European AIDS Clinical Society (EACS)

Guidelines on the Prevention and Management of Metabolic diseases in HIV

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Acknowledgements: The guidelines panel have received helpful comments and suggestions from the following persons: Heiner Bucher, David Burger, Nina Friis-Møller, Jose Gatell, Markku Saraheimo, Signe Worm & Hannele Yki-Järvinen

Abbreviations used throughout this document

- ABC=abacavir
- ART=antiretroviral therapy
- ATV=atazanavir
- CVD=cardiovascular disease
- d4T=stavudine
- ddI=didanosine
- DRV=darunavir
- EFV=efavirenz
- HBV=hepatitis B virus
- HCV=hepatitis C virus
- HDL-c=HDL-cholesterol
- IHD=ischemic heart disease
- LDL-c=LDL-cholesterol
- IDV=indinavir
- LPV=lopinavir
- NFV=nelfinavir
- NNRTI=non-nucleoside reverse transcriptase inhibitors
- NRTI=nucleos(t)ide reverse transcriptase inhibitors
- NVP=nevirapine
- PI=protease inhibitors
- PI/r=protease inhibitors pharmacologically boosted with ritonavir
- RTV=ritonavir (if used as booster= /r)
- SQV=saquinavir
- TC=total cholesterol
- TG=triglycerides
- TDF=tenofovir
- TPV=tipranavir
- ZDV=zidovudine

HIV specific issues to be considered in managing metabolic diseases

In HIV infection, both uncontrolled replication of HIV, co-infections (e.g. HCV) and ART contribute to metabolic diseases. The prevention and management of metabolic diseases in HIV should take all these factors into consideration.

Health care professionals involved with the care of HIV-infected persons who are not familiar with the use of ART should consult HIV specialists before introducing or modifying any type of treatment that HIV patients receive.

Conversely, many HIV physicians are not specialists in metabolic diseases, and should seek proper consultation prior to engaging in the prevention and management of such conditions. Situations where consultation is generally recommended are indicated where appropriate in these guidelines.

Preventing or managing metabolic diseases in HIV often involves polypharmacy, which increases the risk of suboptimal adherence and hence may compromise the continued benefit of ART. Additionally, the possibility of drug-drug interactions with ART should be carefully considered prior to introducing any treatment. Several web-sites exist for this purpose: www.HIV-druginteractions.org, www.HIVpharmacology.com, www.AIDSinfo.nih.gov.

There is limited amount of evidence from randomised controlled trials on how to most effectively manage metabolic diseases in HIV. As a result *management currently is mainly extrapolated from general medical guidelines*. Based on future clinical research findings, these guidelines will be regularly updated, at www.eacs.eu. The guidelines posted on the web, as well as updated versions will contain much more detailed information and links to any other relevant websites.

The current guidelines highlight metabolic diseases, which are seen frequently in the routine care of HIV-infected persons and those for which specific issues should be considered.

Other related conditions in the management of HIV disease that are not or not extensively discussed, but may be included in future versions are:

- *Renal impairment.* Both factors related to HIV and certain antiretroviral drugs may impair renal function. Various drugs used in HIV care may need dose adjustment in case of impaired renal function.
- The contribution of HIV as well as ART to *bone disease, which may include loss of bone mineral content and aseptic necrosis of the femoral head*, remains unclear. For the moment these pathologies should be managed as in the general population.
- *Sexual dysfunction* is frequently encountered and its management often requires a multidisciplinary approach that may include both expert psychological counselling and medical interventions.

Screening for metabolic diseases in patients with HIV

	Assessment	Which Patient?	Frequency of assessment
History	• Family history for premature IHD[i], diabetes, hypertension • Concomitant therapy against dyslipidaemia/hypertension/ diabetes • Concomitant therapy with risk for diabetes/dyslipidaemia[ii] • Current lifestyle (alcohol use, smoking, aerobic exercise)	Every patient	At HIV-diagnosis At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated[iv]
Lipids[iv]	• Fasting[iii] TC • Fasting[iii] TG • Fasting[iii] LDL-c+HDL-c	Every patient	At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated[iv]
Glucose[v]	• Fasting[iii] glucose	Every patient	At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated[iv]
Body composition	• Body-mass index • Waist circumference • Waist-to-hip ratio • Clinical lipodystrophy assessment	Every patient	At HIV-diagnosis, before start of ART, annually thereafter
Hypertension	• Blood pressure	Every patient	HIV-diagnosis, before ART, annually thereafter unless specifically indicated[iv]
Cardiovascular disease	• Risk assessment[vi] • ECG	Every patient	Before ART, and annually thereafter Annually
Renal failure	• Estimated glomerular filtration rate[vii]	Patient receiving drugs cleared via the kidneys	Before initiation of drug in question, after 4 weeks, 6 months and if remaining normal then once annually

i Cardiovascular events in a first degree male relative < 55 years or in a first degree female relative < 65 years.

