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Abbreviations

Antiretroviral drug (ARV) abbreviations

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
COBI	cobicistat
d4T	stavudine
ddI	didanosine
DLV	delavirdine
DRV	darunavir
EFV	efavirenz
EVG	elvitegravir
ENF	enfuvirtide
ETV	etravirine
FI	fusion inhibitor
FPV	fosamprenavir
FTC	emtricitabine
IDV	indinavir
INSTI	integrase strand transfer inhibitor
LPV	lopinavir
MVC	maraviroc
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
BP	blood pressure
cART	combination antitroviral treatment
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
DAA	direct acting antiviral drug
DXA	dual energy X-ray absorptiometry
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
FBC	full blood count
FDC	fixed dose combination
FRAX	fracture risk assessment tool
HAV	hepatitis A virus
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
IM	intramuscular
IV	intravenous
IVDU	intravenous drug use
LDL-c	LDL-cholesterol
LGV	lymphogranuloma venereum
Mg	magnesium
MSM	men who have sex with men
PO	per oral
PAP	papanicolaou test
PEG-IFN	pegylated-interferon
PPI	proton pump inhibitor
PPD	purified protein derivative
PSA	prostate specific antigen
PTH	parathyroid hormone
RBV	ribavirin
SC	subcutaneous
SVR	sustained virological response
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 (HIV-RNA)
WB	western blot
Zn	zinc

Part I Assessment of HIV-positive Persons at Initial & Subsequent Visits

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
HISTORY						
Medical	Complete medical history including	+	+	First visit	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)	30-32
	• Concomitant medications[(i)]	+	+			
	• Past and current co-morbidities	+	+			
	• Vaccination history	+			Measure antibody titres and offer vaccinations where indicated	
Psychosocial	Current lifestyle (alcohol use, smoking, diet, aerobic exercise, drug use)	+	+	6-12 months	Adverse lifestyle habits should be addressed more frequently	29
	Employment	+	+	As indicated Every visit	Provide advice and support if needed Provide counselling if needed	
	Social and welfare	+	+			
	Psychological morbidity	+	+			
	Partner and children	+			Test partner and children if at risk	
Sexual and Reproductive health	Sexual history	+		6-12 months	Address issues concerning sexual dysfunction Risk of sexual transmission should be addressed where indicated	54-56
	Safe sex	+		As indicated		
	Partner status and disclosure	+		As indicated	Consider starting ART in serodifferent couples	
	Conception issues	+	+	As indicated		
HIV DISEASE						
Virology	Confirmation of HIV Ab pos	+		3-6 months	More frequent monitoring of HIV-VL at start of ART Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection	7-11
	Plasma HIV-VL	+	+			
	Genotypic resistance test and sub-type	+	+/-	At virological failure		
	R5 tropism (if available)		+/-		Screen if considering R5 antagonism in regimen	
Immunology	CD4 absolute count and % (optional: CD8 and %)	+	+	3-6 months	Consider less frequent monitoring for stable persons on ART with high CD4 counts[(ii)]	7-11
	HLA B5701 (if available)	+	+/-		Screen before starting ABC containing ART, if not previously tested	
CO-INFECTIONS						
STIs	Syphilis serology	+		Annual/as indicated	Consider more frequent screening if at risk	54
	STI screen	+		Annual/ as indicated	Screen if at risk	
Viral Hepatitis	HAV serology	+		Annual /as indicated	Screen at risk; vaccinate if non-immune	53-54, 62
	HCV screen	+			Annual screen if ongoing risk. Measure HCV-RNA if HCV Ab pos or if acute infection suspected. Vaccinate if non-immune	
	HBV screen	+	+		Annual screen in susceptible persons	
Tuberculosis	CXR	+		Re-screen if exposure	Consider routine CXR in persons from high TB prevalence populations See Diagnosis and Treatment of Resistant and Latent TB in HIV-positive persons	13
	PPD if CD4 count >400	+				
	IGRA in selected high-risk populations (if available)	+				
Others	Varicella zoster virus serology	+			Offer vaccination where indicated	53
	Measles/Rubella serology	+			Offer vaccination where indicated	
	Toxoplasmosis serology	+				
	CMV serology	+				
	Leishmania serology	+/-			Screen according to travel history/origin	
	Tropical screen (e.g. Schistosoma serology)	+/-			Screen according to travel history/origin	

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
CO-MORBIDITIES						
Haematology	FBC	+	+	3-12 months		
	Haemoglobinopathies	+			Screen at risk persons	
	G6PD	+			Screen at risk persons	
Body composition	Body-mass index	+	+	Annual		29
Cardiovascular disease	Risk assessment (Framingham score[iii])	+	+		Should be performed in all men > 40 years and women > 50 years without CVD	30
	ECG	+	+/-	Annual	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
Hypertension	Blood pressure	+	+	Annual		31-32
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	36
Glucose	Serum glucose	+	+	6-12 months	Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL)	34-35
Pulmonary disease	CXR	+/-		As indicated	Consider CXR if prior history of pulmonary disease	
	Spirometry			As indicated	Screen for COPD in at risk persons[xii]	
Liver disease	Risk assessment[v]	+	+	Annual		44-46
	ALT/AST, ALP, Bilirubin	+	+	3-12 months	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs	
Renal disease	Risk assessment[vi]	+	+	Annual	More frequent monitoring if CKD risk factors present and/or prior to starting and on treatment with nephrotoxic drugs[ix]	40-41
	eGFR (aMDRD)[vii]	+	+	3-12 months		
	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[vii]	
Bone disease	Bone profile: calcium, PO^4, ALP	+	+	6-12 months		37, 39
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons	
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons	38
Neurocognitive impairment	Screening questionnaire	+	+	2 years	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 61 for further assessment.	61
Depression	Questionnaire	+	+	1-2 years	Screen at risk persons	57-59
Cancer	Mammography			1-3 years	Women 50-70 years	28, 46
	Cervical PAP			1-3 years	Sexually active women	
	Anoscopy and PAP (MSM)			1-3 years	Evidence of benefit not known	
	Ultrasound and alpha-foetoprotein			6 months	Controversial/Persons with cirrhosis and persons with HBV irrespective of fibrosis stage	
	Others				Controversial	

i Review all concomitant medications which may potentially interact with ARVs or increase co-morbidities, see Drug-drug Interactions between Antidepressants and ARVs Drug-drug Interactions between Antihypertensives and ARVs Drug-drug Interactions between Analgesics and ARVs Drug-drug Interactions between Antimalarial Drugs and ARVs and www.hiv-druginteractions.org

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

iii A risk equation developed from HIV populations is available, see www.cphiv.dk/tools.aspx. Of note, if individual persons receive medication to control dyslipidaemia and/or hypertension, the estimation should be interpreted with caution.

iv A 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 and hepatotoxic drugs.

vi Risk factors for CKD: hypertension, diabetes, CVD, family history, black African ethnicity, viral hepatitis, low current CD4 count, smoking, older age, concomitant nephrotoxic drugs.

vii eGFR: use the abbreviated modification of diet in renal disease (aMDRD) formula based on serum creatinine, gender, age and ethnicity; see www.cphiv.dk/tools.aspx. The Cockcroft-Gault (CG) equation may be used as an alternative.

viii Some experts recommend UA/C (urinary albumin creatinine ratio) or UP/C (urinary protein creatinine ratio) as a screening test for proteinuria in all persons. UA/C predominantly detects glomerular disease. Use in persons with diabetes. UP/C detects total protein secondary to glomerular and tubular disease.

ix Additional screening is required for persons receiving TDF and perhaps for certain PIs e.g. ATV and LPV/r, see ARV-associated Nephrotoxicity

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 (FRAX®) tool: www.shef.ac.uk/FRAX

xii A diagnosis of COPD should be considered in persons over the age of 35 who have a risk factor (current or ex- smoker) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze.

Part II ART of HIV-positive Persons

Assessing HIV-positive Persons´ Readiness to Start and Maintain ART

Goal: to help persons start and/or maintain ART	
Successful ART requires a person´s readiness to start and adhere to the regimen over time. The trajectory from problem awareness to maintenance on ART can be divided into five stages. Knowing a person´s stage, health care providers use appropriate techniques to assist them to start and maintain ART.	Identify the person to start's stage of readiness using WEMS[i] techniques, and start discussion with an open question/invitation: "I would like to talk about HIV medication." <wait> "What do you think about it?" Based on the person´s response, identify his/her stage of readiness and intervene accordingly[ii]

Stages of readiness to start ART	
Precontemplation: *"I don't need it, I feel good."* *"I don't want to think about it."*	Support: Show respect for the person´s attitude. / Try to understand the person's health and therapy beliefs. / Establish trust. / Provide concise, individualized information. / Schedule next appointment.
Contemplation: *"I am weighing things up and feel torn about what to do about it."*	Support: Allow ambivalence. / Support the person in weighing pros and cons. / Assess the person's information needs and support his/her information seeking. / Schedule the next appointment.
Preparation: *"I want to start, I think the drugs will allow me to live a normal life."*	Support: Reinforce the person´s decision. / Decide with the person which is the most convenient regimen. / Educate the person on adherence, resistance, side effects. / Discuss integration into daily life. / Respect the person´s self assessment. Ask: How confident are you that you can take your medication as we discussed (specify) once you have started? Use VAS 0-10[iii] Consider skills training: • Medication-taking training, possibly MEMS • Directly observed therapy with educational support • Use aids: mobile phone alarm, pillboxes • Involve supportive tools/persons where appropriate
Action: ***"I will start now."***	**'Final check': With a treatment plan established, is the person capable of taking ART?**
Maintenance: *"I will continue" or "I have difficulties continuing over the long run"* Caveat: A person can relapse to an earlier stage, even from "maintenance" to "precontemplation"	Assess: Adherence every 3-6 months[iv] Evaluate adherence: For persons with good adherence: show respect for their success. Assess: The person´s own perception of ability to adhere to, and continue, treatment. Ask: In the next 3-6 months, how confident are you that you can take your medication? Use VAS 0-10[iii] For a person without sufficient adherence: use mirroring techniques[v] on problems, ask open questions to identify dysfunctional beliefs. Assess: Stage of readiness and provide stage-based support Assess: Barriers and facilitators[vi] Schedule next appointment and repeat support

START ART

Screen for and talk about problems and facilitators	
Consider systematic assessment of: • Depression[vii], see page 57-58 • Cognitive problems[viii], see page 61 • Harmful alcohol or recreational drug use, see page 27, 29	Consider talking about: • Social support and disclosure • Health insurance and continuity of drug supply • Therapy-related factors
Recognise, discuss and reduce problems wherever possible in a multidisciplinary team approach.	

i WEMS: Waiting (> 3 sec), Echoing, Mirroring, Summarising [1]

ii The person presenting in the clinic may be at different stages of readiness: precontemplation, contemplation or preparation. The first step is to assess this stage, and then to support/intervene accordingly. In the case of late presentation (< 350 CD4 cells/µL), the initiation of ART should not be delayed. The person should be closely followed and optimally supported. Schedule the next appointment within a short time, i.e. 1-2 weeks.

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

iv Suggested adherence questions: "In the past 4 weeks how often have you missed a dose of your HIV medication: every day, more than once a week, once a week, once every 2 weeks, once a month, never?" / "Have you missed more than one dose in a row?" [2].

v Mirroring: reflecting back on what a person has said or non-verbally demonstrated (e.g. anger or disappointment) WITHOUT introducing new material by asking questions or giving information.

vi Adherence to long-term therapies [3].

vii 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% [4].

viii Ask: "Do you feel having problems to concentrate in your daily life?" / "Do you feel slowed in your thinking?" / "Do you feel having problems with your memory?" / "Did relatives or friends express that they feel you have problems with your memory or difficulty concentrating?" [5].

ix We recommend the AUDIT-Fast tool to determine harmful alcohol use: "How often have you had 6 or more units (if female), or 8 or more (if male), on a single occasion in the last year?" If the answer is weekly or daily, i. e. screening positive, stop here. If the answer is less than that, ask three more questions. When screening for harmful substance use, drop the first quantitative question and replace "drinking" with "recreational substance" [6].

