EACS

European AIDS Clinical Society

Guidelines

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The European AIDS Clinical Society (EACS) is a not-for-profit group of European physicians, clinicians and researchers in the field of HIV/AIDS.

It aims to bring together scientists from all over Europe to help exchange the latest medical and scientific knowledge regarding clinical aspects of HIV/AIDS and its complications.

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Abbreviations used throughout this document

ARV ABBREVIATIONS

- 3TC=lamivudine
- ABC=abacavir
- ATV=atazanavir
- d4T=stavudine
- ddI=didanosine
- DRV=darunavir
- EFV=efavirenz
- ENF=enfuvirtide
- ETV=etravirine
- FDC=fixed dose combination
- FPV=fosamprenavir
- FTC=emtricitabine
- IDV=indinavir
- ITI=integrase transfer inhibitor
- LPV=lopinavir
- MVC=maraviroc
- NFV=nelfinavir
- NRTI=nucleos(t)ide reverse transcriptase inhibitors
- NNRTI=non-nucleoside reverse transcriptase inhibitors
- NVP=nevirapine
- PI=protease inhibitors
- PI/r=protease inhibitors pharmacologically boosted with ritonavir
- RAL=raltegravir
- RPV=rilpivirine
- RTV=ritonavir (used as booster= /r)
- SQV=saquinavir
- TDF=tenofovir
- TPV=tipranavir
- ZDV=zidovudine

OTHER ABBREVIATIONS

- 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
- BMD=bone mineral density
- BMI=body mass index
- CKD=chronic kidney disease
- CMV=cytomegalovirus
- CNS=central nervous system
- COPD=chronic obstructive pulmonary disease
- CSF=cerebrospinal fluid
- CVD=cardiovascular disease
- CXR=chest X-ray
- DXA=dual energy X-ray absorptiometry
- ECG=electrocardiogram
- eGFR=estimated glomerular filtration rate
- FBC=full blood count
- FRAX=fracture risk assessment tool
- HBV=hepatitis B virus
- HCV=hepatitis C virus
- HDL-c=HDL-cholesterol
- HIVAN=HIV-associated nephropathy
- HPV=human papillomavirus
- HSR=hypersensivity reaction
- IGRA=interferon-gamma release assay
- IHD=ischaemic heart disease
- IV=intravenous
- LDL-c=LDL-cholesterol
- LGV=lymphogranuloma venereum
- Mg=magnesium
- MSM=men who have sex with men
- PPD=purified protein derivative
- PSA=prostate specific antigen
- PTH=parathyroid hormone
- RBV=ribavirin
- STI=sexually transmitted infection
- TC=total cholesterol
- TDM=therapeutic drug monitoring
- TG=triglycerides
- UA/C=urine albumin/creatinine ratio
- UP/C=urine protein/creatinine ratio
- VL=viral load
- WB=western blot
- Zn=zinc

Part I Assessment of HIV-infected patients at initial and subsequent visits

	Assessment	At HIV diagnosis	Prior to starting cART	Follow-up frequency	Comment	See page
HISTORY						
Medical	Complete medical history including	+	+		On transfer of care repeat assessment	
	• Family history (e.g. premature CVD, diabetes, hypertension, CKD)	+			Premature CVD: Cardiovascular events in a first degree relative: male < 55, female < 65 years	26
	• Concomitant medications [(i)]	+	+	Every visit		22
	• Past and current co-morbidities	+	+		Consider CXR if prior history of pulmonary disease	
	• Vaccination history	+			Measure antibody titres and offer vaccinations where indicated	44
Psychosocial	• Current lifestyle (alcohol use, smoking, diet, aerobic exercise, drug use)	+	+	6-12 m	Adverse lifestyle habits should be addressed more frequently	Appendix: Lifestyle interventions
	• Employment	+	+			
	• Social and welfare	+	+	As indicated	Provide advice and support if needed	
	• Psychological morbidity	+	+	Every visit	Provide counselling if needed	
	• Partner and children	+			Test partner and children if at risk	
Sexual and reproductive health	• Sexual history	+		6-12 m	Address issues concerning sexual dysfunction	46
	• Safer sex	+		As indicated	Risk of sexual transmission should be addressed where indicated	
	• Partner status and disclosure	+		As indicated		
	• Conception issues	+	+	As indicated		
HIV DISEASE						
Virology	• Confirmation of HIV Ab +ve test	+				12-21
	• Plasma HIV RNA	+	+	3-6 m	More frequent monitoring of HIV RNA at start of ART	
	• Genotypic resistance test and sub-type	+	+	At virological failure	Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection	
	• R5 tropism (if available)	+/-	+		Screen if considering R5 antagonist in regimen	

	Assessment	At HIV diagnosis	Prior to starting cART	Follow-up frequency	Comment	See page
Immunology	• CD4 absolute count and % (optional: CD8 and %)	+	+	3-6 m [(ii)]	Consider less frequent monitoring for stable patients on ART with high CD4-counts [(ii)]	12-21
	• HLA B5701(if available)	+	+/-		Screen before starting abacavir containing ART, if not previously tested	
COINFECTIONS						
STIs	• Syphilis serology	+		Annual/as indicated	Consider more frequent screening if at risk	
	• STI screen	+		Annual/as indicated	Screen if at risk	
Viral Hepatitis	• Hep A serology	+			Screen at risk, vaccinate if non-immune	44
	• Hep C screen	+		Annual/as indicated	Annual screen if ongoing risk Measure HCV-RNA if HCV Ab+ve or if acute infection suspected If HCV-RNA +ve	46
	• Hep B screen	+	+		Vaccinate if non-immune Annual screen in susceptible patients If Hep B sAg +ve	52
Tuberculosis	• CXR	+			Consider routine CXR in patients from high prevalence TB populations	
	• PPD if CD4-count > 400	+		Re-screen if exposure		
	• IGRA in selected high risk populations (if available)	+				
Others	• Varicella zoster virus serology	+			Offer vaccination where indicated	44
	• Measles/Rubella serology	+			Offer vaccination where indicated	44
	• Toxoplasma serology	+				
	• CMV serology	+				
	• Leishmania serology	+/-			Screen according to travel history/origin	
	• Tropical parasites: e.g. schistosomiasis, strongyloides serology	+/-			Screen according to travel history/origin	

	Assessment	At HIV diagnosis	Prior to starting cART	Follow-up frequency	Comment	See page
NON-INFECTIOUS CO-MORBIDITIES						
Haematology	• FBC	+	+	3-12 m		
	• Haemoglobinopathies	+			Screen at risk patients	
	• G6PD	+			Screen at risk patients	
Body composition	• Body mass index	+	+	Annual		Appendix: Lifestyle interventions
Cardiovascular disease	• Risk assessment (Framingham score [iii])	+	+	Annual	Should be performed in all men > 40 and women > 50 years without CVD	26
	• ECG	+	+/-		Consider baseline ECG prior to starting PIs associated with potential conduction problems	
Hypertension	• Blood pressure	+	+	Annual		27
Lipids	• TC, HDL-c, LDL-c, TG [iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	31
Glucose	• Plasma glucose	+	+	6-12 m	Consider oral glucose tolerance test/HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100 125 mg/dL)	29
Liver disease	• Risk assessment [v]	+	+	Annual	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs	39
	• ALT/AST, ALP, Bilirubin	+	+	3-12 m		
Renal disease	• Risk assessment [vi]	+	+	Annual		37
	• eGFR (aMDRD) [vii]	+	+	3-12 m	More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs [ix]	
	• Urine Dipstick analysis [viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min; if proteinuria ≥ 1+ and/or eGFR < 60 mL/min perform UP/C or UA/C [viii]	
Bone disease	• Bone profile: calcium, PO4, ALP	+	+	6-12 m		35
	• Risk assessment [x] (FRAX® [xi] in patients > 40 years)	+	+	2 yrs	Consider DXA in at risk patients	
Vitamin D	• 25 OH Vitamin D	+		As indicated	Screen at risk patients	36
Neurocognitive impairment	• Screening questions	+	+	2 yrs	Screen all patients without highly confounding conditions. If abnormal or symptomatic, refer to algorithm page for further assessment	48

	Assessment	At HIV diagnosis	Prior to starting cART	Follow-up frequency	Comment	See page
Depression	• Screening questions	+	+	1-2 yrs	Screen at risk patients	32
Cancer	• Mammography			1-3 yrs	Women 50-70 years	25
	• Cervical PAP			1-3 yrs	Sexually active women	
	• Anoscopy and PAP (MSM)			1-3 yrs	Evidence of benefit uncertain	
	• Ultrasound and alphafoetoprotein			6 m	Persons with cirrhosis	40
	• Others				Controversial	

i Review all concomitant medications which may potentially interact with ART drugs or increase co-morbidities.

ii If stable on ART with undetectable VL and CD4-count > 350/µL, consider less frequent CD4-count monitoring every 6-12 months.

iii 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, interpretation of the estimation should be done with caution.

iv Calculator for LDL-cholesterol in cases where TG is not high can be found at www.cphiv.dk/tools.aspx.

v Risk factors for chronic liver disease include: alcohol, viral hepatitis, obesity, diabetes, insulin resistance, hyperlipidaemia, hepatotoxic drugs.

vi Risk factors for chronic kidney disease (CKD): hypertension, diabetes, CVD, family history, black African ethnicity, viral hepatitis, concomitant nephrotoxic drugs.

vii eGFR: use the abbreviated modification of diet in renal disease formula (aMDRD) based on serum creatinine, gender, age and ethnicity (see: www.cphiv.dk/tools.aspx).

viii Some experts recommend UA/C or UP/C as a screening test for proteinuria in all patients. UA/C: urinary albumin creatinine 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.

ix Additional screening is required for patients receiving tenofovir (see p. 38).

x Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m^2), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (> 3 units/day), steroid exposure (minimum 5 mg for > 3 months).

xi WHO fracture risk assessment tool (FRAX®): (www.shef.ac.uk/FRAX).

Part II ARV treatment of HIV-infected patients

Assessing patients' readiness to start ART [i]

Goal: Facilitate decision making and starting ART for patients who qualify according to international guidelines

Before initiating ART, screen for decision making and adherence barriers:	
Patient-related factors: A. Depression [ii] B. Harmful alcohol or recreational drug use [iii] C. Cognitive problems [iv] D. Low health literacy	System-related factors: E. Health insurance and drug supply F. Continuity of drug supply G. Social support and disclosure
Recognise, discuss and reduce problems wherever possible!	

Assess patients' readiness and support progress between stages: [v]

"I would like to talk about HIV medication." <wait> *"What do you think about it?"* [vi]

Remember:

• Set the agenda before every interview • Use open questions whenever possible • Use the WEMS-technique [vii]

Precontemplation: "I don't need it, I feel good". "I don't want to think about it"

Support: Show respect for patient attitude / Try to understand health and therapy beliefs / Establish trust / Provide individualised short information / Schedule the next appointment

Restage again

Contemplation: "I am weighing things up and feel torn about what to do about it"

Support: Allow ambivalence / Support to weigh pros and cons together with patient / Assess information needs and support information seeking / Schedule the next appointment

NO

Restage again

Preparation: "I want to start, I think the drugs will allow me to live a normal life"

Support: Reinforce decision / Make shared decision on most convenient regimen / Educate: adherence, resistance, side effects / Discuss integration into daily life / Assess self-efficacy

Ask: Do you think you can manage to take cART consistently once you have started?

Use: VAS 0-10 [viii]

0 ..... 5 10

NO

Patients presenting in the clinic may be at different stages of readiness: Precontemplation, contemplation or preparation [Transtheoretic model; Prochaska JO. Am Psychol 47:1102-1114, 1992]. The first step is to assess this stage, and then to support/intervene accordingly. An exception is if a patient presents late or very late, i.e. < 200 or < 50 CD4/µL. In this case the initiation of ART should not be delayed; the clinician should try to identify the most important adherence barriers which may be present, and support the patient to be prepared for prompt initiation of ART.

Consider skills training:

- Medication-taking training, possibly MEMS (2-4wk) [ix]
- Directly Observed Therapy with educational support
- Use aids: Pillboxes, cell phone alarm, involve contact persons where appropriate

START AND MAINTAIN ADHERENCE

Screen: For adherence problems in each meeting [x]

Support: Discuss side effects, educate about surrogate markers, discuss integration of drug-taking schedule

Empower: Give positive feedback

Comments on the table “Assessing patients’ readiness to start ART”

i This table should facilitate the initiation of ART. Matters for consideration listed in this table, such as decision making or barriers to adherence, have to be judged clinically in their context. For instance, the clinician has to judge whether ART has to be initiated immediately despite the detection of possible barriers to adherence or whether delaying initiation is justified. Consider patient’s cultural background.

ii Ask: *“During the past month, have you often been bothered by feeling down, depressed or hopeless?” “During the past month, have you often been bothered by little interest or pleasure in doing things?” “Is this something with which you would like help?”* If answers are positive, then sensitivity is 96 %, specificity 89 % (Arroll B et al. BMJ 327:1144-1146. 2003).

iii Ask: *“Have you thought about cuttting down?”; “Have you ever become annoyed when people talk to you about your drinking?”; “Have you ever felt guilty about your drinking?”; “Do you ever have a drink first thing in the morning (eye opener)?”*. An affirmative answer to more than two CAGE questions means a sensitivity and specificity for problematic alcohol use of more than 90 % (Kitchens JM. JAMA 272(22): 1782-1787. 1994). Ask similar questions for recreational drug use.

iv Ask: *“Do you feel that you are having problems concentrating in your daily life?”; “Do you feel slow in your thinking?”; “Do you feel that you are having problems with your memory?”; “Have relatives or friends expressed that they feel you are having problems with your memory or difficulty concentrating?”*

v Patients presenting in the clinic may be at different stages of readiness: Precontemplation, contemplation or preparation [Transtheoretic model; Prochaska JO. Am Psychol 47:1102-1114, 1992]. The first step is to assess this stage, and then to support/intervene accordingly. An exception is if a patient presents late or very late, i.e. < 200 or < 50 CD4/µL. In this case the initiation of ART should not be delayed; the clinician should try to identify the most important adherence barriers which may be present, and support the patient to be prepared for prompt initiation of ART.

vi This is a suggested opening question to assess the patient’s stage of readiness. Further discussion will indicate which of the three initial stages the patient has reached: he/she might even be ready for therapy.

vii WEMS: Waiting (> 3 sec), Echoing, Mirroring, Summarising (Langewitz W et al. BMJ 325:682-683. 2002).

viii VAS (= Visual Analogue Scale; Range from 0 to 10 i.e. 0 = I will not manage, 10 = I am sure I will manage).

ix Medication training/MEMS training could be done with vitamins before starting ART.

x Suggested adherence questions: *“In the past 4 wks, how often have you missed a dose of your HIV medication: every day, more than once a wk, once a wk, once every 2 wks, once a month, never?” “Have you missed more than one dose in a row?”* (Glass TR et al. Antiviral Therapy 13(1):77-85. 2008).

Adapted from: J. Fehr, D. Nicca, F. Raffi, R. Spirig, W. Langewitz, D. Haerry, M. Battegay, NEAT, 2008.

Recommendations for initiation of ART in HIV-positive persons without prior ART exposure [i]

Recommendations are graded while taking into account both the degree of progression of HIV disease and the presence of or high risk for developing various types of (co-morbid) conditions

Condition	Current CD4+ lymphocyte count [ii,iii]	
	350-500	> 500
Asymptomatic HIV infection	C	D
Symptomatic HIV disease (CDC B or C conditions) incl. tuberculosis	R	R
Primary HIV infection	C	C
Pregnancy (before third trimester)	R	R
Conditions (likely or possibly) associated with HIV, other than CDC stage B or C disease:		
HIV-associated kidney disease	R	R
HIV-associated neurocognitive impairment	R	R
Hodgkin's lymphoma	R	R
HPV-associated cancers	R	R
Other non-AIDS-defining cancers requiring chemo- and/or radiotherapy	C	C
Autoimmune disease – otherwise unexplained	C	C
High risk for CVD (> 20 % estimated 10-yr risk) or history of CVD	C	C
Chronic viral hepatitis		
HBV requiring anti-HBV treatment	R	R
HBV not requiring anti-HBV treatment	C/R [iv]	D
HCV for which anti-HCV treatment is being considered or given	R [v]	D [vi]
HCV for which anti-HCV treatment not feasible	R	C

i The consideration to start ART should be individualized regardless of CD4-count and plasma HIV RNA level, especially if a patient is requesting ARV therapy and ready to start, and/or for any other personal reasons. **In serodifferent partners, early initiation of ART as one aspect of the overall strategy to reduce HIV transmission to the seronegative partner should be strongly considered and actively discussed.**

Time should be taken to prepare the patient, in order to optimize compliance and adherence.

Genotypic resistance testing and subtype determination is recommended prior to initiation of ART; ideally at the time of HIV diagnosis, otherwise before initiation of ART. If genotypic testing is not available, it is recommended to include a ritonavir-boosted PI in the first-line regimen.

Before starting treatment, the HIV RNA level and CD4-count should be repeated to obtain a baseline to assess subsequent response.

ii **ART is always recommended in any HIV-positive person with a current CD4-count below 350 cells/μL.**

iii **C**=use of ART should be considered; for patients under these circumstances, some experts would recommend starting ART whereas others would recommend deferral of ART; this clinical equipoise reflects that whereas certain evidence supports starting ART, this needs to be balanced against the risk of known or undiscovered adverse drug reactions from use of ART, and hence the risk/benefit ratio for use of ART under these circumstances has not yet been well defined.

D=defer initiation of ART.

R=use of ART is recommended.

iv Initiation of ART is recommended in those who are HBeAg-positive.

v Initiation of ART is recommended to optimize the outcome of HCV treatment.

vi HCV treatment to attempt eradication of HCV should be prioritized and ART deferred.

Initial combination regimen for antiretroviral-naive adult patients

Recommended regimens (*)

A drug from column A should be combined with the drugs listed in column B (**)

A	B	Remarks
NNRTI	**NRTI**	
• EFV (i) • RPV (ii)	ABC/3TC (vii) or TDF/FTC	• TDF/FTC co-formulated • ABC/3TC co-formulated • EFV/TDF/FTC co-formulated • RPV/TDF/FTC co-formulated
• NVP (iii)	TDF/FTC	• TDF/FTC co-formulated
Ritonavir-boosted PI		
• ATV/r (iv) • DRV/r (iv) • LPV/r (v)	ABC/3TC (vii) or TDF/FTC	• ATV/r: 300/100 mg qd • DRV/r: 800/100 mg qd • LPV/r: 400/100 mg bid or 800/200 mg qd
ITI		
• RAL	TDF/FTC	• RAL: 400 mg bid

Alternative regimen components

Ritonavir-boosted PI	Remarks
• SQV/r	1000/100 mg BID
• FPV/r	700/100 mg bid or 1400/200 mg QD
NRTI	
• TDF-3TC • ZDV/3TC • ddI/3TC or ddI/FTC (viii)	ZDV/3TC co-formulated
CCR5 inhibitor	
MVC (vi)	Only if CCR5 tropic HIV (viii)

* Only drugs currently licensed for initiation of therapy by the European EMA are taken into consideration.

