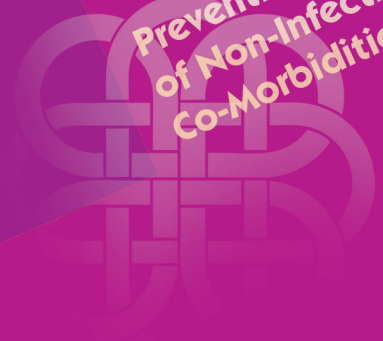


European AIDS Clinical Society

Guidelines
Prevention and Management
of Non-Infectious
Co-Morbidities in HIV



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Available online at

www.europeanaidscinicalsociety.org/Guidelines/G2.htm

- Indications and tests for proximal renal tubulopathy (PRT)
- Dose adjustment of antiretrovirals for impaired renal function
- International HIV Dementia Scale (IHDS)
- CNS penetration of antiretroviral drugs
- Classification, doses, safety and side effects of antidepressants
- Interactions between antidepressants and antiretroviral agents
- List of selected dermal/soft tissue fillers used for restorative treatment

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Abbreviations used throughout this document

- ABC=abacavir;
 - ACE=angiotensin converting enzyme;
 - ALP=alkaline phosphatase;
 - ALT=alanine aminotransferase;
 - aMDRD=abbreviated Modification of Diet in Renal Disease formula;
 - ART=antiretroviral therapy;
 - AST=aspartate aminotransferase;
 - ATV=atazanavir;
 - BMD=bone mineral density;
 - CKD=chronic kidney disease;
 - CNS=central nervous system;
 - COPD=chronic obstructive pulmonary disease
 - CSF=cerebrospinal fluid;
 - CVD=cardiovascular disease;
 - d4T=stavudine;
 - DXA=dual energy X-ray absorptiometry;
 - ddl=didanosine;
 - DRV=darunavir;
 - EFV=efavirenz;
 - eGFR=estimated glomerular filtration rate;
 - ENF=enfuvirtide;
 - ETV=etravirine;
 - FPV=fos-amprenavir;
 - FRAX=Fracture Risk Assessment Tool;
 - FTC=emtricitabine;
 - HBV=hepatitis B virus;
 - HCV=hepatitis C virus;
 - HDL-c=HDL-cholesterol;
 - HIVAN=HIV associated nephropathy;
 - IDV=indinavir;
 - IHD=ischaemic heart disease;
 - LDL-c=LDL-cholesterol;
 - LPV=lopinavir;
 - MVC=maraviroc;
 - 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;
 - PSA=prostate specific antigen;
 - PTH=parathyroid hormone;
 - RAL=raltegravir;
 - RTV=ritonavir (used as booster= /r);
 - SQV=saquinavir;
 - 3TC=lamivudine;
 - TC=total cholesterol;
 - TG=triglycerides;
 - TDF=tenofovir;
 - TPV=tipranavir;
 - UAC/ : urine albumin/creatinine ratio;
 - UP/C: : urine protein/creatinine ratio;
 - ZDV=zidovudine
- Acknowledgements: The guidelines panel has received helpful comments and suggestions from the following persons: EACS executive committee, T Brown, A Carr, U Gschwandtner, E Negrodo, P Portegies, SW Worm.

HIV specific issues to be considered in managing “non-infectious” co-morbidities

Non-infectious co-morbidities include cardiovascular, renal, hepatic, metabolic, neoplastic, bone pathologies and depression. Although HIV and other infections may be involved in their pathogenesis, these guidelines focus on preventive and/or management principles other than use of antivirals and other anti-infectious agents in adults and adolescent HIV-infected persons.

These co-morbidities are becoming increasingly important for HIV-infected persons as a consequence of increased life expectancy resulting from effective ART. Additionally, several demonstrated and proposed HIV-associated risk factors may contribute to their development including immune activation, inflammation and coagulation associated with (uncontrolled) replication of HIV, co-infections (e.g. HCV), ART itself and persistent immunodeficiency.

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-infected patients receive.

Conversely, many HIV physicians are not specialists in non-infectious co-morbidities, and should seek expert advice where appropriate in the prevention and management of such conditions. Situations where consultation is generally recommended are indicated in these guidelines.

Preventing or managing these 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 websites exist for this purpose: www.HIV-druginteractions.org, www.HIVpharmacology.com, www.AIDSinfo.nih.gov.

These guidelines are intended to provide the best guide to clinical management, and it is recognised that the level of evidence to support the advice varies. Indeed, there is limited evidence from randomised controlled trials on best management of non-infectious co-morbidities in HIV. As a result current management is mainly derived from general medical guidelines. These guidelines therefore represent the collective consensus opinion of a panel of experts in the field of HIV and the respective range of co-morbidities, and no attempt to rate the underlying evidence and strength of the panel's recommendations was undertaken.

Dependent on future clinical research findings, these guidelines will be regularly updated as required. The online version of guidelines, at www.europeanaidsclinicalsociety.org, contains more detailed information, links to other relevant websites and will be regularly updated.

The current guidelines highlight non-infectious co-morbidities that 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 extensively discussed, but may be included in future versions are:

- Sexual dysfunction. This is frequently encountered and often requires a multi-disciplinary approach for its management that may include both expert psychological counselling and medical interventions.
- Hypogonadism,
- Other women's health issues, and
- Neuropathy which may be caused by infections (e.g. HIV), some ARV ([see p. 39](#)), other neuropathic drugs, and by metabolic diseases (eg. diabetes).