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

Present condition/circumstance	Current CD4 count[ii,iii]	
	350-500	> 500
Asymptomatic HIV infection	C	C
To reduce transmission of HIV	C	C
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:	R	R
• 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	R[iv]	C
• HCV for which anti-HCV treatment is being considered or given	R[v]	C
• HCV for which anti-HCV treatment not feasible	R	C

i,ii **ART is always recommended in any HIV-positive person with a current CD4 count below 350 cells/μL.**
For persons with CD4 counts above this level, the decision to start ART should be individualized and considered, especially if a person is requesting ART and ready to start, has any of the conditions mentioned above and/or for any other personal reasons. Priority should be taken to treat persons with CD4 counts below 350 cells/μL and for persons with higher CD4 counts if they suffer from one of the above-mentioned conditions before placing resources into treatment as prevention.
Time should always be taken to prepare the person, in order to optimize compliance and adherence.
Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis; otherwise before initiation of ART. If ART needs to be initiated before genotypic testing results are available, it is recommended to include a ritonavir-boosted PI in the first-line regimen. Before starting treatment, the HIV-VL level and CD4 count should be repeated to obtain a baseline to assess subsequent response.

iii **R** use of ART is recommended
C use of ART should be considered and actively discussed with the HIV-positive person; under these circumstances, some experts would recommend starting ART whereas others would consider deferral of ART; this clinical equipoise reflects that whereas certain data, such as hypotheses on pathophysiology and chronic immune activation, 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.

iv See figure page 63 for indication of HBV treatment in HBV/HIV co-infected persons

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

Initial Combination Regimen for ART-naive Adult HIV-positive Persons

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	ABC/3TC co-formulated TDF/FTC co-formulated EFV/TDF/FTC co-formulated RPV/TDF/FTC co-formulated
PI/r		
ATV/r(iv) DRV/r(iv)	ABC/3TC(vii) or TDF/FTC	ATV/r: 300/100 mg qd DRV/r: 800/100 mg qd
INSTI		
RAL	TDF/FTC or ABC/3TC	RAL: 400 mg bd

Alternative Regimen Components

PI/r	Remarks
FPV/r LPV/r(v) SQV/r	700/100 mg bd or 1400/200 mg qd 400/100 mg bd or 800/200 mg qd 1000/100 mg bd
NNRTI	
NVP(iii)	
NRTI	
ddI/3TC or ddI/FTC(viii) TDF-3TC ZDV/3TC	ZDV/3TC co-formulated
CCR5 inhibitor	
MVC(vi)	Only if CCR5 tropic HIV(viii)
INSTI	
EVG + COBI	TDF/FTC co-formulated(ix)

* Only drugs currently licensed for initiation of therapy by the EMA are taken into consideration (in alphabetical order)

** 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 EFV is already started before pregnancy; not active against HIV-2 and HIV-1 group O strains.

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

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

iv Castle study (LPV/r vs. ATV/r) showed better tolerability of ATV/r; [7]. Coadministration with PPI is contraindicated for treatment-experienced persons. If coadministration is judged unavoidable, close clinical monitoring is recommended and doses of PPI comparable to omeprazole 20 mg should not be exceeded and must be taken approximately 12 hours prior to the ATV/r.
Artemis study (LPV/r vs. DRV/r) showed better eficacy and tolerability of DRV/r [8].

v ACTG 5142 study showed lower virological efficacy of LPV/r vs. EFV. No PI mutations emerged with LPV/r plus 2 NRTI failures. PI mutations were seen with LPV/r + EFV failures. LPV to be used in cases where oral absorption is the only alternative, especially in intensive care [9].

vi Unlicensed in Europe for naive persons.

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 persons with a high CVD risk and/or persons with a VL > than 100,000 copies/mL.

viii Only if unavailability or intolerance to other recommended NRTIs.

ix Should not be initiated in persons with eGFR < 70 mL/min. It is recommended that EVG/COBI/TDF/FTC not be initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment.

Acute HIV infection

Definition of Acute primary HIV infection

High-risk exposure within previous 2-8 weeks, and
- Detectable HIV-VL in the plasma (p24 Ag and/or HIV-VL > 1000 copies/mL) and/or
- Negative or indeterminate serologic testing (negative or weakly positive ELISA, and WB ≤ 1 band) plus HIV-VL
- Recommendation: confirm HIV infection by HIV antibody test (WB) performed 2 weeks later

Treatment

Treatment indicated if, see page 7:
- Asymptomatic recent HIV infection with HIV-VL > 1000 copies/mL or p24 Ag positive
- Confirmed CD4 count < 350 cells/μL at month 3 or beyond
- Symptomatic primary infection
- AIDS-defining events
- Severe illness/prolonged symptoms (especially CNS symptoms)

In all cases persons should be preferably recruited into a clinical trial.

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, HBV and HCV, see page 54
- Counsel newly diagnosed person on high risk of transmission and preventive measures (condoms) including notifying and testing partners

Switch Strategies for Virologically Suppressed Persons

Definition of virologically suppressed

Confirmed HIV-VL< 50 copies/mL

Indication

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

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.

Switch for simplification
Wish to simplify regimen
Actual regimen no longer recommended

Principles

1. A PI/r may be switched for simplification, prevention or improvement of metabolic abnormalities or adherence facilitation to unboosted ATV, an NNRTI or RAL 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 persons with 1) substitution of drugs difficult to administer (ENF) 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 and adherence facilitation. NVP and RPV have the advantage of their metabolic profile. EFV and RPV have the advantage of possible FDC of 3 drugs (Atripla, Eviplera).
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 RTV or 1 NRTI + RAL, or 2 NRTIs
c. Triple NRTI combinations

Other strategy

PI/r monotherapy with qd DRV/r or bd LPV/r might represent an option in persons with intolerance to NRTIs or for treatment simplification or in illicit drug users with documented frequent interruption of cART. Such a strategy only applies to persons without history of failure on prior PI-based therapy and who have had HIV-VL < 50 copies/mL in at least the past 6 months and who do not have chronic HBV.

Virological Failure

Definition	Confirmed HIV-VL > 50 copies/mL 6 months after starting therapy (initiation or modification) in persons that remain on ART
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 HIV-VL levels > 350-500 copies/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 HIV-VL > 50 and < 500-1000 copies/mL
	Check for adherence
	Check HIV-VL 1 to 2 months later
	If genotype not possible, consider changing regimen based on past treatment and resistance history
	If HIV-VL 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: HIV-VL < 400 copies/mL after 3 months, HIV-VL < 50 copies/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. DRV/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. ETV), assessed by genotypic testing
	Defer change if < 2 active drugs available, based on resistance data, except in persons 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 HIV-VL (> 1*$\log_{10}$ 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

Treatment of HIV-positive 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-VL 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 planning to be pregnant while already on ART	1. If under EFV, switch to another NNRTI or boosted PI because of risk of neural tube defects
2. Women becoming pregnant while already on ART	2. Maintain ART unless under EFV: switch to another agent (NVP or PI/r) if before 8 weeks (because of risk of neural tube defects)
3. Women becoming pregnant while treatment naive irrespective of whether they fulfil the criteria (CD4) for initiation of ART	3. Starting ART at beginning of 2nd trimester is highly recommended
4. Women whose follow-up starts after week 28 of pregnancy	4. Start ART immediately and consider adding raltegravir to obtain rapid VL decline in case of high VL
5. Women whose viral load is not undetectable at third trimester	5. Perform resistance testing and consider adding raltegravir to obtain rapid VL decline
Antiretroviral regimen in pregnancy	Same as non pregnant
	NVP not to be initiated but continuation is possible if started before pregnancy
	EFV should be avoided during first trimester because of increase in neural tube defects*
	Among PI/r, prefer LPV/r or SQV/r or ATV/r
	If RAL, DRV/r: could be continued
Drugs contra-indicated during pregnancy	ddI + d4T, triple NRTI combinations
IV ZDV during labour	Benefit uncertain if plasma HIV-VL < 50 copies/mL
Single dose NVP during labour	Not recommended
Caesarean section	Benefit uncertain if plasma HIV-VL < 50 copies/mL at week 34-36. In this case, consider vaginal delivery only

* According to prospective studies [10-11]

ART in TB/HIV Co-infection

Principles

Persons with TB should be started on standard TB therapy with 2 months rifampicin/isoniazid/pyrazinamide +/- ethambutol followed by 4 months rifampicin/isoniazid (choice of drugs and length of treatment depends on drug susceptibility and site of disease), see Diagnosis and Treatment of Resistant and Latent TB in HIV-positive Persons

All persons with TB/HIV co-infection should start ART irrespective of CD4 count. Treatment supervision and adherence evaluation are very important

Suggested timing of ART initiation in TB/HIV co-infection according to CD4

< 100 cells/μL(*) As soon as TB treatment is tolerated and wherever possible within 2 weeks

> 100 cells/μL(**) Can be deferred until between 8 and 12 weeks of TB treatment, especially when there are difficulties with drug-drug interactions, adherence and toxicities

* Be aware of IRIS reaction in persons starting ART at low CD4 levels and with early initiation of ART. Corticosteroids should be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response.

** Although the data suggests a cut-off of 50 cells/μL, because of the daily variability in CD4, a cut-off of 100 cells/μL may be more appropriate.

Recommended 1st line ARV combination with anti-TB medication

EFV/TDF/FTC or EFV/ABC/3TC

Alternatives

1. If HIV-VL < 100,000 copies/mL, fixed-dose combination of ZDV/ABC/3TC bd +/- TDF could also represent a short-term alternative until anti-TB treatment has been completed.
2. Rifampicin plus double dose LPV/r or with RTV super boosted (400 mg bd) plus LPV

Where combinations are not recommended or to be used with caution or because of resistance/intolerance, specialist HIV treatment advice should be sought.

- PI/r + TDF/FTC, using rifabutin instead of rifampicin
- Use with caution

Important Drug-Drug Interactions between ART and Rifampicin / Rifabutin

ARV drug class	Specific ARVs	Drug- drug interactions and recommended adjustment of dose of either or both drugs
NRTIs		Rifampicin: standard dose of all drugs
		Rifabutin: standard dose of all drugs
PI/r	ATV/r, DRV/r, LPV/r or SQV/r	Rifampicin: not recommended
	Monitor liver enzymes and, whenever possible, perform TDM for PI/r	Rifabutin: dose as 150 mg x 3/week. PI/r at standard dose
NNRTIs	EFV	Rifampicin: No dose change required. EFV: standard dose (some recommend 800 mg if not black African); ARV TDM recommended after 2 weeks
		Rifabutin: 450 mg daily. EFV: standard dose
	NVP	Neither Rifampicin nor Rifabutin recommended
	RPV	Rifampicin: not recommended
		Rifabutin: standard dose. RPV dose should be increased (use with caution)
	ETV	Rifampicin: not recommended
		Rifabutin: standard dose of both drugs (few data – use with caution)
INSTI	EVG	Rifampicin: not recommended
		Rifabutin: 150 mg x 3/week. EVG: standard dose
	RAL	Rifampicin: standard dose. RAL 800 mg bd (standard dose may also work)
		Rifabutin: standard dose of both drugs

Post-exposure Prophylaxis

Post-exposure Prophylaxis (PEP) recommended in case of

Risk	Nature of exposure	Status of source person
Blood	Subcutaneous or intramuscular penetration with iv or im needle, or intravascular device	HIV-positive 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-positive
Genital secretions	Anal or vaginal sex	HIV-positive or serostatus unknown but presence of HIV risk factors
	Receptive oral sex with ejaculation	HIV-positive
Intravenous drug use	Exchange of syringe, needle, preparation material or any other material	HIV-positive

- Rapid testing of the source person for HCV and HIV (if HIV-status unknown) recommended
- If source person HIV-positive on ART, 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 bd
- 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 person HCV-positive (observed or suspected)
  - Repeat HIV serology after 2 and 4 months, syphilis serology after 1 month if sexual exposure