ii E.g. neuroleptic drugs including clozapin, olanzapin; pentamidine, glucocorticoids, IFN-a, thiazide diuretics, furosemide, phenytoin, diazoxide, and others.

iii Fasting defined as a time period without caloric intake of at least 8 hours

iv Assessment and monitoring should increase in frequency in case of severe dyslipidaemia (see 26), elevated blood pressure (see 36) or elevated fasting blood glucose levels (see 32) and/or if medical interventions are instituted to correct these conditions.

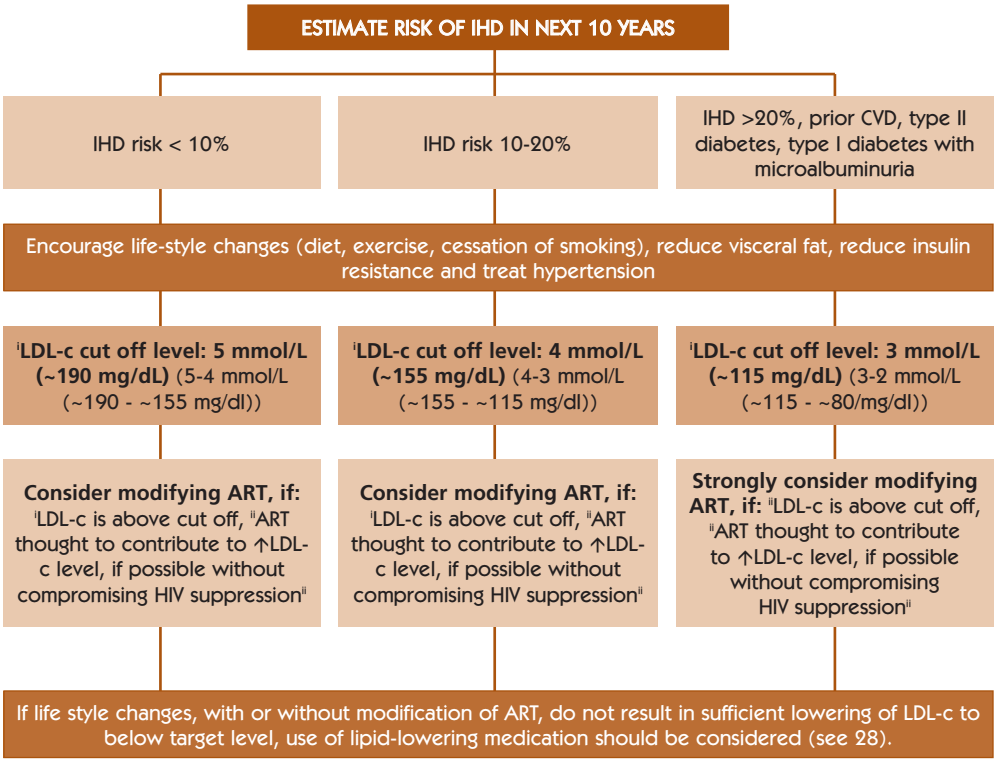
v Oral glucose tolerance test may be considered if repeated fasting glucose levels are in the range of 6.1-6.9 mmol/L (110-125 mg/dL) as it may reveal the presence of diabetes in such patients

vi Use risk calculators for estimating 10-year risk of developing IHD events - http://www.chip.dk/tools.aspx. Of note, if individual patients receive medication to control dyslipidaemia and/or hypertension, interpretation of the estimation should be done with caution.

vii Use calculator to estimate glomerular filtration rate (eGFR) according to Cockcroft- Gault - http://www.cphiv.dk/TOOLS.aspx