Screening for non-infectious co-morbidities

	Assessment	At HIV diagnosis	Prior to starting cART	Follow up frequency		Comment	See page
				with cART	without cART		
History	<ul style="list-style-type: none"> Past and current co-morbidities Family history (eg premature CVD, diabetes, hypertension, CKD) Concomitant medicationsⁱ Current lifestyle (alcohol use, smoking, diet, aerobic exercise) 	+	+	every visit 6-12 m	every visit annual	On transfer of care repeat assessment Premature CVD: Cardiovascular events in a first degree relative: male <55, female <65 years	44
		+	+				
Body composition	<ul style="list-style-type: none"> Body-mass index Clinical lipodystrophy assessment 	+	+	annual	annual		61
Cardiovascular disease	<ul style="list-style-type: none"> Risk assessment (Framingham scoreⁱⁱ) ECG 	+	+	annual	annual	Should be performed in every older patient without CVD (Men > 40 years; Women >50 years)	44
Hypertension	<ul style="list-style-type: none"> Blood pressure 	+	+	annual	annual		46
Dyslipidaemia	<ul style="list-style-type: none"> TC, HDL-c, LDL-c, TGⁱⁱⁱ 	+	+	annual		Repeat in fasting state if used for medical intervention (i.e. ≥8h without caloric intake)	51
Diabetes mellitus	<ul style="list-style-type: none"> Serum glucose 	+	+	6-12 m		Consider oral glucose tolerance test if repeated fasting glucose levels of 6.1-6.9 mmol/L (110-125 mg/dL)	49
Liver disease	<ul style="list-style-type: none"> Risk assessment^{iv} ALT/AST, ALP 	+	+	annual 3-6 m	annual 6-12 m	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs	62
Renal disease	<ul style="list-style-type: none"> Risk assessment^v eGFR (aMDRD)^{vi} Urine Dipstick analysis^{vii} 	+	+	annual 3-6 m	annual 6-12 m	More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs ^{viii} Every 6 months if eGFR <60 ml/min; If proteinuria ≥1+ and/or eGFR<60 ml/min perform UP/C or UAC ^{vii}	59
Bone disease	<ul style="list-style-type: none"> Risk assessment^{ix} FRAX®^x in patients >40 years) 25-OH vitamin D 	+	+	2 yrs	2 yrs	If not using FRAX®, consider DXA of spine and hip in specific patients Repeat according to risk factors	52
Neurocognitive impairment	<ul style="list-style-type: none"> Questionnaire 	+	+	1-2 yrs	1-2 yrs	Screen risk patients	64
Depression	<ul style="list-style-type: none"> Questionnaire 	+	+	1-2 yrs	1-2 yrs	Screen risk patients	56
Cancer	<ul style="list-style-type: none"> Mammography Cervical PAP Others 			1-3 yrs 1-3 yrs	1-3 yrs 1-3 yrs	Women 50-70 years Sexually active women, frequency depending on CD4 Controversial	37

Notes

Screening for non-infectious co-morbidities

- i Review all concomitant medications that increase the risk of co-morbidities: eg diabetes: neuroleptic drugs including clozapine, olanzapine; pentamidine, glucocorticoids, IFN- α , thiazide diuretics, furosemide, phenytoin, diazoxide, beta-blockers and others; renal disease: NSAIDs
- ii A risk equation developed from HIV populations is under development (see: www.cphiv.dk/tools.aspx). Of note, if individual patients receive medication to control dyslipidaemia and/or hypertension, any risk estimation should be interpreted with caution.
- iii Calculator for LDL-cholesterol in cases where TG is not high can be found at www.cphiv.dk/tools.aspx.
- iv Risk factors for chronic liver disease include: alcohol, viral hepatitis, obesity, diabetes, insulin resistance, hyperlipidaemia, hepatotoxic drugs
- v Risk factors for chronic kidney disease (CKD): hypertension, diabetes, CVD, family history, black African ethnicity, viral hepatitis, concomitant nephrotoxic drugs.
- vi eGFR: use aMDRD based on serum creatinine, gender, age and ethnicity (see: www.cphiv.dk/tools.aspx).
- vii Some experts recommend UA/C or UP/C as screening test for proteinuria in all patients. UA/C: urinary albumin creatine ratio (mg/mmol) predominantly detects glomerular disease. Use in patients with diabetes mellitus. UP/C: urinary total protein creatinine ratio (mg/mmol) detects total protein secondary to glomerular and tubular disease
- viii Additional screening is required for patients receiving tenofovir ([see p. 60](#))
- ix Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m²), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (>3 units/day), steroid exposure (minimum prednisone 5mg or equivalent for >3 months)
- x See: www.shef.ac.uk/FRAX

Cancer - screening methods¹

Problem	Patients	Procedure	Evidence of benefit	Screening interval	Additional comments
Breast cancer	Women 50-70 yrs	Mammography	↓ breast cancer mortality	1-3 years	
Cervical cancer	Sexually active women	Papnicolau test	↓ cervical cancer mortality	1-3 years	Target age group should include at least the age range 30 to 59 years. Longer screening interval if prior screening tests repeatedly negative
Anal cancer	Homosexual men	Digital rectal exam ± Papanicolau test	Unknown - advocated by some experts	1-3 years	If Pap test abnormal, anoscopy
Colorectal cancer	Persons 50-75 yrs	Fecal Occult Blood test	↓ colorectal cancer mortality	1-3 years	Benefit is marginal
Prostate cancer	Men >50 yrs	Digital rectal exam ± Prostate specific antigen (PSA)	Controversial	1-3 years	Pros: ↑ early diagnosis Cons: Overtreatment, no ↓ cancer-related mortality

- i Screening recommendations derived from the general population. These screenings should preferably be done as part of national general population-screening programs. Although non-Hodgkin lymphoma has a higher incidence in HIV-infected patients than in the general population, it is currently unknown whether it can be screened. Careful examination of skin should be performed regularly to detect cancers such as Kaposi's sarcoma, basal cell carcinoma and malignant melanoma.

