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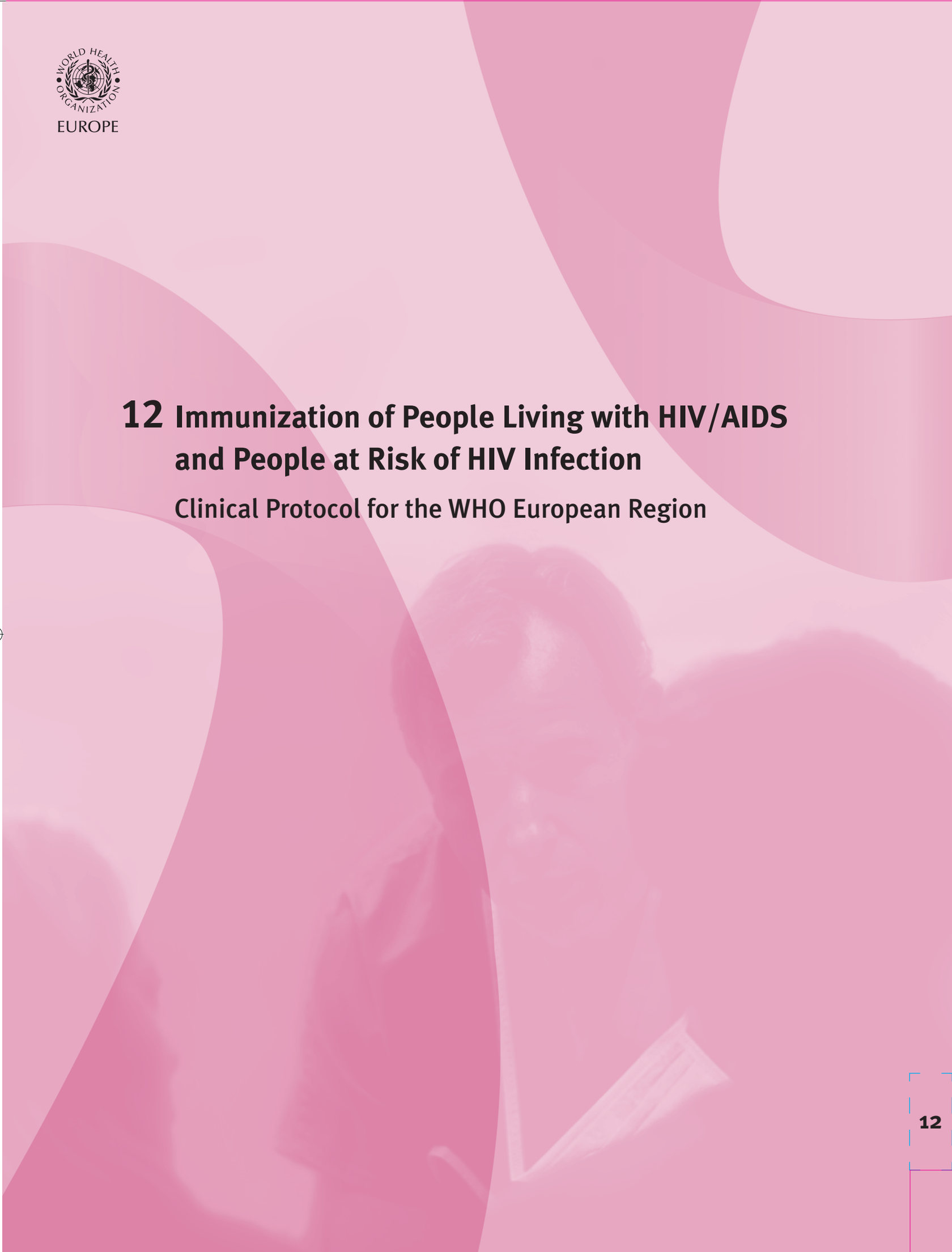
12 Immunization of People Living with HIV/AIDS and People at Risk of HIV Infection

Clinical Protocol for the WHO European Region



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12 Immunization of People Living with HIV/AIDS and People at Risk of HIV Infection

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Table of contents

Abbreviations

AEFI	adverse event following immunization
AIDS	acquired immune deficiency syndrome
ART	antiretroviral treatment
BCG	bacille Calmette-Guérin
CD4 cell	cluster of differentiation antigen 4 cell (a subgroup of T lymphocytes)
DT	diphtheria and tetanus toxoids (for paediatric use)
DTaP	diphtheria, tetanus and acellular pertussis
DTP	diphtheria, tetanus and pertussis
HAV	hepatitis A virus
HBcAb	hepatitis B core antibody
HBIg	hepatitis B immunoglobulin
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HiB	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HNIg	human normal immunoglobulin
HRIg	human rabies immunoglobulin
Ig	immunoglobulin
IPV	inactivated poliovirus vaccine
IgIV	intravenous immunoglobulin
IU	international unit
M	measles
MCV	measles-containing vaccine
MMR	measles, mumps and rubella
MR	measles and rubella
MSM	men who have sex with men
OPV	oral poliovirus vaccine
PCV	pneumococcal conjugate vaccine
PLWHA	people living with HIV/AIDS
PPV	pneumococcal polysaccharide vaccine
R	rubella
STI	sexually transmitted infection
TB	tuberculosis
Td	tetanus and diphtheria toxoids (for adult use)
TIg	tetanus immunoglobulin
TLC	total lymphocyte count
TT	tetanus toxoid
Ty21a	a live, attenuated typhoid strain
VZIg	varicella-zoster immunoglobulin
VZV	varicella-zoster virus
WHO	World Health Organization

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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 PLWHA

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/AIDS (PLWHA) 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 PLWHA 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 PLWHA 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)*.