** Generic HIV drugs are becoming more available and can be used as long as they replace the same drug and do not break recommended fixed dose combinations.

i EFV: not recommended to be initiated in pregnant women or women with no reliable and consistent contraception; continuation is possible if already started before pregnancy; not active on HIV-2 and HIV-1 group O.

ii RPV: only if VL < 100 000 c/mL; PPI contraindicated, H2 antagonists to be taken 12h before or 4h after RPV.

iii NVP: Use with extreme caution in women with CD4 > 250 and men with CD4 > 400 µL and only if benefits outweigh the risk; not active on HIV-2 and HIV-1 group O.

iv Castle study (LPV/r vs. ATV/r) has shown better tolerability of ATV/r and Artemis study (LPV/r vs. DRV/r) better efficacy and greater tolerability of DRV/r.

v ACTG 5142 randomised study showed lower virological efficacy of LPV/r vs. EFV while no PI mutations were seen in the LPV/r plus two nucleoside failures. However, PI mutations were seen on LPV/r + EFV.

vi Unlicensed in Europe for naive patients.

vii ABC contra-indicated if HLA B*5701 positive. Even if HLA B*5701 negative, counselling on HSR risk still mandatory. ABC should be used with caution in patients with a high CVD risk and/or patients with a VL > than 100,000 c/mL.

viii Only if unavailability or intolerance to other recommended NRTIs.

Acute HIV infection

Definition of Acute primary HIV infection

- High-risk exposure within previous 2-8 weeks,
- and clinical symptoms,
- and detectable HIV in the plasma (p24 Ag and/or HIV RNA > 10 000 c/mL)
- and negative or indeterminate serologic testing (negative or weakly positive ELISA, and WB ≤ 1 band)
- Recommendation: confirm HIV infection by HIV antibody test (WB) performed 2 weeks later.

Treatment:

- Treatment indicated if:
  - AIDS defining events
  - Confirmed CD4 < 350 c/µL at month 3 or beyond
- Treatment should be considered if:
  - Severe illness/prolonged symptoms (especially CNS symptoms)
- If treatment of PHI is considered, patient should be preferably recruited into a clinical trial
- Treatment optional, if based only on theoretical considerations. In most situations, wait till month 6 (with CD4 and plasma HIV-RNA monitoring) and follow criteria for initiation of treatment in chronic HIV infection. Some experts recommend treatment as a tool for prevention of HIV transmission.
- Duration of treatment should be lifelong.
- Maintain closer follow-up in case of treatment interruption

Resistance testing:

- Recommended in all situations as soon as acute HIV infection is diagnosed, even if treatment not initiated
- In case it cannot be performed, store a plasma sample for testing.

Transmission:

- Recognize STIs, including syphilis, gonorrhoea, chlamydia (urethritis and LGV), HPV, hepatitis B and hepatitis C
- Counsel newly diagnosed patient on high risk of transmission and preventive measures (condoms) including notifying and testing partners.

Switch strategies for virologically suppressed patients (confirmed plasma viral load < 50 c/mL)

Indication:

1. Switch for toxicity
- Documented toxicity
- Management of potential drug interactions
- Side effects
- Planned pregnancy

2. Switch for prevention of long-term toxicity
- Prevention of long-term toxicity (pre-emptive switch)
- Ageing and/or co-morbidity with a possible negative impact of drug(s) in current regimen, e.g. on CVS risk, metabolic parameters.

3. Switch for simplification
- Wish to simplify regimen
- Actual regimen no longer recommended

Principles:

1. A boosted PI may be switched for simplification, prevention or improvement of metabolic abnormalities or adherence facilitation to unboosted atazanavir, an NNRTI or raltegravir only if full activity of the 2 NRTIs remaining in the regimen can be guaranteed.
2. Simplification of a complex multidrug regimen in antiretroviral-experienced patients with **1)** substitution of drugs difficult to administer (enfuvirtide) and/or with poor activity (NRTI in case of multiple NRTI resistance) and/or poor tolerability and **2)** addition of new well-tolerable, simpler and active agent(s).
3. Bid to qd NRTI switch for simplification, prevention of long-term toxicity
4. Intra-class switch if drug-specific related adverse event
5. PI/r to NNRTI switch for simplification, prevention or improvement of metabolic abnormalities, adherence facilitation. NVP has the advantage of its metabolic profile. EFV has the advantage of possible FDC of 3 drugs (Atripla).
6. Review the complete ARV history and available resistance test results
7. Avoid switching to a drug with a low genetic barrier in the presence of a backbone compromised by the possibility of archived class resistance

Strategies not recommended:

a. Intermittent therapy, sequential or prolonged treatment interruptions

b. 2-drug combination, i.e. 1 NRTI + 1 NNRTI or 1 NRTI + 1 PI without ritonavir or 1 NRTI + RAL, or 2 NRTIs

c. Triple NRTI combinations

Other strategy:

PI/r monotherapy with bid LPV/r or qd DRV/r might represent an option in patients with intolerance to NRTI or for treatment simplification. Such a strategy only applies to patients without history of failure on prior PI-based therapy and who have had viral loads < 50 c/mL in at least the past 6 months.

Virological failure

Definition	Confirmed plasma HIV RNA > 50 copies/mL 6 months after starting therapy (initiation or modification) in patients that remain on ART [(i)]
General measures	• Review expected potency of the regimen • Evaluate adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues • Perform resistance testing on failing therapy (usually routinely available for VL levels > 350-500 c/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations • Tropism testing • Consider TDM • Review antiretroviral history • Identify treatment options, active and potentially active drugs/combinations
Management of virological failure (VF)	If plasma HIV RNA > 50 and < 500-1000 copies/mL • Check for adherence • Check plasma HIV RNA 1 to 2 months later If genotype not possible, consider changing regimen based on past treatment and resistance history If plasma HIV RNA confirmed > 500/1000 copies/mL, change regimen as soon as possible. What to change will depend on the resistance testing results: • No resistance mutations found: re-check for adherence, perform TDM • Resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary expert discussion advised Goal of new regimen: plasma HIV RNA < 400 c/mL after 3 months, plasma HIV RNA < 50 c/mL after 6 months
In case of demonstrated resistance mutations	**General recommendations:** • Use at least 2 and preferably 3 active drugs in the new regimen (including active drugs from previously used classes) • Any regimen should use at least 1 fully active PI/r (e.g. darunavir/r) plus 1 drug from a class not used previously e.g. fusion, integrase or CCR5 antagonist (if tropism test shows R5 virus only), or 1 NNRTI (e.g. etravirine), assessed by genotypic testing • Defer change if < 2 active drugs available, based on resistance data, except in patients with low CD4-count (< 100 cells/μL) or with high risk of clinical deterioration for whom the goal is the preservation of immune function through partial reduction of plasma HIV RNA (> 1 log reduction) by recycling • If limited options, consider experimental and new drugs, favouring clinical trials (but avoid functional monotherapy) • Treatment interruption is not recommended • Consider continuation of 3TC or FTC in particular situations even if documented resistance mutation (M184V/I) If many options are available, criteria of preferred choice include: simplicity of the regimen, toxicity risks evaluation, drug-drug interactions, future salvage therapy

i Depending on the viral load assay, this limit could be higher or lower.

Treatment of HIV pregnant women

Pregnant women should be monitored every month and as close as possible to the predicted delivery date.

Criteria for starting ART in pregnant women (see different scenarios)	Same as for non pregnant
Objective of treatment in pregnant women	Full plasma HIV RNA suppression at least by third trimester and specifically at time of delivery
Resistance testing	Same as for non pregnant, i.e. before starting ART and in case of virological failure
SCENARIO 1. Women becoming pregnant while already on ART 2. Women becoming pregnant while treatment naive irrespective of whether they fulfil the criteria (CD4) for initiation of ART 3. Women whose follow-up starts after W28 of pregnancy	 1. Maintain ART 2. Starting ART at beginning of 2nd trimester is highly recommended 3. Start ART immediately
Antiretroviral regimen in pregnancy	**Same as non pregnant** • NVP and EFV not to be initiated but continuation is possible if started before pregnancy • Among PI/r, prefer LPV/r, SQV/r or ATV/r • RAL, DRV/r: use only in special conditions; little data available in pregnant women
Drugs contra-indicated during pregnancy	ddI + d4T, triple NRTI combinations
IV zidovudine during labour	Benefit uncertain if plasma HIV RNA < 50 c/mL
Single dose nevirapine during labour	Not recommended
Caesarean section	Benefit uncertain if plasma HIV RNA < 50 c/mL at W34-36. In this case, consider vaginal delivery only

ART in TB/HIV coinfection

Suggested timing of ART initiation in TB/HIV coinfection according to CD4/µL

CD4-COUNT, CELLS/µL	WHEN TO START ART
< 100	As soon as possible and ideally within 2 weeks [i]
100–350	As soon as practical, but can wait until after completing 2 months TB treatment especially when there are difficulties with drug interactions, adherence and toxicities
> 350	At physician discretion

Concomitant use of anti-TB medications and antiretrovirals

- **NRTIs:** no significant interaction with rifampicin or rifabutin
- **NNRTIs:**
  - EFV and rifampicin: No dose change for Efavirenz in black Africans. In Caucasians, consider EFV 800 mg qd if weight > 60 kg, 600 mg qd if < 60 kg; rifampicin at standard dose. In any case, TDM is recommended after 2 weeks
  - EFV and rifabutin: EFV at standard dose; rifabutin 450 mg daily
  - NVP: not recommended
  - Etravirine: not recommended
- **PIs:**
  - and rifampicin: not recommended
  - and rifabutin: rifabutin 150 mg x 3 per week with ATV/r, DRV/r, LPV/r or SQV/r; PI/r at standard dose; monitor liver enzyme tests and, whenever possible, perform TDM for PI
- **Raltegravir:**
  - and rifampicin: use with caution (only if no alternative), if used: raltegravir 800 mg bid
  - and rifabutin: can be given with raltegravir both in normal doses
- **Maraviroc:**
  - and rifampicin: use with caution at double dose 600 mg bd maraviroc
  - and rifabutin: standard doses
- **Enfuvirtide:** no significant interaction with rifampicin or rifabutin

Where combinations are not recommended, specialist HIV treatment advice should be sought. TDM of NNRTI and PI should be performed when drug regimens contain one of these drugs. Drug levels of anti-tuberculosis drugs should be measured when there is clinical concern regarding absorption or response to TB therapy.

Recommended 1st line ARV combination in patients receiving anti-TB medication

Among recommended regimens for antiretroviral-naive patients, preference should be given to EFV/TDF/FTC with dose adaptation of EFV if needed (see above).

Alternative

- Recommended PI/r + TDF/FTC, using rifabutin instead of rifampicin
- Use with caution
  1. Raltegravir 800 mg bid + TDF/FTC with rifampicin
  2. If plasma viral load < 100,000 c/mL, fixed-dose combination of ZDV/ABC/3TC bid +/- tenofovir could also represent a short-term alternative until TB treatment has been completed.

If it is not possible to use these drugs because of resistance/intolerance, seek expert help.

i Be aware of IRIS reaction in patients starting ARV at low CD4 levels and at early initiation. Corticoids could be considered as treatment of IRIS in some settings

Post-exposure prophylaxis

	POST EXPOSURE PROPHYLAXIS (PEP) RECOMMENDED IF	
	Nature of exposure	**Status of source patient**
Blood	Subcutaneous or intramuscular penetration with IV or IM needle, or intravascular device	HIV + Or serostatus unknown but presence of HIV risk factors
	• Percutaneous injury with sharp instrument (lancet), IM or SC needle, suture needle • Contact > 15 min of mucous membrane or non intact skin	HIV +
Genital secretions	Anal or vaginal sex	HIV + Or serostatus unknown but presence of HIV risk factors
	Receptive oral sex with ejaculation	HIV +
Intravenous drug use	Exchange of syringe, needle, preparation material or any other material	HIV +

- Rapid testing of the source patient for HCV and HIV (if HIV status unknown) recommended
- If source patient HIV+ on ARV therapy, order resistance testing if VL detectable
- Individualise PEP according to the source's treatment history and previous resistance tests
- PEP to be started ideally < 4 hours after the exposure, and no later than 48 hours
- Duration of PEP: 4 weeks
- Standard PEP regimen: TDF/FTC (alternative: ZDV/3TC) + LPV/r tablets 400/100 mg bid
- Full sexual health screen in case of sexual exposure
- Follow-up:
  - HIV serology + HBV and HCV, pregnancy test (women) within 48 hours of exposure
  - Re-evaluation of PEP indication by HIV expert within 48-72 hours
  - Assess tolerability of PEP regimen
  - Transaminases, HCV-PCR and HCV serology at month 1 if source of exposure was HCV+ (observed or suspected)
  - Repeat HIV serology after 2 and 4 months, syphilis serology after 1 month if sexual exposure

Antiretroviral drugs & drug classes: **frequent/severe** side effects (i) 1/2

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genitourinary	Nervous	Body fat	Metabolic	Other
NRTI										
ZDV	Nail pigmentation	Nausea	Steatosis		Myopathy			**Lipoatrophy**	Dyslipidaemia **Hyperlactataemia**	Anaemia
d4T		**Pancreatitis**	**Steatosis**				**Peripheral neuropathy**		**Dyslipidaemia** **Hyperlactataemia**	
ddI		**Pancreatitis**	Steatosis, Liver fibrosis	**IHD**					**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 Reduced vitamin D level
NVP	**Rash**		**Hepatitis**							**Systemic hypersensitivity (CD4, gender, ART experience dependent)**
ETV	Rash									

Antiretroviral drugs & drug classes: **frequent/severe** side effects [i] 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	
SQVI									Dyslipidaemia	
LPV				**IHD**					**Dyslipidaemia**	
FPV	Rash			**IHD**					**Dyslipidaemia**	
ATV			Jaundice			**Nephrolithiasis**		↑ abdominal fat	Dyslipidaemia	
DRV	Rash								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 red. "Frequent events" (events expected in at least 10 % of treated patients) are marked in bold.

ii Frequency and severity differs between individual agents.

Drug-drug interactions between HIV drugs and non-HIV drugs [i]

	Non-HIV drugs	ATV	DRV	LPV	RTV [ii]	EFV	ETV	NVP	MVC	RAL
CARDIOVASCULAR DRUGS	atorvastatin	↑	↑	↑	↑	↓	↓	↓*	↔	↔
	fluvastatin	↔*	↔*	↔*	↔*		↑*		↔*	↔*
	pravastatin	↔*	↑	↔	↔	↓	↓*	↔*	↔	↔
	rosuvastatin	↑	↑*	↑	↑	↔	↑*	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓	↓*	↓*	↔	↔
	amlodipine	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	↔*	↔
	diltiazem	↑[iii]	↑*	↑	↑	↓	↓*	↓	E*	↔
	metoprolol	↑*	↑*	↑*	↑*	↔*	↔*	↔*	↔*	↔*
	verapamil	↑*[iii]	↑*	↑*	↑*	↓*	↓*	↓*	E*	↔*
	warfarin	↑ or ↓*	↓	↓	↓	↑ or ↓*	↑*	↑ or ↓*	↔*	↔*
CNS DRUGS	diazepam	↑*	↑*	↑*	↑*	↓*	↑*	↓*	↔*	↔*
	midazolam	↑	↑	↑	↑	↑			↔	↔
	triazolam	↑	↑	↑	↑	↑			↔*	↔*
	citalopram	↑*	↑*	↑*	↑*	↓*	↑*	↓*	↔*	↔*
	mirtazapine	↑*	↑*	↑*	↑*	↓*	↓*	↓*	↔*	↔*
	paroxetine	↑*	↓	↑*	↑	↔	↔	↔*	↔*	↔*
	sertraline	↑*	↓	↑*	↑	↓	↓*	↓*	↔*	↔*
	pimozide	↑	↑	↑	↑	↑			↔*	↔*
	carbamazepine	↑D	↑	↑D	↑	↓D	D	↓D	D	D
	lamotrigine	↔**	↔*	↓	↓	↔*	↔*	↔*	↔*	↔*
	phenytoin	D	D	D	↓	↓D	D	↓D	D	D
ANTI-INFECTIVES	clarithromycin	↑E	↑	↑	↑	↓	↓E	↓	E	↔*
	fluconazole	↔	↔*	↔	↔	↔	E	E	↔	↔
	itraconazole	↑E	↑E	↑E	↑	↓	↓E	↓	E	↔
	rifabutin	↑	↑E	↑	↑	↓	D			↔
	rifampicin	D	D	D	D	D	D	D	D	D
	voriconazole	↓	↓	↓	↓	↓E	↓E	↓E	E	↔
MISCELLANEOUS	antacids	D	↔	↔		↔	↔*	↔	↔*	E
	PPIs	D	↔	↔	↔	↔	↔	↔	↔*	E
	H2 blockers	D	↔	↔	↔	↔	↔	↔	↔*	E
	alfuzosin	↑	↑	↑	↑	↓*	↓*	↓*	↔*	↔*
	buprenorphine	↑	↑	↔	↑	↓	↓*	↓*	↔	↔
	budesonide inhal.	↑	↑	↑	↑	↔*	↔*	↔*	↔*	↔*
	ergot derivatives	↑	↑	↑	↑	↑	↑*		↔*	↔*
	ethinylestradiol	↑**	↓	↓	↓		↔	↓	↔	↔
	fluticasone inhal.	↑	↑	↑	↑	↔*	↔*	↔*	↔*	↔*
	methadone	↔	↓	↓	↓	↓	↔	↓	↔*	↔
	salmeterol inhal.	↑	↑	↑	↑	↔*	↔*	↔*	↔*	↔*
	sildenafil	↑*	↑	↑	↑	↓*	↓	↓*	↔*	↔
	St John's wort	D	D	D	D	D	D	D	D	↔

Comments:

i This table summarizes the drug-drug interactions between HIV therapy and some commonly prescribed co-medications as well as the drug-drug interactions of particular clinical relevance. This table is not exhaustive; for additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, refer to www.hiv-druginteractions.org.

ii Ritonavir dosed as a pharmacokinetic enhancer or as an antiretroviral agent.

iii ECG monitoring is recommended.