Antiretroviral drugs & drug classes: **frequent/severe side effectsⁱ - 1/2**

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genitourinary	Nervous	Body fat	Metabolic	Other
NRTI										
ZDV	Nail pigmentation	Nausea	Steatosis		Myopathy			Lipoatrophy	Dyslipidaemia, Hyperlactataemia	Anemia
d4T		Pancreatitis	Steatosis				Peripheral neuropathy	Lipoatrophy	Dyslipidaemia Hyperlactataemia	
ddI		Pancreatitis	Steatosis, Liver fibrosis	IHD			Peripheral neuropathy		Hyperlactataemia	
3TC										
FTC										
ABC	Rash*			IHD						*: Systemic Hypersensitivity (HLA B*5701 dependent)
TDF					↓ BMD, Osteomalacia	↓ GFR, Fanconi syndrome				
NNRTI										
EFV	Rash		Hepatitis				Depression, Suicidal ideation, Dizziness, Sleep disturbances		Dyslipidaemia Gynaecomastia	Teratogenesis
NVP	Rash		Hepatitis							Systemic Hypersensitivity (CD4- and gender-dependent)
ETV	Rash									

Antiretroviral drugs & drug classes: **frequent/severe** side effectsⁱ - 2/2

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genitourinary	Nervous	Body fat	Metabolic	Other	
PI											
IDV	Dry skin Nail dystrophy	Nausea and diarrhoea ⁱⁱ	Jaundice	IHD		Nephrolithiasis		↑abdominal fat	Dyslipidaemia Diabetes mellitus		
SQV									Dyslipidaemia		
LPV					IHD				Dyslipidaemia		
FPV	Rash				IHD				Dyslipidaemia		
ATV				Jaundice			Nephrolithiasis			Dyslipidaemia	
DRV										Dyslipidaemia	
TPV				Hepatitis				Intracranial haemorrhage		Dyslipidaemia	
Fusion inhibitors											
ENF	Injection site reactions									Hypersensitivity, ↑risk for pneumonia	
Integrase inhibitors											
RAL		Nausea			Myopathy		Headache				
CCR5 inhibitors											
MVC			Hepatitis	IHD						↑risk for infections	

i “Severe events” (events that can put patient’s life at risk and represent a medical emergency) are marked in bold letters. “Frequent events” (events expected in at least 10% of treated patients) are marked in red. Background knowledge on tolerability of ENF, DRV, ETV, RAL, and MVC is limited because of its recent introduction into the clinical armamentarium.

ii Frequency and severity differs between individual agents.

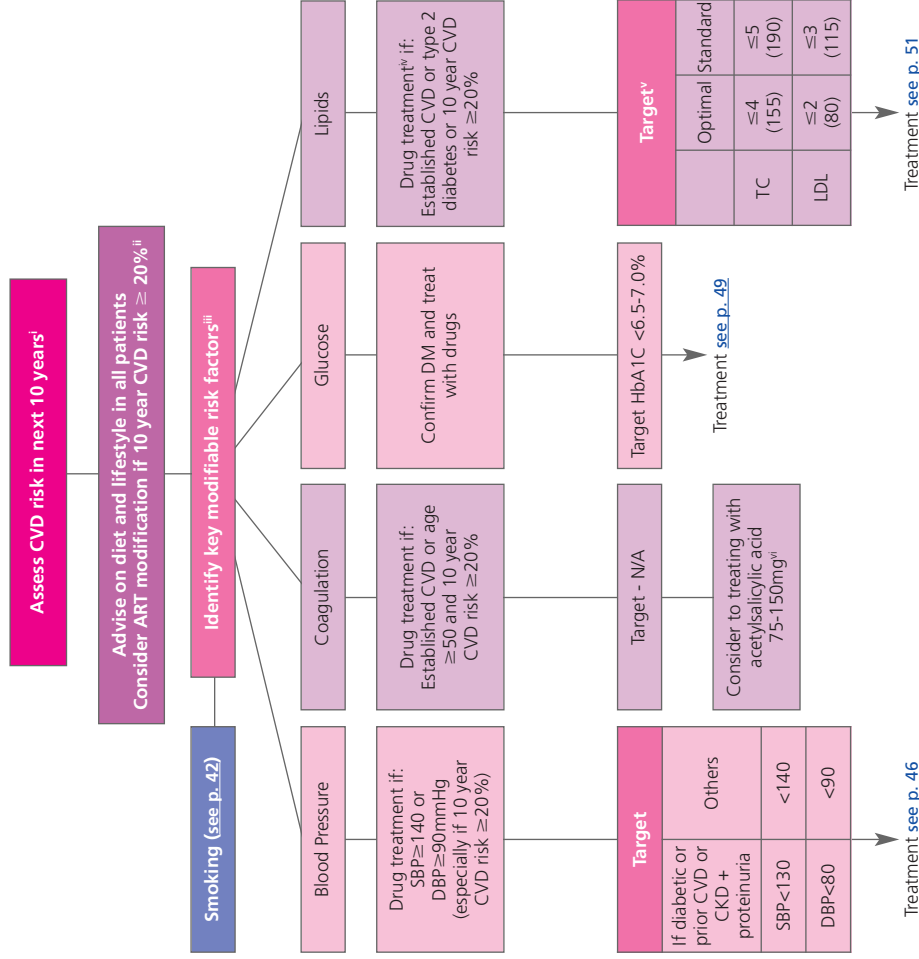
Lifestyle interventionsⁱ

INTERVENTION	PRINCIPLES
<p>Smoking cessation</p>	<ul style="list-style-type: none"> - 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: both drugs may cause central nervous system side effects including suicide; 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
<p>Dietary counselling</p>	<ul style="list-style-type: none"> - Dietary intervention should not interfere with the dietary requirements required for appropriate absorption of ART drugs - Keep caloric intake balanced with energy expenditure - Limit intake of saturated fat, cholesterol and refined carbohydrates - 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) and lean meat - 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
<p>Exercise promotion</p>	<ul style="list-style-type: none"> - Patients who are obviously overweight should be motivated to lose weight. Starvation diets are not recommended (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/m² - Intake of alcohol should be restricted to <20-40g/d
	<ul style="list-style-type: none"> - Promote active lifestyle to prevent and treat obesity, hypertension and diabetes - Encourage self-directed moderate level physical activity (take the stairs, cycle or walk to work, cycling, swimming, hiking etc.) - Emphasize regular moderate-intensity exercise rather than vigorous exercise - Achieve cardiovascular fitness (e.g. 30 minutes brisk walking >5 days a week) - Maintain muscular strength and joint flexibility

ⁱ Based on recommendations by the US Preventive Services Task Force.

Prevention of CVD

Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated. The preventive efforts are diverse in nature and require involvement of a relevant specialists, in particular if the risk of CVD is high and always in patients with a history of CVD.



