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ORIGINAL RESEARCH

European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV*

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Background

Metabolic diseases are frequently observed in HIV-infected persons and, as the risk of contracting these diseases is age-related, their prevalence will increase in the future as a consequence of the benefits of antiretroviral therapy (ART).

Summary of guidelines

All HIV-infected persons should be screened at regular intervals for a history of metabolic disease, dyslipidaemia, diabetes mellitus, hypertension and alteration of body composition; cardiovascular risk and renal function should also be assessed. Efforts to prevent cardiovascular disease will vary in intensity depending on an individual's absolute risk of ischaemic heart disease and should be comprehensive in nature. Lifestyle interventions should focus on counselling to stop smoking, modify diet and take regular exercise. A healthy diet, exercise and maintaining normal body weight tend to reduce dyslipidaemia; if not effective, a change of ART should be considered, followed by use of lipid-lowering medication in high-risk patients. A pre-emptive switch from thymidine analogues is recommended to reduce the risk of development or progression of lipoatrophy. Intra-abdominal fat accumulation is best managed by exercise and diet. Prevention and management of type 2 diabetes mellitus and hypertension follow guidelines used in the general population. When using medical interventions to prevent and/or treat metabolic disease(s), impairment of the efficacy of ART should be avoided by considering the possibility of pharmacokinetic interactions and compromised adherence. Specialists in HIV and specialists in metabolic diseases should consult each other, in particular in difficult-to-treat cases.

Conclusion

Multiple and relatively simple approaches exist to prevent metabolic diseases in HIV-infected persons; priority should be given to patients at high risk of contracting these diseases.

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*These guidelines will be updated as new evidence emerges. Please check on www.eacs.eu for the most recent version. Any conflict of interest of panel members can also be found on this website.

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‡See www.eacs.eu for current roster.

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Introduction

Prevention and management of metabolic diseases have emerged as major challenges to physicians responsible for the care of HIV-infected persons [1,2]. The prevalence of metabolic diseases has increased in the last decade in conjunction with the introduction of combination antiretroviral therapy (ART) [1–4], and will continue to

increase in the next several years as the beneficial effects of ART allow the treated population to age.

In HIV infection, uncontrolled replication of HIV, co-infections [e.g. with hepatitis C virus (HCV)] and ART contribute to metabolic diseases [1,2]. The prevention and management of metabolic diseases in HIV should take all these factors into consideration.

Healthcare professionals involved in 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-infected 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 in which consultation is generally recommended are indicated where appropriate in these guidelines.

Preventing or managing metabolic diseases in HIV often involve *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 websites exist for this purpose, for example www.hiv-druginteractions.org, www.hivpharmacology.com and www.aidsinfo.nih.gov.

There is a limited amount of evidence from randomized controlled trials on how to most effectively manage metabolic diseases in HIV. As a result, *management is currently 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 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 whom specific issues related to HIV infection 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 the following.

- *Renal impairment*. Both factors related to HIV and certain antiretroviral drugs may impair renal function [5]. Various drugs used in HIV care may need dose adjustment in the 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.

Summary of guidelines

Screening for metabolic diseases in patients with HIV infection

All HIV-infected persons should be screened for a history of metabolic disease, dyslipidaemia, diabetes mellitus, hypertension and alteration of body composition at regular intervals. The composite of cardiovascular risk factors for individual patients should be summarized by the calculation of the 10-year absolute risk of contracting ischaemic heart disease (IHD). Renal function and tubular damage should also be assessed (Table 1).