Adverse Effects of ARVs & Drug Classes

Bold: Frequent effects
Red: Severe effects
Black: Neither Frequent nor Severe[i]

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genito-urinary	Nervous	Body fat	Metabolic	Other
NRTI										
ABC	Rash*	Nausea* Diarrhoea*		IHD						*Systemic hyper-sensitivity syndrome (HLA B*5701 dependent)
AZT	Nail pig-mentation	Nausea	Steatosis		Myopathy, Rhabdo-myolysis			**Lipoatrophy**	Dyslipi-daemia, Hyperlacta-taemia	Anaemia
d4T		Pancreatitis	**Steatosis**				**Peripheral neuropathy**		**Dyslipi-daemia,** Hyperlacta-taemia	
ddI			Steatosis, Liver fibrosis	IHD					Hyperlacta-taemia	
3TC										
FTC										
TDF					↓ BMD, Osteomalacia ↑ fractures risk	↓ GFR, Fanconi syndrome				
NNRTI										
EFV	Rash		Hepatitis				**Dizziness, Sleep disturban-ces,** Depression		**Dyslipi-daemia,** Gynaeco-mastia	**↓ plasma 25(OH) vitamin D,** Teratoge-nesis
ETV	Rash									
NVP	Rash*		Hepatitis*							*Systemic hypersen-sitivity (CD4- and gender-dependent)
RPV	Rash		Hepatitis				Depression, Sleep distur-bances, headache			
PI										
ATV		**Nausea and diarrhoea**[ii]	Jaundice Cholelithiasis			↓ GFR, Nephro-lithiasis			Dyslipi-daemia	
DRV	Rash					Nephro-lithiasis			Dyslipi-daemia	
FPV	Rash			IHD					**Dyslipi-daemia**	
IDV	**Dry skin,** Nail dystrophy		Jaundice	IHD		**Nephro-lithiasis**		**↑ abdominal fat**	**Dyslipi-daemia,** Diabetes mellitus	
LPV				IHD		↓ GFR			**Dyslipi-daemia**	
SQV									Dyslipi-daemia	
TPV			Hepatitis				Intracranial haemorrhage		Dyslipi-daemia	

FI										
ENF	Injection nodules									Hypersensitivity
ITI										
RAL		Nausea			Myopathy, Rhabdomyolysis		Headache			
CCR5 inhibitors										
MVC			Hepatitis	IHD						↑ Infections risk

i **"Severe effect" (events that can put a person´s life at risk and represent a medical emergency), in bold**
"Frequent effects" (events expected in a least 10% of treated HIV-positive persons), in red.
Neither frequent nor severe effects, in black
ii Frequency and severity differs between individual ARVs.
* Refers to effects seen in relation to hypersensitivity reactions.

Note: the adverse effects included in the table above are not exhaustive, but represent the most important effects with a likely causal relation. Nausea, diarrhoea and rash are frequently observed in persons on ART, and these symptoms are indicated in the table for drugs where clinical experience suggests a possible causal link.

Drug-drug Interactions between ARVs and Non-ARVs[i]

	non-ARV drugs	ATV/r	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	RAL	ABC	FTC	3TC	TDF	ZDV
cardiovascular drugs	atorvastatin	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↔	↔	↔	↔	↔
	fluvastatin	↔	↔	↔	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pravastatin	↔	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
	rosuvastatin	↑213%	↑48%	↑107%	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	amlodipine	↑[iii]	↑	↑[iii]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[iii]	↑	↑[iii]	↓69%	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
	metoprolol	↑[iii]	↑	↑[iii]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑[iii]	↑	↑[iii]	↓	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
	warfarin	↑or ↓	↓	↓	↑or ↓	↑	↑or ↓	↔	↔	↔	↔	↔	↔	↔	↔
CNS drugs	diazepam	↑	↑	↑	↓	↑	↓	↔	↔	↔	↔	↔	↔	↔	↔
	midazolam (oral)	↑	↑	↑	↑	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	triazolam	↑	↑	↑	↑	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	citalopram	↑[iii]	↑	↑[iii]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	mirtazapine	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↓39%	↑↓?	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	sertraline	↓	↓49%	↓	↓39%	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	bupropion	↓	↓	↓57%	↓55%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔
	pimozide	↑[iii]	↑	↑[iii]	↑	↓	↓	↔[iv]	↔	↔	↔	↔	↔	↔	↔
	carbamazepine	↑D	↑	↑D	↓27%D36%	D	↓D	D	D	D	↑	↔	↔	↔	↑[ix]
	lamotrigine	↓39%[ii]	↓[ii]	↓50%	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenytoin	↓D	↓D	↓D	↓D	D	↓D	D	D	D	D	↔	↔	↔	↓
anti-infectives	boceprevir	D35%	↓32%D44%	↓45%D34%	↓19%E20%	↑10%D23%	↓E	E	E	↔	↔	↔	↔	↔	↔[ix]
	clarithromycin	↑[iii]	↑	↑[iii]	↓	↓E	↓	E	E	↔	↔	↔	↔	↔	D
	fluconazole	↔	↔	↔	↔	E86%	E100%	E	↔	↔	↔	↔	↔	↔	E74%
	itraconazole	↑E	↑E	↑E	↓	↓E	↓61%	E	E	↔	↔	↔	↔	↔	↔
	rifabutin	↑	↑E50%	↑	↓	D37%	↑17%	D	*	↔	↔	↔	↔	↔	↔
	rifampicin	D72%	D	D	D26%	D	D58%	D80%	D	D40%	D	↔	↔	↔	D47%
	telaprevir	↓20%E17%	↓35%D40%	↓54%	↓26%D7%	↓16%	↓?	↓5%E	E	E31%	↔	↔	↔	E30%	↔[ix]
	voriconazole	↓	↓	↓	↓E	↑E	↓E	E	E	↔	↔	↔	↔	↔	↔
miscellaneous	antacids	D	↔	↔	↔	↔	↔	D	↔	D	↔	↔	↔	↔	↔
	PPIs	D	↔	↔	↔	↔	↔	D	↔	E	↔	↔	↔	↔	↔
	H2 blockers	D	↔	↔	↔	↔	↔	D	↔	E	↔	↔	↔	↔	↔
	alfuzosin	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	beclometasone inhal.	↑?[v]	↓11%	↑?[v]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	buprenorphine	↑67%	↑6	↔	↓50%	↓25%	↔	↔	↔	↔	↔	↔	↔	↔	↔
	budesonide inhal.	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ergot derivatives	↑	↑	↑	↑	↑	↓	E	↔	↔	↔	↔	↔	↔	↔
	ethinylestradiol	↓[vii]	↓	↓	↔v[iii]	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔
	fluticasone inhal.	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	methadone	↓[ii, iii]	↓16%	↓53%[iii]	↓52%	↑6%	↓≈50%	↓16%	↔	↔	↓	↔	↔	↔	E29-43%
	salmeterol inhal.	↑[iii]	↑	↑[iii]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	sildenafil (erec. dys.)	↑	↑	↑	↓	↓37%	↓	↔	↔	↔	↔	↔	↔	↔	↔
	St John's wort	D	D	D	D	D	D	D	D	↔	↔	↔	↔	↔	↔
	varenicline	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

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, see www.hiv-druginteractions.org (University of Liverpool).

Colour legend

- no clinically significant interaction expected.
- these drugs should not be coadministered.
- potential interaction which may require a dosage adjustment or close monitoring.
- potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC). A dosage adjustment is *a priori* not recommended unless the drug has a narrow therapeutic index.

Note: the symbol (green, amber, red) used to rank the clinical significance of the drug interaction is based on www.hiv-druginteractions.org.

Legend:

- ↑ potential elevated exposure of non-ARV drug
- ↓ potential decreased exposure of non-ARV drug
- ↔ no significant effect
- E potential elevated exposure of ARV
- D potential decreased exposure of ARV

  Numbers refer to decreased/increased AUC of non-ARV/ARV drugs as observed in drug interactions studies
- ii no PK changes with unboosted PI
- iii ECG monitoring is recommended
- iv rilpivirine's manufacturer recommends caution when coadministering with another drug susceptible to prolong QT interval
- v increase in concentration of active metabolite observed with RTV 100 mg bd alone but without significant effect on adrenal function
- vi concentration of parent drug unchanged but concentration of metabolite increased
- vii increase in ethinylestradiol with unboosted ATV
- viii no effect on ethinylestradiol but ↓ progestin
- ix potential haematological toxicity
- * no dose adjustment for MVC in absence of PI. With PI (except TPV/r; FPV/r), give MVC 150 mg bd

Drug-drug Interactions between Antidepressants and ARVs

antidepressants		ATV/r	DRV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	RAL
SSRI	citalopram	↑ [a]	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↔
	escitalopram	↑ [a]	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↔
	fluvoxamine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	fluoxetine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↓39%	↑↓?	↑↓?	↔	↔	↔	↔	↔	↔
	sertraline	↓	↓49%	↓	↓	↓39%	↓	↓	↔	↔	↔
SNRI	duloxetine	↑↓	↑↓	↑↓	↑↓	↔	↔	↔	↔	↔	↔
	venlafaxine	↑	↑	↑	↑	↓	↓	↓	↔	D	↔
TCA	amitriptyline	↑	↑	↑	↑ [b]	↔	↔	↔	↔	↔	↔
	clomipramine	↑	↑	↑	↑ [b]	↓	↓	↓	↔	↔	↔
	desipramine	↑	↑	↑5%	↑	↔	↔	↔	↔	↔	↔
	doxepin	↑	↑	↑	↑ [b]	↔	↔	↔	↔	↔	↔
	imipramine	↑ [a]	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↔
	nortriptyline	↑ [a]	↑	↑ [a]	↑ [ab]	↔	↔	↔	↔	↔	↔
	trimipramine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
TeCA	maprotiline	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	mianserine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔
Others	bupropion	↓	↓	↓57%	↓	↓55%	↔	↓	↔	↔	↔
	lamotrigine	↓32%	↓	↓50%	↓	↔	↔	↔	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↓	↓ E	↓	E	E	↔
	St John's wort	D	D	D	D	D	D	D	D	D	↔
	trazodone	↑	↑	↑	↑ [b]	↓	↓	↓	↔	↔	↔

Legend

↑ potential elevated exposure of the antidepressant
↓ potential decreased exposure of the antidepressant
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
a ECG monitoring is recommended
b coadministration contraindicated in the European SPC. However, US prescribing information recommends TDM for antidepressants. The charts reflect the more cautious option. Numbers refer to decreased AUC of the antidepressant as observed in drug-drug interactions studies.
SSRI selective serotonin reuptake inhibitors
SNRI serotonin and norepinephrine reuptake inhibitors
TCA tricyclic antidepressants
TeCA tetracyclic antidepressants

Colour legend

no clinically significant interaction expected.
these drugs should not be coadministered.
potential interaction which may require a dosage adjustment or close monitoring.
potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC). A dosage adjustment is *a priori* not recommended.

Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on www.hiv-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Drug-drug Interactions between Antihypertensives and ARVs

antihypertensives		ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	RAL	ABC	FTC	3TC	TDF	ZDV
ACE inhibitors	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↓	↓	↓	↓	↓	↓	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	losartan	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↑[b]	↑[b]	↔	↔	↔	↔	↔	↔	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↔[d]	↔	↔	↔	↔[d]	↔[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bisoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	carvedilol	↑↓[d]	↑↓	↑↓	↑↓	↑↓[d]	↑↓[d]	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	propanolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
calcium channel blockers	amlodipine	↑[c]	↑	↑	↑80%	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[c]	↑	↑	↑	↑	↑[c]	↓69%	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
	felodipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	lacidipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	nicardipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
	nifedipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	nisoldipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bendroflumethia-zide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chlortalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E	↔
	indapamide	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	torasemide	↓	↓	↓	↓	↓	↓	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Others	doxazosin	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	spironolactone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Legend

↑	potential elevated exposure of the antihypertensive
↓	potential decreased exposure of the antihypertensive
↔	no significant effect
D	potential decreased exposure of ARV drug
E	potential elevated exposure of ARV drug
a	[parent drug] decreased but [active metabolite] increased
b	[parent drug] increased but [active metabolite] decreased
c	ECG monitoring recommended
d	risk of PR interval prolongation

Numbers refer to decreased AUC of the antihypertensive as observed in drug-drug interactions studies.