- i Use the Framingham equation; a risk equation developed from HIV populations is under development (see: www.cphiv.dk/tools.aspx). This assessment and the associated considerations outlined in this figure should be repeated annually in all patients under care (see p. 34) to ensure that the various interventions are initiated in a timely way.
- ii Options for ART modification include: (1) replace PI/r with NNRTI or by another PI/r known to cause less metabolic disturbances (see p. 38); (2) consider replacing d4T, ZDV or ABC with TDF.
- iii Of the modifiable risk factors outlined, drug treatment is reserved for certain subgroups where benefits are considered to outweigh potential harm. Of note, there is a combined benefit of various interventions in target groups identified. Per 10 mmHg reduction in systolic blood pressure, per 1 mmol/L (39 mg/dL) reduction in TC and with use of acetylsalicylic acid, each reduces risk of IHD by 20-25%, the effect is additive. Observational studies suggest that smoking cessation results in greatest reductions in risk of IHD 50% - and this is additive to other interventions. This benefit only becomes apparent up to 5 years from when intervention was first applied.
- iv See discussion on drug treatment of patients with lower CVD risk at www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm.
- v Target levels are to be used as guidance and are not definitive – expressed as mmol/L with mg/dL in parenthesis. In case LDL cannot be calculated because of high triglyceride levels, the non-HDL-c (TC minus HDL-c) target should be used which is 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-c target. Target levels for TG are not listed because an independent contribution from TG to CVD risk is uncertain and hence whether this condition should be treated (see p. 51).
- vi Evidence for benefit when used in persons without a history of CVD (including diabetics) is less compelling.

Hypertension: diagnosis and management - 1/2

		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 ⁱ
1-2 risk factors ^{iv}	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
	Lifestyle changes ⁱ	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 ⁱ
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 ⁱ	Drug therapy ⁱⁱⁱ and lifestyle changes ⁱ	Drug therapy ⁱⁱⁱ and lifestyle changes ⁱ	Drug therapy ⁱⁱⁱ and lifestyle changes ⁱ	Immediate drug therapy ⁱⁱⁱ and lifestyle changes ⁱ
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 ⁱ	Immediate drug therapy ⁱⁱⁱ and lifestyle changes ⁱ	Immediate drug therapy ⁱⁱⁱ and lifestyle changes ⁱ	Immediate drug therapy ⁱⁱⁱ and lifestyle changes ⁱ	Immediate drug therapy ⁱⁱⁱ and lifestyle changes ⁱ

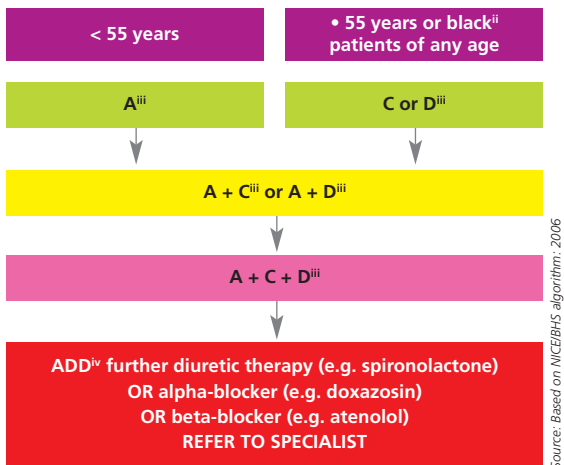
- i SBP =systolic blood pressure; DBP = diastolic blood pressure. Repeated blood pressure measurements should be used for stratification
- ii Recommended life style interventions - [see p. 42](#). Table adapted from J. Hypertension 2003; 21:1779-86.
- iii [See next page](#)
- iv Risk factors include 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.

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

Hypertension: diagnosis and management - 2/2

Choosing drugsⁱ for patients newly diagnosed with hypertension



Abbreviations + details:

- A = ACE inhibitor (e.g. perindopril, lisinopril, ramipril)
(consider angiotensin-II receptor antagonist (e.g. losartan, candesartan) if ACE intolerant)
- C = Dihydropyridine calcium-channel blocker (e.g. amlodipine). If not tolerated, verapamil (note: dose with caution with PIs which may increase plasma concentrations leading to toxic reactions), or diltiazem may be used.
- D = thiazide-type diuretic

- i Several anti-hypertensive drugs interact with the pharmacokinetics of ART – check always for drug-drug interactions
- ii Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients
- iii Await 2-6 weeks to assess whether target (p. 44) is achieved – if not go to next step.
- iv Requirement of 4-5 drugs to manage hypertension requires specialist training

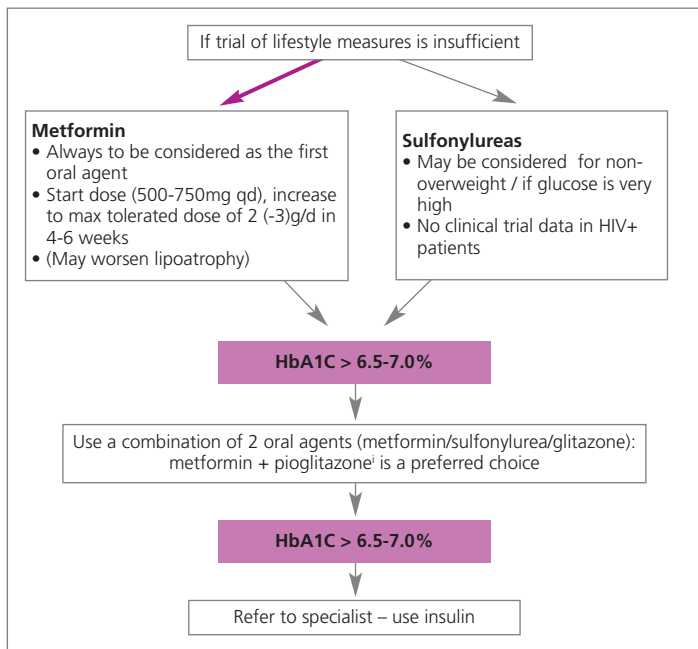
Type 2 diabetes: diagnosis and management

Diagnostic criteriaⁱ

	Fasting plasma glucose mmol/L (mg/dl) ⁱⁱ	Oral glucose tolerance test (OGTT) 2-h value mmol/L (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 identify 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



i some experts consider pioglitazone as first-line monotherapy for a lipotrophic diabetic patient

Management of patients with diabetes

Treatment goals: 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 < 130/80 mmHg (see p. 51 and p. 46). Acetylsalicylic acid (75-150mg/d) considered in diabetics with elevated underlying CVD risk (see p. 44) Nephropathy, polyneuropathy and retinopathy screening should be performed as in diabetic patients without HIV Consultation with a specialist in diabetology is recommended.