Prevention of cardiovascular disease

The intensity of efforts to prevent cardiovascular disease depends on the absolute risk of IHD, which is calculated using the Framingham equation [6] (see www.cphiv.dk/tools.aspx) (Fig. 1), and possible history of cardiovascular disease, type 2 diabetes mellitus or type 1 diabetes mellitus with microalbuminuria. Based on this, the population can be stratified into three risk categories: low risk ($<10\%$ 10-year risk of IHD), medium risk (10–20% 10-year risk of IHD) and high risk ($>20\%$ 10-year risk of IHD). The preventive efforts are diverse in nature [7,8] and require the involvement of cardiologists, in particular if the risk of IHD is high. Lifestyle interventions – in particular smoking cessation [8] – should be prioritized (Table 2; see below). Additional interventions should be based on low-density lipoprotein (LDL)-cholesterol levels; threshold values are indicated for each risk category in Fig. 1. For patients with higher-than-stipulated LDL-cholesterol threshold values, modification of ART should be considered, provided that one or more drugs used as part of the therapy is believed to contribute to LDL-cholesterol increases, and if substitution of this (these) drug(s) by other drugs will not compromise the antiviral efficacy. Figure 2 indicates a rough stratification of the metabolic impact of various antiretroviral drugs. If the LDL-cholesterol levels still remain above threshold values, consideration should be given to the initiation of lipid-lowering medication (Tables 3 and 4; see below).

Additional recommended medical interventions to prevent cardiovascular disease are as follows.

- Treat hypertension (see Table 10 below).
- Provide low-dose acetylsalicylic acid: only indicated in high-risk patients (right column in Fig. 1) as risk of

Table 1 Screening for metabolic disease in patients with HIV

	Assessment	Patient's condition	Frequency of assessment
History	Family history for premature IHD,[¶] diabetes, hypertension	Every patient	At HIV-diagnosis
	Concomitant therapy against dyslipidaemia/hypertension/diabetes		
	Concomitant therapy with risk for diabetes/ dyslipidaemia		At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated*
	Current lifestyle (alcohol use, smoking, aerobic exercise)		
Lipids	Fasting[†] TC	Every patient	At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated*
	Fasting[†] TG		
	Fasting[†] LDL-c + HDL-c		
Glucose[‡]	Fasting[†] glucose	Every patient	At HIV-diagnosis, before start of ART, and annually thereafter unless specifically indicated*
Body composition	Body mass index	Every patient	At HIV-diagnosis, before start of ART, annually thereafter
	Waist circumference		
	Waist-to-hip ratio		
	Clinical lipodystrophy assessment		
Hypertension	Blood pressure	Every patient	At HIV-diagnosis, before ART, annually thereafter unless specifically indicated*
Cardiovascular disease	Risk assessment[§]	Every patient without IHD (Men > 40 years; women > 50)	Before ART, and annually thereafter
	ECG		Annually
Renal failure	Estimated glomerular filtration rate**	Patients receiving drugs cleared via the kidneys	Before initiation of drug in question, after 4 weeks, 6 months, and if remaining normal then once annually

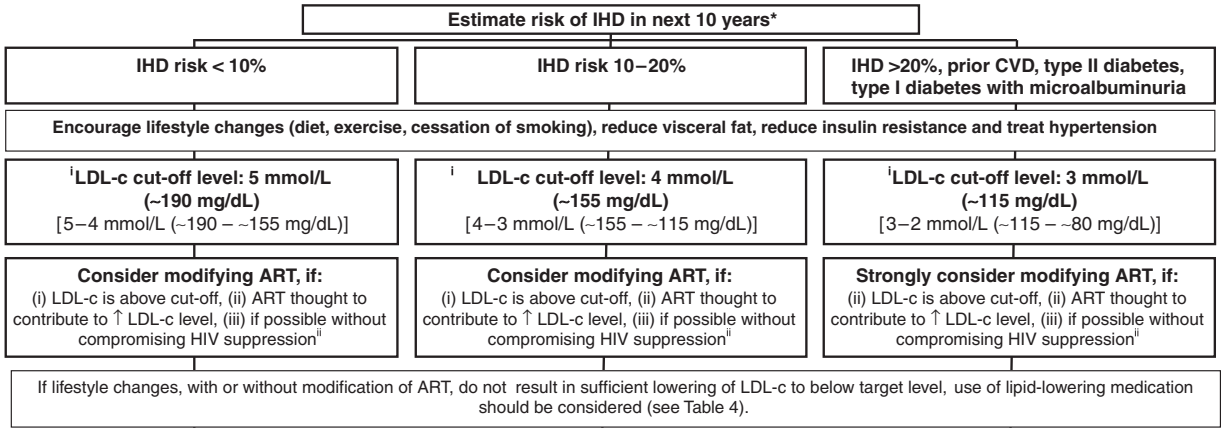
[¶]Cardiovascular events in a first degree male relative < 55 years or in a first degree female relative < 65 years.
*Assessment and monitoring should increase in frequency in cases of severe dyslipidaemia (see Table 4), elevated blood pressure (see Table 10) or elevated fasting blood glucose levels (see Table 6) and/or if medical interventions are instituted to correct these conditions.
[†]Fasting defined as a time period without caloric intake of at least 8 h.
[‡]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.
[§]Use risk calculators for estimating 10-year risk of developing IHD events – www.cphiv.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.
**Use calculator to estimate glomerular filtration rate (eGFR) according to Cockcroft–Gault – www.cphiv.dk/tools.aspx.
HDL-c, HDL-cholesterol; IHD, ischaemic heart disease; LDL-c, LDL-cholesterol; TC, total cholesterol; TG, triglycerides.