Legend:

↑ =	elevated exposure of non-HIV drug
↓ =	decreased exposure of non-HIV drug
↔ =	no significant effect
E =	elevated exposure of HIV drug
D =	decreased exposure of HIV drug
* =	prediction based on metabolic profiles of the drugs only, no clinical data from interaction study, absence of * indicates that clinical data are available
** =	effect with unboosted ATV. Boosted ATV ↓ lamotrigine and ethinylestradiol

Colour legend:

red =	these drugs should not be coadministered
amber =	potential interaction which may require close monitoring or alteration of drug dosage or timing of administration
green =	no clinically significant interaction expected

Note: the "traffic light" used to rank the clinical significance of the drug interaction refers to www.hiv-druginteractions.org

Part III Prevention and management of non-infectious co-morbidities in HIV

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

Non-infectious co-morbidities include cardiovascular, renal, hepatic, metabolic, neoplastic and bone pathologies, central nervous system disorders and sexual dysfunction. Although HIV and other infections may be involved in their pathogenesis, this section of the EACS guidelines focuses 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, coinfections (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. For this purpose, refer to **www.hiv-druginteractions.org**.

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.

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

- Women's health issues not already covered
- Neuropathy which may be caused by infections (e.g. HIV), some ARV (see p. 20), other neuropathic drugs, and metabolic diseases (e.g. diabetes)

Cancer - screening methods [(i)]

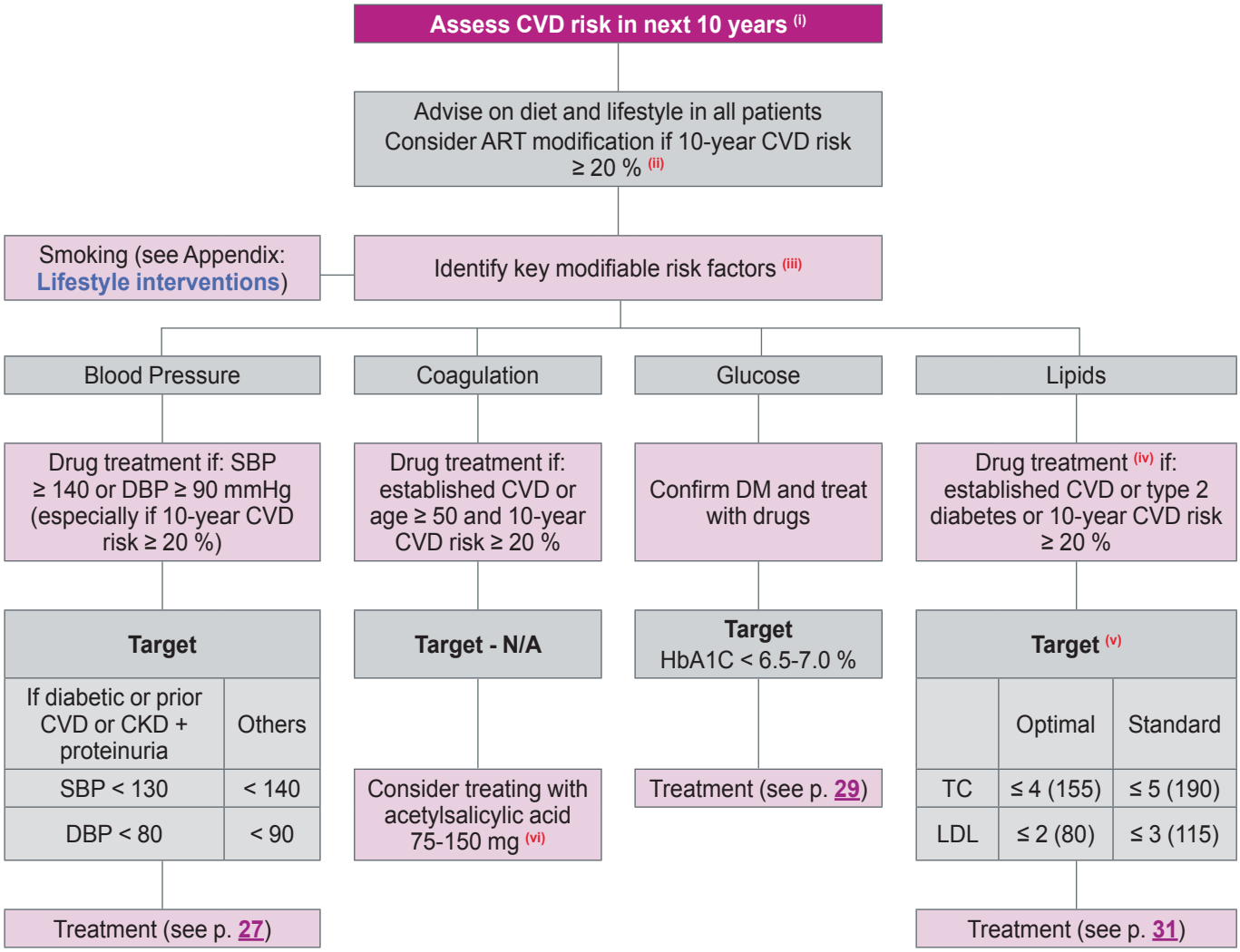
Problem	Patients	Procedure	Evidence of benefit	Screening interval	Additional comments
Anal cancer	Homosexual men	Digital rectal exam ± Papanicolau test	Unknown advocated by some experts	1-3 years	If Pap test abnormal, anoscopy
Breast cancer	Women 50-70 yrs	Mammography	↓ Breast cancer mortality	1-3 years	
Cervical cancer	Sexually active women	Papanicolau 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
Colorectal cancer	Persons 50-75 yrs	Faecal Occult Blood test	↓ Colorectal cancer mortality	1-3 years	Benefit is marginal
Hepatocellular carcinoma	Persons with cirrhosis	Ultrasound and alphafoetoprotein	Diagnosis earlier allowing for improved ability for surgical eradication	Every 6 months	
Prostate cancer	Men > 50 yrs	Digital rectal exam ± prostate specific antigen (PSA)	Use of PSA is 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 programmes. Although non-Hodgkin's 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.

Prevention of CVD

Principles: The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated [i]. The preventive efforts are diverse in nature and require involvement of a relevant specialist, 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 has been developed (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. 6) to ensure that the various interventions are initiated in a timely way.

ii Options for ART modification include: **(1)** replace PI/r with NNRTI, RAL or by another PI/r known to cause less metabolic disturbances (see p. 20); **(2)** consider replacing d4T, ZDV or ABC with TDF or use a NRTI sparing regimen.

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.

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. 31).

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: SBP 140-159 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]**

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

ii Recommended lifestyle interventions - See Appendix: **Lifestyle interventions**. Table adapted from J. Hypertension 2003; 21:1779-86.

iii See next page

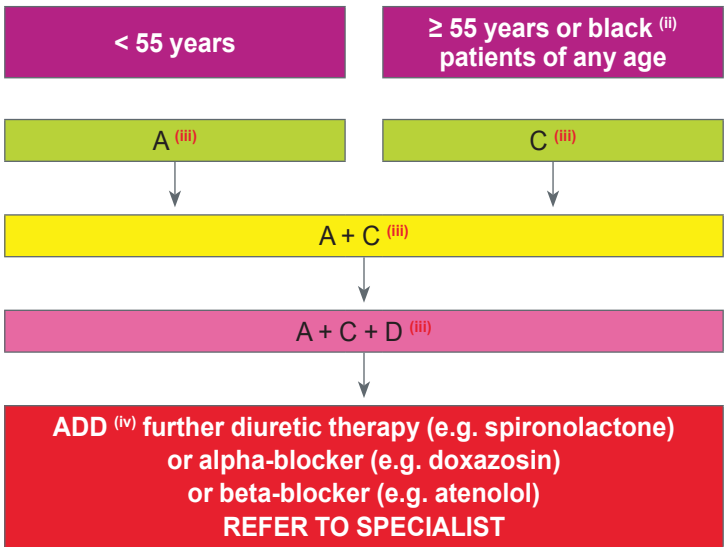
iv Risk factors include age (> 45 years for men; > 55 years for women), smoking, family history of premature CVD.

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.

Choosing drugs [i] for patients newly diagnosed with hypertension



Abbreviations + details:

A ACE inhibitor (e.g. perindopril, lisinopril or ramipril) or low cost angiotensin receptor blockers (ARB) (e.g. losartan, candesartan)

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 e.g. indapamide or chlorthalidone

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. 26) is achieved – if not go to next step

iv Requirement of 4-5 drugs to manage hypertension needs specialist training

Diagnostic criteria [i]

	Fasting plasma glucose mmol/L (mg/dL) [ii]	Oral glucose tolerance test (OGTT) 2-h value mmol/L (mg/dL) [iii]	HbA1c [iv]
Diabetes	≥ 7.0 (126) OR →	≥ 11.1 (200)	≥ 6.5 %
Impaired glucose tolerance (IGT)	< 7.0 (126) AND →	7.8 – 11.0 (140 – 199)	Prediabetes
Impaired fasting glucose (IFG)	5.7– 6.9 (100 – 125)	< 7.8 (140)	5.7-6.4 %

i As defined by WHO and International Diabetes Federation (2005)

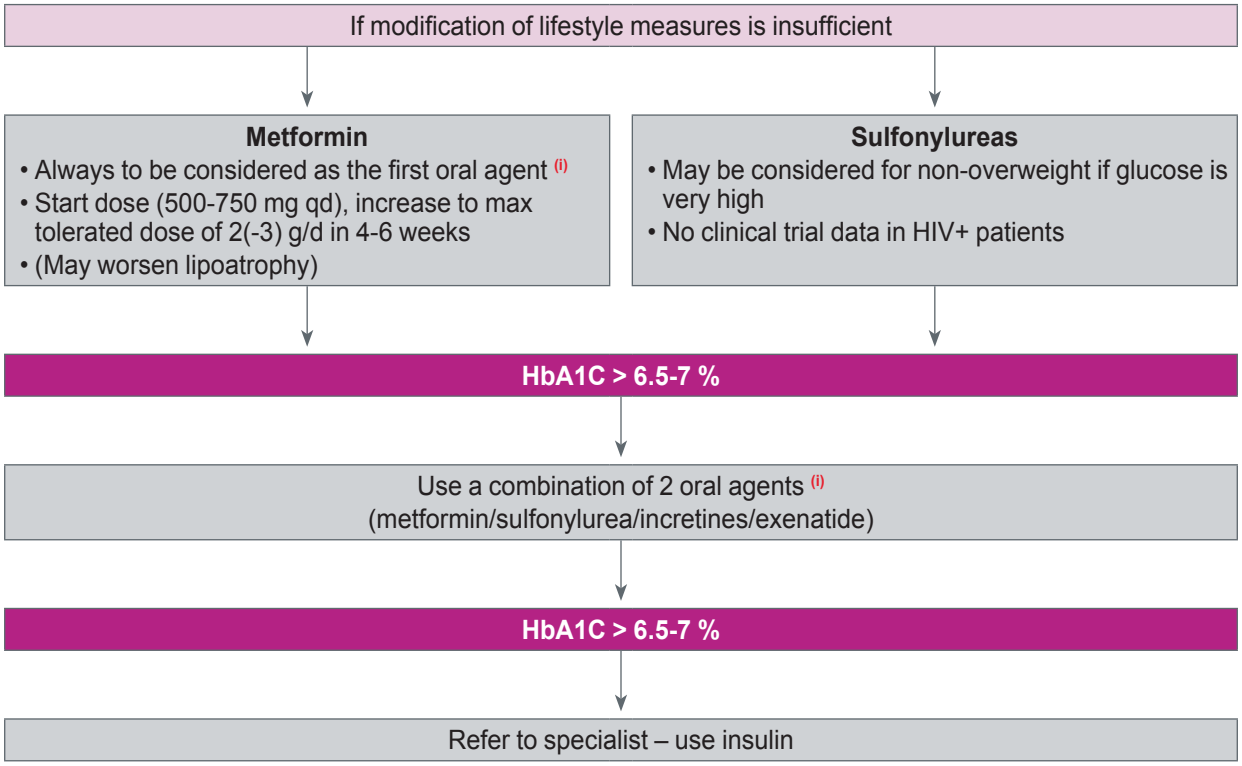
ii An abnormal finding should be repeated before confirming the diagnosis

iii Recommended in patients with fasting blood glucose 5.7 - 6.9 mmol/L (100-125 mg/dL) as it may identify patients with overt diabetes

iv Do not use HbA1c in presence of hemoglobinopathies, increased erythrocyte turnover and severe liver or kidney dysfunction. Falsely high values are measured under supplementation with iron, vitamin C and E as well as older age (age > 70: HbA1c +0.4 %)

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 lifestyle intervention, and their CV risk factors must be evaluated and treated.

Interventions for treatment of diabetes



i Very limited data for incretins (e.g. liraglutide, saxagliptine, sitagliptine, vildagliptine) and exenatide in HIV patients; no clinically significant drug-drug interaction expected; clinical use of pioglitazone questioned by its side effects

Management of patients with diabetes

Treatment goals: glucose control (HbA1c < 6.5-7 % without hypoglycaemia, fasting plasma glucose 4-6 mmol/L (73-110 mg/dL)

- Normal blood lipids (see p. 31) and blood pressure < 130/80 mmHg (see p. 27)
- Acetylsalicylic acid (75-150 mg/d) considered in diabetics with elevated underlying CVD risk (see p. 26)
- Nephropathy, polyneuropathy and retinopathy screening should be performed as in diabetic patients without HIV
- Consultation with a specialist in diabetology is recommended

Principles:

Higher LDL-c levels increase risk of CVD and reduction thereof reduces this risk (see table below for drugs used on this indication); the reverse is true for HDL-c. The CVD risk implications from higher than normal TG levels are less clear, as TG independently does not predict well the risk of CVD and since the clinical benefit of treating moderate hypertriglyceridaemia is uncertain; very high TG (> 10 mmol/L or > 900 mg/dL) may increase risk of pancreatitis although direct evidence is lacking.

Diet (more fish), exercise, maintaining normal body weight, reducing alcohol intake 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. 26).

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 (iii)	20-80 mg qd		Consider higher dose (vi)	Consider higher dose (vi)
	Pravastatin (iii)	20-80 mg qd		Consider higher dose (vi,vii)	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)	10-40 mg qd		**Contraindicated**	Consider higher dose (vi)
Cholesterol uptake↓ (i)	Ezetimibe (iv)	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. 26. In persons where LDL-c targets are difficult to achieve, consult/refer to specialist

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

v, vi The ART drug may **v** 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**

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 • 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 and other neurotropic - incl. recreational - drugs	• Screen every 1-2 years • Two main questions: 1. Have you often felt depressed, sad or without hope in the last few months? 2. Have you lost interest in activities that you usually enjoy? • Special symptoms in men: - 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** At least 2 weeks of depressed mood OR A. Loss of interest OR B. Diminished sense of pleasure **PLUS 4 out of 7 of the following:** 1. Weight change of ≥ 5 % in one month or a persistent change of appetite 2. Insomnia or hypersomnia on most days 3. Changes in speed of thought and movement 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 [(i)], recommend physical activity	• Severe depression • Depression not responding to treatment • Suicidal ideation • Complex situations such as drug addiction, anxiety disorders, personality disorders, dementia, acute severe life events
Intermediate	5-6	Start antidepressive treatment [(i)], 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: sertralin, paroxetin, venlafaxine, citalopram, mirtazapin, but other antidepressants may also be given. Citalopram may be preferred because of low interactions. For classification, doses, safety and side effects of antidepressants, see p. 34

For interactions with antidepressants, see www.hiv-druginteractions.org and **Interactions between antidepressants and antiretroviral agents**

Classification, doses, safety and side effects of antidepressants

Mechanisms of action and classification	Starting dose	Standard dose	Lethality in overdose	Insomnia and agitation	Sedation	Nausea or gastro-intestinal effects	Sexual dysfunction	Weight gain
	mg/day							
Selective serotonin-reuptake inhibitors (SSRIs)								
Paroxetine	20	20-40	low	+	- or +	+	+	+
Sertraline	50	50-150	low	+	- or +	+	+	+
Citalopram	20	20-40	low	+	- or +	+	+	+
Mixed or dual-action reuptake inhibitors								
Venlafaxine	37-75	75-225	moderate	+	- or +	+	+	- or +
Mixed-action newer agents								
Mirtazapine (5-HT2 plus 5-HT3 plus α2-adrenergic receptors)	30	30-60	low	- or +	++	- or +	- or +	++

- = none; + = moderate; ++ = severe

Bone disease: diagnosis, prevention and management

CONDITION	CHARACTERISTICS	RISK FACTORS	DIAGNOSTIC TESTS
Osteopenia • Postmenopausal women and men aged ≥ 50 years T-score -1 to ≥ -2.5 **Osteoporosis** • Postmenopausal women and men aged ≥ 50 years T-score < -2.5 • Premenopausal women and men aged < 50 years Z-score ≤ -2 and fragility fracture	• Reduced bone mass • Increased risk of fractures • Asymptomatic until fractures occur **Common in HIV** • Up to 60 % prevalence of osteopenia • Up to 10-15 % prevalence of osteoporosis • Aetiology multifactorial • Loss of BMD observed with antiretroviral initiation	Consider classic risk factors [i] Consider DXA in any patient with ≥ 1 of: [ii] 1. Postmenopausal women 2. Men ≥ 50 years 3. History of low impact fracture or high risk for falls [iii] 4. Clinical hypogonadism (symptomatic - see table on sexual dysfunction, p. 47) 5. Oral glucocorticoid use (minimum 5 mg prednisone equivalent for > 3 months) Preferably perform DXA in those with above risk factors prior to ART initiation. Assess effect of risk factors on fracture risk by including DXA results in the FRAX® score (www.shef.ac.uk/FRAX) - Only use if > 40 years - May underestimate risk in HIV patients - Consider using HIV as secondary cause of osteoporosis [iv]	**DXA scan** **Rule out secondary causes if BMD abnormal** [v] **Lateral spine X-rays** (lumbar and thoracic) if BMD suggests osteoporosis, or significant height loss or kyphosis develops
Osteomalacia	• 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	• Dietary deficiency • Lack of sunlight exposure • Dark skin • Malabsorption • Renal phosphate wasting	Measure 25-OH vitamin D in all patients at presentation ng/mL / nmol/L Deficiency: < 10 / < 25 Insufficiency: < 20 / < 50 If deficient, check PTH levels Consider vitamin D replacement if clinically indicated (see vitamin D table, p. 36)
Osteonecrosis	• Infarct of epiphyseal plate of long bones resulting in acute bone pain • Rare but increased prevalence in HIV	**Risk factors:** • Advanced HIV disease (low CD4 + T-cell counts) • Glucocorticoid exposure • Intravenous drug use	**MRI**

i Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m^2), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (> 3 units/day), steroid exposure (minimum prednisone 5 mg or equivalent for > 3 months)

ii 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.