Prevention of cardiovascular disease

Principles: The intensity of efforts to prevent cardiovascular disease depends on the absolute risk of IHD, using Framingham equation (see http://www.cphiv.dk/tools.aspx). The preventive efforts are diverse in nature and require involvement of cardiologists, in particular if the risk of IHD is high.



i LDL-c cut off levels (unit: mmol/L (mg/dL)) are higher than in guidelines for the general population (more stringent levels where some experts would consider intervention also indicated in parenthesis below). In cases where LDL-c cannot be reliably calculated because of high triglyceride levels, the non-HDL-c target level should be used which is 0.8 mmol/L (30 mg/dl) higher than the corresponding LDL-c target.

ii Options for ART modification include: (1) replacing PI(/r) by NNRTI, by another PI(/r) known to cause less metabolic disturbances (see 30) or by abacavir; should not be done if patient is known or suspected to harbour archived virus containing drug-related mutations against the new drug the patient is switched to (switch to abacavir should not be done in case (archived) thymidine analogue mutations are known or suspected to be present (e.g. due to prior use of suboptimal mono- or dual NRTI therapy)); (2) replacing d4T or ZDV by ABC or TDF. In patients with >20% 10 year risk or with prior CVD, the risk of CVD events and cardiac death will usually be higher than risk of progression to AIDS or death and in such patients a strategy to reduce risk of CVD by switching ART is hence most appropriate.

- Blood-pressure: ↑treat hypertension (see 36).
- TG levels: Uncertain if TG↑ contributes to CVD risk and whether it should be treated (see 28).
- Low dose acetylsalicylic acid: Only indicated in high-risk patients (right column above) as risk of intracerebral bleeding increased by 25% and extracerebral bleeding by 50%; harm likely exceeds benefit if risk of IHD is lower.
- Combined benefit of interventions: Per 10 mmHg reduction of systolic blood pressure, per 1 mmol/L reduction in TC and with use of low dose acetylsalicylic acid, each reduces risk of IHD by 20-25%; the effect is additive. Smoking cessation reduces risk of IHD the most - by 50% - and this is additive to other interventions.

Life style interventions[i]

Intervention	Principles
Stop smoking counselling	• Brief unambiguous statement about need to stop smoking • If patient is not contemplating, try to motivate and emphasize positive short-term aspects (more money for better things, better taste for food, better skin, less dyspnoea), and long-term benefits (prevention of COPD, IHD, stroke, lung cancer) • If patient is contemplating, try to fix stop date, establish reward system • Use nicotine substitution (patch, chewing gum, spray), varenicline, or bupropion (note: bupropion may interact with PI and NNRTI) during weaning phase if necessary • Consider referring patient to specialized stop smoking clinic • Anticipate relapses, explain and consider them as part of the weaning process to final nicotine abstinence
Diet counselling	• Limit intake of saturated fat and cholesterol • Reduce total fat intake to < 30% and dietary cholesterol to <300mg/day • Emphasize intake of vegetables, fruits, grain products with fibre • Emphasize consumption of fish, poultry (without skin), lean meat and low fat dietary intake • Keep caloric intake balanced with energy expenditure • Consider referral to dietician, one week food and drink diary to discover 'hidden' calories • Avoid binge eating ('yo-yo dieting') • In patients with HIV-related wasting and dyslipidaemia address wasting first and consider referral to dietician • Patients with BMI >30 kg/m^2 should be motivated to lose weight. Starvation diets are not recommended in an HIV-infected person (immune defence mechanisms potentially decreased). Malnutrition has to be addressed where observed. Normal BMI range: 18.5-24.9; Overweight: 25.0-29.9, Obesity: > 30.0 kg/m^2
Exercise	• Promote active lifestyle to prevent obesity, hypertension and diabetes • Emphasize regular moderate-intensity exercise rather than vigorous exercise • Encourage self-directed moderate level physical activity (take the stairs, bike or walk to work, cycling, swimming, hiking etc.) • Achieve cardiovascular fitness (e.g. 30 minutes brisk walking 5/7 days a week) • Maintain muscular strength and joint flexibility

i Based on recommendations by the US Preventive Services Task Force. Detailed guidelines with evidence grading (fulltext) available at http://odphp.osophs.dhhs.gov/pubs/guidecps/pcpstoc.htm

Management of dyslipidaemia

Principles: Higher LDL-c levels increase risk of CVD and reduction thereof reduces this risk; the reverse is true for HDL-c.