Dyslipidaemia: management

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 TG levels are less clear, as is the clinical benefit of treating moderate hypertriglyceridaemia; very high TG (>10 mmol/L or > 90mg/dL) may increase risk of pancreatitis, although direct evidence is lacking. Diet, exercise, maintaining normal body weight and stopping smoking tends to improve dyslipidaemia; if not effective, consider change of ART and then consider lipid-lowering medication in high-risk patients (see p. 44).

Drugs used to lower LDL-c

Drug class	Drug	Dose	Side effects	ADVISE ON USE OF STATIN TOGETHER WITH ART	
				Use with PI/r	Use with NNRTI
Statin ⁱ	Atorvastatin ⁱⁱ	10-80 mg QD	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Start with low dose ^v (max: 40 mg)	Consider higher dose ^{vi}
	Fluvastatin ⁱⁱ	20-80 mg QD		Consider higher dose ^{vi}	Consider higher dose ^{vi}
	Pravastatin ⁱⁱ	20-80 mg QD		Consider higher dose ^{vi,vi}	Consider higher dose ^{vi}
	Rosuvastatin ⁱⁱ	5-40 mg QD		Start with low dose ^v (max: 20 mg)	Start with low dose ^v
	Simvastatin ⁱⁱ	10-80 mg QD		Contraindicated	Consider higher dose ^{vi}
Cholesterol uptake ^j	Ezetimibe ^v	10 mg QD	Gastrointestinal symptoms	No known drug-drug interactions with ART	

i A statin is preferred first-line therapy; different statins have variable intrinsic LDL-c lowering ability^{ii,iii,iv}. Target levels for LDL-c see p. 44. In persons where LDL-c targets are difficult to achieve, consult/refer to specialist.
 ii, iii, iv Expected range of reductions of LDL-c: ⁱⁱ1.5-2.5 mmol/L (60-100) mmol/L, ⁱⁱⁱ0.8-1.5 mmol/L (35-60 mg/dL), ^{iv}0.2-0.5 mmol/L (10-20 mg/dL)
 v, vi The ART drug may inhibit (statin toxicity, ↓ dose) or ^{vi}induce (≈less effect of statin, ↑ dose gradually to achieve expected benefit^{ii,iii}) the excretion of the statin.
 vii **Exception:** If used with **DRV/r**, start with lower dose of **pravastatin**.

Bone disease: diagnosis, prevention and management

CONDITION	CHARACTERISTICS	RISK FACTORS	DIAGNOSTIC TESTS									
<p>Osteopenia</p> <ul style="list-style-type: none"> • Postmenopausal women and men aged ≥ 50 years T-score -1 to ≥ -2.5 • Premenopausal women and men aged < 50 years Z-score ≤ -2 <p>Osteoporosis</p> <ul style="list-style-type: none"> • Postmenopausal women and men aged ≥ 50 years T-score < -2.5 • Premenopausal women and men aged < 50 years Z-score ≤ -2 and fragility fracture 	<ul style="list-style-type: none"> • Reduced bone mass • Increased risk of fractures • Asymptomatic until fractures occur <p>Common in HIV</p> <ul style="list-style-type: none"> • Up to 60% prevalence of osteopenia • Up to 10-15% prevalence of osteoporosis • Aetiology multifactorial 	<p>Consider classic risk factorsⁱ</p> <p>Assess risk score or need for DXA of spine and hip using FRAX® (www.shef.ac.uk/FRAX)</p> <ul style="list-style-type: none"> - Only use if >40 years - May underestimate risk in HIV patients - Consider using HIV as secondary cause of osteoporosisⁱⁱ - Assess risk biannually <p>If not using FRAX® consider DXA in any patient with ≥ 1 of:ⁱⁱⁱ</p> <ol style="list-style-type: none"> 1. Postmenopausal women 2. Men ≥ 50 years 3. History of low impact fracture or high risk for falls^{iv} 4. Hypogonadism 5. Oral glucocorticoid use (minimum 5mg prednisone equivalent for >3 months) 	<p>DXA scan</p> <p>Rule out secondary causes if BMD abnormal^v</p> <p>Lateral spine Xrays if low BMD (lumbar and thoracic)</p>									
<p>Osteomalacia</p>	<ul style="list-style-type: none"> • Defective bone mineralisation • Increased risk of fractures and bone pain • Vitamin D deficiency may cause proximal muscle weakness • High prevalence ($>80\%$) of vitamin D insufficiency in some HIV cohorts 	<ul style="list-style-type: none"> • Dietary deficiency • Lack of sunlight exposure • Dark skin • Malabsorption • Renal phosphate wasting 	<p>Measure 25-OH vitamin D in all patients</p> <table> <thead> <tr> <th></th> <th>ng/ml</th> <th>nmol/L</th> </tr> </thead> <tbody> <tr> <td>Deficiency</td> <td><10</td> <td><25</td> </tr> <tr> <td>Insufficiency</td> <td><20</td> <td><50</td> </tr> </tbody> </table> <p>If low, check serum calcium, phosphate, alkaline phosphatase and PTH levels</p> <p>If hypophosphataemic, consider Fanconi syndrome (page 60)</p>		ng/ml	nmol/L	Deficiency	<10	<25	Insufficiency	<20	<50
	ng/ml	nmol/L										
Deficiency	<10	<25										
Insufficiency	<20	<50										
<p>Osteonecrosis</p>	<ul style="list-style-type: none"> • Infarct of epiphyseal plate of long bones resulting in acute bone pain • Rare but increased prevalence in HIV 	<p>Risk factors:</p> <ul style="list-style-type: none"> - Advanced HIV disease (low CD4+ T-cell counts) - Glucocorticoid exposure - Intravenous drug use 	<p>MRI</p>									

i Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m²), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (>3 units/day), steroid exposure (minimum prednisone 5mg or equivalent for >3 months)

ii Although use of HIV as a secondary risk factor in FRAX® has not been validated, including HIV as a secondary cause in a risk assessment will help identify those patients NOT requiring further assessment / DXA

iii If T-score normal, repeat after 3-5 years in groups 1 and 2, no need for re-screening with DXA in groups 3 & 4 unless risk factors change and only rescreen group 5 if steroid use ongoing

iv Falls Risk Assessment Tool (FRAT) (www.health.vic.gov.au/agedcare/maintaining/falls/downloads/ph_frat.pdf)

v Hyperparathyroidism, hyperthyroidism, malabsorption, hypogonadism / amenorrhoea, autoimmune disease, diabetes mellitus, chronic liver disease