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

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

Vitamin D deficiency: diagnosis and management

Vitamin D	Test	Therapy [i]
Deficiency: < 10 ng/mL (< 25 nmol/L) [ii] **Insufficiency:** < 20 ng/mL (< 50 nmol/L)	25-hydroxyvitamin D (25[OH]D) If deficient, consider checking parathyroid hormone (PTH), calcium, phosphate [iii], alkaline phosphatase	If vitamin D deficient, replacement recommended. Various regimens suggested [iv] After replacement, maintenance with 800-2000 IU vitamin D daily
Factors associated with lower vitamin D: • Dark skin • Dietary deficiency • Avoidance of sun exposure • Malabsorption • Obesity • Chronic kidney disease • Some antiretrovirals [v]	Check vitamin D status in patients with history of: • low bone mineral density and/or fracture • high risk for fracture • chronic kidney disease Consider assessment of vitamin D status in patients with other factors associated with lower vitamin D levels (see left column)	Consider replacement in patients with vitamin D insufficiency [vi] and: • osteoporosis • osteomalacia • increased PTH (once the cause has been identified) Consider retesting after 6 months of vitamin D intake

i Can be provided according to national recommendations/availability of preparations (oral and parenteral formulations). Combine with calcium where there is insufficient dietary calcium intake. Consider that in some countries food is artificially fortified with vitamin D.

ii Some experts consider a value of ≤ 30 ng/mL as vitamin D deficiency. Low vitamin D has a prevalence of up to 80 % in HIV cohorts and was associated with increased risk for osteoporosis, type 2 diabetes, mortality and AIDS events. Consider seasonal differences (during winter approximately 20 % lower than during summer).

iii Consider that hypophosphataemia can be associated with TDF therapy. This phosphate loss through proximal renal tubulopathy may be independent of low vitamin D (see table "**Drug-associated nephrotoxicity**"). A combination of low calcium + low phosphate +/- high alkaline phosphatase may indicate osteomalacia and lack of vitamin D.

iv Expect that 100 IU vitamin D daily leads to an increase of 1 ng/mL. Some experts prefer a loading dose of e.g. 10,000 IU vitamin D daily for 8-10 weeks in patients with vitamin D deficiency. The principal goal is to achieve a serum level > 20 ng/mL and to maintain normal serum PTH levels. The therapeutic aim is to maintain skeletal health; vitamin D supplementation has not been proven to prevent other co-morbidities in HIV-patients.

v The role of HIV-therapy or specific drugs remains unclear. Some studies suggest an association of efavirenz with reductions in vitamin D.

vi The implications of vitamin D levels that are below the physiological reference range but not markedly reduced and the value of supplementation are incompletely understood.

		eGFR [i]		
		≥ 60 mL/min	30-59 mL/min	< 30 mL/min
Proteinuria [ii]	UP/C [iii] < 50	Regular Follow-up		• Check risk factors for CKD and nephrotoxic medication including ART [iv] • Discontinue or adjust drug dosages where appropriate [v] • Perform renal ultrasound • Urgent referral to nephrologist
	UP/C [iii] 50-100	• Check risk factors for CKD and nephrotoxic medication including ART [iv] • Discontinue or adjust drug dosages where appropriate [v] • Perform renal ultrasound • If haematuria present with any level of proteinuria refer to nephrologist. • Refer to nephrologist if new CKD or progressive decline in eGFR		
	UP/C [iii] > 100			

Management of HIV-associated renal disease [vi]

Prevention of progressive renal disease	Comment
1. Antiretroviral therapy	Start ART immediately where HIV-associated nephropathy (HIVAN) [vii] or HIV immune complex disease strongly suspected. Renal biopsy to confirm histological diagnosis recommended
2. Start ACE inhibitors or angiotensin-II receptor antagonists if: 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: a. Avoid nephrotoxic drugs b. Lifestyle measures (smoking, weight, diet) c. Treat dyslipidaemia [viii] and diabetes [ix] d. Adjust drug dosages where necessary	CKD and proteinuria are independent risk factors for CVD

i eGFR: use aMDRD based on serum creatinine, gender, age and ethnicity. If not previously known to have CKD, reassess within 2 weeks

ii Urinalysis: use urine dipstick to screen for haematuria. To screen for proteinuria, use urine dipstick and if ≥ 1+ check UP/C, or screen with UP/C. Proteinuria defined as persistent if confirmed on ≥ 2 occasions > 2-3 weeks apart. If UP/C not available, use UA/C (see note **iii**)

iii UP/C in spot urine (mg/mmol) is preferred to UA/C as detects total urinary protein secondary to glomerular AND tubular disease. UA/C largely detects glomerular disease and can be used for screening for HIV associated renal disease where UP/C is not available, but is not appropriate for screening for tubular proteinuria secondary to drug nephrotoxicity (e.g. tenofovir). Screening values for UA/C are: < 30, 30-70 and > 70. UA/C should be monitored in patients with diabetes mellitus. UPC ratio is calculated as urine protein (mg/L) / urine creatinine (mmol/L), may also be expressed as mg/mg. Conversion factor for mg to mmol creatinine is x 0.000884.

iv Check risk factors for CKD, and repeat eGFR and urinalysis as per screening table (see p. 6)

v Dose modification of ARVs in case of impaired renal function: see Appendix for **"Indications and tests for proximal renal tubulopathy"**

vi Joint management with a nephrologist

vii HIVAN suspected if black ethnicity & UP/C > 100 mg/mmol & no haematuria

viii See p. 31

ix See p. 29

ART: Drug-associated nephrotoxicity

Renal abnormality	Antiretroviral drug	Management
Proximal tubulopathy: 1. Proteinuria: urine dipstick > 1, or confirmed clinically significant increase in UP/C [(i)] 2. Progressive decline in eGFR and eGFR < 90 mL/min [(ii)] 3. Phosphaturia [(iii)]: confirmed hyophosphataemia secondary to increased urine phosphate leak	**Tenofovir**	**Assessment:** • Tests for proximal renal tubulopathy/renal Fanconi syndrome [(iii)] • Bone DEXA scan if hypophosphataemia with phosphaturia **Consider stopping tenofovir if:** • Progressive decline in eGFR and no other cause • Confirmed significant hypophosphataemia of renal origin and no other cause • Significant osteopaenia in the presence of phosphaturia/renal tubulopathy
Nephrolithiasis: 1. Crystalluria 2. Haematuria [(iv)] 3. Leucocyturia 4. Loin pain 5. Acute renal insufficiency	**Indinavir** **Atazanavir**	**Assessment** • Urinalysis for crystalluria/stone analysis • Exclude other cause for nephrolithiasis • Renal tract imaging including CT scan **Consider stopping atazanavir/indinavir if:** • Confirmed renal stones. • Recurrent loin pain +/- haematuria
Interstitial nephritis: 1. Progressive decline in eGFR [(ii)] 2. Proteinuria/haematuria 3. Eosinophiluria (if acute)	**Indinavir** **(atazanavir)** [(v)]	**Assessment:** • Renal ultrasound • Refer nephrologist **Consider stopping indinavir if:** • Progressive decline in eGFR and no other cause

i UP/C in spot urine: urine protein/creatinine ratio in 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.

ii eGFR: estimated glomerular filtration rate, according to the abbreviated MDRD formula (Modification of Diet in Renal Disease)

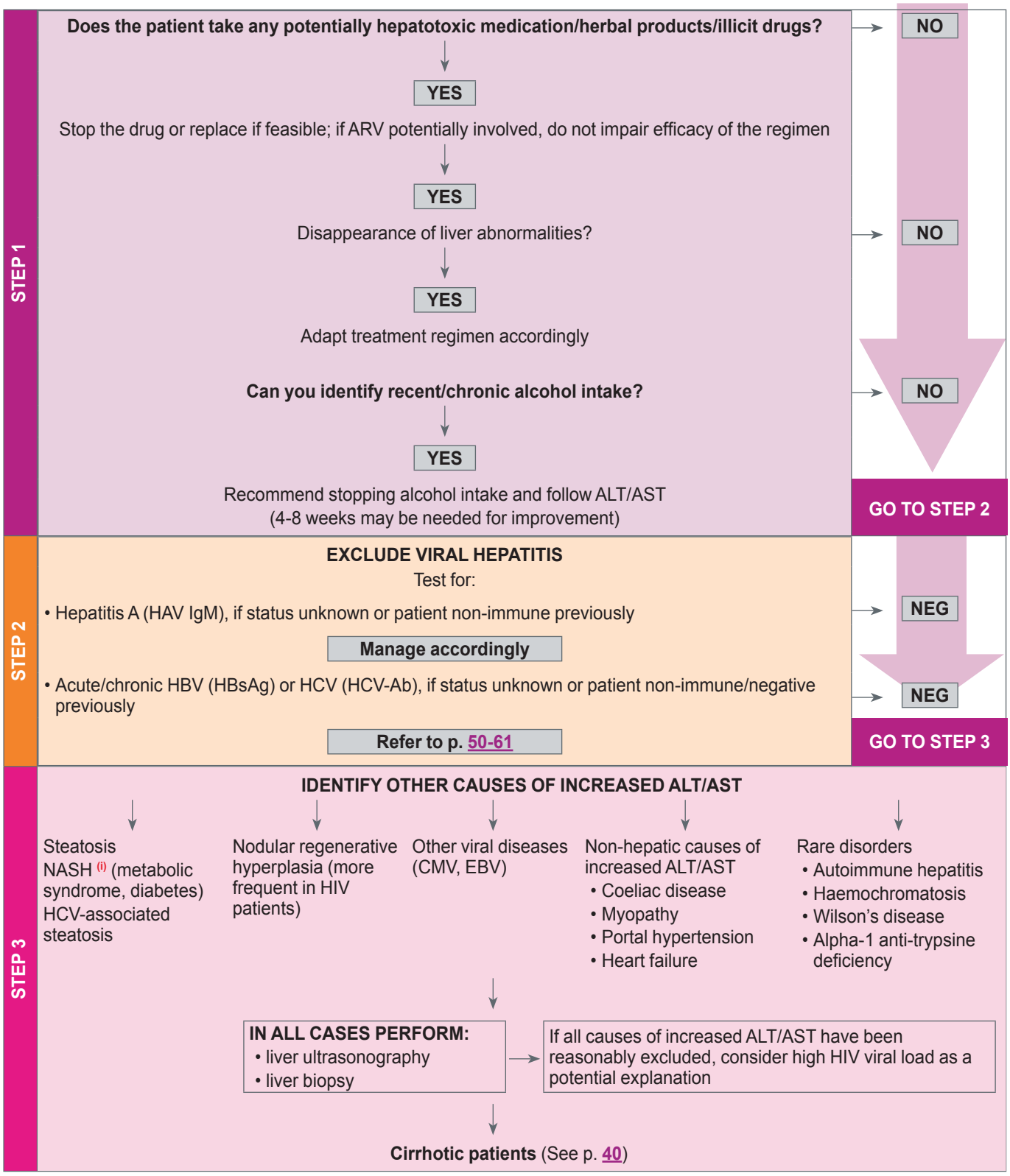
iii See Appendix for **"Indications and tests for proximal renal tubulopathy"**

iv Microscopic haematuria is usually present

v Atazanavir may cause decline in eGFR – also without clinical detected nephrolithiasis – but exact pathology and clinical significance remains unclear

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

Management of HIV-positive patients with cirrhosis

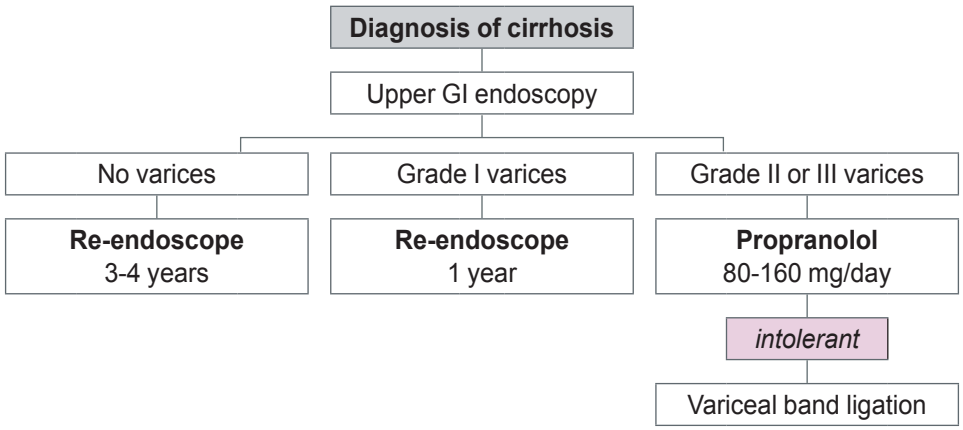
Management of patients with cirrhosis should be done in collaboration with experts in liver disease. More general management guidance is depicted below – for management of established complications from cirrhosis, see Appendix: **Management of HIV patients with liver cirrhosis**

Certain antiretrovirals with increased risk for hepatotoxicity such as tipranavir or nevirapine should preferably not be used in this particular patient population.

In ESLD, increased drug levels of Efavirenz have been described to occur and may increase the risk for CNS toxicity. Nevertheless, it is important to highlight that ART initiation in cirrhotic patients independently has been demonstrated to improve overall survival and is therefore strongly recommended in these patients when indicated

Child-Pugh classification of the severity of cirrhosis			
	Point (*)		
	1	2	3
Total bilirubin, mg/dL (µmol/L)	< 2 (< 34)	2-3 (34-50)	> 3 (> 50)
Serum albumin, g/L (µmol/L)	> 35 (> 507)	28-35 (406-507)	< 28 (< 406)
INR	< 1.7	1.71-2.20	> 2.20
Ascites	None	Mild/Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)
(*) 5-6 points: Class A 7-9 points: Class B 10-15 points: Class C			

Algorithm for surveillance for varices and primary prophylaxis



Nutrition of cirrhotic patient

Caloric requirements

- 25-30 Kcal/Kg/day of normovolemic body weight

Protein requirements

- Protein restriction is controversial but still routinely implemented (esp. in patients with TIPSS) (i)
- Amount: 40-60 g/day or 0.8 g/Kg.day (of normovolemic body weight)
- Type: rich in branched chain (non-aromatic) amino acids
- Some studies support that parental proteins carry less risk of encephalopathy since not converted by colonic bacteria into NH3

Micronutrients

- Thiamine, folic acid, Mg, Zn.

Analgesia in patient with hepatic failure

- Although high-dose **acetaminophen** is a well-known hepatotoxin, most hepatologists permit the use of acetaminophen in patients with cirrhosis at doses up to 2 g/d.
- **NSAID** use may predispose patients with cirrhosis to develop GI bleeding. Patients with decompensated cirrhosis are at risk for NSAID-induced renal insufficiency, because of prostaglandin inhibition and worsening of renal blood flow
- **Opiate** analgesics are not contraindicated but must be used with caution in patients with preexisting hepatic encephalopathy.

Surveillance for hepatocellular carcinoma

- Ultrasound + alpha FP (ii) every 6 months
- In case of suspicious lesion at US, perform CT scan (+arterial phase) or MRI
- Confirm diagnosis by fine needle aspiration or biopsy
- In case of alpha FP > 400 mg/mL (ii) and hypervascular lesion, no histology is needed

When to refer for liver transplantation (iii)

Best to refer early as disease progresses rapidly
= MELD (iii) score 10-12 (listing at 15)

- Decompensated cirrhosis
  - Ascites
  - Encephalopathy
  - Variceal bleeding
- Early hepatocellular carcinoma

(i) TIPSS = Transjugular Intrahepatic Portosystemic Stent Shunt

ii Alphafoetoprotein (alpha FP) may also be expressed in µg/L (cut-off value of 400 is the same)

iii Unit for both S-creatinine and S-bilirubin is mg/dL (see p. 40 for conversion from µmol/L). MELD Score = 10 {0,957 Ln (serum creatinine (mg/dL)) + 0.378 Ln (total bilirubin (mg/dL)) + 1.12 Ln (INR) + 0.643}

Lipodystrophy: prevention and management

LIPOATROPHY	LIPOHYPERTROPHY
Prevention • Avoid d4T and ZDV or pre-emptively switch away from them • Regimens containing ritonavir-boosted PIs lead to more limb fat gain than regimens containing NNRTIs • Regimens not containing NRTIs lead to more fat gain than regimens containing NRTIs • CCR5 and integrase inhibitors have not been associated with lipoatrophy in registrational studies, although not in formal comparative studies	**Prevention** • No proven strategy. • ATV/r has been associated with more central fat gain than EFV • Weight gain expected with effective ART reflecting "return to health" type of response • Weight reduction or avoidance of weight gain may decrease visceral adiposity • Avoid inhaled fluticasone (and potentially other inhaled corticosteroids) with ritonavir-boosted PI as it may cause Cushing syndrome or adrenal insufficiency
Management • Modification of ART - Switch d4T or ZDV to ABC or TDF: ▪ Only ART modification proven to partially restore subcutaneous fat; increase in total limb fat ~400-500 g/year ▪ Risk of toxicity from new drug (see p. 20) - Switch to regimen not including NRTIs ▪ Increase in total limb fat ~400-500 g/year ▪ May increase risk of dyslipidaemia • Surgical intervention - Offered for relief of facial lipoatrophy only	**Management** • Diet and exercise may reduce visceral adiposity - Limited data, but possible reduction in 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 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 and insulin resistance - Tesamorelin (i) - 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 Tesamorelin (growth hormone releasing factor) was shown to reduce visceral adipose tissue volume but this effect was lost on discontinuation; the drug is not currently licensed in Europe

Travel

General precautions	• Delay travel until clinically stable and treatment established • Provide drug prescription and referral letter for emergencies • Provide medical certificate for import of personal medication/syringes • Carry antiretrovirals split between suitcase and hand luggage • Beware of fake drugs
Antiretroviral treatment	• Maintain hours of medication (e.g. 23.00) when switching time zones, shortening the interval to the next dose when flying east
Acknowledge increased susceptibility [i] of HIV+	**1. Observe food hygiene** • Bacterial enterocolitis e.g. Salmonella, Shigella, Campylobacter • Intestinal parasitosis Cyclospora, Cryptosporidium, Isospora, Microsporidia **2. Prevent insect bites** • Repellents (DEET ≥ 30 %, Permethrin) • Malaria Chemoprophylaxis/emergency treatment [ii] • Yellow fever **See vaccination table** • Leishmaniasis Beware of sand flies (dogs)

Advice on travel restrictions – see: **www.hivtravel.org**

i Higher susceptibility due to HIV-associated GALT destruction, low CD4

ii According to malaria risk at travel destination and national guidelines; adherence counselling is particularly important in patients visiting friends and relatives

Vaccination

- Vaccinate according to national guidelines for healthy population
- As vaccine responses may be significantly lower in HIV+, antibody titres should be considered to assess the indication and effectiveness of vaccinations
- Consider repeating vaccines performed at CD4 < 200/µL (14 %) after immune reconstitution
- For attenuated live vaccines [i] (in addition to restrictions for general population):
  - **Varicella, measles, mumps, rubella, yellow fever** contraindicated if CD4 < 200/µL (14 %) and/or AIDS
  - **Oral typhoid, oral polio (OPV)** contraindicated as inactivated vaccines are available

	Vaccination rationale in HIV+	comment
Varicella	Higher rate and severity of both chickenpox and zoster	Vaccinate if seronegative
Streptococcus pneumoniae	Higher rate and severity of invasive disease	• In adults use PPV-23 polysaccharide vaccine [ii] • Consider delaying vaccination until CD4 ≥ 200/µL • Consider (single) booster after 5 years [iii]
Influenza		Yearly
Human Papillomavirus	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	Vaccination of women and men according to national guidelines
Hepatitis B	Shared risk with HIV of contracting infection. HIV accelerates liver disease progression	Consider double dose (40 µg) and intradermal vaccination in non-responders, in particular with low CD4 and high viraemia. Repeat doses until HBs antibodies ≥ 10 IU/L / ≥ 100 IU/L according to national guidelines
Hepatitis A	According to risk profile (travel, MSM, IVDU, active hepatitis B or C infection)	Check antibody titres in high risk population
Yellow fever	Mandatory for travel to selected countries (provide exemption letter if no true risk of exposure)	• Contraindicated if past or current haematological neoplasia or thymus affection • Relatively contraindicated at age > 60y

i Administer live vaccines simultaneously or with an interval of 4 weeks

ii 13-valent conjugated vaccine may replace 23-valent polysaccharide vaccine as more immunogenic

iii Repetitive boosting may attenuate immune response

Hyperlactataemia: diagnosis, prevention and management [(i)]

Risk factors	Prevention/Diagnosis	Symptoms
• Use of ddI > d4T > ZDV • HCV/HBV coinfection • 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 for symptoms if > 1 risk factor	• Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, elevated ALT and/or AST, weight loss • Acidaemia: asthenia, dyspnoea, arrhythmias • Guillain-Barré-like syndrome

i For management of lactic acidosis, see Appendix: **Management of hyperlactataemia and management of lactic acidosis**.