Conversely, the CVD risk implications from higher than normal levels of TG are less clear, as is the clinical benefit of treating moderate hypertriglyceridaemia. Diet, exercise and maintaining normal body weight tends to reduce dyslipidaemia; if not effective, consider change of ART and then consider lipid-lowering medication in high-risk patients (see 22).

Drugs used to treat dyslipidaemia

Drug class	Drug	Dose	Benefit		Side effects	Advise on use of statin together with ART	
						Use with PI/r	Use with NNRTI
Statin	Atorvastatin	10-80 mg QD	LDL-c↓[ii]		Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Relative contraindicated	Consider higher dose[iv]
	Fluvastatin	20-80 mg QD	LDL-c↓[i]			Consider higher dose[iv]	Consider higher dose[iv]
	Pravastatin	20-80 mg QD	LDL-c↓[i]			Consider higher dose[iv-vi]	Consider higher dose[iv]
	Rosuvastatin	5-40 mg QD	LDL-c↓[ii]			Start with low dose[v]	Start with low dose[v]
	Simvastatin	10-80 mg QD	LDL-c↓			Contraindicated	Consider higher dose[iv]
Cholesterol uptake↓	Ezetimibe	10 mg QD	LDL-c↓[iii]		Gastrointestinal symptoms	No known drug-drug interactions with ART	
Nicotinic acid derivative	Acipimox	1.0-1.5 g QD	TG↓		Flushing, rash, headache, gastrointestinal symptoms		
Fibrate	Bezafibrate	400 mg QD	TG↓		Gastrointestinal symptoms, toxic hepatitis, myopathy and rhabdomyolysis		
	Fenofibrate	67-267 mg QD	TG↓				
	Ciprofibrate	100 mg QD	TG↓				
	Gemfibrozil	900 mg QD/600 bid	TG↓				
Omega 3 acid ester	MaxEPA	5 g bid	TG↓				
	Omacor	1-2 g bid	TG↓				

i, ii, iii Expected range of reductions of LDL-c: [i]0.8-1.5 mmol/L (35-60 mg/dL), [ii]1.5-2.5 mmol/L (60-100) mmol/L, [iii]0.2-0.5 mmol/L (10-20 mg/dL)

iv, v The ART drug may [iv]induce (=less effect of statin, ↑dose gradually to achieve expected benefit[i,ii]) or [v]inhibit (statin toxicity, ↓dose) the excretion of the statin.

vi **Exception:** If used with **DRV/r**, start with **lower** dose of pravastatin.

Treatment recommendations

Type of dyslipidaemia	First choice[i]	Combination therapy [i]
Isolated hypercholesterolaemia (LDL-c > cut-off (see 22))	Statin[ii]	+ Ezetimibe
Combined hyperlipidaemia (LDL-c > cut-off (see 22) and TG 5 - 10 mmol/l[iii])	Statin[ii]	+ Fibrate[iv] (/nicotinic acid derivative)
Isolated hypertriglyceridaemia (TG 2.3-10 mmol/L[iii])	Diet, alcohol abstinence	–
Severe hypertriglyceridaemia (> 10 mmol/l[iii])	Fibrate	+ Omega 3 acid ester (/nicotinic acid derivative)
Isolated low HDL-c (< 0.9 mmol/L)	Fibrate	+ Nicotinic acid derivative

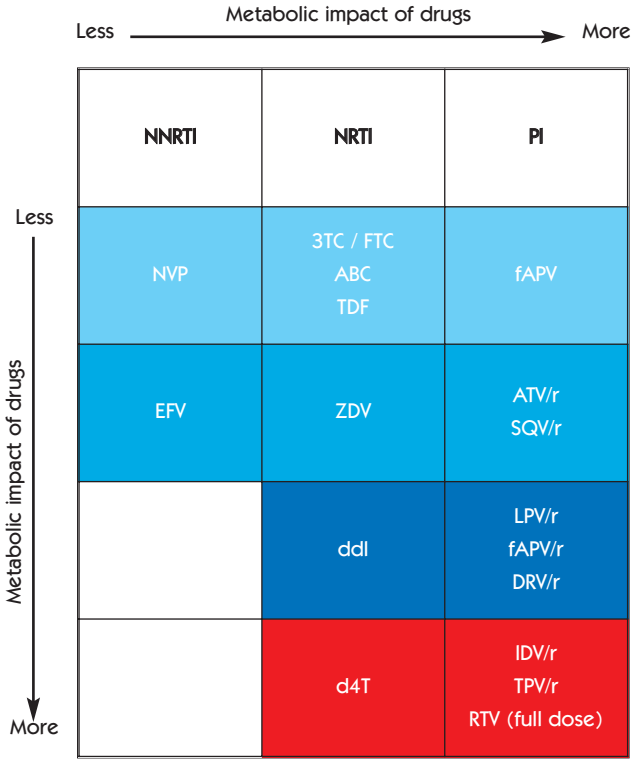
i Treatment goal is to reduce LDL-c < cut-off levels (see 22). Check lipids (fasting) prior to initiation of therapy, 4-12 weeks after initiation or modification of therapy, and annually once levels are below cut off levels. Consult with lipid expert if treatment goal cannot be reached.

