zoster IV***				
	Aciclovir	10–20 mg/kg	TID	IV	7–10 days
	Children with mild immune suppression and mild oral disease				
	Aciclovir	20 mg/kg (max: 200 mg/dose)	QID	PO	7–10 days
For patients not responding to acyclovir[a]					
	Foscarnet	40–60 mg/kg	TID	IV	7–10 days

[a] Valaciclovir is approved for use in adult and adolescents with zoster at a dose of 1 gram PO BID 7–10 days; data on dosing in children is limited.

7.3. Herpes simplex virus (HSV)

7.3.1. Prophylaxis

HIV-infected children with severe oral recurrences (more than 3–6 severe episodes a year) or previous disseminated disease may benefit from prophylaxis with oral acyclovir *(82)*.

7.3.2. Diagnosis

Neonatal HSV can appear as disseminated multi-organ disease (occurring in approximately 25% of neonates with HSV infection), localized disease of the CNS (approximately 35% of infected neonates) or localized disease of the skin, eyes and mouth (approximately 40% of infected neonates) *(83)*. Vesicular rash is present in approximately 80% of children with localized skin, eye or mouth disease, but only in approximately 60% of children with CNS or disseminated disease *(84, 85)*.

Outside of the neonatal period, the most common appearance of HSV infection in children is orolabial disease. Fever, irritability, tender submandibular lymphadenopathy and superficial, painful ulcers in the gingival and oral mucosae and perioral area characterize primary HSV gingivostomatitis. HIV-infected children who experience primary infection when they are immunocompromised can have severe local lesions or, more rarely, disseminated HSV with visceral involvement and generalized skin lesions with primary infection. Other sites of involvement among severely immunocompromised HIV-infected children include the oesophagus, CNS and genitals and disseminated disease in the liver, adrenals, lungs, kidneys, spleen and brain.

Among children with suspected HSV encephalitis, detection of HSV DNA by PCR is the diagnostic test of choice *(86)*. CSF cultures for HSV are usually negative. Definitive diagnosis of HSV oesophagitis requires endoscopy with biopsy (histological evidence of multinucleated giant cells with intranuclear viral inclusion) and culture.

7.3.3. Treatment

Table 19. Treatment of HSV disease

Condition	Antimicrobial agenta	Dose	Frequency	Route	Duration
Skin, eye and mouth disease	Acyclovir	20 mg/kg	TID	IV	14 days (63)
Disseminated HSV disease or encephalitis		20 mg/kg or 500 mg/m^2	TID	IV	21days
Symptomatic HSV gingivostomatitis		5–10 mg/kg *Or* 20 mg/kg	TID TID	IV PO	7–14 days 7–14 days
Alciclovir-resistant HSV infection					
	Foscarnet	120 mg/kg/day	2–3 divided doses over 1–2 hours (administer slowly over 2 hours or no faster than 1 mg/kg/min.)	IV	Until the infection resolves

Aciclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA PCR assay is negative at day 19–21 of treatment.

Because episodes of HSV disease can be treated successfully, chronic therapy with aciclovir is not required after lesions resolve. However, people with frequent or severe recurrences can be administered daily suppressive treatment with oral aciclovir or valaciclovir.

V. Paediatric HIV pain management

1. Background

Pain in children with HIV AIDS is a multifactor, biologically complex problem associated with diminished quality of life and increased mortality *(87)*. Pain elimination, pain amelioration and (when appropriate) palliative administration of analgesics and sedatives are essential aspects of the care of every HIV-infected child.

Despite advances in the treatment and control of HIV infection in children, pain may still complicate medical management and diminish quality of life for some children with advanced disease. Because pain in this population is often complex, optimal management will best be achieved through the coordinated collaboration of several specialists, including anaesthesiologists, pain specialists, social workers, nursing staff and others.

Patients with pain are more than five times more likely to die than those who do not report pain. Pain is also associated with lower CD4 cell percentages and more severe immunosuppression *(88)*.

2. Pain management strategies

Pain management in HIV-infected children should combine pharmacological and non-pharmacological therapies. The latter include:

- relaxation techniques and behaviour modification;
- environmental management: play, music, scheduled medical and nursing interventions, and structured time for sleep and rest;
- gentle handling and supportive positioning;
- nutritional support, adequate hydration and electrolyte replacement;
- optimized tissue perfusion and oxygenation;
- transcutaneous electrical nerve stimulation (TENS), gentle massage, whirlpool baths and physical therapy; and
- electrical or needle stimulation of acupuncture meridians by HIV-knowledgeable practitioners *(88, 89)*.

VI. Suggested minimum data to be collected at the clinical level

The suggested minimum data to be collected is important in the development of key indicators on access to diagnosis and treatment and their success. Such indicators assist managers in decision making on ways to strengthen and expand these services to all who need them.

The following data should be collected at each clinical facility on a regular basis (e.g. monthly, quarterly or semi-annually):

- number of infants <18 months of age born to HIV-infected mothers;
- number of infants <18 months of age born to HIV-infected mothers and have had PCR testing;
- number of HIV diagnosed infected infants <18 months of age;
- number of infants ≥18 months of age born to HIV-infected mothers
- number of infants ≥18 months of age born to HIV-infected mothers and have had only serological HIV testing;
- number of HIV-infected infants ≥18 months of age diagnosed only serologically;
- number of HIV-infected children (<15 years old) seen for care who are eligible for HAART;
- number of HIV-infected children(<15 years old) seen for care and receiving first-line HAART regimen;
- number of HIV-infected children(<15 years old) on HAART changing from first-line HAART to second-line HAART;
- number of HIV-infected children(<15 years old) interrupting HAART, including the reasons (e.g. death, toxicity/side effects, loss to follow-up, ARVs not available, etc.);
- number of HIV-infected children who died while on HAART, including cause of death (e.g.HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, etc.);
- number of HIV-infected children who died within first 12 months of initiating HAART;
- number of death among all HIV infected children including cause of death (e.g. HIV/AIDS related mortality or non-HIV/AIDS related mortality such as accident, etc).

Annex 1. Revised WHO clinical staging of HIV/AIDS for infants and children

Revised WHO clinical staging of HIV/AIDS
for infants and children
(Interim European Region version for people <15 years old
with confirmed laboratory evidence of HIV infection –
HIV antibody test if ≥18 months old, virological or p24 antigen test if <18 months)

Clinical Stage 1
- Asymptomatic
- Persistent generalized lymphadenopathy (PGL)

Clinical Stage 2
- Hepatosplenomegaly
- Papular pruritic eruptions
- Extensive molluscum contagiosum
- Fungal nail infections
- Recurrent oral ulcerations
- Lineal gingival erythema (LGE)
- Angular cheilitis
- Parotid enlargement
- Herpes zoster
- Asymptomatic lymphocytic interstitial pneumonitis (LIP)
- Recurrent or chronic respiratory tract infections (otitis media, otorrhoea, sinusitis)

Clinical Stage 3
- Moderate unexplained malnutrition not adequately responding to standard therapy
- Unexplained persistent diarrhoea (14 days or more)
- Unexplained persistent fever (intermittent or constant, for longer than one month)
- Oral candidiasis (excluding first two months of life)
- Oral hairy leukoplakia
- Acute necrotizing ulcerative gingivitis or periodontitis
- Lineal gingival hyperplasia
- Severe recurrent presumed bacterial pneumonia
- Extensive and confluent warts
- Giant disfiguring molluscum
- Chronic HIV-associated lung disease, including bronchiectasis
- Symptomatic lymphocytic interstitial pneumonitis (LIP)
- Unexplained anaemia (<8 g/dl) and/or neutropenia (<500/mm^3)
- Unexplained thrombocytopenia (<50 000/mm^3) for more than one month

Clinical Stage 4
- Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy
- Recurrent severe presumed bacterial infections (e.g. empyema, pyomyositis, bone or joint infection or meningitis, but not pneumonia)
- Chronic herpes simplex infection (orolabial or cutaneous and of more than one month's duration)
- Extrapulmonary TB
- Kaposi sarcoma
- Oesophageal candidiasis
- CNS toxoplasmosis (after the neonatal period)
- HIV encephalopathy
- CMV infection (CMV retinitis or infection of organs other than liver, spleen or lymph nodes; onset at age one month or more)
- Extrapulmonary *Cryptococcus*, including meningitis
- Any disseminated endemic mycosis (e.g. extrapulmonary histoplasmosis, coccidiomycosis, penicilliosis)
- Cryptosporidiosis
- Isosporiasis

continued on next page

- Disseminated non-tuberculous mycobacteria infection
- Candida of trachea, bronchi or lungs
- Visceral herpes simplex infection
- Acquired HIV-associated rectal fistula
- Cerebral or B-cell non-Hodgkin lymphoma
- Progressive multifocal leukoencephalopathy (PML)
- HIV-associated cardiomyopathy or HIV-associated nephropathy[a]
- Leiomyosarcoma and other HIV-related solid tumours

[a] WHO is seeking further information and evidence relating to the occurrence and definitions of these conditions.
Source: WHO Regional Office for Europe *(90)*.

Annex 2. WHO classification of HIV-associated immunodeficiency in infants and children

Table 20. Classification of HIV-associated immunodeficiency

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤11 months (%)	12–35 months (%)	36–59 months (%)	≥5 years[a] (cells/mm^3)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–29	20–24	15–19	200–349
Severe	<25	<20	<15	<200 or <15%

[a] Including adolescents and adults.
Source: WHO *(30).*

Annex 3. ARV dosage ranges

Table 21. ARV DOSAGE RANGES

Surface area (m^2)		Weight range (kg)		Abacavir			Didanosine (twice daily)			Efavirenz		Lamivudine			Nelfinavir		
				Formulation	DOSE (ml or tablets)		Formulation	Dose (ml or tablets)		Formulation	Dose (capsules, tablets)	Formulation	Dose (ml, tablets)		Formulation	Dose (tablets)	
Bottom	Top	Bottom	Top		AM	PM		AM	PM	Age 3 years and above. Dose given ONCE daily			AM	PM		AM	PM
0.30	0.34	5.0	5.9	20 mg/ml syrup	2 ml	2 ml	10 mg/ml suspension	4 ml	4 ml			10 mg/ml solution	3 ml	3 ml	250 mg tablets	2	2
							or										
							25 mg chew tablets	2	2								
0.34	0.38	6.0	6.9	20 mg/ml syrup	3 ml	3 ml	10 mg/ml suspension	5 ml	5 ml			10 mg/ml solution	3 ml	3 ml	250 mg tablets	2	2
							or										
							25 mg chew tablets	2	2								
0.38	0.40	7.0	7.9	20 mg/ml syrup	4 ml	4 ml	10 mg/ml suspension	6 ml	6 ml			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	2
							or										
							25 mg chew tablets	2	2								
0.40	0.43	8.0	8.9	20 mg/ml syrup	4 ml	4 ml	10 mg/ml suspension	6 ml	6 ml			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	3
							or										
							25 mg chew tablets	2	2								
0.43	0.45	9.0	9.9	20 mg/ml syrup	4 ml	4 ml	10 mg/ml suspension	6 ml	6 ml			10 mg/ml solution	4 ml	4 ml	250 mg tablets	3	3
							or										
							25 mg chew tablets	2	2								
0.45	0.49	10	10.9	20 mg/ml syrup	5 ml	5 ml	10 mg/ml suspension	6 ml	6 ml	200 mg capsule	1	10 mg/ml solution	5 ml	5 ml	250 mg tablets	3	3
							or										
							25 mg chew tablets	3	2								
0.49	0.53	11	11.9	20 mg/ml syrup	5 ml	5 ml	10 mg/ml suspension	7 ml	7 ml	200 mg capsule	1	10 mg/ml solution	5 ml	5 ml	250 mg tablets	3	3
				or			or										
				300 mg tablets	0.5	0.5	25 mg chew tablets	3	3								
0.53	0.58	12	13.9	20 mg/ml syrup	6 ml	6 ml	10 mg/ml suspension	7 ml	7 ml	200 mg capsule	1	150 mg tablet	0.5	0.5	250 mg tablets	4	4
				or			or										
				300 mg tablets	0.5	0.5	25 mg chew tablets	3	3								
0.58	0.70	14	16.9	300 mg tablets	0.5	0.5	10 mg/ml suspension	8 ml	8 ml	200 mg capsule + 50 mg capsule	1 + 1	150 mg tablet	0.5	0.5	250 mg tablets	4	4
							or										
							25 mg chew tablets	4	3								
0.70	0.80	17	19.9	300 mg tablets	0.5	0.5	10 mg/ml suspension	9 ml	9 ml	200 mg capsule + 50 mg capsule	1 + 1	150 mg tablet	0.5	0.5	250 mg tablets	5	5
							or								or		
							25 mg chew tablets	4	4						625 mg tablets	2	2
0.80	0.95	20	24.9	300 mg tablets	1	0.5	25 mg chew tablets	5	5	200 mg capsule + 100 mg capsule	1 + 1	150 mg tablet	1	0.5	250 mg tablets	5	5
															or		
															625 mg tablets	2	2
0.95	1.10	25	29.9	300 mg tablets	1	1	25 mg chew tablets	5	5	200 mg capsule + 100 mg capsule + 50 mg capsule	1 + 1 + 1	150 mg tablet	1	1	250 mg tablets	5	5
															or		
															625 mg tablets	2	2
1.10	1.20	30	34.9	300 mg tablets	1	1	25 mg chew tablets	5	5	200 mg capsule	2	150 mg tablet	1	1	250 mg tablets	5	5
															or		
															625 mg tablets	2	2
		35	39.9				25 mg chew tablets	5	5	200 mg capsule	2				250 mg tablets	5	5
															or		
															625 mg tablets	2	2
		40	and over							200 mg capsule	3						
										or							
										600 mg tablet	1						