Assessment of sexual dysfunction in people living with HIV

Sexual dysfunction has been reported as a common problem in HIV-positive men (M) and women (W). The reduction in quality of life is also likely to be under-diagnosed. Guidelines for treatment of sexual dysfunction in the general population are available for men but not women.

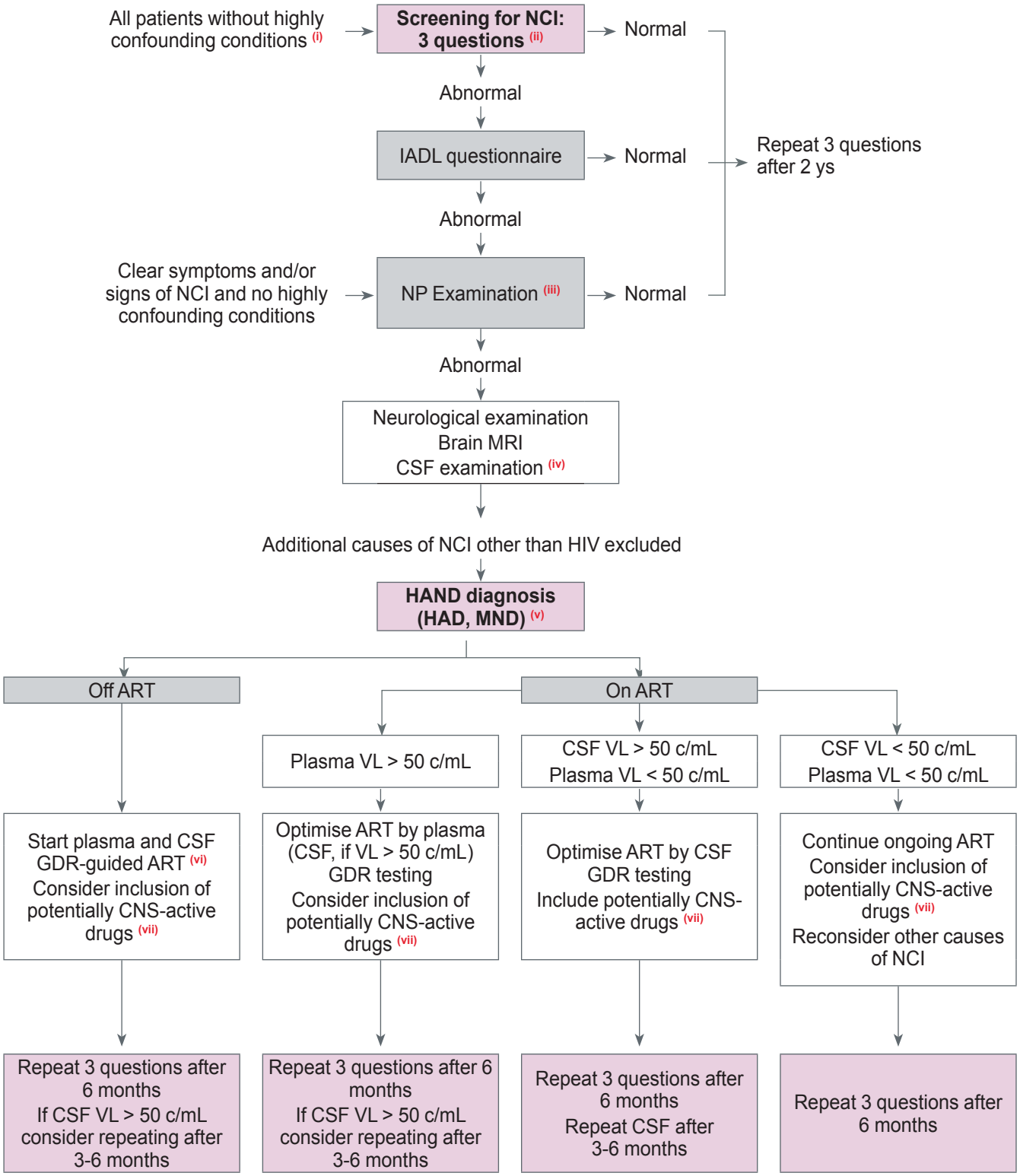
Referral to endocrinologist, clinical psychologist, cardiologist or clinical pharmacologist, where appropriate, should be advised.

STEP 1	**Taking a general sexual history:**	Screening questions for all HIV+ persons:	*How satisfied are you about your sex life? Do you experience sexual difficulties that need attention? Need for STD prevention? Contraception? Hopes of starting a family?*	
STEP 2	**When sexual complaints exist:**	*What is the exact nature of the problem? In which phase(s) of the sexual response cycle does the problem occur?*	**1. Desire** (lack of sexual desire or libido; desire discrepancy with partner; aversion to sexual activity)	
			2. Arousal (difficulties with physical and/or subjective sexual arousal; difficulties or inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse **(M)**—i.e. erectile dysfunction; lack or impaired nocturnal erections **(M)**; difficulties lubricating **(W)**; difficulties sustaining arousal)	
			3. Orgasm (difficulties experiencing orgasm)	
			4. Pain (pain with sexual activity; difficulties with vaginal/anal penetration—anxiety, muscle tension; lack of sexual satisfaction and pleasure)	
STEP 3	**Identify the causes:**	*Psychological or sociological problems?*	Stigma, body image alteration, depression? Fear of infecting an HIV-negative partner?	**Refer to clinical psychologist**
		Relevant co-morbidity?	Cardiovascular disease (note: if complete sexual response possible - e.g. with another partner, with masturbation or nocturnal - then no major somatic factors are involved)	**Refer to urologist, andrologist, cardiologist**
		Relevant medication, drugs, lifestyle factors?	Drugs associated with sexual dysfunction: **(1)** psychotropics (antidepressants, antiepileptics, antipsychotics, benzodiazepines), **(2)** lipid-lowering drugs (statins, fibrates), **(3)** antihypertensives (ACE-inhibitors, beta-blockers, alpha-blockers), **(4)** others (omeprazole, spironolactone, metoclopramide, finasteride, cimetidine); **(5)** contribution from antiretroviral drugs is controversial and benefit from switching studies is not proven.	**Refer to clinical pharmacologist**
		Signs of hypogonadism in men?	Signs of testosterone insufficiency (reduced sexual arousability and libido; decreased frequency of sexual thoughts and fantasies; decreased or absent nocturnal erections; decreased genital sensitivity; loss of vitality; fatigue; loss of muscle mass and muscle strength and decreased body hair)	**Refer to endocrinologist**

Treatment of sexual dysfunction in men living with HIV

Treatment of Erectile dysfunction	Treatment of Premature ejaculation
Primarily oral PDE5-Is (sildenafil, tadalafil, vardenafil). • All at least 30 minutes before initiation of sexual activity • Use lower dose if on PI/r - sildenafil (25 mg every 48 hours) - tadalafil 5 mg initial dose with maximum dose 10 mg in 72 hours - vardenafil 2.5 mg maximum dose in 72 hours • Higher doses may be required if on EFV • Tadalafil also licensed for use as an everyday ongoing therapy	Consider behavioural interventions and/or psychosexual counselling. SSRIs, tricyclic antidepressant, clomipramine, and topical anaesthetics. • Use lower dose of clomipramine and other tricyclic antidepressants if on PI/r • Dapoxetine, short-acting SSRI, only drug approved for the on-demand treatment of premature ejaculation in Europe • Treatment must be maintained as recurrence is highly likely following withdrawal of medication

Algorithm for diagnosis and management of HIV-associated Neurocognitive Impairment (NCI)



Abbreviations

- ANI=asymptomatic neurocognitive impairment
- CSF=cerebrospinal fluid
- GDR=genotypic drug resistance test
- HAD=HIV-associated dementia
- HAND=HIV-associated neurocognitive disorder
- IADL=instrumental activities of daily living
- MND=mild neurocognitive disorders
- MRI=brain magnetic resonance imaging
- NP=neuropsychological

i **Highly confounding conditions**

1. Severe psychiatric conditions
2. Abuse of psychotropic drugs
3. Alcohol abuse
4. Sequelae from previous CNS-OIs or other neurological diseases
5. Current CNS-OIs or other neurological diseases

ii **3 questions** (ref. Simioni et al., AIDS 2009)

1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have difficulties paying attention (e.g. to a conversation, a book, or a movie)?

For each question, patients can answer: a) never, b) hardly ever, or c) yes, definitely.

Patients are considered to have an "abnormal" result when answering "yes, definitely" on at least one question.

iii NP examination will have to include tests exploring the following cognitive domains: fluency, executive functions, speed of information processing, attention/working memory, verbal and visual learning, verbal and visual memory, motor skills (ref. Antinori et al., Neurology 2007).

iv **Brain MRI and CSF examination**

These are required to further exclude other pathologies and to further characterize HAND, by including assessment of CSF HIV-RNA level and, where appropriate, evidence for genotypic drug resistance (GDR) in a paired CSF and plasma sample.

v **HAD and MND definitions** (ref. Antinori et al., Neurology 2007).

- **HAD is defined in the presence** of **1) marked** acquired impairment in cognitive functioning involving **at least 2** cognitive domains, as documented by performance of at least 2 SD below the mean for age-education appropriate norms on NP tests; **2) marked** interference in daily functioning; **3)** no evidence of another pre-existing cause for the dementia
- **MND is defined in the presence** of **1)** acquired impairment in cognitive functioning involving at least 2 cognitive domains, as documented by performance of **at least 1 SD** below the mean for age-education appropriate norms on NP tests; **2) mild** interference in daily functioning; **3)** no evidence of another pre-existing cause for the MND

vi If GDR in CSF and/or plasma not available, store aliquots for possible future use

vii **Definition of 'potentially CNS-active' drugs**

ARV drugs with either demonstrated clear CSF penetration when studied in healthy HIV-infected populations (concentration above the **IC90** in > 90 % examined patients) or with proven short-term (3-6 months) efficacy on cognitive function or CSF viral load decay when evaluated as single agents or in controlled studies in peer-reviewed papers.

- Agents with demonstrated clear CSF penetration:
  - NRTIs: ZDV, ABC
  - NNRTIs: EFV, NVP
  - Boosted PIs: IND/r, LPV/r, DRV/r
  - Other classes: MAR
- Drugs with proven "efficacy":
  - NRTIs: ZDV, d4T, ABC
  - Boosted PIs: LPV/r

Part IV Clinical management and treatment of chronic hepatitis B and C coinfection in HIV-infected adults

These Euroguidelines result from:

- The short statement of the first European Consensus conference on the treatment of chronic hepatitis B and C in HIV coinfected patients (J Hepatol 2005; 42:615-624)
- The updated recommendations from the HCV-HIV International Panel (Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, Mauss S, Bräu N, Hatzakis A, Pol S, Rockstroh J: Care of patients coinfected with HIV and hepatitis C virus. AIDS 2007; 21:1073-1089)
- The previous recommendations from the hepatitis panel of the European AIDS Clinical Society (JK Rockstroh, S Bhagani, Y Benhamou, R Bruno, S Mauss, L Peters, M Puoti, V Soriano & C Tural) and the EACS Governing Board: European AIDS Clinical Society (EACS) Guidelines for the Clinical Management and Treatment of Chronic Hepatitis B and C Coinfection in HIV-infected Adults. HIV Medicine 2008; 9, 82–88)
- The revised website version from 2011
- A discussion with the following panel:

Chair: Jürgen Rockstroh	Bonn, *Germany*
Sanjay Bhagani	London, *United Kingdom*
Raffaele Bruno	Pavia, *Italy*
Diego García	Alicante, *Spain*
Maxime Journiac	Paris, *France*
Karine Lacombe	Paris, *France*
Stefan Mauss	Dusseldorf, *Germany*
Lars Peters	Copenhagen, *Denmark*
Massimo Puoti	Milan, *Italy*
Vicente Soriano	Madrid, *Spain*
Cristina Tural	Barcelona, *Spain*

General recommendations in patients with HIV and hepatitis coinfection

SCREENING

1. All HIV-infected patients should be screened for hepatitis C at diagnosis and then on an annual basis. Screening for HCV in HIV-infected patients should be done using an anti-HCV antibody test. A positive result should be followed by evaluation for the presence of HCV-RNA and the genotype should also be determined. Patients with risk factors (ongoing IVDU, mucosal traumatic sex, ongoing unprotected anal intercourse, recent sexually transmitted infection) with unexplained increase in hepatic transaminases and a negative HCV antibody test should be tested for HCV-RNA for early detection of a recent infection.
2. HIV-infected patients should be screened for hepatitis A and B. Patients who are anti-HBc positive and HBsAg negative, in particular those with elevated liver transaminases should be screened for HBV-DNA in addition to HBsAg to rule out occult HBV infection.
3. Hepatitis delta antibodies should be screened for in all HBsAg+ patients.
4. Patients with liver cirrhosis should be screened at 6-monthly intervals with serum alphafoetoprotein and hepatic ultrasound for the occurrence of hepatocellular carcinoma. Routine screening is also advised for oesophageal varices at the time of diagnosis mainly when there is evidence of portal hypertension and at 2-year intervals thereafter if not present initially. For non-cirrhotic HBV co-infected patients, HCC screening with 6-monthly US scans may be advisable for African patients over the age of 20, Asian patients over the age of 40, patients with a family history of HCC, and patients with high HBV DNA levels (> 200 000 IU/L).

VACCINATION

5. Patients lacking anti-HAV IgG antibodies or anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4-count. The response to the HBV vaccine is influenced by the CD4-count and level of HIV-RNA. In patients with low CD4-counts (< 200/µL) and ongoing HIV replication, ART should be initiated first prior to respective vaccination. Because of the lack of data on the impact of immunization in isolated anti-HBc Ab patients (HBs Ag negative, anti-HBc positive and anti-HBs negative profile), vaccination is not presently recommended in this population. This guideline might be revised when more data is available from current trials. Occult HBV (HBsAg negative and HBV-DNA positive) should be ruled out in all cases.

6 In HIV individuals vaccinated for HBV showing insufficient response (anti-HBs < 10 IU/l), re-vaccination should be considered. Double-dose (40µg) at 3-4 time points (months 0, 1, 6 and 12) may help to improve response rates to the HBV vaccine. Patients who fail to seroconvert after hepatitis B vaccination and remain at risk for HBV infection should have annual serological tests for evidence of HBV infection.

ART

7. Hepatitis B and/or C coinfected patients benefit from early ART because liver fibrosis progression is reduced with immune reconstitution and suppression of HIV-RNA. Thus, ART initiation with a tenofovir-based regimen is recommended in all HBV coinfected patients with the need of anti-HBV therapy irrespective of CD4-counts, and in all HBs-Ag positive patients with less than 500 CD4-cells irrespective of HBV disease status to prevent transition to a more active HBV disease state due to immune suppression.
8. In patients with chronic hepatitis C, ART initiation is recommended when CD4-counts drop below 500/µL. Stopping ART has been associated with enhanced risk for AIDS and non-AIDS related events; indeed the risk for non-AIDS events was particularly enhanced for patients with hepatitis coinfection. Stopping anti-HBV containing ART should be avoided in HIV/HBV coinfected patients because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis.

END STAGE LIVER DISEASE (ESLD)

9. HIV-positive patients require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative patients.
10. HIV-coinfected patients who suffer from ESLD warrant particular attention in the management of liver insufficiency. Apart from considerations of treatment of HBV or HCV, some antiretrovirals metabolized by the liver may need to be dose adjusted and in individual cases, therapeutic drug monitoring of the respective drug could be advisable. Certain antiretrovirals with increased risk for hepatotoxicity such as tipranavir or nevirapine should preferably not be used in this particular patient population. High exposure to efavirenz may occur in ESLD patients, increasing the risk for CNS toxicity. Nevertheless, it is important to highlight that ART initiation in cirrhotic patients generally improves overall survival and is therefore strongly recommended in these patients when indicated.
11. Creatinine clearance using Cockcroft Gault estimation in the setting of advanced or decompensated liver cirrhosis overestimates the true glomerular filtration rate and use of the arithmetic mean urea and creatinine clearance is recommended. When not accessible, MDRD and CKD-EPI formulas should be preferred.
12. Patients with HCC or a MELD-score > 15* (model for ESLD), CD4-cell count > 100/µL and options for efficacious and durable ART should be evaluated for liver transplantation (OLTX). OLTX outcomes in HIV/HBV coinfected patients are particularly promising, whereas post-transplant survival in HIV/HCV coinfected patients has been somewhat lower than in HCV-monoinfected patients mainly due to the complicated course of HCV re-infection after transplantation.