Colour legend

- no clinically significant interaction expected.
- these drugs should not be coadministered.
- potential interaction which may require a dosage adjustment or close monitoring.
- potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC). A dosage adjustment is *a priori* not recommeded.

Note: although some drug interactions are predicted to potentially require a dosage adjustment based on the drug's metabolic pathway, clinical experience with a particular antihypertensive and ARV drug may indicate that dosage adjustments are not an *a priori* requirement.

Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on www.hiv-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Drug-drug Interactions between Analgesics and ARVs

	analgesics	ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	RAL	ABC	FTC	3TC	TDF	ZDV
non-opioid analgesics	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	j	↔
	celecoxib	↔	↔	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	j	↔
	diclofenac	↔	↔	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↑[j]	↔
	ibuprofen	↔	↔	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↑[j]	↔[b]
	mefenamic acid	↔	↔	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↑[j]	↔
	naproxen	↔	↔	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↑[j]	↔[b]
	nimesulide	↔	↔	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	j	↔
	paracetamol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	piroxicam	↔	↔	↔	[c]	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	j	↔
opioid analgesics	alfentanil	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	buprenorphine	↑67%	↑[d]	↔	↑	↔	↑	↓50%	↓25%	↔	↔	↔	↔	↔	↔	↔	↔	↔
	codeine	↑[g]	↑[g]	↑[g]	↑[g]	↑[g]	↑[g]	↓[g]	↓[g]	↓[g]	↔	↔	↔	↔	↔	↔	↔	↔
	dihydrocodeine	↓↑	↓↑	↓↑	↓↑	↓↑	↓↑	↓↑	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	fentanyl	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	methadone	↓[e]	↓16%	↓18%	↓	↓53%[e]	↓19%[ef]	↓52%	↑6%	↓≈50%	↓16%[e]	↔	↔	↓	↔	↔	↔	E
	morphine	↓	↓	↓	↓	↓	↓	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	oxycodone	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	pethidine	↓[h]	↓[h]	↓[h]	↓[ch]	↓[h]	↓[h]	↓[h]	↔	↓[h]	↔	↔	↔	↔	↔	↔	↔	↔
	sufentanil	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	tramadol	↑[g]	↑[g]	↑[g]	↑[g]	↑[g]	↑[g]	↓[i]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Legend

↑ potential elevated exposure of the analgesic
↓ potential decreased exposure of the analgesic
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
a clinical significance unknown. Use the lowest recommended dose particularly in persons with risk factors for cardiovascular disease, those persons at risk of developing gastrointestinal complications, persons with hepatic or renal impairment, and in elderly persons
b potential additive haematological toxicity
c manufacturer's recommendation
d [parent drug] unchanged but [metabolite] increased
e both drugs can potentially prolong the QT interval; ECG monitoring recommended
f coadministration contraindicated in the European SPC. However, US prescribing information advises caution. The charts reflect the more cautious option
g potential decrease of the analgesic effect due to the reduced conversion to the active metabolite
h [parent drug] decreased and increase [neurotoxic metabolite]
i [parent drug] decreased but no change [more active metabolite]
j potential risk of nephrotoxicity which is increased if NSAID is used for a long duration, if the person has a pre-existing renal dysfunction, has a low body weight or receives other drugs that may increase TDF exposure. Concurrent use of NSAIDs with TDF warrants monitoring of renal function. Numbers refer to increased or decreased AUC of the analgesic as observed in drug-drug interactions studies.

Colour legend

no clinically significant interaction expected.
these drugs should not be coadministered.
potential interaction which may require a dosage adjustment or close monitoring.
potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC). A dosage adjustment is *a priori* not recommeded.

Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on www.hiv-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Drug-drug Interactions between Antimalarial Drugs and ARVs

Antimalarial	Indication[i]	NNRTI EFV, NVP, ETV	RPV, RAL, MVC	PI COBI (C)
Mefloquine (M) CYP 3A4	P/T	↓	→	→ M may reduce PI/C (RTV ca 35%)
Artemisinins/ **Artemether (A)**[ii] CYP 2B6, 3A4, 2A6, 2C19	T	↓ A & Dihydroartemisin; A & metabolites reduce NVP, but not EFV/ETR	→ A may reduce RPV, MVC	↑ A monitor toxicity (liver)
Lumefantrin (L) CYP 3A4	T	↓	→	↑LPV increases L 2-3x
Atovaquone (At)[iii] **Proguanil (P)**[iv] CYP 2C19	P/T	↓ ETV is increased	→	↓ At & P take with fat meal, consider dose increase
Doxycycline	P	possibly ↓	→	→
Chloroquine CYP 3A4, 2D6	T	→	→	possibly ↑
Quinine (Q) CYP 3A4	T	↓ consider dose increase	→	↑ RTV increases Q 4x: consider dose reduction, monitor toxicity (tinnitus). **CAVE:** PI & Q prolong QT
Primaquine CYP 2E1, 2B6, 1A2, 2D6, 3A4	(P)/T	possibly ↑ haemolytic metabolites	→	NA

CYP: cytochrome p450 subtypes which the drug is metabolised via

Legend

↑↓ indicate effect of antiretrovirals on antimalarial drug/key metabolite

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

ii (A) Artemether and the key metabolite, dihydroartemisinin, are active compounds

iii (At) increases ZDV levels by 35%

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

Colour legend

- no clinically significant interaction expected
- potential interaction (consider treatment ahead of travel and therapeutic drug monitoring)
- clinically relevant interaction; do not use or use with caution

Dose Adjustment of ARVs for Impaired Hepatic Function

NRTIs	
ABC	**Child-Pugh Score** 5–6: 200 mg bd (use oral solution)
	Child-Pugh Score > 6: Contraindicated
ddI	Contraindicated
	If used no dosage adjustment
d4T	Contraindicated
	If used no dosage adjustment
FTC	No dosage adjustment
3TC	No dosage adjustment
TDF	No dosage adjustment
FTC + TDF	No dosage adjustment
ZDV	Reduce dose by 50% or double the interval between doses if Child-Pugh > 9
NNRTIs	
DLV	No dosage recommendation; use with caution in persons with hepatic impairment
EFV	No dosage adjustment; use with caution in persons with hepatic impairment
EFV + FTC + TDF	
ETV	**Child-Pugh score** < 10: no dosage adjustment
NVP	**Child-Pugh score** > 6: contraindicated

PIs	
ATV	Child-Pugh Score 7–9: 300 mg once daily
	Child-Pugh Score > 9: not recommended
	RTV boosting is not recommended in persons with hepatic impairment (Child-Pugh Score > 7)
DRV	Mild to moderate hepatic impairment: no dosage adjustment
	Severe hepatic impairment: not recommended
FPV	**PI-naive persons only:**
	Child-Pugh Score 5–9: 700 mg bd
	Child-Pugh Score 10–15: 350 mg bd
	PI-experienced persons:
	Child-Pugh Score 5–6: 700 mg bd + RTV 100 mg qd
	Child-Pugh Score 7–9: 450 mg bd + RTV 100 mg qd
	Child-Pugh Score 10–15: 300 mg bd + RTV 100 mg qd
IDV	Mild to moderate hepatic insufficiency: 600 mg q8h
LPV/r	No dosage recommendation; use with caution in persons with hepatic impairment
NFV	Mild hepatic impairment: no dosage adjustment
	Moderate to severe hepatic impairment: not recommended
RTV	Refer to recommendations for the primary PI
SQV	Mild to moderate hepatic impairment: use with caution
	Severe hepatic impairment: contraindicated
TPV	Child-Pugh score < 7: use with caution
	Child-Pugh score > 6: contraindicated
FI	
ENF	No dosage adjustment
CCR5 Inhibitor	
MVC	No dosage recommendations. Concentrations will likely be increased in persons with hepatic impairment
INSTI	
RAL	No dosage adjustment

Note: Hepatic dysfunction is a good indication for TDM as clinical experience with these dose adjustments is very limited

Dose Adjustment of ARVs for Impaired Renal function

		eGFR[i] (mL/min)				Haemodialysis
		≥ 50	30-49	10-29	< 10	
NRTIs						
ABC	300 mg q12h	No dose adjustment required	No dose adjustment required	No dose adjustment required		
ddI[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**	
d4T	> 60 kg	30 mg q12h	15 mg q12h	15 mg q24h	15 mg q24h	15 mg q24h AD[iv]
	< 60 kg	40 mg q12h	20 mg q12h	20 mg q24h	20 mg q24h	20 mg q24h AD[iv]
FTC		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h
3TC		300 mg q24h	150 mg q24h	100 mg q24h[iii]	50-25 mg q24h[iii]	50-25 mg q24h[iii] AD[iv]
TDF[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]
ZDV		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h
ABC/3TC		Use individual drugs				
ZDV/3TC						
ZDV/3TC/ABC						
FTC/TDF		q24h	q48h	Use individual drugs		
NNRTIs						
EFV		600 mg q24h	No dose adjustment required			
ETV		200 mg q12h	No dose adjustment required			
NVP		200 mg q12h	No dose adjustment required			

	eGFR[i] (mL/min)				Haemodialysis
	≥ 50	30-49	10-29	< 10	
PIs					
ATV/r	300/100 mg q24h	No dose adjustment required[v,vi]			
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required[v]			
FPV/r	700/100 mg q12h	No dose adjustment required[v]			
LPV/r	400/100 mg q12h	No dose adjustment required[v]			
SQV/r	1000/100 mg q12h	No dose adjustment required[v]			
TPV/r	500/200 mg q12h	No dose adjustment required[v]			
Other ART					
RAL	400 mg q12h	No dose adjustment required[v] (dose AD[iv])			
FTC/TDF/COBI/EVG	Do not initiate if eGFR < 70 mL/min	Discontinue if eGFR < 50 mL/min			
MVC: co-administered without CYP3A4 inhibitors[viii]	300 mg q12h	No dose adjustment required			
MVC: co-administered with CYP3A4 inhibitors[viii]	if eGFR < 80 mL/min 150 mg q24h[viii] except: 150 mg q12h if co-administered with FPV/r				

i eGFR according to the abbreviated MDRD (Modification of Diet in Renal Disease) formula. The Cockcroft-Gault (CG) equation may be used as an alternative.
ii Dose reduction if combined with TDF
iii 150 mg loading dose
iv AD: after dialysis
v Limited data available in persons 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