				Nevirapine (maintenance)			Stavudine			Zidovudine			Lopinavir/ritonavir		
Surface area (m^2)		Weight range (kg)		Formulation	DOSE (ml or tablets)		Formulation	Dose (ml or tablets)		Formulation	Dose (ml or capsules)		Formulation	Dose (ml, capsules or tablets)	
Bottom	Top	Bottom	Top		AM	PM		AM	PM		AM	PM		AM	PM
0.30	0.34	5.0	5.9	10 mg/ml syrup	6 ml	6 ml	1 mg/ml syrup	6 ml	6 ml	10 mg/ml syrup	6 ml	6 ml	80 mg lop/20mg rit per ml solution	1 ml	1 ml
0.34	0.38	6.0	6.9	10 mg/ml syrup	7 ml	7 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	7 ml	7 ml	80 mg lop/20mg rit per ml solution	1.5 ml	1.5 ml
0.38	0.40	7.0	7.9	10 mg/ml syrup	8 ml	8 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	8 ml	8 ml	80 mg lop/20mg rit per ml solution	1.5 ml	1.5 ml
													or		
													133 mg lop/33 mg rit per capsule	1	1
0.40	0.43	8.0	8.9	10 mg/ml syrup	9 ml	9 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	9 ml	9 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
										or			or		
										100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.43	0.45	9.0	9.9	10 mg/ml syrup	9 ml	9 ml	20 mg capsule	0.5	0.5	10 mg/ml syrup	9 ml	9 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or						or			or		
				200 mg tablets						100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.45	0.49	10	10.9	10 mg/ml syrup	10 ml	10 ml	15 mg capsule	1	1	10 mg/ml syrup	10 ml	10 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or						or			or		
				200 mg tablets	0.5	0.5				100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.49	0.53	11	11.9	10 mg/ml syrup	10 ml	10 ml	15 mg capsule	1	1	10 mg/ml syrup	10 ml	10 ml	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or						or			or		
				200 mg tablets	0.5	0.5				100 mg capsules	1	1	133 mg lop/33 mg rit per capsule	1	1
0.53	0.58	12	13.9	10 mg/ml syrup	11 ml	11 ml	15 mg capsule	1	1	100 mg capsules	1	1	80 mg lop/20mg rit per ml solution	2 ml	2 ml
				or									or		
				200 mg tablets	0.5	0.5							133 mg lop/33 mg rit per capsule	2	1
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.58	0.70	14	16.9	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsules	2	1	80 mg lop/20mg rit per ml solution	2 ml	2 ml
										or			or		
										300 mg tablets	0.5	0.5	133 mg lop/33 mg rit per capsule	2	1
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.70	0.80	17	19.9	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsules	2	1	80 mg lop/20mg rit per ml solution	2.5 ml	2.5 ml
										or			or		
										300 mg tablets	0.5	0.5	133 mg lop/33 mg rit per capsule	2	1
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.80	0.95	20	24.9	200 mg tablets	1	0.5	20 mg capsule	1	1	100 mg capsules	2	2	80 mg lop/20mg rit per ml solution	3 ml	3 ml
										or			or		
										300 mg tablets	0.5	0.5	133 mg lop/33 mg rit per capsule	2	2
													or		
													200 mg lop/50 mg rit per tablet	1	1
0.95	1.10	25	29.9	200 mg tablets	1	1	30 mg capsule	1	1	100 mg capsules	2	2	80 mg lop/20mg rit per ml solution	3.5 ml	3.5 ml
										or			or		
										300 mg tablets	1	0.5	133 mg lop/33 mg rit per capsule	2	2
													or		
													200 mg lop/50 mg rit per tablet	2	1
1.10	1.20	30	34.9	200 mg tablets	1	1	30 mg capsule	1	1	100 mg capsules	3	3	80 mg lop/20mg rit per ml solution	4 ml	4 ml
										or			or		
										300 mg tablets	1	1	133 mg lop/33 mg rit per capsule	3	3
													or		
													200 mg lop/50 mg rit per tablet	2	2
		35	39.9										80 mg lop/20mg rit per ml solution	5 ml	5 ml
													or		
													133 mg lop/33 mg rit per capsule	3	3
													or		
													200 mg lop/50 mg rit per tablet	2	2
		40	and over										80 mg lop/20mg rit per ml solution	5 ml	5 ml
													or		
													133 mg lop/33 mg rit per capsule	3	3
													or		
													200 mg lop/50 mg rit per tablet	2	2

Source: WHO *(27)*.

Annex 4. Developmental assessment checklist

Table 22. Developmental assessment checklist

Age	Developmental milestones	Date Accomplished
1 month	Raises head Crawling movement Alerts to sound	
2 months	Holds head at midline Lifts chest off table Smiles socially	
4 months	Rolls front to back Laughs	
6 months	Sits unsupported Babbles	
9 months	Pulls to stand Says “mama”	
12 months	Walks alone Uses a couple of words together	
18 months	Can remove some clothing Scribbles Uses 6 or more words together Runs	
24 months	Can wash hands Jumps up Combines words	
36 months	Begins to dress (puts on shirt) Understandable speech Able to balance on one foot	
48 months	Dresses alone Draws a person Uses complex speech Hops	

Source: Adapted from Abrams, El-Sadr, Rabkin *(56)*.

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EUROPE

12 Immunization of People Living with HIV and People at Risk of HIV Infection

Clinical Protocol for the WHO European Region

Contents

I. Introduction

This protocol is based on the global WHO recommendations for vaccinating people who are HIV-infected. At the same time, it reflects the epidemiological situation and immunization programme priorities of the WHO European Region. This protocol diverts from global recommendations regarding the use of bacille Calmette-Guérin (BCG) vaccine, oral poliovirus vaccine (OPV) and measles-containing vaccines (MCVs) including measles, mumps and rubella (MMR) vaccine. It also provides additional recommendations on the vaccines and immunoglobulins used outside the routine national immunization programmes.

This protocol is designed primarily for HIV/AIDS clinicians. It is recommended as a basis for developing national recommendations that take into account local epidemiological situations.

II. General principles for the immunization of PLHIV

As HIV infection results in a progressive deterioration of the immune system, there has been concern that some vaccines could result in severe adverse events in HIV-infected individuals.

Since no immunobiological product is completely safe, general recommendations for vaccinating infants, children and adults are based on:
- the characteristics of immunobiological products
- scientific knowledge of the principles of active and passive immunization
- the epidemiology of infection
- the risk and benefits of achieving optimal protection against infectious disease.

Until further research can clearly define the risks and benefits, administration of certain vaccines to people living with HIV (PLHIV) should be restricted or administered with caution after a thorough risk assessment by experts in clinical and preventive medicine.

The terms vaccination and immunization are often used interchangeably. Vaccination denotes the physical act of administering an immunobiological product (a vaccine or toxoid) to a person and refers to active immunization. “Immunization” is a more inclusive term denoting the process of inducing or providing immunity artificially, and it can be active or passive.

General principles for vaccination of PLHIV are as follows.
- Killed or inactivated vaccines do not represent a danger to immunocompromised people and generally should be administered as recommended for other people.
- Live-virus or live-bacteria vaccines such as BCG, oral poliovirus, typhoid (Ty21a), varicella and yellow fever vaccines may pose a risk to HIV-infected people, who should not be given them without careful consideration of the risks and benefits, given their individual stage of HIV disease and level of immune suppression.

For further information, please refer to section III below for vaccine-specific considerations and to Annex 1 for a summary of recommendations.

III. Use of vaccines and immunoglobulins

General aspects of immunogenicity of vaccines should be taken into consideration when immunizing PLHIV against vaccine-preventable diseases.

- Although the capacity to mount both cellular and humoral immune response starts declining after birth in HIV-infected neonates, most children still have an immune response capacity during the first two years of life. Studies of the immunogenicity of immunization programmes with recommended vaccines[1] have shown satisfactory seroconversion rates in the early stages of HIV infection. Each vaccine has its own seroconversion rate, some of which can be found in this section. However, the proportion of responders decreases with progression from HIV infection to AIDS *(1)*.
- Symptomatic HIV-infected children and adults have suboptimal immunologic responses to vaccines *(1–5)*. The response to both live and killed antigens may decrease as the HIV disease progresses *(1)*. However, the response to higher doses of vaccine and the persistence of antibodies in HIV-infected patients have not been systematically evaluated. Although higher doses or more frequent boosters may be considered for such patients, firm recommendations cannot be made at this point.

Specific considerations for the safety[2] and efficacy of individual vaccines and immunoglobulins include the epidemiology of the particular disease and the patient's level of immunosuppression.

The degree to which a patient is immunocompromised should be determined by a physician, using the WHO clinical staging system[3] and/or age-specific CD4 counts and percentages (see Annex 2).

1. Live attenuated vaccines

1.1. BCG vaccine

BCG vaccine protects children younger than 2 against disseminated and severe tuberculosis (TB), including TB meningitis and miliary TB. BCG has little or no effect in reducing the number of adult cases of pulmonary tuberculosis.

It is not known if HIV infection reduces the protection conferred by BCG in children. There is some evidence that conversion to a positive tuberculin test after BCG is less frequent in HIV-infected children *(6)*, but the significance of this finding is not clear. There have been case reports of local complications and disseminated BCG infection, even years after vaccinating HIV-infected children. However, prospective studies comparing BCG immunization in HIV-infected and uninfected infants have shown no difference in risk for complications *(6)*. There needs to be closer monitoring for adverse events in areas of high HIV prevalence, with specific efforts to distinguish BCG infection from TB *(7)*.

[1] BCG vaccine; diphtheria, tetanus and pertussis (DTP) vaccine; OPV; MMR vaccine; hepatitis B vaccine; and HiB vaccine.
[2] It should be noted that the safety information on administration of certain vaccines to PLHIV is limited, and that countries are encouraged to report any encountered adverse events following immunization (AEFIs) to their pharmacovigillance or AEFI surveillance systems, keeping in mind that some AEFIs may occur with large latency in PLHIV.
[3] For clinical staging, refer to Protocol 1, *Patient evaluation and antiretrovital treatment for adults and adolescents*, Annex 2, and Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 1.

Until further research can clearly define the risks and benefits of BCG vaccination, it should be restricted to asymptomatic children (due to its potential to cause disseminated disease) who are at high risk of tuberculosis infection *(8, 9)*, which in turn depend on the local prevalence of TB.[4] Where the risk is high, the possible benefits of BCG immunization outweigh the possible disadvantages.

1.1.1. Recommendations

- Where TB incidence is low,[5] BCG should not be administered to HIV-infected children, regardless of their clinical stage or immunodeficient status. In all other areas, BCG vaccination should be restricted to HIV-positive children who are asymptomatic. Children with symptoms of HIV infection should not receive BCG vaccine.
- BCG is not recommended for adolescents and adults, including those with HIV infection, because it has little or no effect in reducing the number of adult cases of pulmonary tuberculosis *(6)*.
- TB preventive therapy should be strongly recommended for PLHIV thought to be infected with *Mycobacterium tuberculosis* and at risk of developing TB (for further information, please refer to Protocol 4, *Management of tuberculosis and HIV coinfection)*.

1.2. Cholera vaccine (CVD 103-HgR)

1.2.1. Recommendations

- Live, attenuated oral cholera vaccine (using CVD 103-HgR strain) is contraindicated in HIV-infected people due to insufficient safety data *(11)*.
- The killed WC/rBs cholera vaccine is the recommended vaccine for HIV-infected people (see section III.2.1. below for cholera vaccine WC/rBs).

1.3. Measles, mumps and rubella vaccines (MMR, MR, M and R vaccines[6])

HIV-infected asymptomatic children or children with signs of mild immunosuppression should routinely receive MMR and other measles-containing vaccines (MCVs), the same as non-infected children. It is important to remember that immunogenicity of measles vaccine is decreased if the vaccine is administered in a period less than six months after human normal immunoglobulin (HNIg) administration.

Although studies among both asymptomatic and symptomatic HIV-infected patients immunized with MMR vaccine and other MCVs have not documented any serious or unusual adverse events *(1)*, they are not recommended for PLHIV with evidence of severe immunosuppression. The lack of a recommendation is primarily due to:

- a report of a pneumonia case following measles vaccine in an individual with severe HIV-related immunosuppression *(12)*;
- other evidence indicating a diminished antibody response to measles vaccination among severely immunocompromised people *(13)*; and
- evidence linking measles vaccine viral infection to subsequent death in at least six severely immunocompromised people *(14)*.

1.3.1. Recommendations

- MMR and other MCVs should not be administered to PLHIV, either children or adults, who show evidence of severe immunosuppression. Severe immunosuppression is defined as CD4 <200 cells/mm^3 in adults and children ≥5 years, for severe immunosuppression in children younger than 5 years, see Annex 2 *(15–17)*.

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[4] It should be noted that even among countries with a generally low prevalence of TB, there may be high prevalence in given subpopulations, making a subnational policy desirable.

[5] Countries in the WHO European Region with a crude notification rate of <20 per 100 000 population are defined as low-incidence *(10)*.

[6] MMR: measles, mumps and rubella; MR: measles and rubella; M: measles; R: rubella.

- MMR and other MCVs should be considered for HIV-infected patients who are asymptomatic or mildly immunosuppressed, as per the routine national schedule.
- For infants with high risk of exposure to measles virus, an additional dose of single-antigen measles vaccine administered at 6–11 months of age is recommended, followed by a first dose of routine MMR or another measles-containing vaccine (MCV) at age 12 months or older (with a minimum interval of 1 month between doses).
- HIV-infected symptomatic patients who are exposed to measles should receive HNIg regardless of their prior vaccination status (see section III.3.2.1 below for further information on HNIg).
- Healthy susceptible close contacts of immunocompromised people (including PLHIV) should also be vaccinated.

1.4. Oral poliovirus vaccine (OPV)

Although asymptomatic HIV-infected children may be vaccinated with OPV *(1, 18)*, data show that administration of OPV to children with congenital immunodeficiency can result in severe, progressive neurological involvement (paralytic disease) *(19–22)*. Therefore, inactivated poliovirus vaccine (IPV) is recommended for both symptomatic and asymptomatic children (see section III.2.9 below for IPV).

In addition, persons immunized with OPV can shed vaccine virus into their environment for up to one month, consequently, HIV-positive individuals should have limited contact with persons vaccinated with OPV. If OPV is inadvertently administered to a household member or other close contact[7] of an HIV-infected individual, regardless of prior immunization status, close contact between them should be avoided for one month post-vaccination.

1.4.1. Recommendation

- OPV should not be administered to PLHIV, either children or adults, regardless of their immunodeficiency status, or to members of their household or other close contacts.

1.5. Rotavirus vaccine

1.5.1. Recommendation

- Rotavirus vaccine should not be administered to children infected with HIV regardless of their immunodeficiency status, until more scientific evidence can clarify the safety and immunogenicity profile in HIV-infected children.

1.6. Typhoid (Ty21a) vaccine

While live attenuated typhoid vaccine (using the Ty21a strain) can be administered to HIV-infected asymptomatic individuals without risk as long as the CD4 cell count >200 cells/mm^3, parenteral inactivated vaccine is theoretically a safer alternative *(23)*.

1.6.1. Recommendation

- Ty21a vaccine should not be administered to PLHIV, either children or adults, regardless of their immunodeficiency status.

1.7. Varicella vaccine

Although a recent small study indicated no serious adverse events for 10 HIV-infected children *(24)*, people with moderate or severe cellular immunodeficiency resulting from HIV, including those diagnosed with AIDS, should not receive varicella vaccine. However, children with asymptomatic or mildly symptomatic HIV infection and a CD4 cell count ≥25% should receive the vaccine at 12–15 months of age or later, with a second dose 4–8 weeks after the first. Varicella vaccine should not be administered to HIV-infected children with CD4 cell count <25% because of the potential dissemination of viral infection *(23)*.

[7] Defined as someone who risks transmitting live poliomyelitis vaccine virus to an HIV-infected person through faecal or oral contact.

HIV-infected children and adults who are susceptible to varicella-zoster virus (VZV) – including those who have no history of chickenpox (primary varicella infection), those who have shingles (recurrent infection) and those who are seronegative – should avoid exposure to people with chickenpox or shingles.

Susceptible household contacts (especially children) of PLHIV should be vaccinated with varicella vaccine if they have no history of chickenpox and are seronegative for HIV, so that they will not transmit the virus to their HIV-infected contacts that may be susceptible to VZV *(14)*.

1.7.1 Recommendations

- Varicella vaccine should not be administered to HIV-infected adults, regardless of their immunodeficiency status, or to HIV-infected children with moderate or severe immunosuppression.
- Varicella vaccination should be restricted to children with asymptomatic or mildly symptomatic HIV infection (CD4 levels ≥25%).
- Susceptible household contacts of PLHIV should be vaccinated to prevent possible transmission of VZV.

1.8. Yellow fever vaccine

Yellow fever vaccine virus poses a theoretical risk of encephalitis to HIV-infected people, who should thus not be given it. Yellow fever is endemic to 33 countries in equatorial Africa and 11 countries in South America. If travel to such an area is necessary, patients should be advised on the risks, instructed in methods of avoiding mosquitoes and supplied with vaccination waiver letters by their physicians. Some travel clinics may decide whether or not to administer the vaccine on the basis of a person's CD4 cell count.