Management of osteoporosis and vitamin D deficiency

Vitamin D replacement	<ul style="list-style-type: none"> • Suggested regimens for vitamin D replacement: <ul style="list-style-type: none"> - 800-2,000 IU daily - Can be provided according to national recommendations / availability of preparations (oral and parenteral formulations) - Aim to increase serum 25-OH vitamin D >50nmol/L and maintain serum PTH levels within normal range - Combine with calcium where there is insufficient dietary calcium intake
Reducing risk of fractures	<ul style="list-style-type: none"> • Decrease falls by addressing falls risks • Ensure sufficient dietary calcium (1-1.2g daily) and vitamin D (800-2,000 IU daily) intake • Refer to national / regional guidelines on treatment of osteoporosis <ul style="list-style-type: none"> - if no guidelines available consider bisphosphonateⁱ treatment in all osteoporotic postmenopausal women and men > 50 years old and those with a history of fragility fracture - use bisphosphonateⁱ with calcium and vitamin D replacement - no significant interactions between bisphosphonatesⁱ and antiretrovirals - If on TDF consider renal bone disease (p. 60) • In complicated osteoporotic cases (e.g. young men, premenopausal women, recurrent fracture despite bone protective therapy) refer to endocrinologist • If osteoporotic and on bisphosphonateⁱ treatment, repeat DXA after 2 years

ⁱ Bisphosphonate treatment with either of: Alendronate 70 mg once weekly po; Risedronate 35 mg once weekly po; Ibandronate 150mg oral monthly or 3mg i.v. every 3 months; Zoledronate 5 mg i.v. once yearly

Depression: diagnosis and management

Significance

- Higher prevalence of depression in HIV-infected patients (20-40% versus 7% in general population) due to stigma, sexual dysfunction, side effects of cART, co-morbidities
- Significant disability associated with depression

Screening and diagnosis

Who ?	How to screen ?	How to diagnose
Risk population <ul style="list-style-type: none"> • Positive history of depression in family • Depressive episode in personal history • Older age • Adolescence • Patients with history of drug addiction, psychiatric, neurologic or severe somatic co-morbidity • Use of EFV 	<ul style="list-style-type: none"> • Screen every 1-2 years • Two main questions: <ol style="list-style-type: none"> 1. Did you feel frequently depressed, sad and without hope in the last months? 2. Were you uninterested in undertaking something in the last month? • Special symptoms in men: <ul style="list-style-type: none"> - Stressed, burn out, angry outbursts, coping through work or alcohol - Rule out organic cause (hypothyroidism, Addison's disease, non-HIV drugs, Vit B12 deficiency) 	Symptoms – evaluate regularly with screening questions <ol style="list-style-type: none"> A. At least 2 weeks of depressed mood OR B. loss of interest OR C. diminished sense of pleasure PLUS 4 of 7 of the following: <ol style="list-style-type: none"> 1. Weight change of ≥ 5% in one month or a persistent change of appetite, 2. insomnia or hypersomnia in most days, 3. changes in psychomotor state, 4. fatigue, 5. feelings of guilt and worthlessness, 6. diminished concentration and decisiveness, 7. suicidal ideation or a suicide attempt

Management

Degree of depression	Number of symptoms (see diagnosis: A-C + 1-7)	Treatment	Refer to expert
No	< 4		
Mild	4	problem focused consultation, consider antidepressive treatment, recommend physical activity	<ul style="list-style-type: none"> • Severe depression • Depression not responding to treatment • Suicidal ideation • Complex situations such as drug addiction, anxiety disorders, personality disorders, dementia, acute severe life event
Intermediate	5-6	start antidepressive treatment, consider referral	
Severe	>6	refer to expert	

- i Maximum effectiveness reached after 10 weeks, one episode usually 6 months treatment; optimize treatment, i.e. increase dosage or change drug if side effects; partial or no response after 4-6 weeks of antidepressant treatment at adequate dosage: reassess diagnosis; depression in persons ≥ 65 years generally requires relatively low doses of antidepressants; preferred antidepressants for HIV-infected patients: sertraline, paroxetine, venlafaxine, citalopram, mirtazapin, but also other antidepressants may be given. Citalopram may be preferred because of low interactions. For classification, doses, safety and side effects of antidepressants, see www.europeanaidscinicalsociety.org/Guidelines/index.htm. For interactions with antidepressants see www.hiv-druginteractions.org and www.europeanaidscinicalsociety.org/Guidelines/index.htm

Hyperlactataemia: diagnosis, prevention and management

Risk factors	Prevention / Diagnosis	Symptoms
<ul style="list-style-type: none"> • Use of ddl> d4T > ZDV • HCV/HBV co-infection • Use of ribavirin • Liver disease • Low CD4 cell count • Pregnancy • Female sex • Obesity 	<ul style="list-style-type: none"> • Avoid d4T + ddl combination • Routine monitoring of serum lactate levels not recommended - does <u>not</u> predict risk of lactic acidosis. • Measurement of serum lactate, bicarbonate & arterial blood gases-pH indicated in case of symptoms suggestive of hyperlactataemia • Close monitoring for symptoms if > 1 risk factor 	<ul style="list-style-type: none"> • Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, elevated ALT and/or AST, weight loss • Acidaemia: asthenia, dyspnoea, arrhythmias • Guillain-Barré-like syndrome