ii Check AST (< x 3 ULN) and CK (< x5 ULN) prior to initiation, 4-12 weeks after treatment initiation, and then annually if within normal range.

iii It is not clear whether these levels of elevated TG carry an excess CVD risk; priority should be given to reducing LDL-c to below cut-off levels (see 22).

iv Combination therapy of statin and gemfibrozil (and less so other fibrates) increases risk of rhabdomyolysis and should be avoided whenever possible.

Metabolic impact of individual antiretroviral drugs & drug classes[i]



i Limited data from use of fusion inhibitors (enfuvirtide), integrase inhibitors (raltegravir), and CCR5 inhibitors (maraviroc) suggest these drugs to have little metabolic impact, but length of experience for some of these is limited

Prevention and management of lipodystrophy

Lipoatrophy

Prevention

- Avoid d4T and ZDV or pre-emptively switch away from them

Management

- Modification of ART
  - Switch d4T or AZT to ABC or TDF:
    - ✓ Only ART modification proven to partially restore subcutaneous fat; increase in total limb fat ~400-500g/year
    - ✓ Risk of new toxicity (ABC hypersensitivity reaction?; TDF associated nephrotoxicity?)
  - Switch to regimen not including NRTIs
    - ✓ Increase in total limb fat ~400-500g/year
    - ✓ May increase risk of dyslipidaemia
    - ✓ Less data on virological safety
- Surgical intervention
  - Offered for cosmetic relief of facial lipoatrophy only; fillers may be absorbable (limited effect) or permanent (durability of desired cosmetic effect is unknown)[i]
  - Limited randomized trials and no comparative studies of different approaches
- Pharmacological interventions to treat lipoatrophy have not been proven to be effective and may introduce new complications
  - Pioglitazone - possibly beneficial in patients not taking d4T
  - Rosiglitazone and Pioglitazone - improvement in insulin sensitivity
  - Rosiglitazone: increases in blood lipids and possible IHD.

Lipohypertrophy

Prevention

- No proven strategy
- Weight gain expected with effective ART
- Weight reduction or avoidance of weight gain may decrease visceral adiposity

Management

- Diet and exercise may reduce visceral adiposity;
  - Limited data, but possibly reduction of visceral adipose tissue and improvement in insulin sensivity and blood lipids, especially in obesity associated with lipohyperthrophy
  - No prospective trials in HIV-infected patients to definitely indicate degree of diet and/or exercise needed to maintain reduction in visceral fat.
  - May worsen subcutaneous lipoatrophy
- Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects and may introduce new complications
  - Growth hormone
    - ✓ Decreases visceral adipose tissue
    - ✓ May worsen subcutaneous lipoatrophy, may worsen insulin resistance
  - Metformin
    - ✓ Decreases visceral adipose tissue in insulin resistant persons
    - ✓ May worsen subcutaneous lipoatrophy.
  - Surgical therapy can be considered for localised lipomas/buffalo humps
    - ✓ Duration of effect variable

i See (http://www.eacs.eu/guide/index.htm) for list of arguments for and against the use of various types of fillers and some examples of specific types

Treatment of type 2 diabetes

Diagnostic criteria[i]			
	Fasting plasma glucose mmol/l (mg/dl)[ii]		Oral glucose tolerance test (OGTT) 2-h value mM (mg/dl)[iii]
Diabetes	≥ 7.0 (126)	OR ----------→	≥ 11.1 (200)
Impaired glucose tolerance (IGT)	< 7.0 (126)	AND ----------→	7.8 - 11.0 (140 - 199)
Impaired fasting glucose (IFG)	6.1 - 6.9 (110 - 125)	AND ----------→	< 7.8 (140)

i As defined by WHO and International Diabetes Federation (2005)
ii An abnormal finding should be repeated before confirming the diagnosis.
iii Is recommended in patients with fasting blood glucose 6.1 - 6.9 mmol/L (110 - 125 mg/dL) as it may diagnose patients with overt diabetes.