People who are known to be HIV-infected and who cannot avoid potential exposure to yellow fever virus should be offered the choice of vaccination. Vaccinees should be monitored for possible adverse reactions. Since vaccination may be less effective for HIV-positive people than for HIV-negative people, measuring neutralizing antibody responses before travel may be considered. Family members of immunosuppressed people may also be vaccinated against yellow fever if there are no contraindications *(25)*.

1.8.1 Recommendation

- Yellow fever vaccine should not be administered to people infected with HIV, either children or adults, regardless of their immunodeficiency status, unless benefits exceed risks.

2. Killed or inactivated vaccines

Killed or inactivated vaccines do not present a danger to immunocompromised people and generally should be administered as recommended for other people *(17)*. Frequently, the immune response of immunocompromised people to killed and inactivated vaccine antigens is not as good as that of immunocompetent people; higher doses or more frequent boosters may be required, although even with these modifications, the immune response may be less than optimal.

2.1. Cholera vaccine (WC/rBs)

A vaccine consisting of killed whole-cell *Vibrio cholerae* O1 combination with a recombinant B-subunit of cholera toxin (WC/rBs) has been shown to be safe even in pregnancy and during breastfeeding, and well tolerated by HIV-positive individuals.

Given orally according to a two-dose schedule, 10–14 days apart induces initial protection in 86% of the vaccinees. On average, the vaccine confers 50–60% protection for at least 3 years.
There have been no specific reports of WC/rBs vaccine efficacy in HIV-positive individuals published to date but a recent study conducted in Mozambique demonstrated promising results in a

population in which approximately 25% were HIV-positive. Duration of immunity is unknown in HIV-infected people. HIV-infected adults with CD4 counts <100 cells/mm^3 may be expected to respond poorly to immunization, whereas those with CD4 counts >100 cells/mm^3 show improved responses after two doses *(26)*. These observations indicate a potential benefit of vaccination in those with early and moderately advanced clinical HIV disease *(27)*.

2.1.1 Recommendations

- Vaccination should be considered for selected HIV-infected people if they are due to travel to highly endemic areas, fall in one of the risk groups (long-term travellers and for those who drink untreated water, eat poorly cooked or raw seafood, or live in unsanitary conditions in disease-endemic areas).
- Owing to its low efficacy and short duration of protection, use of old parenteral vaccine (based on inactivated phenol-killed whole-cell V. *cholerae* O1) is not recommended, although this vaccine is still produced in some countries *(28)*.

2.2. Diphtheria, tetanus and pertussis vaccines (DTP, DTaP, DT, TT and Td[8])

2.2.1 Recommendations

- For children infected with HIV, irrespective of their immune status, DTP (and DT) vaccine is indicated on the same schedule and dosage as for non-HIV-infected children, including the use of the acellular pertussis form (DTaP) for boosters or the primary series.
- TT and Td vaccines can be administered to HIV-infected adults irrespective of their immune status, using the same schedule and dose as for non-HIV-infected adults *(25)*.
- Special attention should be paid to vaccinating IDUs with TT or Td to prevent tetanus where there are no needle or syringe exchange programmes.

2.3. *Haemophilus influenzae* type b (HiB) vaccine

In general, children older than 2 years do not need HiB vaccination, due to age-dependent susceptibility to the disease *(11)*. In some people the organism causes an invasive infection. The exact mode of invading the bloodstream is unknown, but previous viral or mycoplasmal infection of the upper respiratory tract may be a contributing factor. The bacteria spread via the bloodstream to distant sites in the body, the meninges in particular. HIV-infected children and adults are at increased risk for invasive HiB disease due to immunosuppression and should therefore be vaccinated.

Individual patient risk for the disease and benefits from vaccination should be considered before deciding whether to vaccinate. In some settings, the incidence of HiB disease may be higher among HIV-infected adults than non-HIV-infected adults *(29, 30)*.

2.3.1 Recommendations

- Previously unvaccinated HIV-infected individuals older than 2 years who are at risk for invasive HiB should be given at least one dose of vaccine.
- Immunocompromised children should be vaccinated with the same dosage and schedule as immunocompetent children.

2.4. Hepatitis A vaccine

The risk of developing symptomatic illness following hepatitis A virus (HAV) infection is directly correlated to age. In children younger than 6, HAV infection is usually asymptomatic, while symptomatic disease occurs more commonly among adults. Infection with HAV induces lifelong immunity. In areas of low endemicity, hepatitis A usually occurs as single cases among people in

[8] DTP: diphtheria and tetanus toxoids and pertussis vaccine; DTaP: diphtheria and tetanus toxoids and acellular pertussis vaccine; DT: diphtheria and tetanus toxoids (for paediatric use); TT: tetanus toxoid; Td: tetanus and diphtheria toxoids (for adult use).

high-risk groups or as outbreaks involving a small number of people. In areas of high endemicity, most people are infected with HAV without symptoms during childhood. In countries of low or intermediate endemicity, adult disease is seen more often, and hepatitis A may represent a substantial medical and economic burden.

Hepatitis A vaccine is highly immunogenic. More than 95% of adults will develop protective antibodies within four weeks of a single dose. Among children and adolescents, more than 97% will be seropositive within a month of the first dose. In clinical trials, all recipients had protective levels of antibodies after two doses. Therefore, post-vaccination testing is not indicated. Testing methods sufficiently sensitive to detect low HAV antibody concentrations after vaccination are not approved for routine diagnostic use *(14)*.

Data concerning the long-term persistence of antibody and of immune memory are limited because the currently available vaccines have been under evaluation for less than 12 years. The need for booster doses will be determined by future surveillance studies *(31)*.

2.4.1. Recommendations

Hepatitis A vaccination (one dose with a booster 6–12 months later) is strongly recommended for people at risk for HAV infection or its complications, irrespective of their HIV or immune status. Risk groups include:

- people with chronic liver disease;[9]
- men who have sex with men (MSM);
- drug users;[10]
- people with clotting-factor disorders;
- people with occupational risk of infection (e.g. some laboratory workers); and
- people ≥1 year old from non-endemic countries who are travelling to countries with high or intermediate risk of HAV infection.[11]

2.5. Hepatitis B vaccine

While there are no data regarding HIV-infected children and the duration of protection afforded by HBV vaccine, available data for uninfected children show that vaccine-induced antibody levels decline with time *(14)*. Nevertheless, immune memory remains intact for more than 15 years following immunization in both adults and children. Adults and children with normal immune status do not require booster doses, nor is routine serological testing indicated, except for children of hepatitis B surface antigen (HBsAg)-positive mothers, who should be tested for HBsAg and hepatitis B surface antibody (HBsAb) after the third dose. If the surface antibody level is <10 mIU/ml, the entire three-vaccine series should be repeated. Testing for HBV core antibodies in these children is discouraged because passively acquired maternal antibodies may be detectable up to 24 months of age. The need for booster doses after longer intervals will continue to be assessed as additional information becomes available.[12]

[9] Susceptible people with chronic liver disease are at increased risk of fulminant hepatitis A should they become infected. HIV-infected people with evidence of chronic hepatitis C or hepatitis B disease should be vaccinated with hepatitis A vaccine *(14)*.
[10] HAV is present in the blood at the onset of the illness and has on rare occasions been transmitted by transfusion; the virus is more easily spread in areas of poor sanitation or personal hygiene, conditions common among drug users *(14, 23, 32)*.
[11] Vaccinate 2–4 weeks before departure. Areas of high or intermediate risk include all areas of the world except Canada, the United States, western Europe and Scandinavia, Japan, New Zealand and Australia *(33)*.
[12] Only for haemodialysis patients should the need for booster doses be assessed by annual testing for antibody levels; booster doses should be provided when antibody levels go below 10 mIU/ml.

2.5.1. Recommendations

- Hepatitis B vaccination is recommended for adults at increased risk for hepatitis B virus (HBV) infection, irrespective of their HIV or immune status, including:
  - MSM;
  - heterosexuals with multiple partners,
  - sexually transmitted infection (STI) patients;
  - sex workers;
  - sexual partners and household contacts of HBV carriers;
  - IDUs;
  - prison inmates, both male and female;
  - people on haemodialysis (although the hepatitis B vaccine is less effective in them, it is recommended for all susceptible haemodialysis patients); and
  - health care workers.[13]
- Hepatitis B vaccination is recommended for all infants at birth and all children to age 18, irrespective of their HIV or immune status. Various schedules include or exclude neonates, but all have the same effectiveness.

2.5.1.1. Recommended schedule for hepatitis B vaccination in patients infected with HIV

HIV-infected patients lacking HBV infection markers or HBsAg negative markers should be vaccinated.

- Hepatitis B vaccination should start with the conventional dose (20 µg at Months 0, 1, 2 and 12 or Months 0, 1 and 6) for patients with CD4 count >500 cells/mm^3.
- Paediatric dosage of hepatitis B vaccine is 10 µg.
- In patients with CD4 count 200–500 cells/mm^3, an intensive schedule is recommended (20 µg at Months 0, 1, 2 and 12) *(34)*.
- Patients who do not respond to the first cycle should receive booster doses or a new vaccination cycle with 40 µg.
- Patients with CD4 counts <200 cells/mm^3 who are not on antiretroviral treatment (ART) should first receive ART. Vaccination should be deferred until a clinically significant immune reconstitution has been achieved, preferentially after the CD4 cell count has increased >200 cells/mm^3.

2.5.1.2. Response to hepatitis B vaccination

- The response to the vaccine is dependent on the CD4 count at the time of vaccination, and may be reduced in patients with a CD4 count <500 cells/mm^3.
- After the hepatitis B vaccination schedule has been completed, the response rate is 87% in HIV-positive patients with CD4 count >500 cells/mm^3, and only 33% in patients with CD4 count 200–500 cells/mm^3 *(35)*.
- Hepatitis C virus (HCV) /HIV coinfection may be associated with impaired responses to hepatitis B vaccine, with fewer HBsAb titres after the third vaccination than in HIV monoinfection.

2.5.1.3. Recommended monitoring of HIV-infected patients after HBV vaccination

- HBsAb titre should be monitored four weeks after the end of the HBV vaccination schedule, and booster vaccination or revaccination (1–3 additional doses) should be considered for patients who do not develop protective antibodies (HBsAb <10 mIU/ml). However, the immunogenicity of higher doses of vaccine is unknown, and firm recommendations on dosage cannot be made at this time *(15)*.
- People who fail to seroconvert after vaccination and remain at risk of HBV infection should be annually monitored for serological markers of HBV (HBsAg and HBcAb (hepatitis B core antibody)).

[13] Risk is often highest during training periods; therefore, it is recommended that vaccination be completed during training in schools of medicine, dentistry, nursing, laboratory technology and other allied health professions *(14)*.

- People who fail to develop detectable HBsAb after six doses should be tested for HBsAg.
- People who are found to be HBsAg-positive should be counselled accordingly.
- Vaccine non-responders who are HBsAg-negative should be considered susceptible to HBV infection and should be counselled regarding precautions to prevent it and the need to obtain hepatitis B immunoglobulin (HBIg) prophylaxis for any likely parenteral or sexual exposure to HBsAg-positive blood.

2.6. Influenza vaccine[14]

Influenza may result in serious illness and complications for people who are immunocompromised. Vaccination can result in protective antibody levels in many immunocompromised recipients *(36)*.

2.6.1 Recommendations

- Although there is currently little information regarding the frequency and severity of influenza in PLHIV *(37)*, vaccination is recommended for all PLHIV before the annual influenza season.
- The antibody response to vaccine may be low in people with advanced HIV disease; however, it has not been shown that a booster dose improves their immune response *(38)*.

2.7. Meningococcal vaccine

2.7.1 Recommendation

- Routine immunization with meningococcal vaccine containing appropriate serotypes[15] is recommended for all travellers, regardless of HIV status, to areas with epidemic meningococcal disease *(32)*, and for those in high-risk groups, including people with terminal complement component deficiencies and anatomic or functional asplenia *(39)*.

2.8. Pneumococcal vaccine

Two types of pneumococcal vaccine are available: pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugate vaccine (PCV). Pneumococcal vaccine is recommended for use in people with chronic illnesses specifically associated with increased risk of pneumococcal disease or its complications, such as conditions associated with immunosuppression, including HIV infection *(40)*.

2.8.1. Pneumococcal polysaccharide vaccine (PPV)

More than 80% of non-HIV-infected healthy adults who receive PPV develop antibodies to its serotypes within 2–3 weeks. Elevated antibody levels persist for at least five years in healthy adults, but fall more quickly in people with certain underlying illnesses, including HIV infection.

2.8.1.1. Recommendations

- One dose of PPV should be administered routinely, irrespective of HIV and immune status, to:
  - everyone who is older than 65;
  - immunocompetent people who are older than 2[16] and have chronic illness (cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis or cerebrospinal fluid leaks); and
  - immunocompromised people (including PLHIV)[17] who are older than 2 and are at risk for pneumococcal disease.

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[14] Since live influenza vaccine is contraindicated in PLHIV, inactivated influenza vaccine should be used.

[15] The meningococcal vaccine should cover serotypes causing meningococcal disease epidemics in the relevant geographical area. Meningococcal serogroups A, B and C are found worldwide; serogroup Y is found in some parts of the United States; serogroup A is found in the "African meningitis belt" from Senegal to Ethiopia; serogroup W125 is found in Saudi Arabia.

[16] In children <2 years old, antibody response with PPV to most serotypes is generally poor.

[17] Including (in addition to PLHIV) people with splenic dysfunction or absence (from either disease or surgical removal), Hodgkin disease, lymphoma, multiple myeloma, chronic renal failure, nephritic syndrome (a type of kidney failure) or other conditions associated with immunosuppression (such as organ transplantation).

- PPV is recommended in HIV-infected adults with CD4 count of >200 cells/mm^3 and are stable on HAART.
- When CD4 count is <200 cells/mm^3 vaccination may be considered for those with an increased risk for the disease; however, it may be less effective as immune response is decreased. Once HAART has been administered and immune function restored so that CD4 count increases to >200 cells/mm^3, revaccination should be considered.
- If vaccination status is unknown, patients with HIV infection and others with immunosuppression (including those receiving long-term systemic corticosteroids) should be vaccinated *(41)*.
- Routine revaccination of immunocompetent people younger than 65 is not recommended.
- People 65 and older should be given a second dose if they received the vaccine more than five years previously and were younger than 65 at the time. PLHIV and others who are immunocompromised and at highest risk should be given a second dose after five years.
- Revaccination is also recommended for children vaccinated at age 2 or older who are at highest risk for serious infection, and for those with certain underlying illnesses that make them likely to experience a rapid decline in pneumococcal antibody levels. The second dose should be administered 3–5 years after the first, though there is no upper time limit for revaccination after 5 years.