intracerebral bleeding is increased by 25% and extracerebral bleeding by 50%; harm probably exceeds benefit if risk of IHD is lower.

The projected benefits of these interventions are as follows: per 10 mmHg reduction of systolic blood pressure, per 1 mmol/L (39 mg/dL) reduction in total cholesterol and with use of low-dose acetylsalicylic acid, each reduces risk of IHD by 20–25%. These benefits are additive [9]. Smoking cessation reduces risk of IHD the most – by 50% – and this is also additive to the other interventions. Hence, by combining the various interventions in patients in whom they are all indicated, the absolute risk can be reduced by more than 80%.

Lifestyle interventions

Cessation of smoking reduces the risk of contracting cardiovascular and malignant diseases, and should be prioritized in all patients (Table 2). If not successful on the first attempt, patients should be referred to a specialized stop smoking clinic [10]. Diet counselling may reduce dyslipidaemia and risk of obesity and should focus on reducing the intake of fat and cholesterol and increasing the intake of vegetables and fibre-containing food.



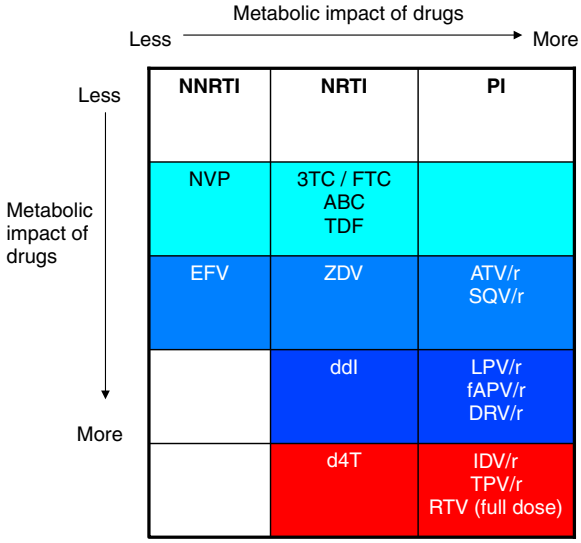
[i] LDL-c cut-off levels [units: mmol/L (mg/dL)] are higher than in guidelines for the general population (more stringent levels where some experts would consider intervention also indicated in parentheses below). In cases where LDL-c cannot be reliably calculated because of hightriglyceride levels, 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, or by another PI(/r) known to cause less metabolic disturbance (see Fig. 2); (2) replacing d4T or ZDV by 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.
* Use Framingham equation (see www.cphiv.dk/tools.aspx).