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.

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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 PLWHA 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 PLWHA.

[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.

[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.

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 PLWHA 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)

Although a live, attenuated oral cholera vaccine (using CVD 103-HgR strain) has been used in HIV-endemic areas without serious adverse events, it 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 PLWHA 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)*.Recommendations
- MMR and other MCVs should not be administered to PLWHA, either children or adults, who show evidence of moderate or severe immunosuppression, defined as CD4 <15% of TLC for children <13 years old or <14% of TLC for those ≥13 years old[7] *(15–17)*.
- MMR and other MCVs should be considered for HIV-infected patients who are asymptomatic or mildly immunosuppressed, if eligible.
- 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 PLWHA) should also be vaccinated.

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[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.

[7] Children with moderate or severe immunosuppression are those with CD4 counts:
- <750 cells/mm3 when <12 months old
- <500 cells/mm3 when 1–5 years old
- <200 cells/mm3 when ≥6 years old.

1.4. Oral poliovirus vaccine (OPV)

Although asymptomatic HIV-infected children can be vaccinated with OPV *(1, 18)*, inactivated poliovirus vaccine (IPV) is the recommended vaccine for both symptomatic and asymptomatic children (see section III.2.9 below for IPV).

HIV-infected individuals should not be vaccinated with OPV, as they may be unable to limit replication of the vaccine virus effectively. Administration of OPV to children with congenital immunodeficiency has resulted in severe, progressive neurological involvement (paralytic disease) *(19–22)*.

If OPV is inadvertently administered to a household member or other familiar[8] (regardless of prior immunization status) of someone with HIV, close contact between them should be avoided for approximately one month after vaccination, which is the period of maximum excretion of the vaccine virus.

Recommendation

- OPV should not be administered to PLWHA, either children or adults, regardless of their immunodeficiency status, or to members of their household or other close contacts.

1.5. Rotavirus vaccine

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)*.

Recommendation

- Ty21a vaccine should not be administered to PLWHA, 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)*.

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.

[8] Defined as someone who risks transmitting live poliomyelitis vaccine virus to an HIV-infected person through faecal or oral contact.

Susceptible household contacts (especially children) of PLWHA 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)*.

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 PLWHA 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)*.

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)

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 (*26*).

A vaccine consisting of killed whole-cell *V. 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 2-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 (*27*). These observations indicate a potential benefit of vaccination in those with early and moderately advanced clinical HIV disease (*28*).

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).

2.2. Diphtheria, tetanus and pertussis vaccines (DTP, DTaP, DT, TT and Td[9])

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 5 do not need HiB vaccination, due to age-dependent susceptibility to the disease. 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 may be vaccinated. Previously unvaccinated HIV-infected individuals older than 5 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.

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)*.

2.4. 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 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.

[9] 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).

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;[10]
- men who have sex with men (MSM);
- drug users;[11]
- 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.[12]

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 *(33)*.

2.5. Hepatitis B vaccine

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.

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

[10] 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).

[11] 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, 31)*.

[12] 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 *(32)*.

[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)*.

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.[14]

2.5.1. 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.

2.5.2. 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.

2.5.3. Monitoring and strategy after HBV vaccination of HIV-infected patients

- 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)).
- 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[15]

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)*. Although there is currently little information regarding the frequency and severity of influenza in PLWHA *(37)*, vaccination is recommended for all PLWHA before the annual influenza season. The

[14] 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.

[15] Since live influenza vaccine is contraindicated in PLWHA, inactivated influenza vaccine should be used.

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

Routine immunization with meningococcal vaccine containing appropriate serotypes[16] 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

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)*. Two types of pneumococcal vaccine are available: pneumococcal polysaccharide vaccine (PPV) and pneumococcal conjugate vaccine (PCV).

2.8.1. Pneumococcal polysaccharide vaccine (PPV)

One dose of PPV should be administered routinely, irrespective of HIV and immune status, to everyone who is older than 65; to immunocompetent people who are older than 2[17] and have chronic illness (cardiovascular disease, pulmonary disease, diabetes, alcoholism, cirrhosis or cerebrospinal fluid leaks); and to immunocompromised people (including PLWHA)[18] who are older than 2 and are at risk for pneumoccal disease. People with asymptomatic or symptomatic HIV infection should be vaccinated as soon as possible after their diagnosis is confirmed *(41)*. If vaccination status is unknown, patients with HIV infection and others with immunosuppression (including those receiving long-term systemic corticosteroids) should be vaccinated *(41)*.