2.8.2. Pneumococcal conjugate vaccine (PCV)

PCV has been shown to be immunogenic in infants and children, including those with HIV infection, regardless of immune status. After four doses of PCV, virtually all healthy infants develop antibodies to all serotypes in the vaccine.[18]

2.6.2.1 Recommendations

- For infants, doses are routinely given at 2, 4 and 6 months of age, and a booster dose is recommended at 12–15 months of age.
- Unvaccinated children 7–11 months old, including those with HIV, should receive two doses of PCV 6–8 weeks apart, followed by a booster at age 12–15 months.
- Unvaccinated children 12–23 months old should receive two doses of PCV, 6–8 weeks apart.
- Unvaccinated healthy children 24–59 months old should receive a single dose of PCV.
- Children 24–59 months old with HIV infection, sickle cell disease, asplenia, chronic illness or immunocompromising conditions should receive two doses of PCV 6–8 weeks apart. In order to improve the booster effect, one dose of PPV 6–8 weeks after the last PCV dose is recommended.
- PCV is not routinely recommended for children older than 5, regardless of HIV status.
- Revaccination after an age-appropriate primary series with PCV is not currently recommended.
- Children 2 and older who receive a primary series of PCV should also have PPV 6–8 weeks after the last dose of PCV.

2.9. Inactivated poliovirus vaccine (IPV)

2.9.1 Recommendations

- In order to prevent transmission of vaccine and/or vaccine-derived polioviruses to PLHIV IPV should be administered to the following people when polio immunization is indicated:
  - infants and children infected with HIV regardless of their immune status;
  - household members or other close contacts; and
  - nursing personnel in close contact with PLHIV.

[18] Presently, there are not much data for PLHIV response to PCV, other than from South Africa and smaller studies in the United States.

- For unvaccinated HIV-infected adults at increased risk of exposure to poliovirus (such as travel to a polio-endemic country), a primary series of IPV is recommended *(25)*.

2.10. Rabies vaccine

Two main types of rabies vaccine are in use: nerve tissue (Semple-type) vaccine and modern cell-derived vaccine.

Immunocompromised HIV-infected people might not develop sufficient immunological response, as immunity depends upon the CD4+ T-cell-dependent neutralizing antibody response to the G protein.

2.10.1. Recommendations

- Rabies vaccines are used for post-exposure protection and pre-exposure immunogenicity. Rabies vaccines are not contraindicated for HIV-infected people and should be administered if indicated (see Annex 3).
- If post-exposure treatment must be given to immunocompromised HIV-positive patients, intramuscular vaccine and rabies immunoglobulin are mandatory, along with serological monitoring of the antibody responses (see section III.3.3 below on rabies immunoglobulin).
- People who have demonstrated less than 0.5 IU/ml neutralizing antibody titres after 4–5 doses of rabies vaccine over four weeks should receive additional doses to achieve the required level *(23)*, as rabies antibody titres >0.5 IU/ml are required for protection.

2.11. Tick-borne encephalitis vaccine

Tick-borne encephalitis, caused by tick-borne encephalitis virus, infections occur in many parts of Europe (Albania, Austria, Croatia, the Czech Republic, Denmark, Estonia, France (Alsace), Germany, Hungary, Latvia, Lithuania, Norway, Poland, the Russian Federation, Slovakia, southern and central Sweden, Switzerland), corresponding to the distribution of the tick reservoir. The disease has been known by several names, including Russian spring-summer encephalitis (RSSE), Far Eastern encephalitis and central European encephalitis (CEE) *(42)*.

Generally risk to the average traveller to affected countries is small. Infections are related to either leisure activities such as hiking, walking and hunting, or working in agriculture and forestry in warm, rural or forested parts of endemic regions. People at risk of infection include foresters, woodcutters, farmers, military personnel, laboratory workers and tourists who camp, hunt and undertake field-work in rural, forested areas.

Pre-exposure prophylaxis is available with the whole virus inactivated vaccines. The standard vaccination schedule consists of 2 doses given over 4–12 weeks apart, followed by a third dose 9–12 months later. In immunocompetent adults, the rate of seroconversion after 3 doses is 85–100%. For those at risk, boosting is recommended every 3 years. The rapid schedules[19] have shown similar efficacy in healthy individuals and are practical for travellers. Whether the rapid vaccination schedule is effective in HIV-infected persons is unknown.

Only two published studies have investigated the immunogenicity of vaccination in HIV-infected patients. These studies suggest that the vaccine is less efficacious in HIV-infected individuals than those not infected with HIV, particularly with a CD4 count <500 cells/mm^3. Although a four-dose vaccination schedule given at 0, 1, 2 and 9–12 months may improve responses in HIV-infected people, evidence in support of this strategy remains limited *(11)*.

[19] For FSME *Immun*: 2 doses 14 days apart as primary course and followed by a third dose 9-12 months later; for *Encepur*: 3 doses on days 0, 7 and 21 as primary course and followed by a fourth dose 12-18 months later.

2.11.1. Recommendations

- Immunization should be considered for HIV-infected people who intend to walk, camp or work in heavily forested regions of affected countries during late spring or summer when the ticks are most active, particularly if staying in areas with heavy undergrowth.
- The vaccine is also recommended for expatriates whose principal area of residence is in an area where tick-borne encephalitis is endemic.
- Either the standard or the rapid vaccination schedule may be considered for HIV-infected people with a CD4 count >400 cells/mm^3.
- In HIV-infected individuals with a CD4 count <400 cells/mm^3, serological testing may be considered one month after the second dose.
- In case of an inadequate antibody response, two further vaccine doses should be given, one immediately and one at 9–12 months after the first dose.
- In the absence of serological testing, a 4-dose vaccination schedule (0, 1, 2 and 9–12 months) should be adopted to improve response rates *(11)*.
- The booster recommendation is the same for HIV-infected individuals as for immunocompetent people.
- Due to the possibility of reduced responses to vaccination in immunocompormised HIV-infected individuals, the importance of protective clothing and insect repellent use should be emphasized.

2.12. Typhoid vaccine (Vi polysaccharide)

HIV-infected people are at increased risk of infection with Salmonella species. In addition, immunodeficiency predisposes patients to bacteraemia, antibiotic resistance, relapsing disease and persistent infection *(11)*.

A parenteral killed vaccine composed of purified Vi polysaccharide *(*from *S. typhi)* has been shown to be moderately (50–80%) effective *(43)*, with one dose administered subcutaneously or intramuscularly. The vaccine confers protection 7 days after injection for at least 2 years. For persons at risk, boosting is recommended every 3 years.

2.12.1. Recommendations

- Owing to low efficacy and high rates of associated adverse events, use of old, heat inactivated whole cell typhoid vaccine is not recommended, although this vaccine is still produced in some countries mainly for economic reasons *(43)*.
- Although not required for international travel, vaccination with the Vi polysaccharide vaccine is recommended for all HIV-infected people who are due to travel to areas in which there is a recognized risk of exposure and who will be intimate with a documented carrier.
- One dose of the vaccine should be given at least 2 weeks before the expected exposure.
- A booster is recommended every 3 years in those who remain at risk, this interval might be considered to be reduced to 2 years, if the CD4 count is <200 cells/mm^3, as typhoid vaccines are not 100% protective and responses may be further reduced in PLHIV.
- Travellers should be advised to follow strict food and drink precautions.

2.13. Other killed antigens

Other vaccines containing killed antigens, including Japanese encephalitis, plague and anthrax, do not pose a risk to PLHIV, regardless of their immunological status.

2.13.1. Recommendation

- These vaccines should be used in the same manner as for non HIV-infected people.

3. Use of immunoglobulins

3.1. Hepatitis B immunoglobulin (HBIg)

Temporary immunity may be obtained using HBIg for post-exposure prophylaxis. HBIg is used for passive immunization of:

- newborn infants of HBsAg-positive mothers;
- people having percutaneous, mucous membrane or sexual exposure to HBsAg-positive blood or body fluids; and
- liver transplant patients.

3.1.1. Recommendations

- Immunocompromised people, including PLHIV, should receive HBIg for the same indications and in the same doses as immunocompetent people.
- As a rule, HBIg should be used as an adjunct to hepatitis B vaccine. All candidates for HBIg are by definition in a high-risk category and should therefore be considered for a concurrent hepatitis B vaccine series.
- The people for whom HBIg is indicated include:
  - premature infants who are born to HBsAg-positive women and women with unknown HBsAg status, and who should receive immunoprophylaxis with hepatitis B vaccine and may receive HBIg[20] at or shortly after birth;
  - infants born to HBsAg-positive mothers, preferably within 12 hours of birth but at a different site from the hepatitis B vaccination;
  - HBsAg-negative people who do not respond to HBV vaccine, and who should be counselled on preventing HBV infection and the need for HBIg prophylaxis against any possible parenteral exposure to HBsAg-positive blood;
  - susceptible sexual contacts of people with acute HBV infection, within 14 days of the last sexual contact;[21]
  - unvaccinated infants whose mothers or primary caregivers have acute HBV infection, in which case the first dose of the hepatitis B vaccine series should also be given;[22] and
  - people who are household contacts of people with acute HBV infection and who have been exposed to the blood of the infected person (for example, by sharing a toothbrush or razor), in which case they should also be given the first dose of the hepatitis B vaccine series.[23]

3.2. Human normal immunoglobulin (HNIg)

3.2.1. Hepatitis A

3.2.1.1. Recommendations

- For the prevention of hepatitis A,[24] HNIg should be administered in the same way to both immunocompromised and immunocompetent people and for the same indications *(25)*. Concurrent administration of HNIg and hepatitis A vaccine does not appear to significantly influence the formation of protective antibodies *(23)*.
- HNIg is indicated to prevent hepatitis A in the following groups of people:
  - people travelling to high-risk areas less than four weeks after an initial dose of hepatitis A vaccine should receive HNIg at a different site from the hepatitis A vaccination;

[20] The protection against perinatally acquired infection achieved by immediate (within 24 hours) hepatitis B vaccination is not significantly improved by the addition of HBIg *(44)*.
[21] If the last sexual contact was more than 14 days prior, hepatitis B vaccination should be initiated, although the amount of protection afforded by post-exposure prophylaxis given this late is not known. HBIg is not recommended in this situation.
[22] HBIg is not needed for infants who have received or are scheduled to receive a second dose of vaccine.
[23] Routine hepatitis B vaccination should also be considered for nonsexual household contacts without blood exposure, especially children and adolescents.
[24] To prevent HAV infection, administration of HNIg is recommended before or within two weeks of HAV exposure. Later administration of HNIg often only attenuates the clinical expression of HAV infection.

  - children younger than 1 travelling to high-risk areas should receive 0.02–0.06 ml/kg, depending on length of stay, since hepatitis A vaccine is not approved for children younger than 1;
  - people exposed to HAV who have not previously received hepatitis A vaccine, who should be given HNIg as soon as possible within two weeks of exposure;
  - people in close contact with a person who has hepatitis A;
  - staff and children at child care centres where a hepatitis A case has been diagnosed; and
  - people in certain common-source exposure situations (for example, patrons of a food establishment with an HAV-infected food handler where the risk of transmission is determined to be high).
- People who received a dose of hepatitis A vaccine at least one month before an exposure do not need HNIg.

3.2.2. Measles

3.2.2.1. Recommendations

- For immunocompromised people (including those with HIV infection), HNIg is indicated to prevent measles following exposure.
- If immediate protection against measles is required for immunocompromised patients with contraindications for measles vaccination, including infants younger than 1, passive immunization with HNIg 0.5 ml/kg of body weight (maximum dose 15 ml) should be administered intramuscularly as soon as possible after exposure.
- Exposed symptomatic HIV-infected patients should receive HNIg regardless of their previous vaccination status, as measles vaccine may not be effective in such patients and the disease may be severe.
- For immunocompromised people receiving HNIg for measles prophylaxis, measles vaccination should be delayed for six months following HNIg administration.

3.3. Human rabies immunoglobulin (HRIg)

3.3.1. Recommendations

- Immunocompromised patients, including those with HIV infection, should receive HRIg for the same indications and in the same doses as immunocompetent patients do.
- HRIg is indicated for Category III contact (single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks), along with the first dose of the rabies vaccine series.
- HRIg treatment is not necessary for people vaccinated against rabies who have demonstrated neutralizing antibody titres of at least 0.5 IU/ml (two intramuscular doses of a cell-derived vaccine separated by three days are sufficient for such cases).
- If post-exposure treatment must be given to an immunocompromised HIV-infected person, HRIg is mandatory, along with the first dose of an intramuscular rabies vaccine series.
- In addition, the antibody responses should be monitored serologically. For further details, see Annex 3.

3.4. Tetanus immunoglobulin (TIg)

3.4.1. Recommendations

- TIg is recommended for people with tetanus and to prevent tetanus in inadequately immunized people with wounds or other conditions associated with tetanus, regardless of their HIV and immune status. TIg neutralizes circulating unbound tetanus toxin. It does not affect toxin that has reached the nervous system.
- Dosage is the same for PLHIV as for others.
- For the treatment of tetanus, a single intramuscular dose of 3000–5000 units is generally recommended for children and adults.
- Indications for TIg are:
  - wounds that are neither clean nor minor in people who have had no more than two prior doses of Td toxoid (vaccine) or who have an uncertain history of TIg immunization, Td toxoids should also be administered;[25]
  - any injury other than a clean minor wound, in combination with a contraindication for tetanus toxoid; or
  - symptoms consistent with tetanus disease.
- Intravenous immunoglobulin (IgIV) contains tetanus antitoxin and may be used if TIg is not available.

3.5. Varicella-zoster immunoglobulin (VZIg)

The most important use of VZIg is for passive immunization of neonates and susceptible severely immunocompromised people, including PLHIV, after significant exposure to chickenpox or zoster. Immunocompromised patients who are exposed to varicella and receive VZIg may have lower rates of complications and infections. The risks of VZIg appear to be negligible, though the cost can be substantial.

3.5.1. Recommendations

- For prophylaxis of chickenpox, susceptible HIV-infected children (those who have no history of chickenpox or shingles or who have no detectable VZV antibodies) should be administered VZIg as soon as possible within 96 hours after close contact with chickenpox or shingles.
- VZIg is also recommended for VZV-susceptible HIV-infected pregnant women within 96 hours after exposure to VZV. If oral aciclovir is used, VZV serology should be performed so that the drug can be discontinued if the patient is seropositive for VZV *(25)*.

[25] Early doses of toxoid do not induce immunity, but only prime the immune system. The TIg provides temporary immunity by directly providing antitoxin, ensuring that a protective level of antitoxin is achieved even if an immune response has not yet occurred.

Annex 1. Summary of immunization recommendations for people immunocompromised due to HIV/AIDS

Table 1. Summary of immunization recommendations for people immunocompromised due to HIV/AIDS[a]

Vaccine/Disease	Infants and children[b]	Adults	Non-routine immunization
Anthrax	—	—	Use if indicated
BCG	Contraindicated/consider[c]	—	Contraindicated
Cholera (CVD 103-HgR)	—	—	Contraindicated
Cholera (WC/rBs)	—	—	Use if indicated
DTP/DTaP/DT	Recommended	—	—
Hepatitis A	—	—	Use if indicated
Hepatitis B	Recommended	Use if indicated	—
HiB	Recommended	Consider[d]	—
Influenza[e]	—	—	Use if indicated
IPV	Recommended	—	Use if indicated
Japanese encephalitis	—	—	Use if indicated
Meningococcal	—	—	Use if indicated
MMR/MR/M/R	Recommended/consider[f]	Consider[f]	—
OPV	Contraindicated	—	Contraindicated
Plague	—	—	Use if indicated
Pneumococcal	—	—	Use if indicated
Rabies	—	—	Use if indicated
Rotavirus	—	—	Contraindicated
Tick-borne encephalitis	—	—	Use if indicated
TT/Td	Recommended	Recommended	—
Typhoid (Ty21a)	—	—	Contraindicated
Typhoid, inactivated	—	—	Use if indicated
Varicella	—	—	Contraindicated/consider[g]
Yellow fever	—	—	Contraindicated

Recommended: the vaccine is either recommended as part of the routine schedule, or HIV immunosuppression indicates its use.
Use if indicated: immunosuppression is not a contraindication unless otherwise indicated.
Contraindicated: HIV immunosuppression is an absolute or relative contraindication to the use of the vaccine.
Consider: the decision to use the vaccine should include consideration of the individual patient's risk of disease and the likely effectiveness of the vaccine.
—: not applicable

[a] Routine and not routine immunization schedules differ from country to country.
[b] Cut off age for infants, children and adults and dosage differs according to vaccine. Check national immunization policies or package insert.
[c] Refer to specific considerations for BCG vaccine in section III.1.1.
[d] Refer to specific considerations for HiB vaccine in section III.2.3.
[e] Note that live influenza vaccines are contraindicated. If influenza vaccine is indicated, use an inactivated one.
[f] Refer to specific considerations for MMR vaccine in section III.1.3.
[g] Refer to specific considerations for varicella vaccine in section III.1.7.