Both IGT and IFG increase CV morbidity and mortality, and increase the risk of developing diabetes by 4-6 fold. These patients should be targeted for life style intervention, and their CV risk factors must be evaluated and treated.

Interventions for treatment of diabetes (only interventions studied in persons receiving ART)				
Intervention	Dose	Expected decrease in HbA1c (%)	Side-effects	Comments
Life-style intervention		1 - 2		Intra-abdominal and subcutaneous fat may↓
Metformin	Start with 500-750mg qd/bid, increase to maximum tolerated dose of 2 (-3) g/d in 4-6 weeks	1.5	Gastrointestinal symptoms, lactic acidosis (rare). Contraindicated in renal insufficiency.	May worsen lipoatrophy
Thiazolidinediones: Rosiglitazone Pioglitazone	4-8mg/d, 15-45 mg/d	0.5 - 1.4	Fluid retention, cardiac failure, weight gain	See also 30
Insulin	See below	No limit	Hypoglycemia, weight gain.	Large doses may be required (1-2 IU/kg).

Individualise treatment: metformin for an overweight patient, pioglitazone (rosiglitazone) for a lipoatrophic patient. Metformin and glitazones can be combined. Diabetes is typically a progressive disease and medication must be modified accordingly. There are currently no data on the use of other antidiabetic drugs (sulfonylureas, glinides, exenatide, alpha-glucosidase inhibitors) in the treatment of HIV-infected patients taking ART. If treatment target cannot be reached with oral agents, insulin should be started. Start with 10 IU of long-acting insulin at bedtime. Teach the patient to self-monitor fasting glucose values and increase the dose by 2 units every 3 days until fasting plasma glucose < 6.1 mmol/l. Oral metformin should be continued with insulin therapy.

Management of patients with diabetes

Treatment goals: glucose control (HbA1c < 6.5-7.0% without hypoglycemias, fasting plasma glucose 4-6 mmol/l (73-110 mg/dl)); normal blood lipids and blood pressure (see 22 and 36).

Acetylsalisylic acid (75-150mg/d) should be considered in all patients with diabetes.

Nephropathy and retinopathy screening should be performed as in diabetic patients without HIV.

Consultation with a specialist in diabetology is recommended.

Further reading: www.easd.org
http://www.who.int/diabetes/publications

Prevention and management of hyperlactataemia

Risk factors	Prevention / Diagnosis	Symptoms
✓ Use of d4T > ZDV > ddI ✓ HCV/HBV co-infection ✓ Use of ribavirin ✓ Liver disease ✓ Low CD4 cell count ✓ Pregnancy ✓ Female sex ✓ Obesity	✓ Avoid d4T + ddI combination ✓ Routine monitoring of serum lactate levels not recommended - does not predict risk of lactic acidosis. ✓ Measurement of serum lactate, bicarbonate & arterial blood gases+pH indicated in case of symptoms suggestive of hyperlactataemia ✓ Close monitoring if > 1 risk factors	✓ Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, weight loss ✓ Acidaemia: asthenia,dyspnoea, arrhythmias ✓ Guillain-Barré-like syndrome

Management

Serum Lactate (mmol/L)	Symptoms	Action
> 5[i]	Yes/No	• Repeat test under standardized conditions to confirm & obtain arterial pH and bicarbonate[i] • If confirmed, exclude other obvious causes ✓ Arterial pH↓ and/or bicarbonate↓[i]: Stop NRTIs ✓ Arterial pH and/or bicarbonate normal: Consider switch from high to low risk NRTI & monitor carefully OR Stop NRTI's
2-5	Yes	• Exclude other causes; if none found: watchfully follow up OR consider switch from high to low risk NRTI, OR Stop NRTI
2-5	No	• Repeat test ✓ if confirmed: watchfully follow up
<2		• None

i Lactic acidosis is a rare but life-threatening situation usually associated with symptoms; high risk if serum lactate > 5 and especially > 10 mmol/L.