Administration of ARVs in Persons with Swallowing Difficulties

Drug	Formulation	Crush tablets	Open capsules	Comment
NRTI				
ABC	tablet (300 mg) solution 20 mg/mL	yes		bitter taste
ddI	capsule (125, 200, 250, 400 mg)	no	no	use powder: contains Ca and Mg antacids, dissolve in ≥ 30 mL of water (add apple juice), take on empty stomach
d4T	capsule (20, 30, 40 mg) oral solution 1 mg/mL	no	yes	take on empty stomach
FTC	capsule (200 mg) solution 10 mg/mL	no	yes	dissolve in ≥ 30 mL of water, contains Na 460 µmol/mL Bioequivalence: 240 mg solution = 200 mg capsule adjust dosage accordingly
3TC	tablet (150, 300 mg) solution 10 mg/mL	yes		
TDF	tablet (245 mg)	yes		better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste)
ZDV	capsule (250 mg)	no	no	sticky, bitter taste
	syrup 10 mg/mL			better: use syrup or iv 6 mg/kg per day in glucose 5%
FTC/TDF	tablet (200/245 mg)	yes		better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste)
3TC/ABC	tablet (300/600 mg)	no		use solution of individual compounds
3TC/ZDV	tablet (150/300 mg)	yes		disperse in ≥ 15 mL water, alternative: use solution of individual compounds
3TC/ABC/ZDV	tablet (150/300/300 mg)	no		use solution of individual compounds
NNRTI				
EFV	tablet (600 mg)	yes		difficult to dissolve; solution has lower bioavailability; if > 40 kg use 720 mg
	capsule (50, 100, 200 mg)	no	yes	
	solution 30 mg/mL			
ETV	tablet (200 mg)	no		disperse in ≥ 5 mL water
NVP	tablet (200, 400 mg[(i)]) suspension 10 mg/mL	yes[(i)]		dissolve in water
FTC/TDF/ EFV	tablet (200/245/600 mg)	no		
FTC/TDF/RPV	tablet (200/245/25 mg)	no		
PI				
ATV	capsule (150, 200, 300 mg)	no	yes	difficult to open; take with food
DRV	tablet (400, 600 mg) solution 100 mg/mL	yes		take with food
FPV	tablet (700 mg) suspension 50 mg/mL			bitter taste; adults take suspension on empty stomach
IDV	capsule (200, 400 mg)	no	no	
LPV/r	tablet (200/50 mg) solution 80, 20 mg/mL	no		42% alcohol, do not dilute with water (risk of precipitation), rinse with milk (no water); take with food, bitter taste: dilute with chocolate milk
NFV	tablet (250 mg)	yes		difficult to dissolve; better: use powder
RTV	tablet (100 mg) solution 80 mg/mL	no		43% alcohol, do not dilute solution (risk of precipitation), rinse with milk (no water); bitter taste; take with food
SQV	tablet (500 mg)	no		
	capsule (200 mg)	no	yes	
TPV	capsule (250 mg) solution 100 mg/mL	no	no	higher bioavailability of oral solution: no dosing recommendation for adults
Others				
MVC	tablet (150, 300 mg)	yes		
RAL	tablet (400 mg)	yes		bitter taste
FTC/TDF/ EVG/COBI	tablet (200/245/150/150 mg)	no		

Drug	Formulation	Crush tablets	Open capsules	Comment
Prophylaxis/treatment of opportunistic infections				
Azithromycin	tablet (250 mg) suspension 40 mg/mL	no		
Cotrimoxazole	tablet (400/80 mg, forte 800/160 mg) solution 40/8 mg per mL	yes; forte difficult		dilute solution 3-5 times with water (high osmolality)
Fluconazole	capsule (50-200 mg) suspension 40 mg/mL	no	yes	
Pyrimethamine	tablet (25 mg)	yes		take with food
Valganciclovir	tablet (450 mg)	no	no	difficult to dissolve
Rifampicin	tablet (450, 600 mg)	yes		take on empty stomach
	capsule (150, 300 mg)	no	yes	
	suspension 20 mg/mL			
Rifabutin	capsule (150 mg)	no	yes	dissolve in water
Isoniazid	tablet (100, 150, 300 mg)	yes		take on empty stomach
Pyrazinamide	tablet (500 mg)	yes		
Ethambutol	tablet (100, 400 mg)	yes		difficult to dissolve better: use iv solution
Rifampicin/Isoniazid	tablet (150/100, 150/75 mg)	yes		take on empty stomach
Rifater (Rifampicin, Isoniazid, Pyrazinamide)	tablet (120/50/300 mg)	yes		take on empty stomach
Rimstar (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol)	tablet (150/75/400/275 mg)	yes		take on empty stomach
Ribavirin	capsule (200 mg)	no	yes	disperse in orange juice, take with food

i Extended release effect lost. Note: NVP 400 mg once daily (immediate release) can lead to sub-therapeutic trough levels in individuals with higher body weight (≥ 90 kg) compared to NVP 200 mg twice daily. Therefore, twice-daily NVP administration should be preferred in individuals with higher body weight

Part III Prevention and Management of Co-morbidities in HIV-positive Persons

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 guidance focuses on preventive and/or management principles other than use of antivirals and other anti-infectious agents in adult and adolescent HIV-positive persons. These co-morbidities are becoming increasingly important for HIV-positive persons as a consequence of increased life expectancy resulting from effective ART. Several demonstrated and proposed HIV-associated risk factors may contribute to their development, which include residual immunodeficiency, immune activation, inflammation and coagulation, co-infections (e.g. HCV, CMV) that may persist in spite of controlled HIV replication, as well as adverse effects of ART.

Health care professionals involved with the care of HIV-positive persons who are not familiar with the use of ART should consult HIV specialists before introducing or modifying any type of medication for co-morbidity in an HIV-positive person.

Conversely, many HIV physicians are not specialists in 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 this document.

Preventing or managing these co-morbidities 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 ARVs should always be carefully considered prior to introducing any other medication, see page 17, www.hiv-druginteractions.org and online documents refered to in the text.

These recommendations are intended to provide the best guide to clinical management, and it is recognised that the level of evidence to support the recommendations may vary substantially. Indeed, there is limited evidence from randomised controlled trials on best management of co-morbidities in HIV. As a result, current management is mainly derived from general medical guidelines. These recommendations 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 recommendations will be regularly updated as required. The online version at www.eacsociety.org and the EACS Guidelines App contain more detailed information and links to other relevant websites; these will be regularly updated.
The current recommendations highlight co-morbidities that are seen frequently in the routine care of HIV-positive persons and those for which specific issues should be considered.

Drug Dependency and Drug Addiction

Characteristics of drugs used as opioid substitution therapy (OST)[i]

Feature	Methadone	Buprenorphine
Dose required to prevent withdrawal symptoms according to degree of opioid dependency	Linear relationship (from 10-300 mg per 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: ↓ 50% • ETV: ↓ < 10% • LPV/r: ↓ 50% • SQV/r, DRV/r, FPV/r: ↓ 15-25% • 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 • EFV: ↓ up to 50% (B) and 70% (N) • ATV/r, IDV, SQV/r: ↑ 50-100% (B&N) • DRV/r: ↑ 50% (N) • **CAVE:** B reduces ATV; do not use without ritonavir or cobicistat boosting
	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)[ii]	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 See Drug-drug Interactions between Analgesics and ARVs

ii 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).

Cancer: Screening Methods[(i)]

Problem	Persons	Procedure	Evidence of benefit	Screening interval	Additional comments
Anal cancer	MSM	Digital rectal exam ± PAP test	Unknown; advocated by some experts	1-3 years	If PAP test abnormal, anoscopy
Breast cancer	Women 50-70 years	Mammography	↓ Breast cancer mortality	1-3 years	
Cervical cancer	Sexually active women	PAP test	↓ Cervical cancer mortality	1-3 years	Target age group should include the 30 to 59-year age range at least. Longer screening interval if prior screening tests repeatedly negative
Colorectal cancer	Persons 50-75 years	Faecal occult blood test	↓ Colorectal cancer mortality	1-3 years	Benefit is marginal
Hepatocellular carcinoma	Persons with cirrhosis & Persons with HBV irrespective of fibrosis stage	Ultrasound and alpha-foetoprotein	Earlier diagnosis allowing for improved ability for surgical eradication	Every 6 months	
Prostate cancer	Men > 50 years	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-positive persons 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.

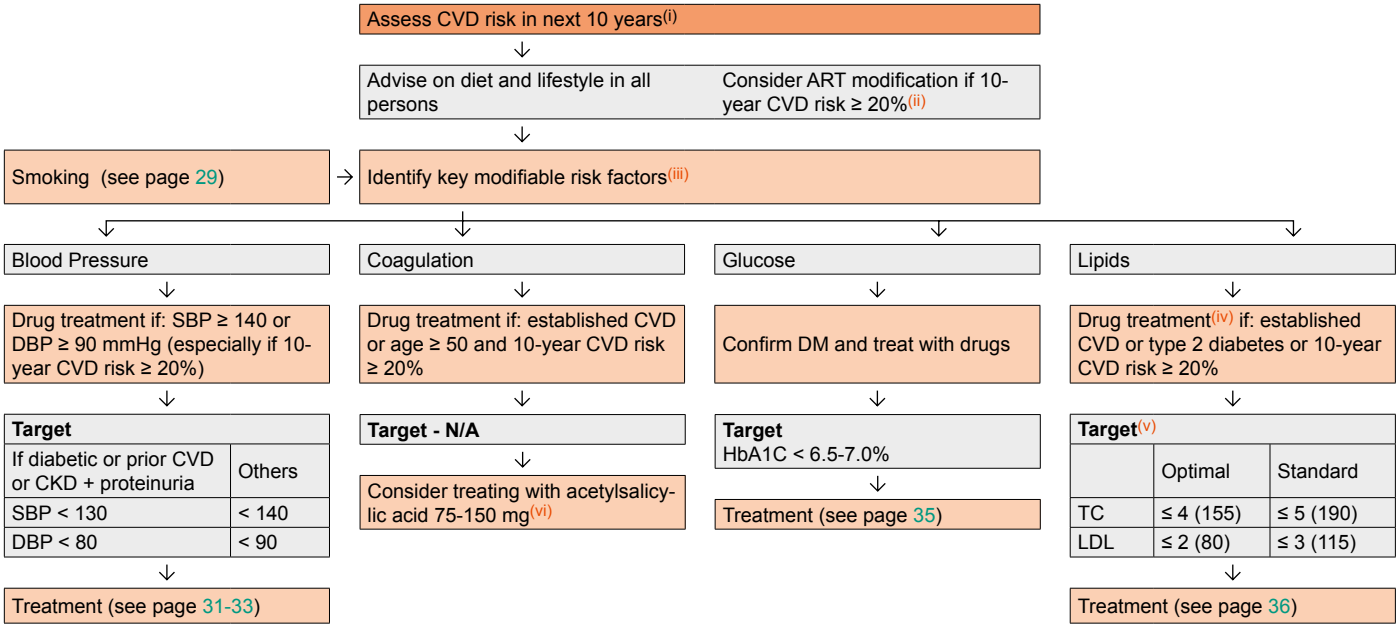
Lifestyle Interventions[i]

Smoking cessation	• Brief unambiguous statement about need to stop smoking • If person 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 person is contemplating, try to fix stop date, establish reward system • Use nicotine substitution (patch, chewing gum, spray), varenicline or bupropion during weaning phase if necessary. Note: both varenicline and bupropion may cause central nervous system side effects including suicide; bupropion may interact with PIs and NNRTIs, see page 17. • Consider referring person 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 • Cut back on beverages and foods with added sugar. • Choose and prepare foods with little or no salt. Aim to eat less than 1,500 mg of sodium per day. • 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 persons with HIV-related wasting and dyslipidaemia, address wasting first and consider referral to dietician • Persons 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
	• The following questions are helpful to determine average alcohol intake **1.** How often do you drink alcohol: never, ≤ 1/month, 2-4x/month, 2-3x/week, > 4x/week **2.** If you drink alcohol, how much typically at a time: 1-2, 3-4, 5-6, 7-9, > 10 drinks **3.** How many times do you have 6 or more alcoholic drinks at one occasion: never, < 1/month, 1x/month, 1x/week, more or less daily. • Intake of alcohol should be restricted to no more than one drink per day for women and two drinks per day for men (< 20-40 g/d). • In particular, persons with hepatic disease, adherence problems, inadequate CD4 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

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 persons with a history of CVD.



i Use the Framingham equation or whatever system local National Guidance recommends; a risk equation developed from HIV populations is available: see www.cphiv.dk/tools.aspx. This assessment and the associated considerations outlined in this figure should be repeated annually in all persons under care, see page 4-5, 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 another PI/r known to cause less metabolic disturbances, see page 15-16
(2) Replace d4T and consider replacing 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 about 50% less risk of IHD – and this is additive to other interventions.

iv See discussion on drug treatment of persons 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 page 36.

vi Evidence for benefit when used in persons without a history of CVD (including diabetics) is less compelling. BP should be reasonably controlled before aspirin use in such a setting.