Fig. 1 Prevention of cardiovascular disease. ABC, abacavir; ART, antiretroviral therapy; CVD, cardiovascular disease; d4T, stavudine; HDL-c, high-density lipoprotein cholesterol; IHD, ischaemic heart disease; LDL-c, low-density lipoprotein cholesterol; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI/r, protease inhibitor boosted with ritonavir; TDF, tenofovir DF; ZDV, zidovudine.

Table 2 Lifestyle interventions*

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 clinics
	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 <300 mg/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, 1 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 min brisk walking 5/7 days a week)
	Maintain muscular strength and joint flexibility

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



[l]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.

Fig. 2 Metabolic impact of individual antiretroviral drugs and drug classes. 3TC, lamivudine; ABC, abacavir; ATZ, atazanavir; d4T, stavudine; ddI, didanosine; DRV, darunavir; EFV, efavirenz; FTC, emtricitabine; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; PI/r, protease inhibitor pharmacologically boosted with ritonavir; RTV, ritonavir (if used as booster,/r); SQV, saquinavir; TDF, tenofovir DF; TPV, tipranavir; ZDV, zidovudine.

Exercise prevents obesity and should include 30 min of brisk walking 5–7 days a week.

Management of dyslipidaemia

Higher LDL-c levels increase the risk of cardiovascular disease, and reduction thereof reduces this risk; the reverse is true for high-density lipoprotein (HDL)-cholesterol [6]. Conversely, the cardiovascular disease risk implications of higher-than-normal levels of triglycerides are less clear, as is the clinical benefit of treating moderate hypertriglyceridaemia.

A healthy diet, exercise and maintaining normal body weight tend to reduce dyslipidaemia; if not effective, consider a change of ART and then consider lipid-lowering medication in high-risk patients (Fig. 1). Co-administration of statins and ART should be carried out with due consideration of possible drug–drug interactions (Table 3). Simvastatin is contraindicated in patients receiving ritonavir-boosted PI-based ART.

Recommendations for use of the various types of lipid-lowering medication are indicated in Table 4. Statins and ezetimibe reduce LDL-cholesterol to a lesser extent; statins are recommended as first-line therapy to reduce elevated LDL-cholesterol levels. Only in cases of combined increases in LDL-cholesterol and triglyceride levels >5 mmol/L is it recommended to initiate therapy aimed at reducing triglyceride levels; the drug class of choice is the fibrates.

Table 3 Drugs used to manage dyslipidaemia

					Advise on use of statin together with ART	
Drug class	**Drug**	**Dose**	**Benefit**	**Side effects**	**Use with PI/r**	**Use with NNRTI**
Statin	Atorvastatin	10–80 mg qd	LDL-c ↓ †	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Relative contraindicated	Consider higher dose§
	Fluvastatin	20–80 mg qd	LDL-c ↓ *		Consider higher dose§	Consider higher dose§
	Pravastatin	20–80 mg qd	LDL-c ↓ *		Consider higher dose§, ‖	Consider higher dose§
	Rosuvastatin	5–40 mg qd	LDL-c ↓ †		Start with low dose¶	Start with low dose¶
	Simvastatin	10–80 mg qd	LDL-c ↓		Contraindicated	Consider higher dose§
Cholesterol uptake ↓	Ezetimibe	10 mg qd	LDL-c ↓ ‡	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 ↓			

Expected range of reductions of LDL-c:
*0.8–1.5 mmol/L (35–60 mg/dL).
†1.5–2.5 mmol/L (60–100 mg/dL).
‡0.2–0.5 mmol/L (10–20 mg/dL).
The ART drug may
§Induce (= less effect of statin, ↑ dose gradually to achieve expected benefit*,†) or
¶Inhibit (statin toxicity, ↓ dose) the excretion of the statin.
‖Exception: If used with darunavir, start with *lower* dose of pravastatin.
LDL-c, LDL-cholesterol; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI/r, protease inhibitors boosted with low dose ritonavir; TG, triglycerides.