Management of lactic acidosis (irrespective of serum-lactate level): Admit patient. Stop NRTI's. Provide intravenous fluid support. Vitamin supplementation can be used (vitamin B complex forte 4 ml bid, riboflavin 20 mg bid, thiamine 100 mg bid; L-carnitine 1000 mg bid), although benefit not well documented

Management based on blood pressure measurement / diagnosis of hypertension -1/2-

Recommendation for intervention from stratification based on blood pressure level and other risk factors

	Blood pressure (mmHg)[i] - levels				+ diagnosis & grading of hypertension	
Other risk factors and disease history	**Normal:** SBP 120-129 or DBP 80-84	**High normal:** SBP 130-139 or DBP 85-89	**Grade 1:** SBP140-159 or DBP 90-99		**Grade 2:** SBP 160-179 or DBP100-109	**Grade 3:** SBP > 180 or DBP > 110
No other risk factors	Average risk	Average risk	Low added risk		Moderate added risk	High added risk
	No BP intervention	No BP intervention	Lifestyle changes for several months[ii], then possible drug therapy[iii]		Lifestyle changes for several months[ii], then drug therapy[iii]	Immediate drug therapy[iii] and lifestyle changes[ii]
1-2 risk factors[iv]	Low added risk	Low added risk	Moderate added risk		Moderate added risk	Very high added risk
	Lifestyle changes[ii]	Lifestyle changes[ii]	Lifestyle changes for several months[ii], then drug therapy[iii]		Lifestyle changes for several months[ii], then drug therapy[iii]	Immediate drug therapy[iii] and lifestyle changes[ii]
3 or more risk factors[iv] or target organ disease[v] or diabetes	Moderate added risk	High added risk	High added risk		High added risk	Very high added risk
	Lifestyle changes[ii]	Drug therapy[iii] and lifestyle changes[ii]	Drug therapy[iii] and lifestyle changes[ii]		Drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]
Associated clinical conditions[vi]	High added risk	Very high added risk	Very high added risk		Very high added risk	Very high added risk
	Drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]		Immediate drug therapy[iii] and lifestyle changes[ii]	Immediate drug therapy[iii] and lifestyle changes[ii]

Management based on blood pressure measurement / diagnosis of hypertension -2/2-

i SBP =systolic blood pressure; DBP = diastolic blood pressure. Repeated blood pressure measurements should be used for stratification

ii Recommended life style interventions - see 24. Table adapted from J. Hypertension 2003; 21:1779-86.

iii Drug therapy can be initiated either with a low dose of a single agent or with a low dose combination of two agents. To reach target blood pressure, a proportion of patients will require combination therapy. For indications and contraindications for the major classes of antihypertensive drugs see (http://www.eacs.eu/guide/index.htm).

Medical treatment of uncomplicated hypertension: 1st choice: Thiazide or ACE-inhibitor, 2nd choice: Amlodipine (start with 5mg QD) or combination of two antihypertensives. Await (2-) 6 weeks of therapy to assess lowering of the blood-pressure. Grade 3 hypertension or lack of achievement of goal (see below) 2-6 weeks after commencing 2nd choice: consult hypertension expert. Coadministration of PIs and calcium channel blockers (CCB) may result in significantly increased CCB-plasma concentrations resulting in increased risk of toxicity and prolonged effect; NNRTI's may decrease plasma concentrations of CCBs and reduce efficacy of CCB. Atenolol is the preferred beta-blocker when combined with ARVs; metoprolol plasma concentrations may be increased by boosted PIs. Consult a clinical pharmacologist or pharmacist when combining another antihypertensive agent with ARVs.

iv Risk factors include age (>45 years for men; > 55 years for women), smoking, family history of premature CVD

v Target organ disease (left ventricular hypertrophy, ultrasound evidence of arterial wall thickening, microalbuminuria)

vi Associated clinical conditions (CVD, IHD, renal disease, peripheral vascular disease, advanced retinopathy);

Goals of treatment: **Reduced SBP to <140/90 mmHg and to lower values if tolerated, with diabetes SBP<130/80 mmHg; SBP values <140 mmHg may be difficult to achieve in the elderly.**

Warning: **Caution regarding drug-drug interactions with antihypertensive drugs and ART.**