PREVENTION/SUPPORT

13. Psychiatric, psychological, social and medical support should be made available to patients with alcohol intake to stop drinking.
14. Substitution therapy (opioid replacement therapy) in patients with active drug abuse as a step towards cessation of active drug use should be encouraged. Help provided (e.g. through needle and syringe exchange programme) reduces the risk of re-infection including parenteral viral transmission (harm reduction strategy).
15. Since HBV and HIV, and occasionally HCV, are transmitted sexually, adequate counselling including the use of condoms is advisable. Information on the risk of HCV transmission due to mucosal traumatic sexual practices associated with a high likelihood of blood contact should be provided and risk reduction should be discussed.

DELTA VIRUS

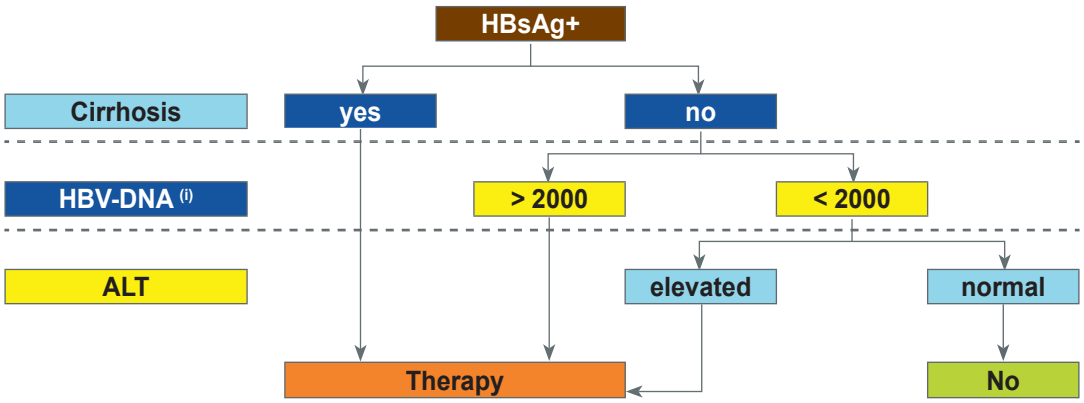
16. In patients with Delta virus co-infection and significant liver fibrosis (≥ F2), long-term (> 18 months) treatment with pegylated interferon might be considered in association with tenofovir-based ART. Because of its anti-HBV activity, TDF should be added to pegylated interferon in order to reduce HBV-DNA load. Treatment efficacy should be monitored with: HBV-DNA and HDV-RNA measurement, when available, and with follow up of biochemical and liver fibrosis estimates.

    Patients with anti-HCV Ab and detectable HCV-RNA should be offered anti-HCV treatment in order to induce a sustained virologic response for HCV coinfection. Persistent off-treatment HDV-RNA negativity and anti-HBs seroconversion are the ideal goals of antiviral treatment for hepatitis delta even if they can only be obtained in a minority of patients.

    Histological remission of liver disease is a less ambitious but more likely to be achieved goal. In delta patients with ESLD or HCC, liver transplantation should be strongly considered especially in the absence of active HCV coinfection. Transplant cures HBV and delta infection.

* MELD calculation (MELD Score = (0.957 * ln(Serum Cr) + 0.378 * ln(Serum Bilirubin) + 1.120 * ln(INR) + 0.643) * 10 (if haemodialysis, value for Creatinine is automatically set to 4.0. Access at www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older)

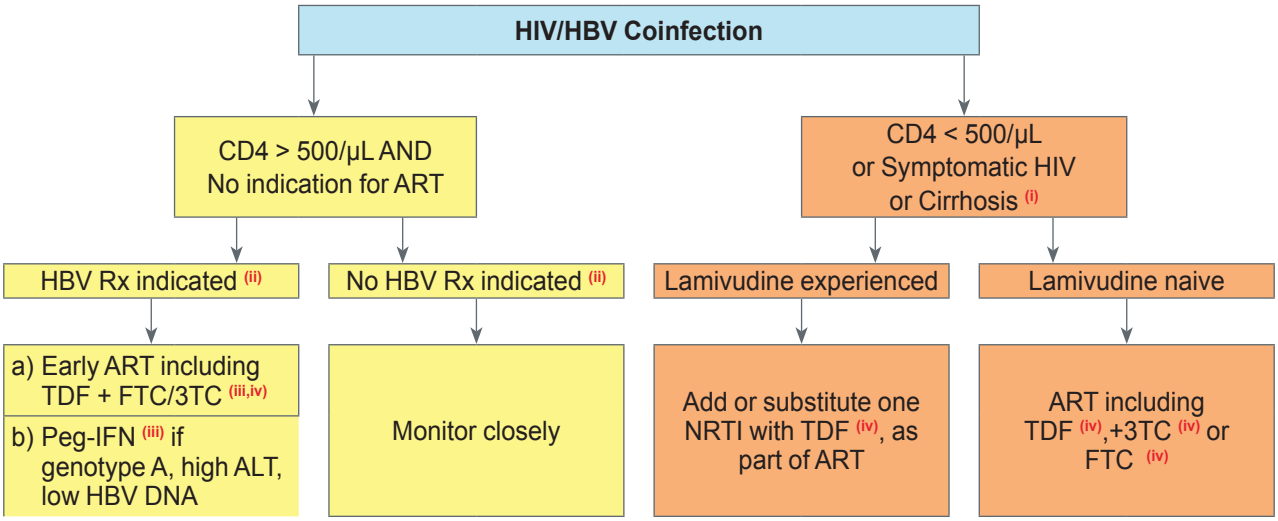
Assessment of treatment indication for HBV infection in HIV-positive individuals



Note: In patients with significant liver fibrosis (F2-F3), anti-HBV treatment might be considered even when serum HBV-DNA is below 2 000 IU/mL and liver enzymes are not elevated.

i IU/mL

Treatment of chronic HBV infection in HIV-positive individuals



i Cirrhotic patients should be referred for variceal assessment, have regular HCC monitoring and be referred early for transplant assessment. Patients with liver cirrhosis and low CD4-counts require careful surveillance in the first months after starting ART in order not to overlook immune-reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes.

ii See Figure on p. 52 for assessment of HBV Rx indication. Some experts strongly believe that any HBV-infected patient requiring ART should receive TDF + 3TC or FTC unless history of TDF intolerance, particularly in HIV/HBV coinfected patients with advanced liver fibrosis (F3/F4). TDF administration should be adapted to creatinine clearance if necessary. In patients with no history of treatment with lamivudine and strict contra-indication of TDF use, entecavir may be used, provided that patients have an optimal ART.

iii Antiretroviral naive Asian, HBe-Ag+, HIV-coinfected patients initiating ART with TDF or TDF+FTC reached unexpectedly high rates of HBe (and even HBs) seroconversion, strengthening the rationale for early ART. If a patient is unwilling to go on early ART, adefovir and telbivudine may be used as an alternative to control HBV alone. No evidence of anti-HIV activity of telbivudine has been reported so far. In patients with HBV genotype A, high ALT and low HBV-DNA, Peg-IFN might be used for a total length of 48 weeks. The addition of an NRTI-based anti-HBV regimen has not been proved to increase Peg-IFN efficacy but results of new trials are awaited. Recent data obtained in HBV mono-infected patients suggests that on-treatment quantification of HBsAg in patients with HBeAg-negative chronic hepatitis B treated with Peg-IFN may help identify those likely to be cured by this therapy and optimize treatment strategies. This does not account for NRTI-based strategies so far, because of the very low rate of HBs seroconversion in this setting. The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy if anti-HBV nucleos(t)ides are given as part of ART. With patients not requiring ART and on treatment with telbivudine +/- adefovir, or those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously in HBeAg+ patients who have achieved HBe-seroconversion for at least six months or after confirmed HBs-seroconversion in those who are HBeAg-. In patients with liver cirrhosis, a stop of effective anti-HBV treatment is not recommended in order to avoid liver decompensation due to flares of liver enzymes.

iv In some cases of tenofovir intolerance (i.e. renal disease), TDF in doses adjusted to renal clearance in combination with effective ART may be advisable. If TDF is strictly contra-indicated, entecavir + adefovir may be tried. However, efficacy and renal toxicity need to be closely monitored, because of the proven renal toxicity of adefovir. In patients with no prior lamivudine exposure, entecavir may be used alone. NRTI substitution should only be performed if feasible and appropriate from the perspective of maintaining HIV suppression. Caution is warranted to switch from a tenofovir-based regimen to drugs with a lower genetic barrier, e.g. FTC/3TC, in particular in lamivudine-pretreated cirrhotic patients as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from tenofovir to entecavir. The addition of entecavir to tenofovir in patients with low persistent HBV replication has not statistically proved to be efficient and should therefore be avoided. Results of trials are awaited.

1. HCV treatment offers the possibility of eradicating HCV within a defined treatment period. This is potentially advantageous for the subsequent management of the patient with HIV, and every coinfected patient should therefore be considered for treatment when the benefits of therapy outweigh the risks. This also needs to be seen in the context of faster liver fibrosis progression in HIV/HCV coinfection and with better HCV treatment outcome with the use of direct acting antivirals (DAAs) in these patients.
2. Information on liver fibrosis staging is important for making therapeutic decisions in coinfected patients. However, a liver biopsy is no longer mandatory for considering treatment of chronic HCV. Current therapy is particularly recommended in patients with a high likelihood of achieving sustained virological response (SVR) such as genotypes 2 or 3 or genotype 1 patients with an IL28B CC genotype or GT 1 patients with a previous relapse under dual therapy which now can be retreated with triple therapy [(i)].
3. Based on 4 baseline variables (serum HCV-RNA, HCV genotype, liver fibrosis staging using elastometry, and IL28B genotyping*), the Prometheus index has recently been developed and can optionally be used as a risk calculator for predicting the likelihood of SVR using Peg-IFN-ribavirin therapy in HIV-HCV coinfected patients. It is freely available on the web (**www.fundacionies/prometheusindex.php**).
4. Insulin resistance (which can be determined using the homeostasis model assessment of insulin resistance HOMA IR) has been reported as a negative predictor of achievement of SVR.
5. In case of the availability of a liver biopsy or FibroScan demonstrating lack of or minimal liver fibrosis (F0-1), regardless of HCV genotype, treatment can be deferred. This may also account for patients with low chances of SVR under the current treatment options for whom improved treatment options will become available within the coming years. This is also relevant in patients with genotype 1 infection who potentially could be treated with DAA based therapy but have expected adherence issues where it appears advisable to defer HCV treatment until easier to take, better tolerated DAAs become available (see figure 1 on **p. 57**). In these cases, fibrosis assessment should be carried out periodically to monitor for fibrosis progression.
6. The combination of Peg-IFN alpha and ribavirin (RBV) remains the treatment of choice for HCV genotype 2, 3 and 4 infection. The standard dose for Peg-IFN 2a is 180 µg once weekly, and for Peg-IFN 2b it is 1.5 µg/kg bodyweight once weekly. An initial weight-adapted dose of RBV of 1000 (wt ≤ 75kg) - 1200 (wt > 75kg) mg/day (administered BID) is recommended for all HCV genotypes in the HIV setting. The treatment paradigm for dual therapy is shown in the figure on **p. 58**).
7. With first pilot studies in HIV/HCV-coinfected subjects demonstrating significant higher SVR12 rates with triple therapy compared to dual therapy, HCV protease inhibitor based therapy with either boceprevir or telaprevir is now the new standard of treatment in HCV genotype 1 infection in HIV-infected individuals where available. Telaprevir is added to Peg-IFN/RBV standard treatment for 12 weeks at 750 mg every 8 hours. In case of successful treatment response at week 4 (HCV-RNA < 1000 IU mL), telaprevir should be continued until week 12 (see figure on **p. 59**). If HCV-RNA at week 12 is still < 1000 IU/mL, dual therapy with Peg-IFN/RBV should be continued until week 24. If HCV-RNA is undetectable at week 24, dual therapy with Peg-IFN/RBV should be continued for another 24 weeks resulting in total treatment duration of 48 weeks. Due to drug-drug interactions, telaprevir can currently only be safely combined with boosted atazanavir, raltegravir, rilpivirine, etravirine or efavirenz (with EFV, telaprevir doses need to be increased to 1125 mg every 8 hours) in combination with tenofovir or abacavir and FTC or 3TC (please also check **www.hep-druginteractions.com**). Boceprevir can be added to Peg-IFN/RBV after a lead-in of 4 weeks of Peg-IFN/RBV dual therapy. Futility rules here are that in case of a HCV-RNA > 100 copies/mL at week 12 or a detectable HCV-RNA at week 24, all HCV therapy needs to be discontinued and interpreted as lack of response and high risk for boceprevir resistance selection. Overall treatment duration of a boceprevir based HCV therapy is 48 weeks. Although shorter treatment durations of triple therapy have been demonstrated to be very efficacious in HCV monoinfected subjects with rapid virological response, this data is so far not available for HIV/HCV coinfected subjects. Due to drug-drug interactions, boceprevir can only be currently safely combined with raltegravir or etravirine in combination with tenofovir or abacavir and FTC or 3TC. The EMEA has also suggested considering boceprevir in combination with boosted atazanavir in patients with no previous HIV treatment failure and no drug resistance who have suppressed HIV-RNA when starting HCV therapy as boceprevir exposure is not impacted by concomitant boosted atazanavir whereas atazanavir AUC decreased significantly but trough levels remained above the recommended IC90 in all patients. Considering the complex treatment issues, in particular drug-drug interactions, inclusion into clinical trials should be preferred and close monitoring for patients treated outside of trials is highly recommended.

i A genetic polymorphism nearby the IL28B gene, encoding interferon-lambda-3 (IFN-lambda-3), was recently associated with an approximately two-fold change in response to Peg-IFN-ribavirin treatment. Because the CC genotype leading to better response is significantly more frequent in European than African populations, this genetic polymorphism also explains approximately half of the difference in response rates between African-Americans and patients of European ancestry.

8. The use of the new HCV PIs is associated with some additional toxicities, in particular higher rates of anaemia for both drugs, rash and anal itching for telaprevir and dysgeusia for boceprevir. Anaemia management is therefore very important and requires more frequent monitoring of haemoglobin levels during the first weeks of HCV treatment. Early ribavirin reduction and EPO use have both been demonstrated to be effective in anaemia management while not lowering overall SVR rates. Data from monoinfected subjects with cirrhosis suggest even higher anaemia rates and clearly haemoglobin values need to be determined in such patients at least every 2 weeks after starting HCV therapy. In addition, careful surveillance should be addressed to severe infectious complications and liver decompensation which have been observed in 3-8% of monoinfected cirrhotic patients on triple therapy in an observational study where they caused a mortality rate greater than 1%. Data in HIV/HCV coinfected patients is still lacking.
9. The primary aim of anti-HCV treatment is sustained virological response defined as undetectable serum HCV-RNA 24 weeks after the end of therapy, evaluated using sensitive molecular tests. Early time points upon completion of treatment, such as SVR12, still need to be examined in HIV-HCV coinfected patients.
10. If chronic hepatitis C is detected early in the course of HIV infection (before the initiation of ART is necessary), treatment for chronic HCV is advised. For patients with a CD4-count < 500/µL, early ART initiation is recommended to optimize HCV treatment outcome. However, if a coinfected patient has significant immunodeficiency (CD4 count < 350 cells/µL), the CD4-count should be improved using ART prior to commencing anti-HCV treatment. Patients with a CD4 relative percentage > 25% are more likely to achieve SVR than those with a lower CD4 percentage.
11. If an early virological response (decline of at least 2 log10 reduction in HCV-RNA at week 12 compared to baseline) is not achieved when treating genotype 2, 3 or 4 infection (or genotype 1 when no DAAs are available), treatment should be stopped (see figure on p. 58). Different stopping rules apply when DAAs are being used and are summarized under point 4.
12. During Peg-IFN plus ribavirin therapy, didanosine is contraindicated in patients with cirrhosis and should be avoided in patients with less severe liver disease. Stavudine and zidovudine should also be avoided if possible. Abacavir can be safely used with concomitant HCV therapy if appropriate ribavirin dosages (weight adapted, see point 4) are being used.
13. Identification of patients with acute hepatitis C is important since treatment in the acute phase leads to higher SVR rates than for treatment of chronic HCV infection. In patients with acute HCV infection, HCV-RNA should be measured at initial presentation and 4 weeks later. Treatment should be offered in patients without a decrease of 2 log10 of HCV-RNA at 4 weeks compared with initial HCV RNA and to patients with persistent serum HCV RNA 12 weeks after diagnosis of acute HCV. Duration of treatment should be based on rapid virological response (RVR) regardless of genotype (see figure on p. 61). Patients who do not achieve a ≥ 2 log10 decrease in HCV-RNA level at week 12 should discontinue therapy. Unfortunately, results from randomized prospective treatment trials are not available so far to allow a more precise recommendation on treatment duration or the role of ribavirin in treatment of acute hepatitis C at this point. Also, no studies have been performed with DAAs in the setting of acute HCV yet. Therefore, considering the high cure rates with IFN/RBV alone in acute HCV, DAAs are currently not recommended unless there is a genotype 1 patient with lack of virological response (at week 12 < 2log decrease in HCV-RNA), a situation in which treatment intensification can be discussed on an individual basis.