Table 4 Treatment recommendations on management of dyslipidaemia

Type of dyslipidaemia	First choice*	Combination therapy*
Isolated hypercholesterolaemia [LDL-c > cut-off (see Table 1)]	Statin†	+ Ezetimibe
Combined hyperlipidaemia [(LDL-c >cut-off (see Table 1) and TG 5–10 mmol/L‡]	Statin†	+ Fibrate§ (/nicotinic acid derivative)
Isolated hypertriglyceridaemia (TG 2.3–10 mmol/L‡)	Diet, alcohol abstinence	–
Severe hypertriglyceridaemia (> 10 mmol/L‡)	Fibrate	+ Omega 3 acid ester (/nicotinic acid derivative)
Isolated low HDL-c (< 0.9 mmol/L)	Fibrate§	+ Nicotinic acid derivative

*Treatment goal is to reduce LDL-c <cut-off levels (see Table 1). 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 can not be reached.
†Check AST (< × 3 ULN) and CK (< × 5 ULN) prior to initiation, 4–12 weeks after treatment initiation, and then annually if within normal range.
‡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 Table 1).
§Combination therapy of statin and gemfibrozil (and less so other fibrates) increases risk of rhabdomyolysis and should be avoided whenever possible.
CVD, cardiovascular disease; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; TG, triglycerides.

Table 5 Prevention and management of lipoatrophy and lipohypertrophy

Lipoatrophy	Lipohypertrophy
Prevention	**Prevention**
Avoid d4T and ZDV or pre-emptively switch away from them	No proven strategy
Management	Weight gain expected with effective ART
Modification of ART	Weight reduction or avoidance of weight gain may decrease visceral adiposity
○ Switch d4T or AZT to ABC or TDF:	**Management**
■ Only ART modification proven to partially restore subcutaneous fat; increase in total limb fat ~ 400–500 g/year	Diet and exercise may reduce visceral adiposity;
■ Risk of new toxicity (ABC hypersensitivity reaction?; TDF associated nephrotoxicity?)	○ Limited data, but possibly reduction of visceral adipose tissue and improvement in insulin sensitivity and blood lipids, especially in obesity associated with lipohypertrophy
○ Switch to regimen not including NRTIs	○ No prospective trials in HIV-infected patients to definitely indicate degree of diet and/or exercise needed to maintain reduction in visceral fat.
■ Increase in total limb fat ~ 400–500 g/year	○ May worsen subcutaneous lipoatrophy
■ May increase risk of dyslipidaemia	Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects and may introduce new complications
■ Less data on virological safety	○ Growth hormone
Surgical intervention	■ Decreases visceral adipose tissue
○ Offered for cosmetic relief of facial lipoatrophy only (fillers may be absorbable (limited effect) or permanent (durability of desired cosmetic effect is unknown)*	■ May worsen subcutaneous lipoatrophy, may worsen insulin resistance
○ Limited randomized trials and no comparative studies of different approaches	○ Metformin
Pharmacological interventions to treat lipoatrophy have not been proven to be effective and may introduce new complications	■ Decreases visceral adipose tissue in insulin resistant persons
○ Pioglitazone – possibly beneficial in patients not taking d4T	■ May worsen subcutaneous lipoatrophy.
○ Rosiglitazone and Pioglitazone – improvement in insulin sensitivity	○ Surgical therapy can be considered for localised lipomas/buffalo humps
○ Rosiglitazone: increases in blood lipids and possible IHD.	■ Duration of effect variable

*See (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.
ABC, abacavir; d4T, stavudine; IHD, ischaemic heart disease; TDF, tenofovir DF; ZDV, zidovudine.

Prevention and management of lipodystrophy

The preferred strategy to prevent lipoatrophy is avoiding exposure to the two thymidine analogues (stavudine and zidovudine) [11,12]. Alternatively, pre-emptive switch away from these drugs should be considered. In cases where lipoatrophy has developed, reversal is slow and gradual (Table 5). Other interventions have either not been sufficiently studied or are known to induce other complications and are hence not generally recommended. It is uncertain whether lipohypertrophy can be induced by specific antiretroviral drugs, and no specific recommendations on medical prevention strategies can be provided at this time.