Management

Serum Lactate (mmol/L)	Symptoms	Action
>5 ⁱ	Yes/No	<ul style="list-style-type: none"> • Repeat test under standardized conditions to confirm & obtain arterial pH and bicarbonateⁱ • If confirmed, exclude other causes <ul style="list-style-type: none"> - 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 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 <ul style="list-style-type: none"> - 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 NRTIs. Provide intravenous fluids. 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 is unproven

Kidney disease: diagnosis, prevention and management

		eGFR		
		•60 ml/min	30-59 ml/min ⁱ	<30 ml/min ⁱ
Proteinuria ⁱⁱ / microhaematuria	UP/C ⁱⁱⁱ <50 or UA/C ^v <30	Regular Follow-up ^v	<ul style="list-style-type: none"> • Check risk factors for CKD and nephrotoxic medication • Discontinue or adjust drug dosages where appropriate^{vi} • Perform renal ultrasound • If haematuria present with any level of proteinuria refer to nephrologist; otherwise consider referral 	<ul style="list-style-type: none"> • Discontinue or adjust drug dosages where appropriate^{vi} • Perform renal ultrasound • Refer to nephrologist
	UP/C ⁱⁱⁱ 50-100 or UA/C ^v 30-70	- haematuria		
		+ haematuria		
	UP/C ⁱⁱⁱ >100 or UA/C ^v >70			

- ⁱ If not previously known to have CKD re-assess within 2 weeks
- ⁱⁱ Proteinuria defined as persistent if confirmed on ≥2 occasions >2-3 weeks apart
- ⁱⁱⁱ UP/C in spot urine (mg/mmol): detects total urinary protein secondary to glomerular and tubular disease
- ^{iv} UA/C in spot urine (mg/mmol): predominantly detects glomerular disease. Use in patients with diabetes mellitus
- ^v Check risk factors for CKD, and repeat eGFR and urinalysis as per screening table ([see p. 34](#))
- ^{vi} Dose modification of ARVs in case of impaired renal function: see www.europeanaidscineticsociety.org/Guidelines/G2_pb.htm

Management of nephropathy in HIV-positive patientsⁱ

Prevention of progressive renal disease	Comment
1. Antiretroviral therapy	Start ART immediately where HIV-associated nephropathy (HIVAN) ⁱⁱ or HIV immune complex disease strongly suspected. Renal biopsy to confirm histological diagnosis recommended
2. Start ACE inhibitors or angiotensin-II receptor antagonists if: <ul style="list-style-type: none"> a) Hypertension, and/or b) Proteinuria 	Monitor eGFR and K+ level closely on starting treatment or increasing dose a) Blood pressure target: <130/ 80 mmHg
3. General measures: <ul style="list-style-type: none"> a) Avoid nephrotoxic drugs b) Life style measures (smoking, weight, diet) c) Treat dyslipidaemiaⁱⁱⁱ and diabetesⁱⁱⁱ d) Adjust drug dosages where necessary 	CKD and proteinuria are important risk factors for CVD

- ⁱ Joint management with a nephrologist
- ⁱⁱ HIVAN suspected if black ethnicity & UP/C >100 mg/mmol & no haematuria
- ⁱⁱⁱ [see p. 51](#) and [49](#)

Screening for tenofovir renal toxicity

Screening	Frequency	Assessment
a) eGFR ⁱ (aMDDR) b) serum phosphate c) urine dipstick analysis ⁱⁱ Measure UP/Cⁱⁱⁱ if <ul style="list-style-type: none"> decline in eGFR (deterioration >10ml/min compared to pre-tenofovir level & eGFR<90 ml/min) confirmed hypophosphatemiaⁱⁱⁱ if urine dipstick proteinuria ≥ 1+ 	Prior to starting tenofovir, after 2-4 and 12 weeks; then every 3-6 months	Consider stopping tenofovir if: <ul style="list-style-type: none"> Confirmed significant hypophosphatemia of renal origin and no other cause^{iv} Progressive decline in eGFR and no other cause Confirmed proximal renal tubulopathy / Renal Fanconi syndrome^v

- i eGFR: estimated glomerular filtration rate, according to aMDDR.
- ii Some experts advocate UP/C in spot urine for screening. UP/C (mg/mmol) detects total urinary protein including protein of glomerular or tubular origin. The urine dipstick analysis primarily detects albuminuria as a marker of glomerular disease and is inadequate to detect tubular disease.
- iii Serum-phosphate <0.8 mmol/L, or according to local thresholds
- iv Hypophosphatemia is common in HIV infected patients. If secondary to increased urinary phosphate loss in the absence of any other renal cause should be attributed to tenofovir toxicity.
Stop TDF if <0.3mmol/L
Consider renal bone disease secondary to proximal tubulopathy, particularly if alkaline phosphatase increased from baseline: measure 25(OH) vitamin D, PTH
- v Indications and tests for proximal renal tubulopathy see online Table (www.europeanaidsclinicalsociety.org/Guidelines/index.htm)