Diagnostic procedures for hepatitis C in HIV coinfection

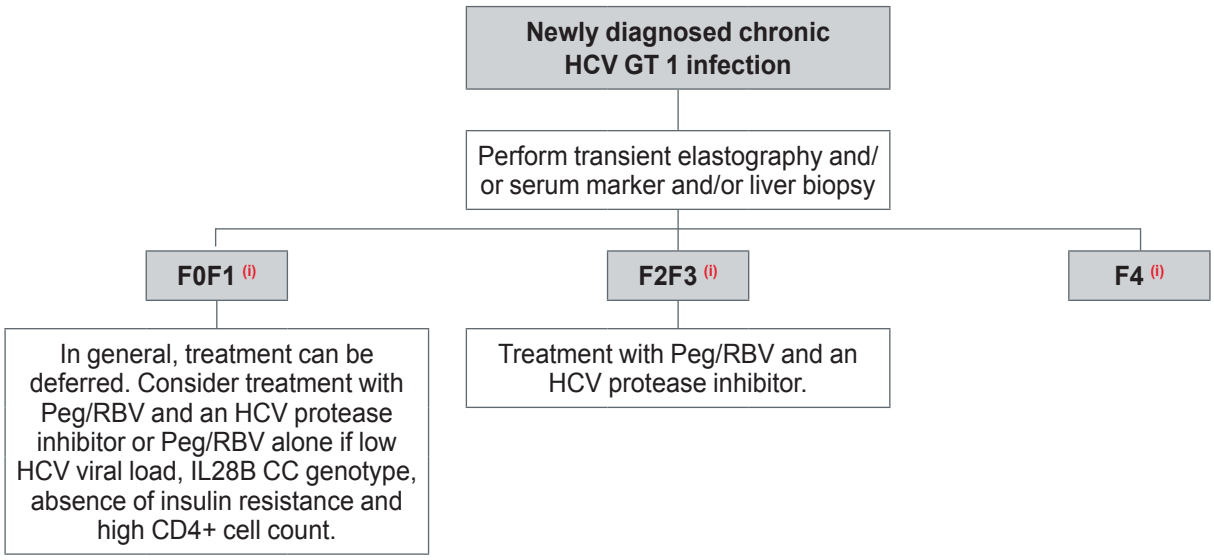
Diagnosis of hepatitis C
HCV-Ab (positive 1-5 months after infection, may rarely be lost with immunosuppression)
HCV-RNA levels [(i)] (in particular, important for the prediction of response to treatment)
Status of liver damage
Grading of fibrosis (e.g. FibroScan, liver biopsy, serum fibrosis markers [(ii)])
Hepatic synthetic function (e.g. coagulation, albumin, CHE)
Ultrasound every 6 months in cirrhotics (gastroscopy upon diagnosis of cirrhosis and every 1-2 years thereafter)
Before HCV treatment
HCV genotype and serum HCV-RNA
IL28B
Autoantibodies (ANA, LKM1) [(iii)]
TSH, thyroid autoantibodies
Monitoring of HCV treatment
Differential blood count and liver enzymes every 2-4 weeks
HCV-RNA at week 4 (to evaluate rapid virological response), and weeks 12, 24 and 48 (72 if applicable) and 24 weeks after stopping HCV therapy
CD4-count every 12 weeks
TSH every 12 weeks

i Low viral load defined as less than 400,000 - 500,000 IU/mL when using Peg-IFN+RBV. There is no standard conversion formula for converting the amount of HCV-RNA reported in copies/mL to the amount reported in IU/mL. The conversion factor ranges from about one to five HCV-RNA copies per IU/mL.

ii Serum fibrosis markers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices; recently more complex tests such as Fibrometer, Fibrotest and Hepascore have shown to more accurately predict liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.

iii Patients with positive anti LKM or ANA with homogeneous pattern should be evaluated for concurrent autoimmune hepatitis, especially in the presence of ALT elevation during treatment.

Management of newly diagnosed HIV/HCV coinfected genotype 1 patients*



Management of HIV-HCV coinfected genotype-1 patients according to fibrosis stage and prior treatment outcome*

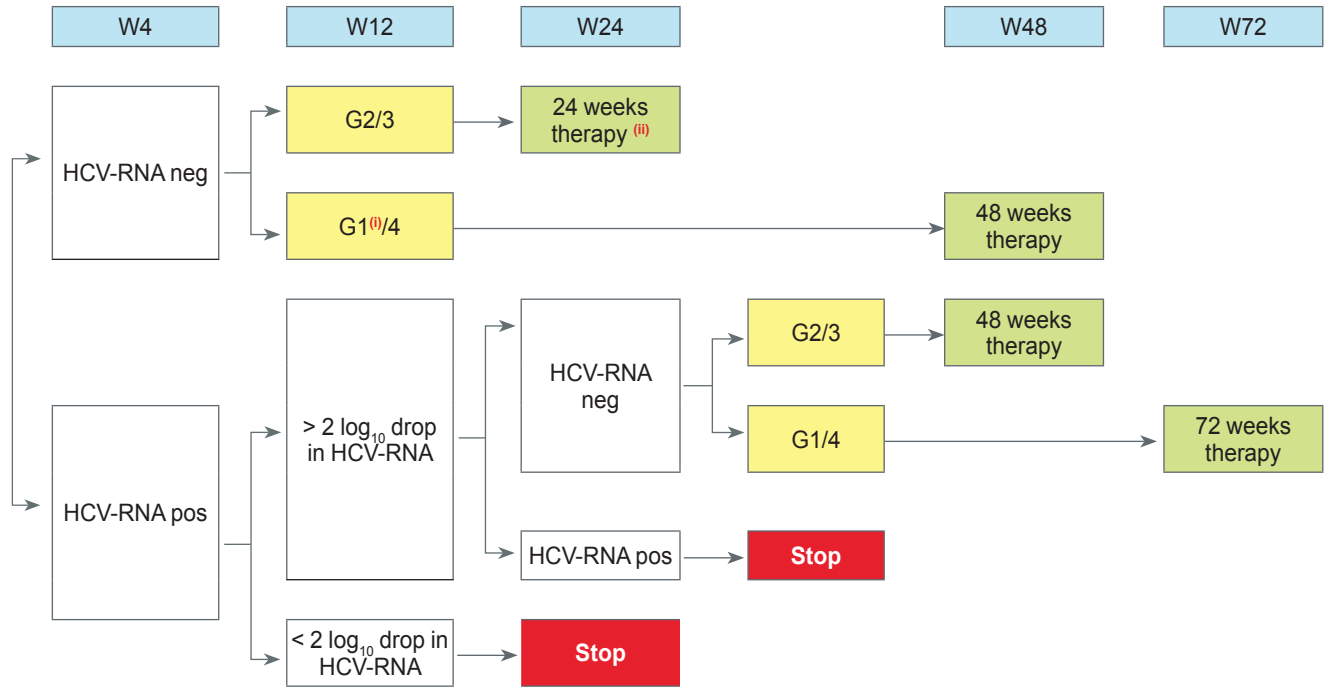
	Naive	Relapser	Non-responder
F0F1	Individual decision	Individual decision/triple therapy	Defer
F2F3	Triple therapy	Triple therapy	Defer (ii)
F4	Triple therapy	Triple therapy	Triple therapy

* Adapted from: Ingiliz P, Rockstroh J. Liver International 2012;32(8):1194-9.

i Metavir fibrosis score: F0=no fibrosis; F1= portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis.

ii Monitor fibrosis stage annually, preferably with two established methods. Treat with triple therapy, if rapid progression.

Proposed optimal duration of dual HCV therapy in HCV/HIV coinfected patients not eligible for triple therapy including direct acting antivirals against HCV



Definitions of treatment response on Peg-IFN and ribavirin

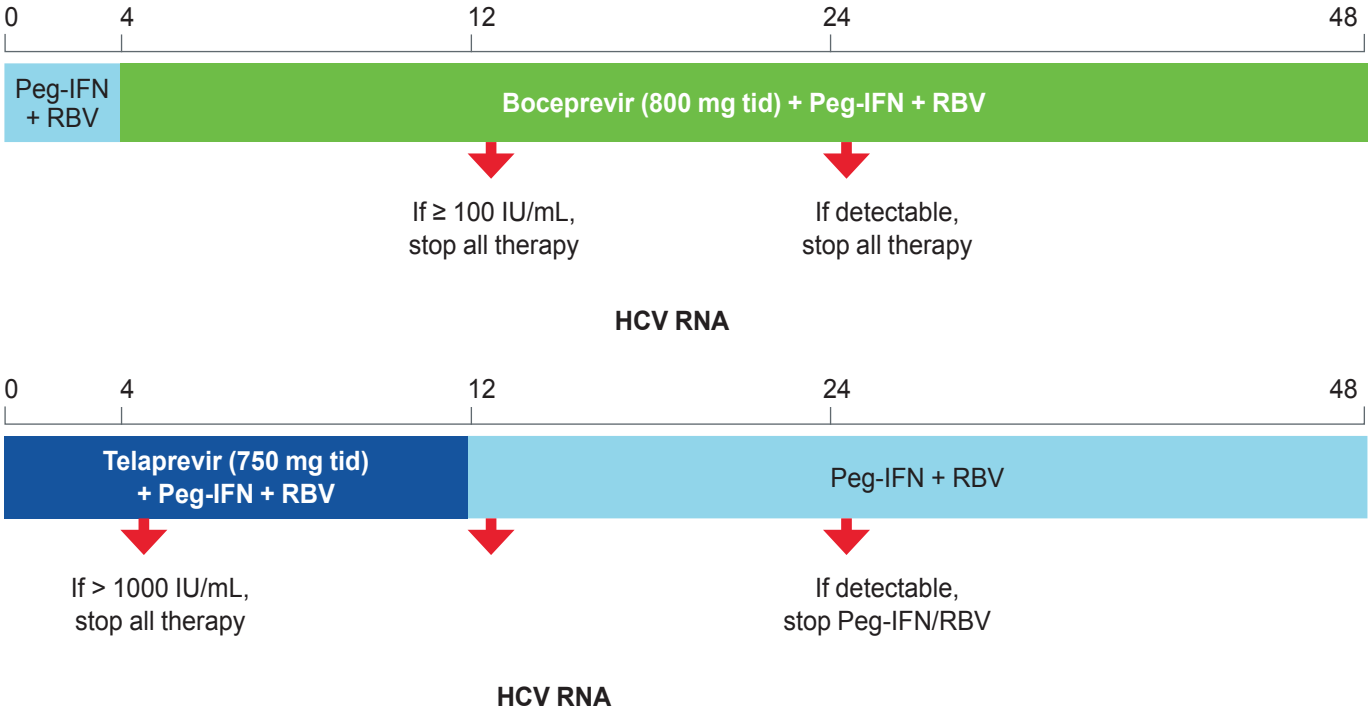
	Time	HCV RNA
Rapid Virological Response (RVR)	Week 4 on treatment	Undetectable (< 50 IU/mL)
Early Virological Response (EVR)	Week 12 on treatment	Undetectable (< 50 IU/mL)
Delayed Virological Response (DVR)	Week 12 on treatment	> 2 log10 decrease from baseline but not undetectable
Null Response (NR)	Week 12 on treatment	< 2 log10 decrease from baseline
Partial Non-Response (PR)	Week 12 and week 24 on treatment	> 2 log10 decrease at week 12 but detectable at week 12 and 24
Sustained Virological Response (SVR)	24 weeks post-treatment	Undetectable (< 50 IU/mL)
Breakthrough	Any time during treatment	Reappearance of HCV RNA at any time during treatment after virological response
Relapse (RR)	End of treatment and week 24 post-treatment	Undetectable HCV RNA at end of therapy, detectable by week 24 post-therapy

Adapted from EASL HCV CPG 2011 (www.easl.eu/assets/application/files/d0df9f948c85a72_file.pdf - accessed 07/05/2011)

i Where no access to DAA available or high chances of cure even with dual therapy (favourable IL28B genotype, low HCV viral load and no advanced fibrosis)

ii In patients with baseline low viral load (< 600 000 IU/mL) and minimal liver fibrosis.

Use of boceprevir or telaprevir in HIV/HCV-coinfected individuals



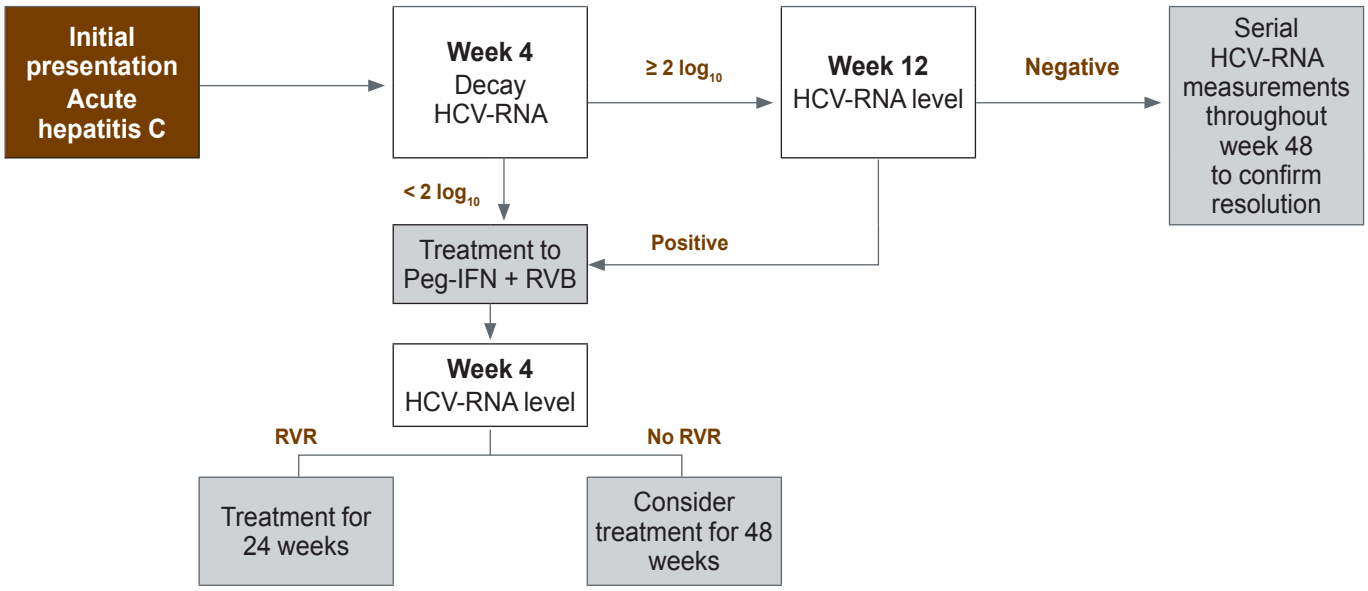
Therapy should be stopped if there is a confirmed increase in HCV RNA by 1log10 following a decline at any stage.

Classification of and interventions for HCV genotype 2, 3 or 4 HIV-coinfected non-responders/relapsers to prior interferon-based therapies

CATEGORY	SUBGROUP	SUGGESTED INTERVENTION
Suboptimal treatment	• Suboptimal schedule • Interferon (monotherapy or with ribavirin) • Low ribavirin dose • Short length of therapy	Re-treatment using combination therapy with Peg-IFN plus weight-based ribavirin dosing
	Limiting toxicities & poor adherence	Optimal support (SSRI, paracetamol/NSAID, adherence support, use of haematopoietic growth factors [i])
Optimal treatment with virological failure	Relapse (HCV-RNA negative at the end of treatment)	• For Genotype 1 patients, wait and monitor if low levels of fibrosis (F0/1) and no or little progression, otherwise re-treat with triple therapy • For Genotypes 2, 3 and 4 for patients with mild fibrosis, wait and monitor. If rapid progression or > moderate fibrosis, re-treatment using combination therapy with Peg-IFN plus weight-based ribavirin dosing (consider longer treatment duration)
	Non response (no undetectable HCV-RNA during treatment)	• For G1 patients with F3/4 fibrosis or those with other stages of fibrosis and rapid progression consider treatment with telaprevir or boceprevir containing triple therapy • In patients without a 2 Log decrease of HCV-RNA or without data on HCV-RNA, decrease in the previous treatment cycle triple therapy is recommended if there is a HCV-RNA decrease of 1 Log after a 4-week lead in phase with pegylated interferon and ribavirin • For others, monitor carefully and wait until new antivirals become available through clinical trials or are licensed.

i Data on the use of haematopoietic growth factors in HIV/HCV coinfection is so far limited to an improvement in quality of life but not antiviral efficacy; treatment with growth factors is currently mostly off-label in Europe.

Algorithm for management of acute HCV in HIV-infected individuals



Adapted from European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel. Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference. AIDS. 2011 Feb 20;25(4):399-409.

Appendix

EACS Guidelines

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Lifestyle interventions [i]

Smoking cessation	• 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
Dietary counselling	• Dietary intervention should not interfere with the dietary requirements necessary 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 < 300 mg/day • Emphasize intake of vegetables, fruit and 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 • 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/m^2 • Intake of alcohol should be restricted to < 20-40 g/d. In particular, patients with hepatic disease, adherence problems, inadequate CD4 T cell increase, tumours, past tuberculosis, diarrhoea and other conditions associated with high alcohol intake should be motivated to decrease or stop alcohol intake.
Exercise promotion	• 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

Interactions between antidepressants and antiretroviral agents

Interacting drug	ARV	Effect of interaction	Recommendation
Sertraline	EFV	sertraline AUC decreased by 39%	titrate to effect
	DRV	sertraline AUC decreased by 49%	
Paroxetine	FPV	paroxetine AUC decreased by 50%	titrate to effect
	DRV	paroxetine AUC decreased by 40%	
	RTV	may increase level of paroxetine	
Venlafaxine	RTV	may increase level of venlafaxine	titrate to effect
Citalopram	RTV	may increase level of citalopram	titrate to effect
Mirtazapine	PIs	may increase level of mirtazapine	titrate to effect

Metabolism of the antidepressants (bold major pathway): **Sertraline:** CYP **2B6**, 2C9, 2C19, 2D6, 3A4 (weak inhibitor of CYP 2D6, 3A4); **Paroxetine:** CYP **2D6** (inhibitor of CYP 2D6); **Venlafaxine:** CYP **2D6**, 3A4 (weak inhibitor of CYP 2D6); **Citalopram:** CYP **2C19**, 2D6, **3A4** (weak inhibitor of CYP 2D6); **Mirtazapine:** CYP **2D6**, **3A4**, 1A2.

Antidepressants do not modify PI and NNRTI concentrations. The antiretroviral agents may alter the antidepressant levels as summarized. No interactions are anticipated between the antidepressants and raltegravir. Venlafaxine (and to a lesser extent mirtazapine) has been associated with prolonged QT. This may be relevant in patients on PI and/or methadone who require antidepressants.