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.

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. PLWHA 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.[19]

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[16] 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.

[17] In children <2 years old, antibody response with PPV to most serotypes is generally poor.

[18] Including (in addition to PLWHA) 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).

[19] Presently, there are not much data for PLWHA response to PCV, other than from South Africa and smaller studies in the United States.

- 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. However 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)

If polio immunization is indicated, IPV should be administered to infants and children infected with HIV regardless of their immune status, and to household contacts and nursing personnel in close contact with PLWHA in order to prevent transmission of vaccine and/or vaccine-derived polioviruses to PLWHA. For unvaccinated HIV-infected adults at increased risk of exposure to poliovirus, 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. 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).

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. Therefore, 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).

Rabies antibody titres >0.5 IU/ml are required for protection. 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)*.

2.11. Tick-borne encephalitis vaccine

Tick-borne encephalitis, caused by tick-borne encephalitis virus, infections occur in many parts of Europe (Austria, Germany, southern and central Sweden, Hungary, France (Alsace), Switzerland, Norway, Denmark, Poland, Croatia, Albania, Estonia, Latvia, Lithuania, Czech and Slovak Republics and Russian Federation, corresponding to the distribution of the tick reservoir. The disease has been known by several names, including the Russian spring-summer encephalitis (RSSE), Far Eastern encephalitis and the 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[20] 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*).

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*).

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. The booster recommendation is the same for HIV-infected individuals as for immunocompetent people.

2.12. Typhoid vaccine (Vi polysaccharide)

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*).

A paranteral 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.

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*). 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.

Typhoid vaccines are not 100% protective and responses may be further reduced in PLWHA. As 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. Travellers should be advised to follow strict food and drink precautions.

[20] 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.

2.13. Other killed antigens

Other vaccines containing killed antigens, including Japanese encephalitis, plague and anthrax, do not pose a risk to PLWHA, regardless of their immunological status. 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)

Immunocompromised people, including PLWHA, should receive HBIg for the same indications and in the same doses as immunocompetent people. 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.

As a rule, HBIg should be used as an adjunct to hepatitis B vaccine. Conversely, 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[21] 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;[22]
- 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;[23] 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.[24]

3.2. Human normal immunoglobulin (HNIg)

3.2.1. Hepatitis A

For the prevention of hepatitis A,[25] 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)*.

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[21] 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)*.

[22] 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.

[23] HBIg is not needed for infants who have received or are scheduled to receive a second dose of vaccine.

[24] Routine hepatitis B vaccination should also be considered for nonsexual household contacts without blood exposure, especially children and adolescents.

[25] 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.

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;
- 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

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)

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)

Immunocompromised people, including PLWHA, should receive TIg for the same indications and in the same doses as the immunocompetent do. TIg is recommended for people with tetanus and to prevent tetanus in inadequately immunized people with wounds or other conditions associated with tetanus. TIg neutralizes circulating unbound tetanus toxin. It does not affect toxin that has reached the nervous system. 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 or who have an uncertain history of TIg immunization, in which cases Td toxoids should also be administered;[26]

[26] 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.

- 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 PLWHA, 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.

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)*.

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

Vaccine	Infants and children	Adults	Non-routine immunization
Anthrax	—	—	Use if indicated
BCG	Contraindicated/consider[a]	—	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[b]	—
Influenza[c]	—	—	Use if indicated
IPV	Recommended	—	Use if indicated
Japanese encephalitis	—	—	Use if indicated
Meningococcal	—	—	Use if indicated
MMR/MR/M/R	Recommended/consider[d]	Consider[d]	—
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[e]
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 for column.
[a] Refer to specific considerations for BCG vaccine in section III.1.1.
[b] Refer to specific considerations for HiB vaccine in section III.2.3.
[c] Note that live influenza vaccines are contraindicated. If influenza vaccine is indicated, use an inactivated one.
[d] Refer to specific considerations for MMR vaccine in section III.1.3.
[e] Refer to specific considerations for varicella vaccine in section III.1.7.

Annex 2. Classification of HIV-associated immunodeficiency

Table 2. Classification of HIV-associated immunodeficiency

Classification	Age-related CD4 values			
	<11 months (%)	**12–35 months (%)**	**36–59 months (%)**	**≥5 yearsa (cells/mm³)**
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–30	20–25	15–20	200–349
Severe	<25	<20	<15	<200 or <15%

[a] Including adolescents and adults.
Source: WHO, 2006 *(45)*.

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[27] who may be exposed to rabies hosts.[28]

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.[29] The indication for post-exposure vaccination with these vaccines (with or without rabies immunoglobulin) depends on the type of contact with the rabid animal.[30] 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.[31] 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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[27] 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)*.

[28] According to age-stratified studies of incidence, those at greatest risk are probably children living in rabies-enzootic regions of the developing world *(23)*.

[29] 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).

[30] 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.

[31] 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 adolescent*s, 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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