Hypertension: Diagnosis and Grading

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 DBP 100-109**	**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	Lifestyle changes for several months[ii], then drug therapy	Immediate drug therapy and lifestyle changes[ii]
1-2 risk factors[iii]	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	Lifestyle changes for several months[ii], then drug therapy	Immediate drug therapy and lifestyle changes[ii]
3 or more risk factors[iii] or target organ disease[iv] or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
	Lifestyle changes[ii]	Drug therapy and lifestyle changes[ii]	Drug therapy and lifestyle changes[ii]	Drug therapy and lifestyle changes[ii]	Immediate drug therapy and lifestyle changes[ii]
Associated clinical conditions[v]	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk
	Drug therapy and lifestyle changes[ii]	Immediate drug therapy and lifestyle changes[ii]	Immediate drug therapy and lifestyle changes[ii]	Immediate drug therapy and lifestyle changes[ii]	Immediate drug therapy 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 page 29.
Table adapted from [1].

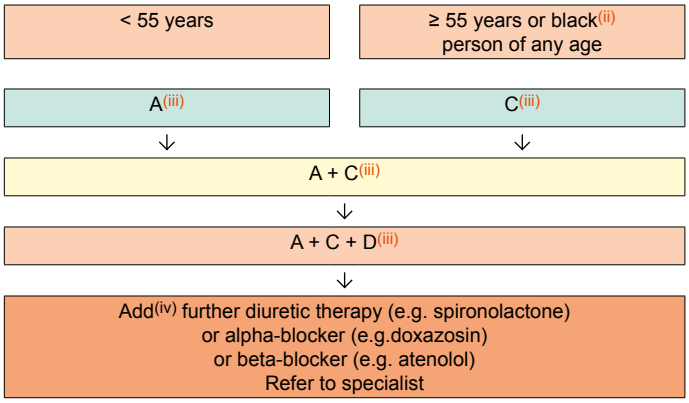
iii Risk factors include age (> 45 years for men; > 55 years for women), smoking, family history of premature CVD and dyslipidaemia.

vi Target organ disease: left ventricular hypertrophy, ultrasound evidence of arterial wall thickening, microalbuminuria.

v Associated clinical conditions: CVD, IHD, CKD, peripheral vascular disease, advanced retinopathy.

Hypertension: Management

Choosing drugs[i] for persons 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 or if deemed at high risk of heart failure, 'D' drugs can be used instead. Where a C drug is preferred but not tolerated, Verapamil or Diltiazem may be used (note: dose with caution with PIs as these may increase plasma concentrations of these calcium-channel blockers, potentially leading to toxic reactions)

D Thiazide-type diuretic* e.g. Indapamide or Chlorthalidone

i Some calcium-channel blockers interact marginally with the pharmacokinetics of ARVs, see Drug-drug Interactions between Antihypertensives and ARVs

ii Black persons are those of African or Caribbean descent, and not mixed race, Asian or Chinese persons

iii Wait 2-6 weeks to assess whether target, see page 30, is achieved; if not, go to next step

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

* This excludes thiazides (e.g. HCTZ, Bendroflumethiazide etc.)

Drug-drug Interactions between Antihypertensives and ARVs

antihypertensives		ATV/r	DRV/r	FPV/r	IDV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	RAL	ABC	FTC	3TC	TDF	ZDV
ACE inhibitors	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↓	↓	↓	↓	↓	↓	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	losartan	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↓[a]	↑[b]	↑[b]	↔	↔	↔	↔	↔	↔	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↔[d]	↔	↔	↔	↔[d]	↔[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bisoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	carvedilol	↑↓[d]	↑↓	↑↓	↑↓	↑↓[d]	↑↓[d]	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	propanolol	↑[d]	↑	↑	↑	↑[d]	↑[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
calcium channel blockers	amlodipine	↑[c]	↑	↑	↑80%	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[c]	↑	↑	↑	↑	↑[c]	↓69%	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
	felodipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	lacidipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	nicardipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
	nifedipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	nisoldipine	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑[c]	↑	↑	↑	↑	↑[c]	↓	↓E	↓	E	E	↔	↔	↔	↔	↔	↔
diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bendroflumethia-zide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chlortalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E	↔
	indapamide	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	torasemide	↓	↓	↓	↓	↓	↓	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Others	doxazosin	↑	↑	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔
	spironolactone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Legend

↑ potential elevated exposure of the antihypertensive
↓ potential decreased exposure of the antihypertensive
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
a [parent drug] decreased but [active metabolite] increased
b [parent drug] increased but [active metabolite] decreased
c ECG monitoring recommended
d risk of PR interval prolongation

Numbers refer to decreased AUC of the antihypertensive as observed in drug-drug interactions studies.

Colour legend

- no clinically significant interaction expected.
- these drugs should not be coadministered.
- potential interaction which may require a dosage adjustment or close monitoring.
- potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC). A dosage adjustment is *a priori* not recommeded.

Note: although some drug interactions are predicted to potentially require a dosage adjustment based on the drug's metabolic pathway, clinical experience with a particular antihypertensive and ARV drug may indicate that dosage adjustments are not an *a priori* requirement.

Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on www.hiv-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

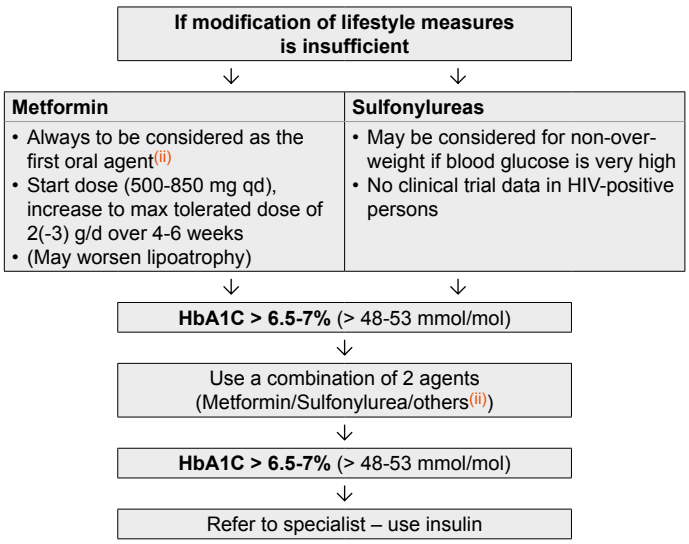
Type 2 Diabetes: Diagnosis

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] (mmol/mol)
Diabetes	≥ 7.0 (126) OR →	≥ 11.1 (200)	≥ 6.5% (≥ 48)
Impaired glucose tolerance (IGT)	< 7.0 (126) AND →	7.8 – 11.0 (140-199)	Prediabetes 5.7-6.4% (39-47)
Impaired fasting glucose (IFG)	5.7– 6.9 (100-125)	< 7.8 (140)	

i As defined by WHO and [2]
ii An abnormal finding should be repeated before confirming the diagnosis
iii Recommended in persons with fasting blood glucose of 5.7 - 6.9 mmol/L (100-125 mg/dL) as it may identify persons with overt diabetes
iv Do not use HbA1c in presence of haemoglobinopathies, 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 %). HbA1c values in treated HIV-persons, particularly when on ABC, tend to underestimate type 2 diabetes. Both IGT and IFG increase CVD morbidity and mortality, and increase the risk of developing diabetes by 4-6 fold. These persons should be targeted for lifestyle intervention, and their CVD risk factors must be evaluated and treated.

Type 2 Diabetes[i]: Management



Treatment goals:

Prevention of hyper-/hypoglycaemia, glucose control (HbA1c < 6.5-7% without hypoglycaemia, fasting plasma glucose 4-6 mmol/L (73-110 mg/dL), prevention of long-term complications

- Normal blood lipids, see page 30, and blood pressure < 130/80 mmHg, see page 31.
- Acetylsalicylic acid (75-150 mg/d) considered in diabetics with elevated underlying CVD risk, see page 30.
- Nephropathy, polyneuropathy and retinopathy screening should be performed as in diabetic persons without HIV
- Consultation with a specialist in diabetology is recommended

i Type 1 diabetes should be treated according to national guidelines.

ii Very limited data for any oral antidiabetic agents in terms of CVD prevention, and no data in HIV-positive persons. Incretins (DDP4 inhibitors [e.g. Saxagliptin, Sitagliptin] and GLP-1 agonists [e.g. Liraglutide & Exenatide] are currently being evaluated in several major morbidity/mortality studies; no clinically significant drug-drug interaction or adverse effects on CD4 cell counts expected; clinical use of Pioglitazone questioned by its side effects; HbA1c targets up to 7.5% can be considered for older persons with long-standing type 2 diabetes and evidence of CVD.

Dyslipidaemia

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 probably true for HDL-c but trial data are less compelling. The CVD risk implications from higher than normal TG levels are even less clear, as TG has not consistently been shown to independently predict the risk of CVD. Furthermore, the clinical benefit of treating moderate hypertriglyceridaemia is uncertain; very high TG (> 10 mmol/L or > 900 mg/dL) may increase risk of pancreatitis.

Diet (more fish), exercise, maintaining normal body weight, reducing alcohol intake and stopping smoking tends to improve HDL and triglyceride levels. Reducing dietary saturated fat intake improves LDL-levels; if not effective, consider change of ART then consider lipid-lowering medication, see page 30. Statins should be used by all those with established vascular disease and among those with type 2 diabetes or at high risk of CVD, irrespective of lipid levels.

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 page 30. 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 ARV 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

Bone Disease: Screening and Diagnosis

CONDITION	CHARACTERISTICS	RISK FACTORS	DIAGNOSTIC TESTS
Osteopenia • Postmenopausal women and men aged ≥ 50 years with T-score -1 to -2.5 **Osteoporosis** • Postmenopausal women and men aged ≥ 50 years with T-score ≤ -2.5 • Premenopausal women and men aged < 50 years with Z-score ≤ -2 and fragility fracture	• Reduced bone mass • Increased prevalence of fractures in people with HIV • 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 • Greater loss of BMD with initiation of certain ARVs[i]	Consider classic risk factors[ii] Consider DXA in any person with ≥ 1 of:[iii] 1. Postmenopausal women 2. Men ≥ 50 years 3. History of low impact fracture 4. High risk for falls[iv] 5. Clinical hypogonadism (symptomatic, see Sexual Dysfunction) 6. Oral glucocorticoid use (minimum 5 mg/d 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-positive persons • Consider using HIV as a cause of secondary osteoporosis[v]	**DXA scan** **Rule out causes of secondary osteoporosis if BMD abnormal**[vi] **Lateral spine X-rays** (lumbar and thoracic) if low spine BMD, osteoporosis on DXA, or significant height loss or kyphosis develops. (DXA-based vertebral fracture assessment [VFA] can be used as an alternative to lateral spine X-ray).
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	• Dark skin • Dietary deficiency • Avoidance of sun exposure • Malabsorption • Obesity • Renal phosphate wasting[vii]	Measure 25(OH) vitamin D in all persons at presentation ng/ml / nmol/L Deficiency: < 10 / < 25 Insufficiency: < 20 / < 50 If deficient or insufficient, check PTH levels Consider vitamin D replacement if clinically indicated, see page 38
Osteonecrosis	• Infarct of epiphyseal plate of long bones resulting in acute bone pain • Rare but increased prevalence in HIV	**Risk factors:** • Low CD4 cell counts • Glucocorticoid exposure • IVDU	**MRI**

i Greater loss of BMD observed with initiation of regimens containing TDF and some PIs. Additional loss and gains in BMD observed with switch to and away from TDF-containing ARV regimens, respectively. Clinical relevance to fracture risk not determined.

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

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

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

v Although use of HIV as a secondary risk factor in FRAX® has not been validated, including HIV as a secondary cause in a risk assessment will help to estimate risk in persons with risk factors for fracture along with low BMD.

vi Causes of secondary osteoporosis include hyperparathyroidism, hyperthyroidism, malabsorption, hypogonadism/amenorrhoea, diabetes mellitus, chronic liver disease.

vii For diagnosis and management of renal phosphate wasting, see Indications and Tests for Proximal Renal Tubulopathy (PRT).