Annex 2. WHO Classification of HIV-associated immunodeficiency in infants and children

Table 2. Classification of HIV-associated immunodeficiency

Classification of HIV associated immunodeficiency	Age-related CD4 values			
	≤11 months (%)	12–35 months (%)	36–59 months (%)	≥5 years[a] (cells/mm^3)
Not significant	>35	>30	>25	>500
Mild	30-35	25-30	20-25	350-499
Advanced	25-29	20-24	15-19	200-349
Severe	<25	<20	<15	<200 *or* <15%

[a] Including adolescents and adults.
Source: WHO *(16)*.

Annex 3. Rabies vaccines

Pre-exposure rabies vaccination may be performed with any of the modern cell-derived vaccines and is recommended for anyone at risk for exposure to rabies virus. Traditionally, this recommendation includes:

- laboratory staff
- veterinarians
- animal handlers
- wildlife officers with frequent exposure to potentially infected animals
- visitors to highly rabies-enzootic areas[26] who may be exposed to rabies hosts.[27]

The pre-exposure schedule of modern cell-derived rabies vaccines requires intramuscular doses of 1 ml or 0.5 ml, depending on the vaccine, given on Days 0, 7 and 28.[28] The indication for post-exposure vaccination with these vaccines (with or without rabies immunoglobulin) depends on the type of contact with the rabid animal.[29] Depending on vaccine type, the post-exposure schedule prescribes intramuscular doses of 1 ml or 0.5 ml given as 4–5 doses over four weeks. For rabies-exposed patients who have previously undergone complete pre-exposure vaccination or post-exposure treatment with cell-derived rabies vaccines, two intramuscular doses of a cell-derived vaccine separated by three days are sufficient. Rabies immunoglobulin treatment is not necessary in such cases. The same rules apply to people vaccinated against rabies who have demonstrated neutralizing antibody titres of at least 0.5 IU/ml.

The human diploid cell rabies vaccine is regarded as the gold standard for cell-derived rabies vaccines.[30] The WHO requirement is a potency of at least 2.5 IU per intramuscular dose for all cell-derived vaccines. Despite the use of potent, modern cell-derived vaccines, about one failure in one million post-exposure treatments does occur. Careful analyses show that such failures are almost always associated with severe lesions on or near the head and/or inappropriate administration of the treatment.

A complete post-exposure treatment using nerve tissue vaccines involves a prolonged and painful immunization course of up to 23 injections. Furthermore, protective potency nerve tissue vaccines are inferior to modern cell-derived vaccines. Obviously, these vaccines are not recommended for pre-exposure immunization.

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[26] More than 2.5 billion people live in regions where rabies is endemic, in Africa, Asia and South America. It is estimated that each year at least 50 000 people die from rabies, and that more than 10 million receive post-exposure vaccination. Children aged 5–15 years are at particular risk *(23)*.

[27] According to age-stratified studies of incidence, those at greatest risk are probably children living in rabies-enzootic regions of the developing world *(23)*.

[28] Major vaccine manufacturers recommend one booster dose after one year, and to ensure protection in people at continued risk, booster vaccinations every five years, or ideally, at intervals dictated by regular testing for rabies antibodies (titres >0.5 IU/ml required for protection).

[29] The types of contact are Category I: touching or feeding animals, or licks on the skin; Category II: nibbling of uncovered skin, minor scratches or abrasions without bleeding, or licks on broken skin; and Category III: single or multiple transdermal bites or scratches, or contamination of a mucous membrane with saliva from licks. For Category I, no treatment is required; for Category II, immediate vaccination is recommended; and for Category III, immediate vaccination and administration of rabies immunoglobulin are recommended, in addition to immediate washing and flushing of all bite wounds and scratches.

[30] Other cell-derived rabies vaccines are vero cell and purified chick embryo cell vaccines. No clinically important differences were observed when these vaccines were evaluated together with human diploid cell vaccines in studies on both post-exposure protection and pre-exposure immunogenicity *(23)*.

Annex 4. Glossary

Active immunity is usually permanent protection produced by a person's own immune system. One way to acquire active immunity is to have the natural disease. In general, once patients recover from infectious diseases, they will be immune to those diseases for the rest of their lives.

Antibodies are proteins that are produced by the immune system in response to specific antigens, thereby helping the body fight infection and foreign substances.

Antigens are substances, foreign to the body, that stimulate the production of antibodies by the immune system. Antigens can either be live (such as viruses and bacteria) or inactivated.

An **antitoxin** is a solution of antibodies (for example, diphtheria antitoxin and botulinum antitoxin) derived from the serum of animals immunized with specific antigens. Antitoxins are used for conferring passive immunity and for treatment and are usually permanent.

An **asymptomatic HIV-infected person** is one with a confirmed HIV diagnosis but with no clinical signs or symptoms of the infection, corresponding to WHO Clinical Stage 1. (For staging, see Protocol 1, *Patient evaluation and antiretrovital treatment for adults and adolescents*, Annex 2, and Protocol 11, *Paediatric HIV/AIDS treatment and care*, Annex 1).

A **contraindication** is a condition in a recipient that greatly increases the likelihood of a serious adverse reaction that could seriously harm the recipient. In general, vaccines should not be administered when a contraindicated condition is present.

An **immune response** is the defence that the immune system develops against antigens. It usually involves the production of protein molecules, antibodies (or immunoglobulins), and of specific cells (also known as *cell-mediated immunity*) whose purpose is to facilitate the elimination of foreign substances.

The **immune system** is a complex system of interacting cells whose primary purpose is to identify foreign substances referred to as antigens, and to defend it against infection, disease and other foreign substances. The body's immune system naturally produces antibodies in this defence process.

Immunity is the ability of the human body to tolerate the presence of material indigenous to the body and to eliminate foreign material. This discriminatory ability provides protection from infectious disease, since the immune system identifies most microbes as foreign. Immunity to a microbe is usually indicated by the presence of an antibody to that organism. Immunity is generally very specific to a single organism or group of closely related organisms. There are two basic mechanisms for acquiring immunity, active and passive.

Immunoglobulin (Ig) is a sterile solution containing antibodies from human blood, also known as human normal immunoglobulin (HNIg), immune serum globulin (ISG) or gamma globulin (IgG). Ig is used to prevent the spread of some diseases among people who are in close contact with each other. Intended for intramuscular administration, it is primarily indicated for routine maintenance of immunity among certain immunodeficient people and for passive immunization against measles and hepatitis A. Ig does not transmit hepatitis B virus, HIV or other infectious diseases.

Immunization is an inclusive term denoting the process of inducing or providing immunity artificially by administering an immunobiological product. Immunization can be active or passive. ***Active immunization*** is the production of antibody or other immune responses through the administration of a vaccine or toxoid. ***Passive immunization*** is the provision of temporary immunity by the administration of preformed antibodies, such as immunoglobulins and antitoxins.

Immunologic memory is persistent protection for many years after an infection. Following exposure of the immune system to an antigen, certain cells (memory B-cells) continue to circulate in the blood (and also in the bone marrow) for many years. Upon exposure to the antigen, these memory cells begin to replicate and produce very rapidly to re-establish protection.

Immunosuppression is the suppressed immune status of an individual caused by diseases (such as HIV/AIDS, congenital immunodeficiency, leukaemia, lymphoma or generalized malignancy) or drugs (such as alkylating agents, antimetabolites or radiation therapy). The level of immunosuppression can be measured by CD4 count or by CD4 percentage of total lymphocytes.

Inactivated vaccines can be composed of whole viruses or bacteria, or fractions of either. Fractional vaccines are either protein-based or polysaccharide-based. Protein-based vaccines include toxoids (inactivated bacterial toxins) and subunit or subvirion products. Most polysaccharide-based vaccines are composed of pure cell-wall polysaccharide from bacteria. Conjugate polysaccharide vaccines are those in which the polysaccharide is chemically linked to a protein. This linkage makes the polysaccharide a more potent vaccine. Vaccine antigens may also be produced by genetic engineering technology. These products are sometimes referred to as recombinant vaccines.

Intravenous immunoglobulin (IgIV) is a product derived from blood plasma from a donor pool similar to the Ig pool, but prepared so it is suitable for intravenous use. IgIV does not transmit infectious diseases. It is primarily used for replacement treatment in primary antibody-deficiency disordersand for the treatment of Kawasaki disease, immune thrombocytopenic purpura, hypogammaglobulinaemia in chronic lymphocytic leukaemia, and some cases of HIV infection.

Live attenuated vaccines are produced by modifying a disease-producing ("wild") virus or bacteria in a laboratory. The resulting vaccine organism retains the ability to replicate and produce immunity, but it usually does not cause illness.

Passive immunity is protection by products produced by an animal or another human and transferred to the recipient, usually by injection. Passive immunity often provides effective protection, but this protection wanes over time, usually a few weeks or months.

Specific immunoglobulins are special preparations obtained from blood plasma from donor pools preselected for high antibody content against a specific antigen (for example, hepatitis B immunoglobulin, varicella-zoster immunoglobulin, rabies immunoglobulin or tetanus immunoglobulin). Like Ig and IgIV, these preparations do not transmit infectious diseases.

A **symptomatic HIV-infected person** is a person presenting with signs and symptoms of HIV infection. Mild, advanced and severe HIV disease corresponds to WHO Clinical Stages 2, 3 and 4, respectively (see Annex 2 and the annexes mentioned under "asymptomatic HIV-infected person" above).

A **toxoid** is a modified bacterial toxin that has been made non-toxic but retains the ability to stimulate the formation of antitoxin.

Vaccination is the physical act of administering any immunobiological agent (vaccine, toxoid or immunoglobulin) to a person to produce active immunity.

Vaccine is a suspension of live (usually attenuated) or inactivated microorganisms (e.g. bacteria, viruses or rickettsiae) or fractions thereof, administered to induce immunity and prevent infectious diseases or their consequences. Some vaccines contain highly defined antigens (such as the polysaccharide of *Haemophilus influenza* type b or the surface antigen of hepatitis B); others contain antigens that are complex or incompletely defined (for example, killed *Bordetella pertussis* or live attenuated viruses). Vaccines interact with the

immune system and often produce an immune response similar to that produced by the natural infection, but do not subject the recipient to the disease and its potential complications. Vaccines produce immunological memory similar to that acquired by having the natural disease.

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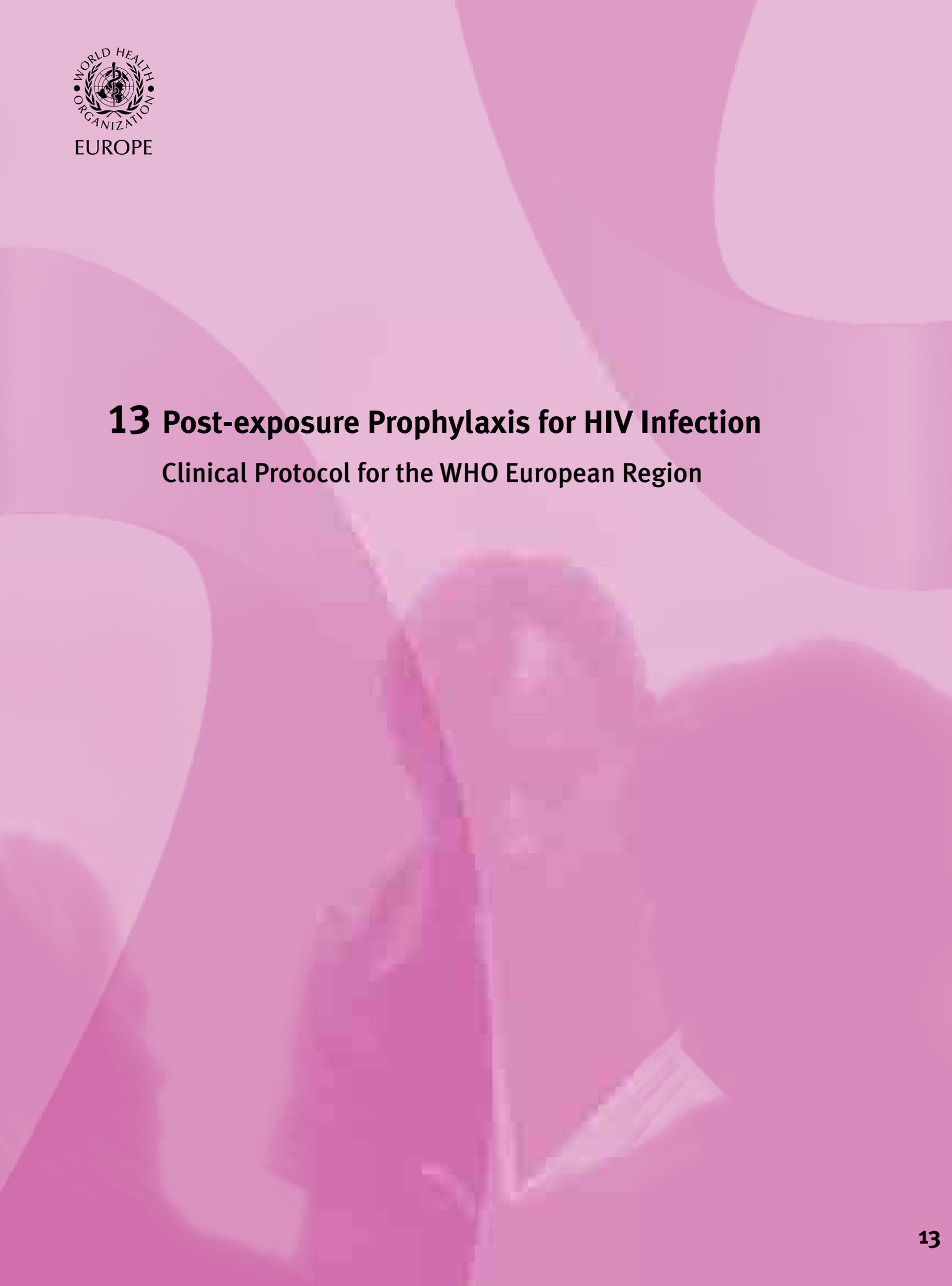
EUROPE

13 Post-exposure Prophylaxis for HIV Infection

Clinical Protocol for the WHO European Region



Contents

I. Policy issues

Following exposure to HIV, there are currently only two known means to reduce the risk of developing HIV infection: post-exposure prophylaxis (PEP) and interventions to prevent mother-to-child transmission (see Protocol 10, *Prevention of HIV transmission from HIV-infected mothers to their infants*).