Treatment of type 2 diabetes

Both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (Table 6) increase cardiovascular morbidity and mortality, and increase the risk of developing diabetes four to six fold. Patients with IGT and IFG should be

Table 6 Diagnostic criteria for diabetes mellitus and its pre-stages*

	Fasting plasma glucose mmol/L (mg/dL)†	Oral glucose tolerance test (OGTT) 2-h value mM (mg/dL)‡
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)

*As defined by WHO and International Diabetes Federation (2005).
†An abnormal finding should be repeated before confirming the diagnosis.
‡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 four to six fold. These patients should be targeted for lifestyle intervention, and their CV risk factors must be evaluated and treated.

targeted for lifestyle intervention [body mass index (BMI) should be reduced in the case of obesity], and their cardiovascular risk factors should be evaluated and treated [13,14]. Both type 1 and type 2 diabetes mellitus and the accompanying metabolic dysregulation may lead to cardiovascular disease and microangiopathy.

The following treatment goals should be aimed for when managing patients with type 2 diabetes.

- Glucose control [HbA1c < 6.5–7.0% without hypoglycaemia; fasting plasma glucose 4–6 mmol/L (73–110 mg/dL)]; normal blood lipids and blood pressure (see Tables 4 and 10). Preferred antihypertensive drug class: angiotensin-converting enzyme (ACE) inhibitors.

Table 7 Selected interventions for treatment of diabetes mellitus

Intervention	Dose	Expected decrease in HbA1c (%)	Side effects	Comments
Lifestyle intervention		1–2		Intra-abdominal and subcutaneous fat may ↓
Metformin	Start with 500–750 mg 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			Fluid retention, cardiac failure, weight gain	See also Table 5.
Rosiglitazone	4–8 mg/d,			
Pioglitazone	15–45 mg/d	0.5–1.4		
Insulin	Refer to text	No limit	Hypoglycaemia, weight gain.	Large doses may be required (1–2 IU/kg).

Table 8 Risk factors for and prevention of hyperlactataemia

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

d4T, stavudine; ddI, didanosine; ZDV, zidovudine.

Table 9 Management of hyperlactataemia

Serum lactate (mmol/L)	Symptoms	Action
> 5*	Yes/no	Repeat test under standardized conditions to confirm & obtain arterial pH and bicarbonate* If confirmed, exclude other obvious causes Arterial pH ↓ and/or bicarbonate ↓ *: stop NRTIs Arterial pH and/or bicarbonate normal: Consider switch from high to low risk NRTI & monitor carefully OR stop NRTIs
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

*Lactic acidosis is a rare but life-threatening situation usually associated with symptoms; high risk if serum lactate > 5 and especially > 10 mmol/L.
NRTI, nucleos(t)ide reverse transcriptase inhibitor.

Table 10 Management based on blood pressure measurements and the diagnosis of hypertension

	Blood pressure (mmHg)* – 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: SBP 140–159 or DBP 90–99**	**Grade 2: SBP 160–179 or DBP 100–109**	**Grade 3: SBP ≥ 180 or DBP ≥ 110**
No other risk factors	Average risk No BP intervention	Average risk No BP intervention	Low added risk Lifestyle changes for several months†, then possible drug therapy‡	Moderate added risk Lifestyle changes for several months†, then drug therapy‡	High added risk Immediate drug therapy‡ and lifestyle changes†
1–2 risk factors§	Low added risk Lifestyle changes†	Low added risk Lifestyle changes†	Moderate added risk Lifestyle changes for several months†, then drug therapy‡	Moderate added risk Lifestyle changes for several months†, then drug therapy‡	Very high added risk Immediate drug therapy‡ and lifestyle changes†
3 or more risk factors§ or target organ disease¶ or diabetes	Moderate added risk Lifestyle changes†	High added risk Drug therapy‡ and lifestyle changes†	High added risk Drug therapy‡ and lifestyle changes†	High added risk Drug therapy‡ and lifestyle changes†	Very high added risk Immediate drug therapy‡ and lifestyle changes†
Associated clinical conditions ‖	High added risk Drug therapy‡ and lifestyle changes†	Very high added risk Immediate drug therapy‡ and lifestyle changes†	Very high added risk Immediate drug therapy‡ and lifestyle changes†	Very high added risk Immediate drug therapy‡ and lifestyle changes†	Very high added risk Immediate drug therapy‡ and lifestyle changes†