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 hydroxy vitamin D (25(OH) vitamin D) If deficient, consider checking parathyroid hormone (PTH), calcium, phosphate[iii], alkaline phosphatase	If vitamin D deficient, replacement recommended. Various regimens suggested[iv] Consider re-checking 25(OH) vitamin D levels 3 months after replacement. After replacement, maintenance with 800-2000 IU vitamin D daily.
Vitamin D deficiency prevalent in both HIV+ and HIV- populations – may not be directly associated with HIV. **Factors associated with lower vitamin D:** • Dark skin • Dietary deficiency • Avoidance of sun exposure • Malabsorption • Obesity • Chronic kidney disease • Some ARVs[v]	Check vitamin D status in persons with history of: • low bone mineral density and/or fracture • high risk for fracture Consider assessment of vitamin D status in persons with other factors associated with lower vitamin D levels (see left column)	Replacement and/or supplementation of 25(OH) vitamin D is recommended for persons 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 (in winter approximately 20% lower than in 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 page 41. A combination of low calcium + low phosphate +/- high alkaline phosphatase may indicate osteomalacia and vitamin D deficiency.

iv Expect that 100 IU vitamin D daily leads to an increase in serum 25(OH) vitamin D of approximately 1 ng/mL. Some experts prefer a loading dose of e.g. 10,000 IU vitamin D daily for 8-10 weeks in persons with vitamin D deficiency. The principal goal is to achieve a serum level > 20 ng/mL (50 nmol/L) and to maintain normal serum PTH levels. Combine with calcium where potential for insufficient dietary calcium intake. The therapeutic aim is to maintain skeletal health; vitamin D supplementation has not been proven to prevent other co-morbidities in HIV-positive persons.

v The role of HIV-therapy or specific drugs remains unclear. Some studies suggest an association of EFV with reductions in 25(OH)D but not 1.25(OH)D. PIs may also affect vitamin D status by inhibiting conversion of 25(OH)D to 1.25(OH)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

Approach to Fracture Reduction in HIV-positive Persons

Reducing risk of fractures	• Aim to decrease falls by addressing fall risks(i) • Ensure sufficient dietary calcium (1-1.2 g daily) and vitamin D (800-2,000 IU daily) intake(ii) • Where appropriate, screen for osteoporosis(iii) and refer to national/regional guidelines on treatment of osteoporosis – If no guidelines available, consider bisphosphonate(iv) treatment in all osteoporotic postmenopausal women and men > 50 years old (BMD T-score ≤ -2.5) and those with a history of fragility fracture. Consider treatment based on BMD alongside consideration of other risk factors for fracture, especially age. – Use bisphosphonate and ensure adequate calcium and vitamin D intake – No significant interactions between bisphosphonates and antiretrovirals – If antiretroviral naive, consider options for ART that preserve BMD(v) – If diagnosed with osteoporosis and requiring therapy, consider optimising ART to preserve or improve BMD(vi) • In complicated cases (e.g. young men, premenopausal women, recurrent fracture despite bone protective therapy), refer to osteoporosis specialist • If on bisphosphonate treatment, repeat DXA after 2 years and reassess need for continued treatment after 3-5 years

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

ii See page 38 for diagnosis and management of vitamin D deficiency.

iii See page 37 for screening and diagnosis of bone disease in HIV.

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

v BMD loss is greatest in the first year after ART initiation, with more BMD loss with ART regimens containing TDF and some PIs. Consider relative risk/benefit of using these agents in persons with high fracture risk.

vi In persons on effective ART, a switch to TDF can lead to further BMD loss while a switch away from TDF (alongside optimisation of vitamin D status) in one study of older men with low BMD resulted in increased BMD.

Kidney Disease: Diagnosis and Management

Diagnosis of Kidney Disease

		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 Kidney Disease[vi]

Prevention of progressive renal disease	Comment
1. ART	Start ART immediately where HIV-associated nephropathy (HIVAN)[vii] or HIV immune complex disease strongly suspected. Immunosuppressive therapy may have a role in immune complex diseases. 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 abbreviated MDRD based on serum creatinine, gender, age and ethnicity. The Cockcroft-Gault (CG) equation may be used as an alternative.
If not previously known to have CKD, confirm pathological eGFR within 2 weeks. Use of Cobicistat, but also PIs, is associated with an increase in serum creatinine/reduction of eGFR due to inhibition of proximal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1-2 months

ii Urinalysis: use urine dipstick to screen for haematuria. To screen for proteinuria, use urine dipstick and if ≥ 1+ check urine protein/creatinine (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 urine albumin/creatinine (UA/C), see note[iii]

iii UP/C in spot urine 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. TDF). If both UP/C and UA/C are measured, UP/C > UA/C suggests tubular proteinuria. Screening values for UA/C are: < 30, 30-70 and > 70. UA/C should be monitored in persons with diabetes. 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 Repeat eGFR and urinalysis as per screening table, see page 5

v See Dose Adjustment of ARVs for Impaired Renal Function

vi Joint management with a nephrologist

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

viii See page 36

ix See page 34-35

ARV-associated Nephrotoxicity

Renal abnormality*	ARV	Management
Proximal tubulopathy with any combination of: 1. Proteinuria: urine dipstick ≥ 1, or confirmed increase in UP/C > 30 mg/mmol(i) 2. Progressive decline in eGFR and eGFR < 90 mL/min(ii) 3. Phosphaturia(iii): confirmed hypophosphataemia secondary to increased urine phosphate leak	**TDF**	**Assessment:** • Tests for proximal renal tubulopathy/renal Fanconi syndrome(iii) • Consider renal bone disease if hypophosphataemia of renal origin: measure 25(OH) vitamin D, PTH, DEXA **Consider stopping TDF if:** • Progressive decline in eGFR and no other cause • Confirmed hypophosphataemia of renal origin and no other cause • Osteopenia/osteoporosis in the presence of increased urine phosphate leak
Nephrolithiasis: 1. Crystalluria 2. Haematuria(iv) 3. Leucocyturia 4. Loin pain 5. Acute renal insufficiency	**IDV** **ATV** **(DRV)**	**Assessment:** • Urinalysis for crystalluria/stone analysis • Exclude other cause for nephrolithiasis • Renal tract imaging including CT scan **Consider stopping IDV/ATV if:** • Confirmed renal stones • Recurrent loin pain +/- haematuria
Interstitial nephritis: 1. Progressive decline in eGFR(ii) 2. Tubular proteinuria(iii)/ haematuria 3. Eosinophiluria (if acute)	**IDV** **ATV**(v)	**Assessment:** • Renal ultrasound • Refer nephrologist **Consider stopping IDV/ATV if:** • Progressive decline in eGFR and no other cause

* Use of COBI, but also PIs, is associated with an increase in serum creatinine/reduction of eGFR due to inhibition of proximal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1-2 months

i UP/C in spot urine 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, according to the abbreviated MDRD (Modification of Diet in Renal Disease) formula. The Cockcroft-Gault (CG) equation may be used as an alternative.

iii See Indications and Tests for Proximal Renal Tubulopathy (PRT)

iv Microscopic haematuria is usually present

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

Dose Adjustment of ARVs for Impaired Renal function

		eGFR[i] (mL/min)				Haemodialysis
		≥ 50	30-49	10-29	< 10	
NRTIs						
ABC	300 mg q12h	No dose adjustment required	No dose adjustment required	No dose adjustment required		
ddI[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**	
d4T	> 60 kg	30 mg q12h	15 mg q12h	15 mg q24h	15 mg q24h	15 mg q24h AD[iv]
	< 60 kg	40 mg q12h	20 mg q12h	20 mg q24h	20 mg q24h	20 mg q24h AD[iv]
FTC		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h
3TC		300 mg q24h	150 mg q24h	100 mg q24h[iii]	50-25 mg q24h[iii]	50-25 mg q24h[iii] AD[iv]
TDF[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]
ZDV		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h
ABC/3TC		Use individual drugs				
ZDV/3TC						
ZDV/3TC/ABC						
FTC/TDF		q24h	q48h	Use individual drugs		
NNRTIs						
EFV		600 mg q24h	No dose adjustment required			
ETV		200 mg q12h	No dose adjustment required			
NVP		200 mg q12h	No dose adjustment required			

	eGFR[i] (mL/min)				Haemodialysis
	≥ 50	30-49	10-29	< 10	
PIs					
ATV/r	300/100 mg q24h	No dose adjustment required[v,vi]			
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required[v]			
FPV/r	700/100 mg q12h	No dose adjustment required[v]			
LPV/r	400/100 mg q12h	No dose adjustment required[v]			
SQV/r	1000/100 mg q12h	No dose adjustment required[v]			
TPV/r	500/200 mg q12h	No dose adjustment required[v]			
Other ART					
RAL	400 mg q12h	No dose adjustment required[v] (dose AD[iv])			
FTC/TDF/COBI/EVG	Do not initiate if eGFR < 70 mL/min	Discontinue if eGFR < 50 mL/min			
MVC: co-administered without CYP3A4 inhibitors[viii]	300 mg q12h	No dose adjustment required			
MVC: co-administered with CYP3A4 inhibitors[viii]	if eGFR < 80 mL/min 150 mg q24h[viii] except: 150 mg q12h if co-administered with FPV/r				

i eGFR according to the abbreviated MDRD (Modification of Diet in Renal Disease) formula. The Cockcroft-Gault (CG) equation may be used as an alternative.
ii Dose reduction if combined with TDF
iii 150 mg loading dose
iv AD: after dialysis
v Limited data available in persons 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 TDF if
• Progressive decline in eGFR[i] & eGFR < 90 mL/min & no other cause and/or • Confirmed hypophosphataemia[ii] and/or • Confirmed increase in UP/C[iii] • Renal insufficiency even if stable (eGFR < 60 mL/min) • 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 according to the abbreviated MDRD formula (Modification of Diet in Renal Disease). The Cockcroft-Gault (CG) equation may be used as an alternative.

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, 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 TDF 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