- PEP policy should be part of a comprehensive national HIV/AIDS policy and also included any occupational health and post sexual assault services policies.
- PEP services should be integrated into existing health services and provided as part of a comprehensive standard precautions package that reduces workplace exposure to infectious hazards.
- Eligibility for and access to PEP should be equitable, without discrimination on grounds of age, gender, sexual orientation, citizenship, occupation or incarceration.
- Decisions about whether to provide PEP should be based on clinical consideration of risk factors.
- PEP services should be provided after:
  - occupational exposure to HIV infection or potential HIV infection;
  - accidental non-occupational exposure to HIV infection or potential HIV infection, including nosocomial exposure.
- The human rights and confidentiality of people accessing PEP should be respected.
- In the context of exposure and/or the provision of PEP, informed consent needs to be obtained for HIV testing and counselling in accordance with both client and provider initiated counselling and testing guidelines. (See Annexes 1 and 2 for examples of informed consent forms.)
- In special situations where the individual has limited or no capacity to consent to an HIV test (such as a child or an unconscious or mentally ill adult), a legal guardian, custodian or other person designated in advance by the patient may be able to provide consent, depending on national or regional legislation.

II. Background and general considerations

PEP is a medical response given to prevent the transmission of pathogens after potential exposure. PEP for HIV refers to a set of comprehensive services to prevent HIV infection in exposed individuals. These services include, first aid care, counselling and risk assessment, HIV testing based on informed consent, and depending on risk assessment, the provision of short term (28 days) antiretroviral (ARV) drugs, with follow up and support.

1. Occupational exposure to HIV

1.1. Definition

According to the ILO/WHO guidelines for occupational PEP, "an occupational exposure is defined as a percutaneous, mucous membrane or non-intact skin exposure to blood or body fluids that occurs during the course of an individual's employment. This applies to health care workers (HCW) and to non-health workers." *(1)* An occupational exposure may place a worker[1] at risk of HIV infection through injuries such as those involving a potentially contaminated needle or sharp instrument or chapped, abraded skin or contact with mucous membranes.

1.2. Risk for transmission

The risks for occupational transmission of HIV vary with the type and severity of exposure *(2, 3)*.

- The average risk for HIV transmission after a percutaneous exposure to HIV-infected blood has been estimated to be approximately 0.23% (95% confidence interval (CI) = 0.00–0.46%) *(3)*.
- The average risk after a mucous membrane exposure is estimated to be approximately 0.09% (CI = 0.006–0.5%) *(4)*.
- Factors associated with an increased likelihood of transmission include:
  - deep (intramuscular) injury
  - injury caused by a device that enters a blood vessel
  - injury with a hollow-bore needle
  - a source patient with a high viral load (VL).
- Episodes of HIV transmission have also been documented after non-intact skin exposure. Although the average risk for transmission by this route has not been precisely quantified, it is estimated to be much less than the risk for mucous membrane exposures.
- The risk for transmission after exposure to HIV-infected fluids or tissues other than blood has not been quantified either, but it is considered probably lower than for blood exposure.

1.3. Potentially infectious body fluids *(5)*

- Blood and visibly bloody body fluids are considered as potentially infectious.
- The risks of HIV transmission from cerebrospinal, synovial, pleural, peritoneal, pericardial and amniotic fluids are unknown.
- Semen and vaginal secretions have not been implicated in occupational transmission from patients to health care providers.
- Faeces, nasal secretions, saliva, sputum, sweat, tears, urine and vomitus are not considered potentially infectious unless they contain visible blood.

[1] Besides health care providers (physicians, dental personnel, nurses, laboratory and autopsy personnel, nursing assistants, medical technicians, pharmacists, medical students et al.), others at risk of workplace exposure include police, fire and ambulance personnel.

1.4. Factors affecting the risk for HIV transmission after an occupational exposure

Epidemiological and laboratory studies suggest that multiple factors might affect the risk for HIV transmission after an occupational exposure *(2, 3)*.

- For percutaneous exposure to HIV, increased risk for HIV infection is associated with exposure to blood from the source person, as indicated by:
  - a device (e.g. a needle) visibly contaminated with blood; or
  - a procedure that involved a needle being placed directly in a vein or artery or in a deep injury.
- High viral load in the source person is also a condition that may increase the risk of HIV transmission.

2. Non-occupational exposure

Due to ethical considerations, it is not possible to make prospective randomized controlled studies to evaluate the efficacy of PEP in preventing HIV after non occupational exposure. Neither are there data from studies or case reports providing definitive evidence of the efficacy of PEP after sexual, injecting drug or other non-occupational exposures to HIV. However, several related data sets from occupational exposure, mother-to-child transmission and animal studies support the biological plausibility of its effectiveness *(6–10)*.

2.1. Definition

Non-occupational exposure is any direct mucosal, percutaneous[2] or intravenous contact with potentially infectious body fluids that occurs outside perinatal or occupational situations *(11)*:

> [N]on-occupational exposure [is considered to be] all accidental and sporadic incidents in which contact with blood or other body fluids (semen, vaginal secretions, etc.) that pose a potential risk for HIV infection occurred … Non-occupational exposure includes unprotected sexual exposure, sexual exposure involving a broken or slipped condom, injecting drug users (IDUs) sharing equipment, accidental needlestick injuries, bite wounds, mucosal exposure, etc.

Non-occupational exposure also includes nosocomial exposure. Accidental exposure to HIV originating in a health care facility includes cases where a patient is exposed by a health care worker (HCW) or another patient *(12)*. Three scenarios can result in a patient being exposed to HIV nosocomially *(13)*:

- an HIV-infected HCW who does not know his/her HIV status performing an exposure-prone procedure;[3]
- an HIV-infected HCW performing a non-exposure-prone procedure (and when there is e.g. a spontaneous nosebleed or a physical assault on the HCW); or
- the event that an invasive device or product contaminated with HIV by use on one patient is accidentally reused on another patient.

[2] Percutaneous non-occupational exposure includes but is not limited to accidental or criminal sticks with needles contaminated with blood or other bodily fluids.

[3] Exposure-prone procedures are those in which there is a risk that injury to the HCW could result in exposure of the patient to the blood of the HCW, including some common procedures found in surgery, obstetrics, gynaecology, midwifery and dentistry *(13)*. HCWs who know that they are HIV infected, should not be involved in such procedures.

2.2. Risk for transmission

The estimated per-act transmission risk from unprotected exposure to a person known to be HIV-infected is low. It varies depending on the type of exposure.

Table 1. Estimated per-act risk for acquisition of HIV, by exposure route[a]

Exposure route	Risk per 10 000 exposures to an infected source	%
Blood transfusion *(3)*	9 250	92.5
Mother-to-child transmission *(15)*	1 500–3 000	15–30
Needle-sharing injecting drug use *(3)*	80	0.80
Receptive anal intercourse *(16, 17)*	50	0.50
Percutaneous needle-stick *(18)*	30	0.30
Mucosal membrane exposure *(19)*	10	0.10
Receptive penile-vaginal intercourse *(16, 17, 20–24)*	1–15	1.01–0.15
Insertive anal intercourse *(16, 17)*	6.5	0.065
Insertive penile–vaginal intercourse *(16, 17)*	1–15	0.01–0.15
Receptive oral intercourse *(17)*	1	0.01
Insertive oral intercourse *(17)*	0.5	0.005

[a] Estimates of risk for transmission from sexual exposure assume no condom use.
Source: adapted from Roland et al. (*14*).

III. Evaluation of the exposure, exposure source and exposed person

1. Evaluation of exposure

An exposure incident should be evaluated for the potential of HIV transmission based on the type of body substance involved, the transmission route and the severity of the exposure. The following factors should be considered in evaluating the risk of transmission:

- the type of exposure:
  - percutaneous injury
  - mucous membrane exposure
  - open wound exposure;
- the type and quantity of fluid/tissue:
  - blood;
  - a fluid that contains blood;
  - a potentially infectious fluid (e.g. seminal, vaginal, cerebrospinal, synovial, pleural, peritoneal, pericardial or amniotic fluid) or tissue;
  - concentrated virus (direct contact); and
- the recency of exposure.

2. Evaluation of the exposure source

When feasible, the person whose blood or body fluid is the source of potential exposure should be evaluated for HIV.

- If an exposure source is known and available, testing the source person for HIV is recommended as soon as possible, or testing the suspected exposure material (blood, tissue, etc) if the person is unavailable.
- Procedures that should be strictly followed for testing the source person include:
  - obtaining informed consent (see suggested form in Annex 1)
  - pre- and post-test counselling
  - referral if positive for appropriate post-test counselling, care and treatment.
- A rapid HIV-antibody test is preferred in situations where enzyme-linked immunosorbent assay (ELISA) tests cannot be completed within 24–48 hours.
- Two positive ELISA or rapid HIV-antibody tests are considered to be highly suggestive of infection, whereas a negative result is an excellent indicator of the absence of HIV antibody.
- In no way should administration of PEP for the exposed person, be delayed while waiting for test results.
- The routine use of direct virus assays (e.g. an HIV p24 antigen enzyme immunoassay (EIA) or HIV RNA tests) to detect infection among exposure sources is usually not recommended *(25)* because:
  - the infrequency of occupational seroconversion and the increased costs of these tests do not warrant routine use in this context; and
  - the relatively high rate of false-positive results for these tests in this context can lead to unnecessary anxiety or treatment *(14, 26)*.
- The exposure source should also be tested for hepatitis C and B viruses (HCV and HBV).
- Information to consider when evaluating an exposure source includes:
  - previous HIV test results; and
  - clinical symptoms (e.g. acute syndrome suggestive of primary HIV infection and history of possible HIV exposure within the last three months) or personal history suggesting possible exposure to HIV; and
  - history of tratment, duration, its success or failure, type of regime and adherence.

- *If the exposure source is unknown, cannot be tested or refuses to be tested*, the risk of HIV transmission should be assessed epidemiologically, if possible. Relevant information includes:
  - type of exposure
  - prevalence of HIV in the population where the source material originates.
- *If the source person is known to have HIV infection*, the following information is also useful to know in determining an appropriate PEP regimen:
  - clinical stage of the HIV infection;
  - CD4 cell count;
  - viral load, as a high plasma viral load increases the risk of transmission in all cases *(27)*;
  - antiretroviral treatment history;
  - genotypic or phenotypic viral resistance results (if available);
  - in a case of sexual exposure, the existence of genito-oral ulcers or other sexually transmitted infections (STIs), and whether menstruation or other bleeding occurred at the time *(24)*; and
  - in the case of an accidental needle-stick exposure, whether fresh blood was present and whether it was a deep injury or intravenous injection (all increase the risk of HIV transmission) *(6)*.
- If this information is not immediately available, initiation of PEP, if indicated, should not be delayed. Appropriate changes in the PEP regimen can be made if new information emerges after PEP has been started.
- If the source person's results are HIV seronegative at post-exposure evaluation and presents no clinical evidence of AIDS or HIV infection, no further testing of the source is indicated. The likelihood of the source person being in the "window period" of HIV infection with no symptoms of acute retroviral syndrome is extremely small.

3. Evaluation of the exposed person

Evaluation of exposed persons (regardless if it is occupational or non-occupational) has to be done as soon as possible and within hours after an exposure. The following evaluations are recommended:
- an HIV serological baseline test to establish infection status at the time of exposure, with pre- and post-test counselling and based on informed consent (see Annex 2);
- direct virus assays for any exposed person who has an illness compatible with an acute retroviral syndrome, regardless of the time elapsed since exposure;
- evaluation of circumstances, medical conditions and medications that might influence drug selection for PEP (e.g. pregnancy or breastfeeding);

It is useful to perform the following baseline tests if resources are available:
- baseline laboratory testing to monitor for adverse reactions:
  - complete blood count (CBC) with differential and platelets
  - liver function tests (LFTs) (asparate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin)
  - urea or serum creatinine; and
- baseline serological tests for hepatitis C and B (HCV antibodies and hepatitis B surface antigen (HBsAg)).

3.1. Additional considerations for non-occupationally exposed people

In addition, those seeking care after potential non-occupational exposure to HIV should also be evaluated for the following information:
- frequency of exposures to HIV;
- history of specific sexual, drug-injecting or other behaviours that might have heightened the risk for acquiring HIV infection;
- if an accidental needle-stick exposure, whether there was fresh blood and whether it was a deep injury or intravenous injection *(6)*; and
- if a sexual exposure:

- condom use
- presence of STIs (as determined by testing)
- need for emergency contraception or pregnancy testing (for females)
- presence of sexual assault, by one or more persons
- whether menstruation or other bleeding was present at time of exposure.

IV. Clinical management of people incidentally exposed to HIV

1. First aid

For a potential exposure to HIV, "first aid" refers to the actions that should be taken immediately afterwards. The aim of first aid is to reduce contact time with the source person's body fluids (including blood) and tissues, and to clean and decontaminate the exposure site to reduce the risk of infection *(28)*.

If the skin is broken following an injury with a used needle or other sharp instrument, take the following steps.

- Wash the injury immediately, using soap.
- Encourage the puncture wound to bleed freely under running water for several minutes or until bleeding ceases.
- If running water is not available, clean site with a gel or hand cleaning solution.
- **Do not** use any strong solutions, such as alcohol, bleach or iodine, as they may irritate the wound and make the injury worse.
- **Do not** squeeze or rub the injury site.
- **Do not** suck a puncture wound.

After a splash of blood or body fluids, do the following:

- *for a splash on unbroken skin:*
  - wash the area immediately;
  - if running water is not available, clean the area with a gel or hand rub solution;
  - **do not** use any strong solutions, such as alcohol, bleach or iodine, as they may irritate the affected area;
  - use mild disinfectants, such as Chlorhexidine gluconate 2–4%;
  - **do not** rub or scrub area;
  - **do not** use a dressing.
- *for a splash in the eye:*
  - irrigate the exposed eye immediately with water or normal saline. Sit in a chair, tilt the head back and have a colleague gently pour water or normal saline over the eye, gently pulling the eyelids up and down to make sure the eye is cleaned thoroughly;
  - if wearing contact lenses, leave them in place while irrigating, as they form a barrier over the eye and will help protect it; once the eye has been cleaned, remove the contact lenses and clean them in the normal manner, which will make them safe to wear again;
  - **do not** use soap or disinfectant on the eye.
- *for a splash in the mouth:*
  - spit the fluid out immediately;
  - rinse the mouth thoroughly, using water or saline, and spit out again. Repeat this process several times.
- **do not** use soap or disinfectant in the mouth.

2. Counselling an exposed person

After the evaluation, health care workers should provide counselling on risk-reduction behaviour to the exposed person regardless of how the individual was exposed, and of whether or not antiretroviral (ARV) drugs will be recommended for PEP, as such, counselling can reduce the risk of future exposures *(29, 30)*.

It should be made clear during the counselling session that PEP is not mandatory. An informed consent form (see Annex 2) should be signed if the exposed person opts for PEP. In addition to the information outlined on the informed consent form, the exposed people should be counselled on:

- avoiding pregnancy and seeking safe alternatives to breastfeeding;
- avoiding blood, tissue or sperm donation;
- using condoms for sexual intercourse up to the sixth month test confirming that the exposed person remains seronegative;
- standard precaution measures for those at risk of workplace exposure; and
- the need for clinical and serological follow-up.