*DBP = diastolic blood pressure; SBP = systolic blood pressure. Repeated blood pressure measurements should be used for stratification.
†Recommended lifestyle interventions, see Table 2. Table adapted from *J. Hypertension* 2003; 21: 1779–1786.
‡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 (www.eacs.eu/guide/index.htm).
Medical treatment of uncomplicated hypertension: first choice: Thiazide or ACE-inhibitor, second choice: Amlodipine (start with 5 mg 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 second 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; NNRTIs may decrease plasma concentrations of CCBs and reduce efficacy of CCB. Atenolol is the preferred β-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.
§Risk factors include age (>45 years for men; >55 years for women), smoking, family history of premature CVD.
¶Associated clinical conditions (CVD, CHD, renal disease, peripheral vascular disease, advanced retinopathy).
‖Target organ damage (left ventricular hypertrophy, ultrasound evidence of arterial wall thickening, microalbuminuria).
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.

- Acetylsalicylic acid (75–150 mg/d) should be considered in all patients.
- Nephropathy and retinopathy screening should be performed as in diabetic patients without HIV infection.
- Consultation with a specialist in diabetology is recommended.

There are several tested interventions available to obtain glucose control in type 2 diabetes (Table 7). These interventions should be individualized as follows.

- 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 oral antidiabetic drugs (sulfonylureas, glinides, exenatide, sitagliptin and α-glucosidase inhibitors) in the treatment of HIV-infected patients taking ART.
- If treatment targets 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 is achieved.
- Oral metformin should be continued with insulin therapy.

Prevention and management of hyperlactataemia

There are multiple risk factors for hyperlactataemia in HIV-infected populations [15], and the symptoms associated with this condition are diverse (Table 8). To reduce the risk of hyperlactataemia it is important to avoid the combination of certain antiretroviral and anti-hepatitis drugs (stavudine, didanosine and ribavirin). Of note, routine measurements of S-lactate to screen for hyperlactataemia are not recommended.

Table 9 depicts the recommended approach for patients for whom an S-lactate measurement has been taken based on a suspicion that the patient may suffer from hyperlactataemia.

Metabolic acidosis associated with increased S-lactate levels (lactic acidosis) is a life-threatening condition. The metabolic acidosis is diagnosed on arterial puncture. For such patients it is recommended to:

- admit the patient;
- stop all ART;
- provide intravenous fluid support;

Perhaps use vitamin supplementation [vitamin B complex forte 4 mL twice a day (bid); riboflavin 20 mg bid; thiamine 100 mg bid; L-carnitine 1000 mg bid], although the benefit is not well documented.

Management based on blood pressure measurement and/or diagnosis of hypertension

The intensity of interventions applied to treat elevated blood pressure varies depending on the measured blood pressure (caution: white-coat hypertension) and on the number of risk factors for various diseases associated with hypertension. The higher the blood pressure and the more risk factors, the more aggressive the approach needs to be (Table 10) [16].

The two principal interventions are lifestyle modification (especially reduction of BMI in the case of obesity) and use of antihypertensives. The footnote to Table 10 describes the recommended approach to the use of antihypertensives. *Of note, there is the potential for drug–drug interactions between calcium-channel blockers and ART.*

The goal of the interventions is to reduce systolic blood pressure to $<140/90$ mmHg and to lower values if tolerated. For patients with diabetes mellitus, the target systolic blood pressure is $<130/80$ mmHg. Of note, in the elderly, it may be difficult to achieve these goals.

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