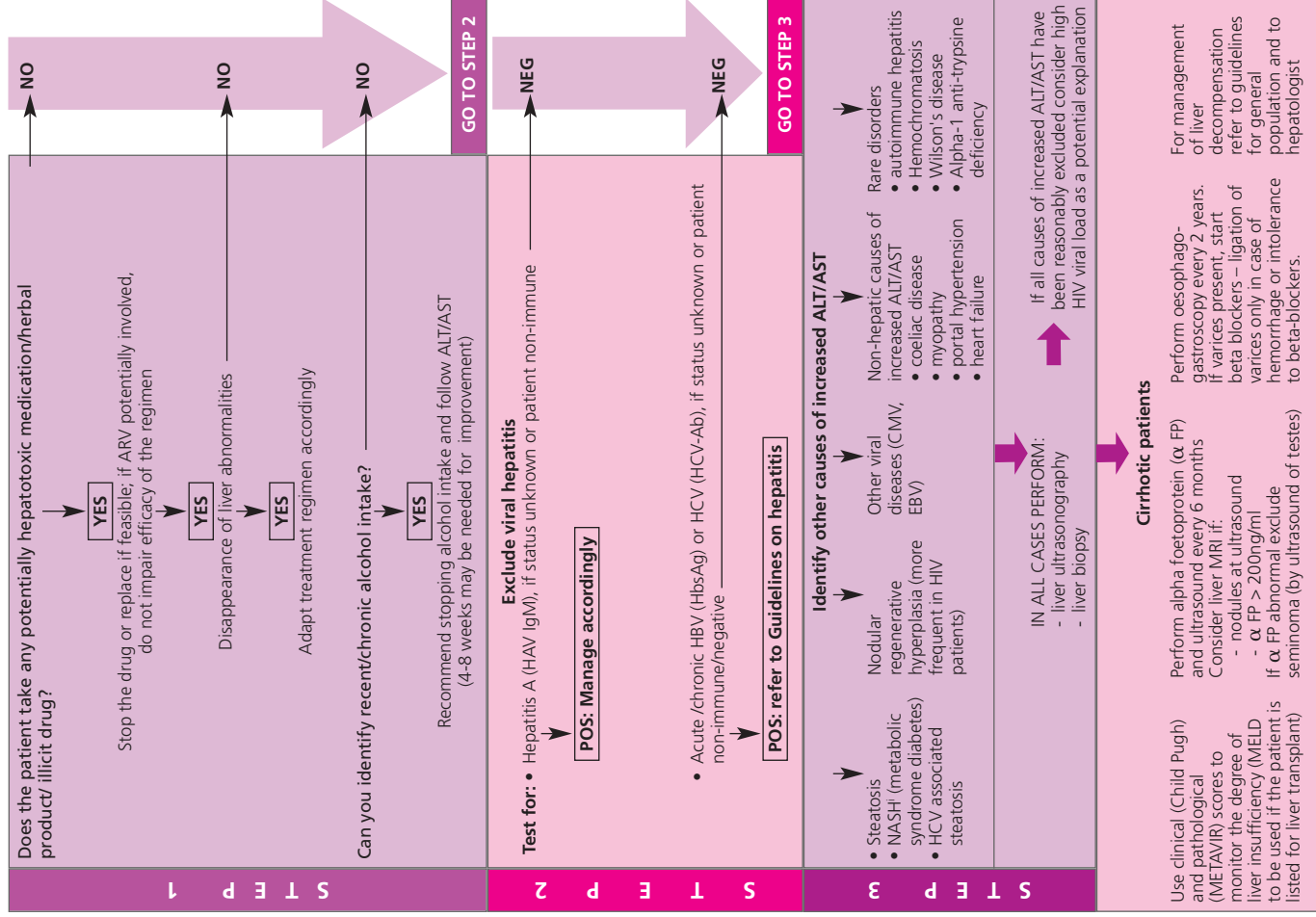
Lipodystrophy: prevention and management

LIPOATROPHY	LIPOHYPERTROPHY
Prevention <ul style="list-style-type: none"> Avoid d4T and ZDV or pre-emptively switch away from them Management <ul style="list-style-type: none"> Modification of ART <ul style="list-style-type: none"> Switch d4T or ZDV to ABC or TDF: <ul style="list-style-type: none"> Only ART modification proven to partially restore subcutaneous fat: increase in total limb fat ~400-500g/year Risk of toxicity from new drug (see p. 38): <ul style="list-style-type: none"> 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 <ul style="list-style-type: none"> Offered for relief of facial lipodystrophy only Pharmacological interventions to treat lipodystrophy have not been proven to be effective and may introduce new complications <ul style="list-style-type: none"> Proglitazone - possibly beneficial in patients not taking d4T Rosiglitazone and Pioglitazone - improvement in insulin sensitivity Rosiglitazone: increases in blood lipids and possible IHD. 	Prevention <ul style="list-style-type: none"> No proven strategy Weight gain expected with effective ART reflecting “healthy” response Weight reduction or avoidance of weight gain may decrease visceral adiposity Avoid inhaled fluticasone with some PI Management <ul style="list-style-type: none"> Diet and exercise may reduce visceral adiposity; Limited data, but possibly reduction of visceral adipose tissue and improvement in insulin sensitivity and blood lipids, especially in obesity associated with lipohypertrophy 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 lipodystrophy Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects and may introduce new complications <ul style="list-style-type: none"> Growth hormoneⁱⁱ <ul style="list-style-type: none"> Decreases visceral adipose tissue May worsen subcutaneous lipodystrophy, may worsen insulin resistance Metformin <ul style="list-style-type: none"> Decreases visceral adipose tissue in insulin resistant persons May worsen subcutaneous lipodystrophy. Surgical therapy can be considered for localised lipomas/buffalo humps <ul style="list-style-type: none"> Duration of effect variable

i See www.europeanaidsclinicalsociety.org/Guidelines/index.htm for list of arguments for and against the use of various types of fillers (with some examples of specific types) and autologous fat transplantation
 ii tesamorelin (growth hormone releasing factor) was shown to reduce visceral adipose tissue volume; the drug is not recently licensed in Europe.

Work-up and Management of the HIV patient with increased ALT/AST

Identify potential cause of increased liver enzymes, using the following steps:



i non alcoholic steato hepatitis

Neurocognitive impairment: diagnosis and management

Any HIV-infected person complaining of disturbances in his/her memory (comprehension, clarity or speed) should be evaluated extensively, including neurological examination, neuropsychological assessment, cerebrospinal examination and imaging of the brain.

- Patients without such symptoms that should be targeted for screening
 - Uncontrolled HIV infection (detectable plasma HIV RNA)
 - Use of antiretroviral agents with limited CNS penetration
 - Low CD4 nadir (<200 cells/mm³)
 - Ongoing depression
- Screening tool
 - International HIV Dementia Scale (IHDS)ⁱ
- Interventions if neurocognitive impairment detected:
 - If patient is not on ART:
 - Consider initiation of ART in which at least 2 drugs penetrate CNSⁱⁱ
 - Consider risk for antiretroviral resistance if prior virological failure
 - If patient is already on ART:
 - Consider changing antiretroviral treatment to active drugs with better CNS penetrationⁱⁱ
 - Consider genotyping of plasma and CSF HIV RNA whenever feasible prior to changing ART

i See www.europeanaidsclinicalociety.org/Guidelines/index.htm for components of the IHDS scale

ii See www.europeanaidsclinicalociety.org/Guidelines/index.htm for list of drugs with favourable and poor CNS penetration