As stated on the consent form, there is a strong need for adherence to PEP regimens, for further information on adherence refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, for information on adherence issues.

Psychological support should be an integral part of counselling and include appropriate referrals as needed.

Counselling on risk-reduction behaviour after non-occupational exposure should also focus, where indicated, on:

- safer injecting practices, with referral to harm-reduction programmes and drug-dependence treatment services;
- STI treatment, with referral to appropriate services; and
- contraception and condom use.

Furthermore, counselling on sexual abuse should be provided, where needed, with appropriate referrals, such as legal services.

3. No indication for ARV use for PEP purposes

Some situations do not require initiation of ARVs for prophylaxis purposes. They include *(26)*:

- if the exposed person has previously tested positive for HIV (this needs to be documented);
- if exposure is chronic (occurring regularly versus occurring occasionally[4]), e.g. between serodiscordant sex partners who rarely use condoms or IDUs who share injecting equipment;
- if the exposure does not pose a risk of transmission, e.g.:
  - exposure of *intact skin* to potentially infectious body fluids;
  - sexual intercourse with proper *condom* use during which the condom remained intact;
  - exposure to *non-infectious body fluids* (such as faeces, saliva, urine, sweat) with no blood contamination;
  - exposure to body fluids from a person *known* to be HIV-seronegative, unless identified as at high risk for recent infection within the "window period"; and
- if the exposure was more than 72 hours previous (however, consider referring for counselling, testing and clinical follow-up).

Note that the final decision for prescribing or not prescribing PEP should be made on the basis of risk evaluation, the patient–physician relationship, bearing in mind that PEP should never be considered a primary prevention strategy *(11)*.

[4] People who are occasionally or episodically exposed to HIV, such as sexually assaulted sex workers who otherwise use condoms, episodically abused children, medical waste workers with repeated sharps injuries, et al should be considered for PEP based on previously described evaluation (see section III of this document).

4. Time of initiation and duration of PEP

PEP should be initiated within hours of exposure – ideally within 2 hours and not later than 72 hours after exposure and should not be delayed while waiting for tests results.

The optimal duration of PEP is unknown. Data show that four weeks of ZDV has appeared protective in occupational and animal studies. PEP should be administered for four weeks if tolerated *(9, 31–33)*.

5. Considerations in choosing an ARV regimen for PEP

The only PEP efficacy data are from a retrospective case control study *(6)* on a zidovudine monotherapy, taken as prophylaxis measure. The model in the study indicates reducing risk of HIV acquisition by approximately 81% in health care workers after percutaneous exposure.

No evidence indicates that a three-ARV combination is more effective than a two-ARV combination, or two-ARV combination is more effective than three-ARV combination. Some data suggest that there is significant toxicity associated with three-ARV regimens, while two-ARV combinations are generally well tolerated *(29, 34)*. Offering a two-drug regimen is a viable option, primarily because the benefit of completing a full course of this regimen exceeds the potential benefit of adding a third agent and risking non-completion *(35)*.

For the vast majority of exposure cases, whether occupational or non-occupational, and whether due to percutaneous injuries or to contact with mucous membrane or non-intact skin, the regimen with two ARVs considered to be sufficient. However, suspected or proven drug resistance in a source person might guide a decision to prescribe a three ARV drug regimen.

If a question exists concerning whether to use a two-drug or three-drug regimen, start the two-drug regimen immediately rather than delay administering PEP.

6. Antiretroviral regimens and drugs for PEP

6.1. Two ARV drug regimens

The two-drug ARV regimen (see Table 2) consists of two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs).

Table 2. Two-drug ARV regimens

Preferred	ZDV + 3TC[a] (or FTC)
Alternatives	TDF + FTC[b] (or 3TC) or d4T + 3TC

[a] The combination ZDV + 3TC is available as a fixed-dose combination (FDC) (Combivir), one tablet twice daily (BID).
[b] The combination TDF + FTC is available as an FDC (Truvada), one tablet once daily (OD).

6.2. Three ARV drug regimens

Expanded ARV regimens (see Table 3) are combinations of three ARVs (two NRTIs + one protease inhibitor (PI)). They are recommended for exposures that pose an increased risk of transmission or that involve a source in whom antiretroviral drug resistance is likely (see section 5).

Table 3.	Thre- drug ARV regimens
Preferred	ZDV + 3TC[a] + LPV/r
Alternatives	ZDV + 3TC[a] + SQV/r or ATV/r or FPV/r or TDF + FTC[b] + SQV/r or ATV/r or FPV/r or d4t + 3TC +SQV/r or ATV/r or FPV/r

[a] The combination of ZDV + 3TC is available as an FDC (Combivir), one tablet BID.
[b] The combination of TDF + FTC is available as an FDC (Truvada), one tablet OD.

6.3. ARV dosages

- ZDV: 300 mg per os (PO), BID with food
- 3TC: 150 mg PO, BID or 300 mg PO, OD
- FTC: 200 mg, PO, OD
- TDF: 300 mg, PO, OD
- d4T: 30 mg PO, BID
- LPV/r: 400 mg/100 mg PO, BID with food
- SQV/r: 1000 mg/100 mg PO, BID
- ATV/r: 300 mg/100 mg PO, OD
- FPV/r: 700 mg/100 mg PO, BID

In cases involving children who need PEP, dosages should be adjusted accordingly (please refer to Protocol 11, *Paediatric HIV/AIDS treatment and care*). For further details regarding essential information about ARVs please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*, Annex 4.

6.4. ARVs not recommended for PEP

Some ARVs are not recommended for use in PEP, primarily because of a higher risk for potentially serious life-threatening events: abacavir (ABC), the combination of didanosine (ddI) and d4T, and NVP *(36, 37)*. Amprenavir (APV) should not be given to pregnant or lactating women *(38–40)*. In addition, EFV is not recommended because of low genetic barrier.

An exceptional use of efavirenz (EFV) may be considered when:
- the exposed person *cannot* tolerate available boosted PIs;
- the source is known to be infected with drug-resistant HIV that is sensitive to EFV.

7. Follow-up of exposed persons

People who have been potentially exposed to HIV, whether occupationally or non-occupationally, should receive follow-up treatment.
- Counselling, post-exposure testing and medical evaluation should be provided to all exposed people, regardless of whether they receive PEP or not.
- If taking ARVs patients should be followed up for adherence and possible side-effects of ARVs (e.g. nausea or diarrhoea) should be managed symptomatically without changing the regimen. For more information, please refer to Protocol 1, *Patient evaluation and antiretroviral treatment for adults and adolescents*.

- After baseline testing at the time of exposure, follow-up testing using enzyme immunoassay should be performed at 6 weeks, 12 weeks, and 6 months after exposure, *even* if PEP is declined.
- Direct virus assays may be performed on any exposed person who has an illness compatible with an acute retroviral syndrome, regardless of the interval since exposure.
- For those who become infected with HCV after exposure to a source coinfected with HIV and HCV, extended HIV follow-up (for 12 months) is recommended *(41)*.
- If an exposed person seroconverts after PEP, he or she should be referred for HIV treatment and care services.
- Psychological support should be provided and referrals suggested as appropriate, including needle and syringe exchange for IDUs.
- If the exposure is due to rape, it is important to arrange for counselling and support. The victim also needs to be provided with information regarding STIs, pregnancy and legal matters.
- If the exposed person is a child or adolescent, or if the exposure is due to rape, it may be worthwhile to cooperate with other specialists, e.g. a paediatrician or a rape counsellor.
- Health care providers caring for people exposed to HIV should report these cases to their health departments regardless of whether or not PEP has been prescribed, and a national PEP registry should be maintained. (See the proposed occupational exposure report in Annex 3 and the proposed non-occupational exposure report in Annex 4).

V. Prevention of occupational and nosocomial exposure

After occupational exposure, it is recommended to evaluate work place safety measures and strengthen standard precautions measures.

The importance of primary prevention in any setting where HIV can be transmitted should be reinforced in every programme that provides PEP. Health care workers (HCW) and other exposed workers should receive appropriate information on PEP availability and the reference centres. It is important to underline that PEP is not ever likely to be 100% effective, and thus it should always be integrated into a larger HIV exposure prevention strategy based on standard precaution principles. Quality control and evaluation of safety conditions at work should be re-evaluated after exposure.

Provided that the procedures for preventing occupational transmission of bloodborne viruses are adhered to at all times, most clinical procedures pose no risk of transmission of HIV from an infected HCW to a patient *(42)*.[5]

1. Standard precautions

Standard precautions are infection control measures that reduce the risk of transmission of bloodborne pathogens through exposure to the blood or other body fluids of patients and health care providers. As it is not possible to identify everyone who may be infected with a bloodborne pathogen, protecting HCWs and patients against HIV and hepatitis viruses should be based on the concept that all patients and HCWs are assumed to be infected with bloodborne diseases.

The application of standard precautions requires that all blood and other body fluids should be regarded as potentially infectious and appropriate protective action taken. To help protect HCWs and patients from bloodborne infections, including HIV, WHO advises that standard infection control precautions be used, as follows.

- Wash hands with soap and water before and after procedures.
- Use protective barriers such as gloves, gowns, aprons, masks and goggles for direct contact with blood and other body fluids.
- Disinfect instruments and other potentially contaminated equipment.
- Handle soiled linen properly (see next section).
- Using new, single-use injecting equipment for all injections is highly recommended.
- Sterilizable injections should only be considered if single-use equipment is not available and if their sterility can be documented with time, steam and temperature indicators.
- Discard contaminated sharps immediately without recapping in puncture- and liquid-proof containers that are closed, sealed and destroyed before completely full.
- Document the quality of sterilization for all medical equipment used in percutaneous procedures *(45)*.

Please see Annex 5 for a checklist of standard precautions for HCWs.

2. Reducing occupational exposure in health care settings

2.1. Basic preventive measures and workplace practices

In addition to standard precautions, workplace practices should be instituted and followed to reduce exposure to bloodborne pathogens and other infectious materials. Avoid accidental injuries

[5] The overall risk of an infected HCW transmitting HIV to a patient is low. Worldwide, only two possible reports of such transmission have been reported, both during exposure-prone procedures *(43, 44)*.

and exposure routes that can transmit bloodborne infections. The following guidelines should be adhered to:

- Institute procedures to ensure and monitor compliance with safety measures.
- Only allow health care professionals to perform a duty involving exposure to body fluids if they have undergone training and education in infection control and preventive measures, including the correct methods for cleaning up accidental spills of blood and other body fluids.
- Avoid splashing, spraying, splattering and generating droplets of blood or other potentially infectious materials.
- Clean all equipment and environment surfaces immediately after contact with blood or other potentially infectious materials.
- Place potentially infectious specimens in properly labelled containers that will prevent leakage during collection, handling, processing, storage, transport and shipping. Use a secondary container if the primary container becomes contaminated or punctured.
- *Hand-washing is essentisal.*
  - Wash hands and any other exposed skin with soap and water before and after procedures, including after removal of gloves and other personal protective equipment or attire.
  - Following the contact of body areas with blood, other potentially infectious materials or contaminated surfaces, wash hands and flush mucous membranes with water immediately or as soon as feasible.
  - Use soap and *running* water. If running water is not available, use an appropriate antiseptic hand cleanser and clean towels or antiseptic towelettes, followed by regular hand-washing as soon as feasible.
  - If minimal skin lesions are already present on hands (e.g. cuts), they need to be properly addressed before using gloves. Bear in mind that glove use requires consideration of additional safety precautions (see Annex 5).
- *Proper handling of soiled linen is essential.*
  - Soiled linen should be handled as little as possible.
  - Gloves and leak-proof bags should be used if necessary.
  - Bags and containers of soiled linen should be labelled.
  - Soiled linen should be cleaned and laundered outside patient areas, using detergent and hot water.
- Place all regulated waste in closable, leak-proof containers.

In addition, health care workers must observe the following restrictions:

- Do not eat, drink, smoke, apply cosmetics, apply lip balm or handle contact lenses in work areas where occupational exposure to bloodborne pathogens is likely.
- Do not keep food and drink in refrigerators or other locations where blood or other potentially infectious materials are present.
- Never use the mouth to pipette or suction blood or other potentially infectious materials.
- Never use hands to pick up broken glassware that may be contaminated.
- Do not bend, recap, break or remove contaminated needles or other contaminated sharps.
- Never use hands to reach into, open, empty or clean reusable sharps containers *(46)*.

2.2. Protective material and equipment

Protective equipment and controls should be instituted in all health care settings. To prevent transmission of bloodborne pathogens, the following precautions should be taken:

- *Protective equipment and clothes* should be made available to and worn by all workers who come into contact with blood or body fluids, including:
  - gloves
  - liquid-resistant gowns
  - face and eye protection.

- *Safety measures for needles and syringes include the following.*
  - Use new, single-use, self-sheathing needles or other new disposable injecting equipment for all injections.
  - Only consider sterilizable injections if single-use equipment is not available and if the sterility can be documented with time, steam and temperature indicators.
  - Use needleless intravenous (IV) access systems.
  - Use a mechanical device that protects the hand or a safe one-handed technique if needle recapping or removal is absolutely necessary.
  - In general, containers for sharps should be wall-mounted when not in use to avoid accidents that may occur from patients (especially children) playing with or trying to open them.
- *Safety measures for other sharps include the following.*
  - Discard contaminated sharps immediately and without recapping in puncture- and liquid-proof containers that are closed, sealed and destroyed before completely full.
  - Position sharps disposal containers so that they are easily accessible and maintained upright throughout use.
  - Replace sharps disposal containers regularly and do not allow them to overfill.
  - Before moving a container of contaminated sharps, close it completely. Place it in a secondary container if leakage is possible.
- *Safety measures for dental instruments, devices and equipment include the following (47).*
  - Follow normal heat-sterilization procedures for surgical instruments, periodontal scalers, scalpel blades, surgical dental burs, dental mouth mirrors, amalgam condensers, reusable dental impression trays and dental handpieces.
  - If disinfecting instruments or other equipment that is heat-sensitive, use high-potency disinfectant.
  - Devices connected to the dental water system that enter a patient's mouth (e.g. handpieces, ultrasonic scalers, air abrasion devices and air/water syringe tips) should operate for a minimum of 20–30 seconds after each patient to discharge water and air and flush out any patient material.
  - Where possible, use dental units that prevent retraction of oral fluids.
  - Components that are permanently attached to dental unit waterlines (e.g. the handles and dental unit attachments of saliva ejectors, high-speed air evacuators and air/water syringe tips) should be covered with impervious barriers that are changed after each use.
- Appropriate first-aid equipment should always be readily available for dealing with spilled body fluids, and staff should be trained to institute safety precautions following any accident.
- Containers appropriate for waste disposal should always be available – as should guidelines for such disposal.

2.3. Technological controls

Technological controls can help isolate and remove bloodborne pathogens from the workplace.

- Document the quality of the sterilization for all medical equipment used for percutaneous procedures.
- Disinfect instruments and other contaminated equipment.
- Before servicing or shipping, decontaminate any equipment that is contaminated with blood or other potentially infectious materials. If decontamination is impossible, attach a label that states which portions of the equipment remain contaminated.
- Set up quality control charts to monitor standard precautions in technical procedures and instrument use.

2.4. Personal protective equipment and its use

If the potential for occupational exposure still remains after an HCW uses up to date technological controls and standard work practice precautions, the employer must also provide personal protective equipment (PPE). This equipment must be provided in a readily accessible location and at no cost to the HCW.