Dose adjustment of antiretrovirals for impaired renal function

		eGFR [i] (mL/min)				Hemodialysis
		≥ 50	30-49	10-29	< 10	
NRTIs						
Didanosine EC [ii]	≥ 60 kg	400 mg q24h	200 mg q24h	150 mg q24h	**> 60 kg: 100 mg/24h**	
	< 60 kg	250 mg q24h	125 mg q24h	100 mg q24h	**< 60 kg: 75 mg/24h**	
Emtricitabine		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h
Tenofovir [vii]		300 mg q24h	300 mg q48h	Not recommended (300 mg q72-96h, if no alternative)	Not recommended (300 mg q7d, if no alternative)	300 mg q7d AD [iv]
Lamivudine		300 mg q24h	150 mg q24h	100 mg q24h [iii]	50-25 mg q24h [iii]	50-25 mg q24h [iii] AD [iv]
Zidovudine		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h
Stavudine < 60 kg		30 mg q12h	15 mg q12h	15 mg q24h	15 mg q24h	15 mg q24h AD [iv]
Stavudine > 60 kg		40 mg q12h	20 mg q12h	20 mg q 24h	20 mg q 24h	20 mg q 24h AD [iv]
Abacavir		300 mg q12h	No dose adjustment required		No dose adjustment required	No dose adjustment required
Abacavir/lamivudine		Use individual drugs				
Zidovudine/lamivudine						
Zidovudine/lamivudine/ abacavir						
Emtricitabine/tenofovir		q24h	q48h	use individual drugs		
NNRTIs						
Nevirapine		200 mg q12h	No dose adjustment required			
Efavirenz		600 mg q24h	No dose adjustment required [v]			
Etravirine		200 mg q12h	No dose adjustment required [v]			

	eGFR [i] (mL/min)				Hemodialysis
	≥ 50	30-49	10-29	< 10	
PIs					
Lopinavir/ritonavir	400/100 mg q12h	No dose adjustment required [v]			
Darunavir/ritonavir	800/100 mg q24h	No dose adjustment required [v]			
Atazanavir/ritonavir	300/100 mg q24h	No dose adjustment required [v,vi]			
Saquinavir/ritonavir	1000/100 mg q12h	No dose adjustment required [v]			
Fosamprenavir/ritonavir	700/100 mg q12h	No dose adjustment required [v]			
Tipranavir/ritonavir	500/200 mg q12h	No dose adjustment required [v]			
Other ART					
Raltegravir	400 mg q12h	No dose adjustment required [v] (dose AD [iv])			
Maraviroc: co-administered without CYP3A4 inhibitors [viii]	300 mg q12h	No dose adjustment required			
Maraviroc: co-administered with CYP3A4 inhibitors [viii]	if eGFR < 80 mL/min dose reduction required [viii]				

i eGFR: estimated glomerular filtration rate, according to the abbreviated MDRD formula (Modification of Diet in Renal Disease)

ii Dose reduction if combined with TDF

iii 150 mg loading dose

iv AD: after dialysis

v Limited data available in patients with renal impairment, pharmacokinetic analysis suggests no dose adjustment required

vi Associated with nephrotoxicity, consider alternative PI if pre-existing CKD

vii Associated with nephrotoxicity, consider alternative ART if pre-existing CKD

viii See summary of product characteristics for specific recommendations, use with caution if eGFR < 30 mL/min

Indications and tests for proximal renal tubulopathy (PRT)

Indications for proximal renal tubulopathy tests	Proximal renal tubulopathy tests [iv], including	Consider stopping tenofovir if
• progressive decline in eGFR [i] & eGFR < 90 & no other cause and/or • confirmed hypophosphataemia [ii] and/or • confirmed increase in UP/C [iii] • renal insufficiency even if stable (eGFR < 60)	• tubular proteinuria [v] • blood phosphate and urinary phosphate excretion [vi] • blood glucose and glucosuria • serum bicarbonate and urinary pH [vii] • blood uric acid level and urinary uric acid excretion [viii] • serum potassium and urinary potassium excretion	• confirmed proximal renal tubulopathy with no other cause

i eGFR: estimated glomerular filtration rate, according to the abbreviated MDRD formula (Modification of Diet in Renal Disease)

ii Serum phosphate < 0.8 mmol/L or according to local thresholds; consider renal bone disease, particularly if alkaline phosphatase increased from baseline: measure 25(OH) vitamin D, PTH

iii UP/C in spot urine: urine protein/creatinine ratio in 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

iv It is uncertain which tests discriminate best for tenofovir renal toxicity. Proximal tubulopathy is characterised by: proteinuria, hypophosphataemia, hypokalaemia, hypouricaemia, renal acidosis, glucosuria with normal blood glucose level. Renal insufficiency and polyuria may be associated. Most often, only some of these abnormalities are observed

v Tests for tubular proteinuria include retinol binding protein, α1- or β2 -microglobulinuria, cystatin C, aminoaciduria

vi Quantified as fractional excretion of phosphate (FE_{Phos}): ($PO4_{(urine)}$ / $PO4_{(serum)}$) / ($Creatinine_{(urine)}$ / $Creatinine_{(serum)}$) in a spot urine sample collected in the morning in fasting state. Abnormal > 0.2 (> 0.1 with serum phosphate < 0.8 mmol/L)

vii Serum bicarbonate < 21 mmol/L and urinary pH > 5.5 suggests renal tubular acidosis

viii Fractional excretion of uric acid ($FE_{UricAcid}$): ($UricAcid_{(urine)}$ / $UricAcid_{(serum)}$ / ($Creatinine_{(urine)}$ / $Creatinine_{(serum)}$) in a spot urine sample collected in the morning in fasting state; abnormal > 0.1

Antiretroviral dosing recommendations in patients with hepatic insufficiency

Nucleoside Reverse Transcriptase Inhibitors

Abacavir	**Child-Pugh Score** 5–6: 200 mg BID (use oral solution)
	Child-Pugh Score > 6: Contraindicated
Didanosine	Contraindicated
	If used no dosage adjustment
Emtricitabine	No dosage adjustment
Lamivudine	No dosage adjustment
Stavudine	Contraindicated
	If used no dosage adjustment
Tenofovir	No dosage adjustment
Emtricitabine (FTC) + tenofovir (TDF)	No dosage adjustment
Zidovudine	Reduce dose by 50% or double the interval between doses

Non-Nucleoside Reverse Transcriptase Inhibitors

Delavirdine	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV) + emtricitabine (FTC) + tenofovir (TDF)	
Etravirine	**Child-Pugh score** < 10: no dosage adjustment
	Child-Pugh score > 9: no dosage recommendation
Nevirapine	**Child-Pugh score** > 6: contraindicated

Protease Inhibitors

Atazanavir	Child-Pugh Score 7–9: 300 mg once daily
	Child-Pugh Score > 9: not recommended
	RTV boosting is not recommended in patients with hepatic impairment (Child-Pugh Score > 7)
Darunavir	Mild to moderate hepatic impairment: no dosage adjustment
	Severe hepatic impairment: not recommended
Fosamprenavir	**PI-naive patients only:**
	Child-Pugh Score 5–9: 700 mg BID
	Child-Pugh Score 10–15: 350 mg BID
	PI-experienced patients:
	Child-Pugh Score 5–6: 700 mg BID + RTV 100 mg QD
	Child-Pugh Score 7–9: 450 mg BID + RTV 100 mg QD
	Child-Pugh Score 10–15: 300 mg BID + RTV 100 mg QD
Indinavir	Mild to moderate hepatic insufficiency: 600 mg q8h
Lopinavir/ritonavir	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir	Mild hepatic impairment: no dosage adjustment
	Moderate to severe hepatic impairment: not recommended
Ritonavir	Refer to recommendations for the primary PI
Saquinavir	Mild to moderate hepatic impairment: use with caution
	Severe hepatic impairment: contraindicated
Tipranavir	Child-Pugh score < 7: use with caution
	Child-Pugh score > 6: contraindicated

Fusion Inhibitor

Enfuvirtide	No dosage adjustment

CCR5 Antagonist

Maraviroc	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment

Integrase Inhibitor

Raltegravir	Mild to moderate hepatic insufficiency: no dosage adjustment. Severe hepatic insufficiency: no recommendation

Note: Hepatic dysfunction is a good indication for Therapeutic Drug Monitoring (TDM) as clinical experience with these dose adjustments is very limited

Diagnosis and management of hepatorenal syndrome (HRS)

Diagnosis	Consider HRS in a patient with cirrhosis and ascites and a creatinine level of > 1.5 mg/dL. It is a diagnosis of exclusion - before making the diagnosis, the following need to be ruled out and treated: • Sepsis (patient needs to be pancultured) • Volume depletion (haemorrhage, diarrhoea, overdiuresis) • Vasodilatators • Organic renal failure (urine sediment; kidney ultrasound) Diuretics should be discontinued and intravascular volume expanded with i.v. albumin If renal dysfunction persists despite above, diagnose HRS		
Recommended therapy	Liver transplant (priority dependent on MELD score). If patient is on transplant list, MELD score should be updated daily and communicated to transplant centre.		
Alternative (bridging therapy)	Vasoconstrictors	**Octreotide**	100-200 mcg subcutaneously t.i.d
			→ Goal to increase mean arterial pressure by 15 mm HG
		+ Midodrine	5-15 mg orally t.i.d
		or Terlipressin [(i)]	0.5-2.0 mg intravenously every 4-6h
	and Intravenous albumin (both for at least 7 days)		50-100 g intravenously q.d.

Antimalarial drugs & cART

Arrows: indicate effect of antiretrovirals on antimalarial drug/key metabolite

Green: no clinically significant interaction expected

Yellow: potential interaction (consider treatment ahead of travel and therapeutic drug monitoring)

Red: clinically relevant interaction, do not use or use with caution

Antimalarial	Indication [i]	NNRTI	PI
Mefloquine (M) CYP 3A4	P/T	↓	↑ M may reduce PI (RTV ca 35%)
Artemisinins (A) [ii] CYP 2B6, 3A4, 2C19	T	↑↓ Increase A (EFV) or key metabolite (NVP)	↑ Increase A: monitor toxicity (liver)
Lumefantrin (L) CYP 3A4	T	↓	↑ **LPV increases L 2-3x**
Atovaquone (A) [iii] **Proguanil** [iv] CYP 2C19	P/T	→	↓ RTV/ATV/LPV reduce A: consider dose increase
Doxycycline	P	→	→
Chloroquine CYP 3A4, 2D6	T	→	→
Quinine (Q) CYP 3A4, 2D6	T	↓ Consider dose increase	↑ RTV increases Q 4x: consider dose reduction, monitor toxicity (tinnitus)
Primaquine CYP 1A2, 2D6, 3A4	(P)/T	NA	NA

i P: use as prophylaxis, T: use as treatment

ii A and its key metabolite, dihydroartemisinin, are active compounds

iii A increases AZT levels by 35%

iv Synergy with A is related to P, not its active metabolite; therefore presumably no net effect of induction/inhibition

Characteristics of drugs used as opioid substitution therapy (OST)

Feature	Methadone	Buprenorphine
Dose required to prevent withdrawal symptoms according to degree of opioid dependency	Linear relationship (from 10-300 mg pr day)	Linear relationship for persons with less opioid dependency only – ceiling effect (max daily dose 24 mg)
Interaction with ARVs	Methadone plasma concentrations are reduced if used together with NNRTIs or PIs: • NVP & EFV: ↓ 40-50% • ETV: ↓ < 10% • LPV/r: ↓ 50% • SQV/r, DRV/r, FPV/r: ↓ 10-25% • ATV, IDV: ↓ < 10%	Buprenorphine (B) and active metabolite norbuprenorphine (N) plasma concentrations are reduced if combined with NNRTIs and increased if combined with some PIs • NVP & EFV: ↓ up to 50% (B) and 70% (N) • ATV/r, IDV, SQV/r: ↑ 50-100% (B&N) • DRV/r: ↑ 50% (N) • LPV/r: ↑ < 10% (B&N) • CAVE: B reduces ATV, do not use without r/
	CAVE: withdrawal symptoms if combined with ARV that decreases plasma concentration and risk of drug toxicity if such ARVs are interrupted – reverse if ARVs increase plasma concentration	
Risk of overdose	Yes	No if used as a co-formulation with naloxone
Causing QT prolongation on ECG	Yes (dose-response relationship) [(i)]	No
Risk of obstipation	High	High
Type of administration	Tablet or liquid	Tablet applied sublingual
Risk of further impairment in persons with existing liver impairment	Yes	Yes

i ECG recommended for daily methadone doses exceeding 50 mg; special caution with concomitant use of other drugs known to cause QT prolongation (e.g. certain PIs such as SQV/r as well as albuterol (USAN) or salbutamol (INN), amiodarone, amitriptyline, astemizole, chloroquine, clomipramine and moxifloxacin).

Management of hyperlactataemia and management of lactic acidosis

Risk factors	Prevention/Diagnosis	Symptoms
• Use of ddI > d4T > ZDV • HCV/HBV coinfection • 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 for symptoms if > 1 risk factor	• 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	• Repeat test under standardized conditions to confirm & obtain arterial pH and bicarbonate (i) • If confirmed, exclude other 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 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

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

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.

IADL (Instrumental Activities of Daily Living) scale

A.	**Ability to use telephone**	
1.	Operates telephone on own initiative; looks up and dials numbers, etc.	1
2.	Dials a few well-known numbers	1
3.	Answers telephone but does not dial	1
4.	Does not use telephone at all	0
B.	**Shopping**	
1.	Takes care of all shopping needs independently	1
2.	Shops independently for small purchases	0
3.	Needs to be accompanied on any shopping trip	0
4.	Completely unable to shop	0
C.	**Food preparation**	
1.	Plans, prepares, and serves adequate meals independently	1
2.	Prepares adequate meals if supplied with ingredients	0
3.	Heats and serves prepared meals, or prepares meals but does not maintain adequate diet	0
4.	Needs to have meals prepared and served	0
D.	**Housekeeping**	
1.	Maintains house alone or with occasional assistance (e.g., “heavy work domestic help”)	1
2.	Performs light daily tasks such as dishwashing, bed making	1
3.	Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
4.	Needs help with all home maintenance tasks	1
5.	Does not participate in any housekeeping tasks	0
E.	**Laundry**	
1.	Does personal laundry completely	1
2.	Launders small items; rinses stockings, etc.	1
3.	All laundry must be done by others	0
F.	**Mode of transportation**	
1.	Travels independently on public transportation or drives own car	1
2.	Arranges own travel via taxi, but does not otherwise use public transportation	1
3.	Travels on public transportation when assisted or accompanied by another	1
4.	Travel limited to taxi or automobile with assistance of another	0
5.	Does not travel at all	0

G.	**Responsibility for own medications**	
	1. Is responsible for taking medication in correct dosages at correct time	1
	2. Takes responsibility if medication is prepared in advance in separate dosages	0
	3. Is not capable of dispensing own medication	0
H.	**Ability to handle finances**	
	1. Manages financial matters independently (budgets, writes cheques, pays rent and bills, goes to bank), collects and keeps track of income	1
	2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.	1
	3. Incapable of handling money	0

Source: Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-186.

Additional questions on job performance

I.	Unable to perform some aspects of previous job (not due to medical symptoms)	0
L.	Reduced efficiency or productivity; or more errors or difficulties meeting expectations; or greater effort to perform the same activities	0

Scoring (TOTAL): If patient receives a score of 0 for at least two of the items above (A-L), then he/she is considered to be functionally impaired

Source: Antinori A, Arendt G, Becker JT, et al. **Updated research nosology for HIV-associated neurocognitive disorders**. Neurology. 2007 Oct 30;69(18):1789-99.

Management of HIV patients with liver cirrhosis

Management of hypervolaemic hyponatraemia	Management strategy of hepatic encephalopathy (HE)	
1 Fluid restriction to 1000-1500 mL/day 2 If fluid restriction is not effective, oral tolvaptan may be used; it should be started in the hospital at a dose of 15 mg/day. This dose should be given for the first few days and then the dose should be titrated to 30 and 60 mg/day until normal values of serum sodium are reached 3 Serum sodium concentration should be monitored closely, particularly during the first days of treatment and whenever the dose of the drug is increased or there are changes in the clinical status of the patient 4 Rapid increases in serum sodium concentration (greater than 8 mmol/day) should be avoided to prevent the potential occurrence of osmotic demyelination syndrome 5 Patients may be discharged after serum sodium levels are stable and no further increase in the dose of the drug is required 6 Treatment with drugs that are either potent inhibitors or inducers of the CYP3A should be avoided 7 The duration of treatment with tolvapan is not known as its efficacy and safety have only been established in short-term studies (1 month)	**General management**	Identity and treat precipitating factor (GI haemorrhage, infection, pre-renal azotemia, constipation, sedatives) Short-term (< 72h) protein restriction may be considered in severe HE
	Specific therapy	Lactulose enemas (300 cm^3 in 1 L of water) in patients who are unable to take it orally or Lactulose 30 cm^3 orally every 1-2h until bowel evacuation, then adjust to a dosage that will result in 2-3 formed bowel movements per day (usually 15-30 cm^3 orally b.i.d.) Lactulose can be discontinued once the precipitating factor has resolved

Management strategy in uncomplicated ascites

General management	• Treat ascites once other complications have been treated • Avoid NSAIDs • Norfloxacin prophylaxis (400 mg orally, q.d.) in patients with **1)** an ascites protein level of < 1.5 gl/dL, **2)** impaired renal function (serum creatinine level = 1.2 mg/dL, BUN = 25 mg/dL, **3)** serum sodium level = 130mE g/L), or **4)** severe liver failure (Child Pugh score = 9 points with serum bilirubin level = 3 mg/dL)
Specific management	• Salt restriction 1-2 g/day • Liberalize if restriction results in poor food intake • Large volume paracentesis as initial therapy only in patients with tense ascites • Administer intravenous albumin (6-8 g/L of ascites removed)
Follow-up and goals	• Adjustment of diuretic dosage should be performed every 4-7 days • Patients should be weighed at least weekly and BUN, creatinine, and electrolytes measured every 1-2 weeks while adjusting dosage • Double dosage of diuretics if: Weight loss < 2 kg a week and BUN, creatinine and electrolytes are stable • Halve the dosage of diuretics or discontinue if: Weight loss ≥ 0.5 kg/day or if there are abnormalities in BUN, creatinine, or electrolytes • Maximum diuretic dosage is spironolactone (400 mg q.d.) and furosemide (160 mg q.d.)

Diagnosis and management of spontaneous bacterial peritonitis (SBP)

Diagnosis	Consider SBP and perform diagnostic paracentesis if: - Symptoms (abdominal pain, fever, chills) - Patient is in emergency room or admitted - Worsening renal function or encephalopathy SBP present if ascites PMN count > 250 cells/μL (if fluid bloody, subtract 1PMN per 250 RBC/μL)
General management	Avoid therapeutic parenteses during active infection Intravenous albumin (1 g/kg of body weight) if BUN > 30 mg/dL, creatinine > 1 mg/dL, bilirubin > 4 mg/dL, Repeat at day 3 if renal dysfunction persists Avoid aminoglycosides
Specific management	Cefotaxime (2 g i.v. every 12h) or Ceftriaxone (2 g every 24h) or Ampicillin/sulbactam (2 g/1g i.v. every 6h)
Follow-up	Continue therapy for 7 days Repeat diagnostic paracentesis at day 2 If ascites PMN count decreases by at least 25% at day 2, intravenous therapy can be switched to oral therapy (quinolone such as ciprofloxacin or levofloxacin 250 mg p.o. b.i.d) to complete 7 days of therapy

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Conflicts of interest

The following panel members have no conflicts of interest to report:

- Sanjay Bhagani
- Mark Bower
- Raffaele Bruno
- Nathan Clumeck
- Simon Collins
- Juliet Compston
- Antonella d'Arminio Monforte
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- Peter Reiss
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Declarations of conflicts of interest provided by the panel members are available for consultation upon request from **info@eacsparis.org**

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The European AIDS Clinical Society (EACS) Guidelines are freely downloadable from www.europeanaidsclinicalsociety.org.
A declaration of potential conflicts of interest of the panel members can be found at the same address.

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