- *Gloves* include special gloves if an HCW is allergic to conventional medical gloves.
  - Single-use gloves should not be reused, nor should reusable gloves that show signs of deterioration.
  - Petroleum-based lubricants should not be used, as they can eat through latex rubber.
- *Gowns/laboratory coats should be used.*
  - Outer garments should be worn in occupational exposure situations.
  - Surgical caps/hoods and shoe covers/boots should be worn only if potential gross contamination of the head or feet is anticipated.
- *Face shields/masks/eye protection should be used.*
  - Chin-length face shields or masks should be worn in combination with eye protection devices and side shields whenever splashes, spray, spatter or droplets of blood or other potentially infectious materials may be generated.
  - Regular eye-glasses do not provide sufficient protection against bloodborne contaminants.

Personal protective equipment must not permit blood or other potentially infectious materials to pass through to or reach work clothes, street clothes, undergarments, skin, eyes, mouth or other mucous membranes under normal conditions of use during the time in which the protective equipment will be used. Heavy gloves and protective clothing and appropriate training should be provided for all cleaners and waste disposal handlers.

If a protective garment is penetrated by blood or another potentially infectious material, it should be removed as soon as possible. Wash the affected area with soap and water. Remove all PPE prior to leaving the work area and place it in a designated receptacle. Employers are responsible for cleaning, laundering, repairing, replacing and disposal of used PPE.

VI. Suggested minimum data to be collected at the clinical level

Based on the proposed occupational and non-occupational reporting forms (Annexes 3 and 4), the clinical level should aggregate the detailed information about patients requiring PEP, receiving PEP and outcomes (patients who become infected or not).

Annex 1. Informed consent form for source person

(Informed consent to perform an HIV test and authorization for release of HIV-related information for purposes of providing post-exposure care to a person accidentally exposed occupationally or non-occupationally[*]*)*

A person has been exposed to your blood or a body fluid in a manner that may pose a risk for the transmission of a bloodborne infection. Many individuals may not know whether they have a bloodborne infection because people can carry these viruses without having any symptoms. We are therefore asking for your consent to test for the presence of human immunodeficiency virus (HIV). You will also be tested for hepatitis B virus (HBV) and hepatitis C virus (HCV). HIV testing is voluntary and requires your consent in writing; consent can be withdrawn for the test at any time. Your blood will be tested by a rapid or enzyme immunoassay serological test. The test result will be used to help determine whether the exposed person is actually at risk for HIV and requires treatment for that exposure.

We will inform you of the test results, helping you understand their implications as well as assisting you in accessing any services you may need.

Meaning of HIV test results

You also are being asked to authorize the release of confidential HIV-related information related to this request to the health professional, named below, who is treating the exposed person. This release is necessary to provide appropriate care and to counsel the exposed person about his or her risk of becoming infected and possibly infecting others. Confidential HIV-related information can only be given to persons you allow to have it by signing a release. These individuals are prohibited by law from subsequently disclosing these test results or your identity.

_____

Name of exposed person's health care provider to whom HIV test result will be disclosed:

Prior to executing this consent, you will be counselled about the implications of HIV testing and your confidentiality protections under the law.

I understand the purpose for which I am being asked to submit a specimen for HIV testing. My questions about the HIV test were answered. I agree to be tested for HIV, and I authorize the release of this information to the health care provider for the exposed person. This release is effective for one year after the date listed below.

_____ _____

Name of person to be tested Date

_____

Signature of the person to be tested, or of the person consenting if different from the person to be tested

I provided pretest counselling. I answered the above individual's questions about the test and offered him/her an unsigned copy of this form.

Signature _____ Title _____

Facility/provider _____

[*] This form is recommended only for cases of accidental non-intentional exposure. In cases of intentional exposure (e.g. a needle-stick or non-consensual sex), the issue of consent to be tested for HIV and the release of information about an individual's HIV status is regulated by national laws.

Annex 2. Informed consent form for exposed person

Name _____ **Record number** _____

I understand that I have had an exposure which may be a risk for HIV transmission.

I have been given the following information about post-exposure prophylaxis (PEP):
- the risk of HIV transmission with and without PEP for the specific exposure;
- the benefits of HIV testing (now, at 6 weeks, at 12 weeks and at 6 months);
- the benefits and risks of taking PEP;
- the use of PEP during pregnancy;
- that PEP is not guaranteed to prevent HIV transmission;
- the importance of receiving post test counselling;
- other recommended blood tests;
- the importance of using methods that will prevent HIV transmission (e.g. using condoms, not sharing needles and not breastfeeding) for the next six months;
- the prohibition against donating blood, semen or tissues for the next six months;
- the usual duration of PEP (four weeks) and my ability to stop at any time (though this will reduce its effectiveness);
- the importance of treatment adherence (taking the correct dose of medications at the right time);
- possible side-effects of and drug interactions with the PEP medications; and
- (for HCWs): the safe work practices that are necessary to observe for the next six months.

I have understood this information and have been given the opportunity to ask questions and have received satisfactory answers.

☐ I voluntarily consent to post-exposure prophylaxis (PEP).

☐ I decline post-exposure prophylaxis (PEP).

Name _____

Date _____ **Signature** _____

I confirm that I have explained information about PEP as above.

Name _____ **Signature** _____

Position _____ **Date** _____

Annex 3. Proposed occupational exposure report (confidential)

<table>
<tr><td colspan="2">Name (last, first, middle)</td><td colspan="2">Address (work)</td><td>Address (home)</td></tr>
<tr><td>Birth date</td><td>Sex</td><td>Position</td><td>Years in practice</td><td>Telephone no</td></tr>
<tr><td>Date/time of exposure

Date/time of consultation</td><td colspan="2">Location exposure occurred</td><td colspan="2">Activity at time of exposure</td></tr>
<tr><td colspan="5">Nature of injury (e.g. cut, splash or needle-stick, including bore of needle)</td></tr>
<tr><td colspan="5">Details of the procedure being performed, including where and how the exposure occurred</td></tr>
<tr><td colspan="5">Details of the exposure, including the type and amount of fluid or material and the severity of the exposure

Reporting officer/procedure</td></tr>
<tr><td colspan="3">Details about exposure source
The source material contained:
HBV:
HCV:
HIV:
Whether the source is HIV-infected:
Clinical disease stage:
Viral load:</td><td colspan="2">Details about exposed person
Infected with:
HBV:
HCV:
HIV:
Concomitant diseases:</td></tr>
</table>

<table>
<tr><td>History of antiretroviral treatment:

Antiretroviral resistance:
Pretest counselling provided:</td><td>Hepatitis B vaccination:
Vaccine-response status:
Pretest counselling provided:</td></tr>
<tr><td rowspan="2">Test results
HBV:
HCV:
HIV:
Post-test counselling provided:
Referral:</td><td>Test results:
HBV:
HCV:
HIV:
Post-test counselling provided:
Referral:</td></tr>
<tr><td>PEP commenced:

Informed consent obtained:

PEP regimen administered:</td></tr>
</table>

Post-exposure management:	CBC with differential	Serum liver enzymes	Signs and symptoms
Week 1 consultation			
Week 2 consultation			
Week 3 consultation			
Week 4 consultation			
HIV antibody test results 1 month: 3 months: 6 months:			
Signature/stamp			Date

Annex 4. Proposed non-occupational exposure report (confidential)

<table>
<tr><td colspan="2">Name (last, first, middle)</td><td rowspan="2">Address (work)</td><td>Address (home)</td></tr>
<tr><td>Birth date</td><td>Sex</td><td>Telephone no.</td></tr>
<tr><td colspan="4">Date/time of exposure

Date/time of consultation

Other possible exposures
• Last month:

• Last six months:</td></tr>
<tr><td colspan="4">Nature of exposure (for example injection, sexual contact)

Risks of exposure</td></tr>
<tr><td colspan="4">Details of exposure, including the type and amount of fluid or material and the severity of exposure
• Related to sexual exposure

• Related to injection exposure</td></tr>
</table>

Details about exposure source	*Details about exposed person*
Source material contained:	Infected with:
HBV:	HBV:
HCV:	HCV:
HIV:	HIV:
Whether source is HIV-infected:	Concomitant diseases:
Clinical disease stage:	
Viral load:	
History of antiretroviral treatment:	
Antiretroviral resistance (if known):	Hepatitis B vaccination:
Pretest counselling provided:	Vaccine-response status:
	Pretest counselling provided:

Test results: HBV: HCV: HIV: Post-test counselling provided: Referral:	Test results: HBV: HCV: HIV: Post-test counselling provided: Referral:
	PEP commenced (date): Informed consent obtained: yes _____ no _____ ARV regimen administered for PEP:

Post-exposure management:	CBC with differential	Serum liver enzymes	Signs and symptoms
Week 1 consultation			
Week 2 consultation			
Week 3 consultation			
Week 4 consultation			
HIV antibody test results 1 month: 3 months: 6 months:			
Pregnancy test result (for female patients)			
Signature/stamp			Date

Annex 5. Standard precautions – an aide memoire[5]

Infection control standard precautions in health care

Background

Standard precautions are meant to reduce the risk of transmission of bloodborne and other pathogens from both recognized and unrecognized sources.

They are the basic level of infection control precautions which are to be used, as a minimum, in the care of all patients.

Hand hygiene is a major component of standard precautions and one of the most effective methods to prevent transmission of pathogens associated with health care. In addition to hand hygiene, the use of **personal protective equipment** should be guided by risk assessment and the extent of contact anticipated with blood and body fluids, or pathogens.

In addition to practices carried out by health workers when providing care, all individuals (including patients and visitors) should comply with infection control practices in health-care settings. The control of spread of pathogens from the source is key to avoid transmission. Among source control measures, **respiratory hygiene/ cough etiquette**, developed during the severe acute respiratory syndrome (SARS) outbreak, is now considered as part of standard precautions.

Worldwide escalation of the use of standard precautions would reduce unnecessary risks associated with health care. Promotion of an **institutional safety climate** helps to improve conformity with recommended measures and thus subsequent risk reduction. Provision of adequate staff and supplies, together with leadership and education of health workers, patients, and visitors, is critical for an enhanced safety climate in health-care settings.

Important advice

- Promotion of a safety climate is a cornerstone of prevention of transmission of pathogens in health care.
- Standard precautions should be the minimum level of precautions used when providing care for all patients.
- Risk assessment is critical. Assess all health-care activities to determine the personal protection that is indicated.
- Implement source control measures for all persons with respiratory symptoms through promotion of respiratory hygiene and cough etiquette.

✓ Checklist

Health policy

- ☐ Promote a safety climate.
- ☐ Develop policies which facilitate the implementation of infection control measures.

Hand hygiene

- ☐ Perform hand hygiene by means of hand rubbing or hand washing (see overleaf for detailed indications).
- ☐ Hands should always be washed with soap and water if hands are visibly soiled, or exposure to spore-forming organisms is proven or strongly suspected, or after using the restroom. For other indications, if resources permit, perform hand rubbing with an alcohol-based preparation.
- ☐ Ensure availability of hand-washing facilities with clean running water.
- ☐ Ensure availability of hand hygiene products (clean water, soap, single use clean towels, alcohol-based hand rub). Alcohol-based hand rubs should ideally be available at the point of care.

Personal protective equipment (PPE)

- ☐ ASSESS THE RISK of exposure to body substances or contaminated surfaces BEFORE any health-care activity. Make this a routine!
- ☐ Select PPE based on the assessment of risk:
  - ☐ clean non-sterile gloves.
  - ☐ clean, non-sterile fluid-resistant gown.
  - ☐ mask and eye protection or a face shield.

Respiratory hygiene and cough etiquette

- ☐ Education of health workers, patients and visitors.
- ☐ Use of source control measures.
- ☐ Hand hygiene after contact with respiratory secretions.
- ☐ Spatial separation of persons with acute febrile respiratory symptoms.

[5] The overall risk of an infected HCW transmitting HIV to a patient is low. Worldwide, only two possible reports of such transmission have been reported, both during exposure-prone procedures *(43, 44)*.
Source: WHO (*48*).

Infection control standard precautions in health care

KEY ELEMENTS AT A GLANCE

1. Hand hygiene[1]

Summary technique:

- Hand washing (40–60 sec): wet hands and apply soap; rub all surfaces; rinse hands and dry thoroughly with a single use towel; use towel to turn off faucet.
- Hand rubbing (20–30 sec): apply enough product to cover all areas of the hands; rub hands until dry.

Summary indications:

- Before and after any direct patient contact and between patients, whether or not gloves are worn.
- Immediately after gloves are removed.
- Before handling an invasive device.
- After touching blood, body fluids, secretions, excretions, non-intact skin, and contaminated items, even if gloves are worn.
- During patient care, when moving from a contaminated to a clean body site of the patient.
- After contact with inanimate objects in the immediate vicinity of the patient.

2. Gloves

- Wear when touching blood, body fluids, secretions, excretions, mucous membranes, nonintact skin.
- Change between tasks and procedures on the same patient after contact with potentially infectious material.
- Remove after use, before touching non-contaminated items and surfaces, and before going to another patient. Perform hand hygiene immediately after removal.

3. Facial protection (eyes, nose, and mouth)

- Wear a surgical or procedure mask and eye protection (face shield, goggles) to protect mucous membranes of the eyes, nose, and mouth during activities that are likely to generate splashes or sprays of blood, body fluids, secretions, and excretions.

4. Gown

- Wear to protect skin and prevent soiling of clothing during activities that are likely to generate splashes or sprays of blood, body fluids, secretions, or excretions.
- Remove soiled gown as soon as possible, and perform hand hygiene.

5. Prevention of needle stick injuries[2]

Use care when:

- handling needles, scalpels, and other sharp instruments or devices
- cleaning used instruments
- disposing of used needles.

6. Respiratory hygiene and cough etiquette

Persons with respiratory symptoms should apply source control measures:

- cover their nose and mouth when coughing/sneezing with tissue or mask, dispose of used tissues and masks, and perform hand hygiene after contact with respiratory secretions.

Health care facilities should:

- place acute febrile respiratory symptomatic patients at least 1 metre (3 feet) away from others in common waiting areas, if possible.
- post visual alerts at the entrance to health-care facilities instructing persons with respiratory symptoms to practise respiratory hygiene/cough etiquette.
- consider making hand hygiene resources, tissues and masks available in common areas and areas used for the evaluation of patients with respiratory illnesses.

7. Environmental cleaning

- Use adequate procedures for the routine cleaning and disinfection of environmental and other frequently touched surfaces.

8. Linens

Handle, transport, and process used linen in a manner which:

- prevents skin and mucous membrane exposures and contamination of clothing.
- avoids transfer of pathogens to other patients and or the environment.

9. Waste disposal

- Ensure safe waste management.
- Treat waste contaminated with blood, body fluids, secretions and excretions as clinical waste, in accordance with local regulations.
- Human tissues and laboratory waste that is directly associated with specimen processing should also be treated as clinical waste.
- Discard single use items properly.

10. Patient care equipment

- Handle equipment soiled with blood, body fluids, secretions, and excretions in a manner that prevents skin and mucous membrane exposures, contamination of clothing, and transfer of pathogens to other patients orthe environment.
- Clean, disinfect, and reprocess reusable equipment appropriately before use with another patient.

[1] For more details, see: WHO guidelines on hand hygiene in health care: (http://www.who.int/patientsafety/information_centre/ghhad_download/en/index.html).
[2] The SIGN Alliance: (http://www.who.int/injection_safety/sign/en/).
Source: WHO (*48*).

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