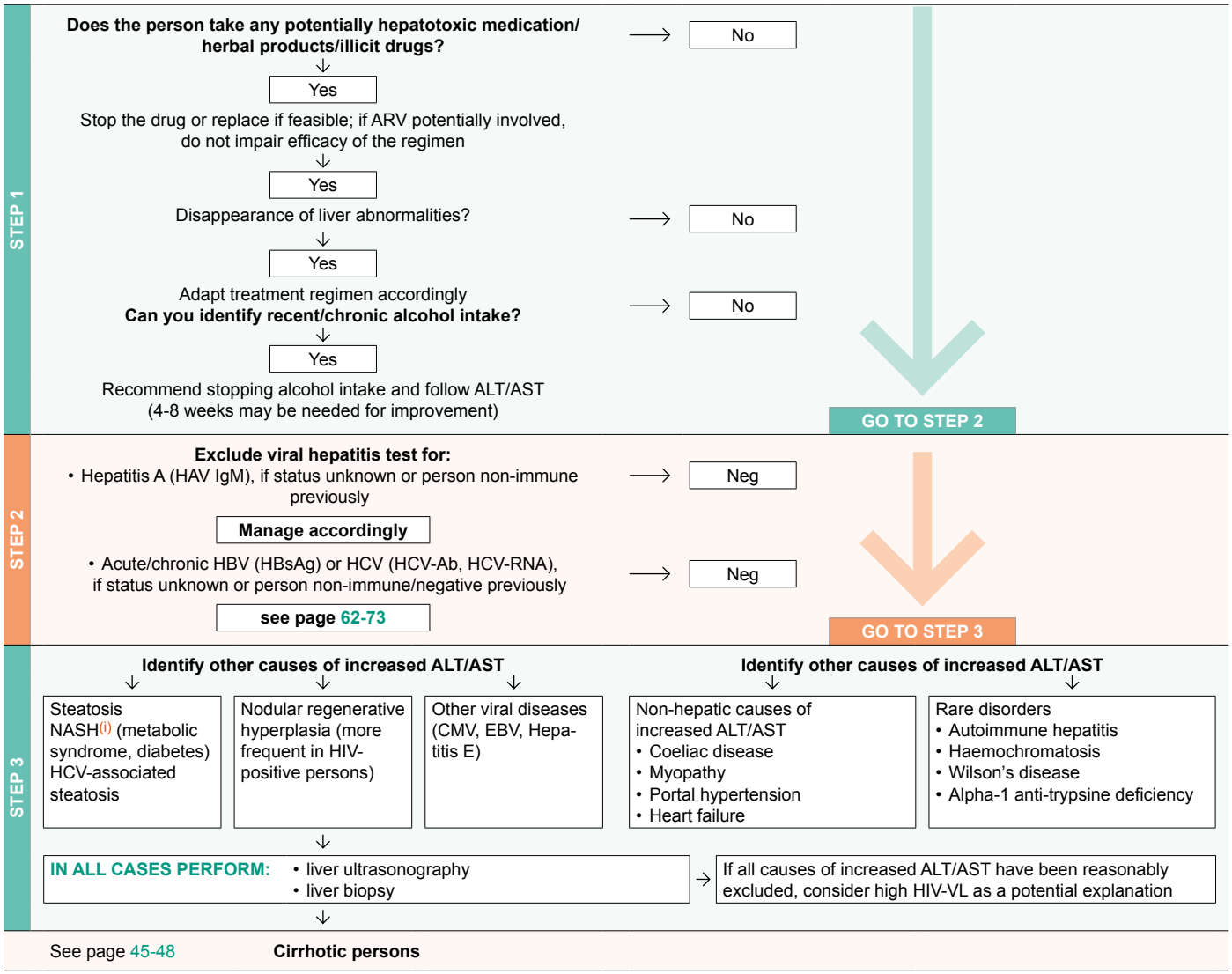
vi Quantified as fractional excretion of phosphate (FEPhos): (PO_4(urine) / PO_4(serum)) / (Creatinine(urine) / Creatinine(serum)) in a spot urine sample collected in the morning in fasting state. Abnormal > 0.2 (> 0.1 with serum phosphate < 0.8 mmol/L)

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

viii Fractional excretion of uric acid (FEUricAcid): (UricAcid(urine) / UricAcid(serum) / (Creatinine(urine) / Creatinine(serum)) in a spot urine sample collected in the morning in fasting state; abnormal > 0.1

Work-up and Management of HIV-positive Persons with Increased ALT/AST

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



i Nonalcoholic steatohepatitis

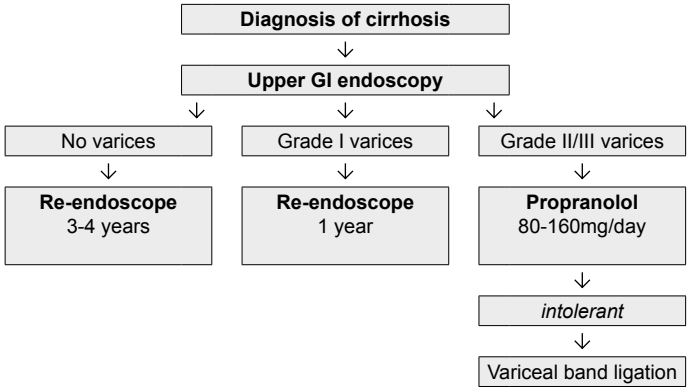
Liver Cirrhosis: Classification and Surveillance

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



Liver Cirrhosis: Management

Management of HIV-positive persons with cirrhosis should be done in collaboration with experts in liver diseases. More general management guidance is described below.
For dosage adjustment of antiretrovirals, see Dose Adjustment of ARVs for Impaired Hepatic Function.
In end-stage liver disease (ESLD), use of EFV may increase risk of CNS symptoms.
ART, if otherwise indicated, also provides net benefit to cirrhotic persons.
See Diagnosis and Management of Hepatorenal Syndrome (HRS).

Management of hypervolaemic hyponatraemia	Management strategy of hepatic encephalopathy (HE)
1. Fluid restriction: 1000-1500 mL/day (consumption of bouillon allowed ad libitum) 2. If fluid restriction is ineffective, consider use of oral Tolvaptan a. To be started in hospital at 15 mg/day for 3-5 days, then titrated to 30-60 mg/day until normal s-Na; duration of treatment unknown (efficacy/safety only established in short-term studies (1 month)) b. S-Na should be monitored closely, particularly after initiation, dose modification or if clinical status changes. c. Rapid increases in s-Na concentration (> 8 mmol/day) should be avoided to prevent osmotic demyelisation syndrome d. Persons may be discharged after s-Na levels are stable and without need to further adjust dose	**General management** 1. Identify and treat precipitating factor (GI haemorrhage, infection, pre-renal azotaemia, constipation, sedatives) 2. Short-term (< 72 hours) protein restriction may be considered if HE is severe **Specific therapy** Lactulose 30 cm³ orally every 1-2h until bowel evacuation, then adjust to a dosage resulting in 2-3 formed bowel movements per day (usually 15-30 cm³ orally bd) Lactulose enemas (300 cm³ in 1L of water) in persons who are unable to take it orally. 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, qd) in persons with **1)** an ascites protein level of < 1.5 mg/dL, **2)** impaired renal function (serum creatinine level > 1.2 mg/dL, BUN > 25 mg/dL), **3)** s-Na level < 130mE g/L), or **4)** severe liver failure (Child Pugh score > 9 points with s-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 persons with tense ascites • Administer intravenous albumin (= 6-8 g per litre ascites removed)
Follow-up and goals	• Adjust diuretic dosage every 4-7 days • Weigh the person at least weekly and BUN, s-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: Spironolactone (400 mg qd) and Furosemide (160 mg qd)

Nutrition of cirrhotic persons	
Caloric requirements • 25-30 Kcal/Kg/day of normal body weight **Protein requirements** • Protein restriction is not recommended (see above for exception if HE)	• 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 NH_3 **Micronutrients** • Mg and Zn

Analgesia in persons with hepatic failure	
• **Acetaminophen** can be used; caution on daily dose (max 2 g/day). • **NSAIDs generally avoided,** predispose persons with cirrhosis to develop GI bleeding. Persons with decompensated cirrhosis are at risk for NSAID-induced renal insufficiency.	• **Opiate** analgesics are not contraindicated but must be used with caution in persons with pre-existing hepatic encephalopathy.

Screening for hepatocellular carcinoma
• Ultrasound (US) every 6 months Alpha-foetoprotein is a suboptimal surveillance tool because of low sensitivity and specificity • In case of suspicious lesions on US, perform CT scan (+arterial phase) or dynamic contrast-enhanced MRI • Confirm diagnosis by fine needle aspiration or biopsy should CT scan or MRI be inconclusive.

When to refer for liver transplantation Best to refer early as disease progresses rapidly
= MELD[ii] score 10-12 (listing at 15) Decompensated cirrhosis (at least one of the following complications) • Ascites • Hepatic encephalopathy • Variceal bleeding • Spontaneous bacterial peritonitis • Hepatorenal syndrome • Hepatopulmonary syndrome • Hepatocellular carcinoma

i Alpha-foetoprotein may also be expressed in µg/L (cut-off value of 400 is the same)
ii Unit for both S-creatinine and S-bilirubin is mg/dL.
MELD score = 10 {0,957 Ln (serum creatinine (mg/dL)) + 0.378 Ln (total bilirubin (mg/dL)) + 1.12 Ln (INR) + 0.643}. See www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/

Diagnosis and Management of Hepatorenal Syndrome (HRS)

Diagnosis	Consider HRS in a person 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 (person 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 iv albumin. If renal dysfunction persists despite above, diagnose HRS		
Recommended therapy	Liver transplant (priority dependent on MELD score). If person is on transplant list, MELD score should be updated daily and communicated to transplant centre.		
Alternative (bridging therapy)	Vasoconstrictors	Octreotide	100-200 mcg subcutaneously td
			→ Goal to increase mean arterial pressure by 15 mm HG
		+ Midodrine	5-15 mg orally td
		or Terlipressin(i)	0.5-2.0 mg iv every 4-6 hours
	and iv albumin (both for at least 7 days)		50-100 g iv qd

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

Dose Adjustment of ARVs for Impaired Hepatic Function

NRTIs	
ABC	**Child-Pugh Score** 5–6: 200 mg bd (use oral solution)
	Child-Pugh Score > 6: Contraindicated
ddI	Contraindicated
	If used no dosage adjustment
d4T	Contraindicated
	If used no dosage adjustment
FTC	No dosage adjustment
3TC	No dosage adjustment
TDF	No dosage adjustment
FTC + TDF	No dosage adjustment
ZDV	Reduce dose by 50% or double the interval between doses if Child-Pugh > 9
NNRTIs	
DLV	No dosage recommendation; use with caution in persons with hepatic impairment
EFV	No dosage adjustment; use with caution in persons with hepatic impairment
EFV + FTC + TDF	
ETV	**Child-Pugh score** < 10: no dosage adjustment
NVP	**Child-Pugh score** > 6: contraindicated

PIs	
ATV	Child-Pugh Score 7–9: 300 mg once daily
	Child-Pugh Score > 9: not recommended
	RTV boosting is not recommended in persons with hepatic impairment (Child-Pugh Score > 7)
DRV	Mild to moderate hepatic impairment: no dosage adjustment
	Severe hepatic impairment: not recommended
FPV	**PI-naive persons only:**
	Child-Pugh Score 5–9: 700 mg bd
	Child-Pugh Score 10–15: 350 mg bd
	PI-experienced persons:
	Child-Pugh Score 5–6: 700 mg bd + RTV 100 mg qd
	Child-Pugh Score 7–9: 450 mg bd + RTV 100 mg qd
	Child-Pugh Score 10–15: 300 mg bd + RTV 100 mg qd
IDV	Mild to moderate hepatic insufficiency: 600 mg q8h
LPV/r	No dosage recommendation; use with caution in persons with hepatic impairment
NFV	Mild hepatic impairment: no dosage adjustment
	Moderate to severe hepatic impairment: not recommended
RTV	Refer to recommendations for the primary PI
SQV	Mild to moderate hepatic impairment: use with caution
	Severe hepatic impairment: contraindicated
TPV	Child-Pugh score < 7: use with caution
	Child-Pugh score > 6: contraindicated
FI	
ENF	No dosage adjustment
CCR5 Inhibitor	
MVC	No dosage recommendations. Concentrations will likely be increased in persons with hepatic impairment
INSTI	
RAL	No dosage adjustment

Note: Hepatic dysfunction is a good indication for TDM as clinical experience with these dose adjustments is very limited

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 INSTI 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 RTV-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 Adverse Effects of ARVs & Drug Classes – 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-positive persons 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 See Diagnosis and Management of Heptatorenal Syndrome (HRS)

Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management

Risk factors	Prevention/Diagnosis	Symptoms
• Use of ddI > d4T > ZDV • HCV/HBV co-infection • Use of ribavirin • Liver disease • Low CD4 cell count • Pregnancy • Female sex • Obesity	• Avoid d4T + ddI combination • Routine monitoring of serum lactate levels not recommended - does not predict risk of lactic acidosis. • Measurement of serum lactate, bicarbonate & arterial blood gases + pH indicated in case of symptoms suggestive of hyperlactataemia • Close monitoring 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

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

Management of lactic acidosis (irrespective of serum-lactate level)

Admit the person. Stop NRTIs. Provide iv fluids. Vitamin supplementation can be used (vitamin B complex forte 4 mL bd, riboflavin 20 mg bd, thiamine 100 mg bd; L-carnitine 1000 mg bd), although benefit is unproven.

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
ART	• Maintain hours of medication (e.g. 23.00 local time) when switching time zones, shortening the interval to the next dose when flying east
Acknowledge increased susceptibility[i] of HIV-positive	**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 page 53 • 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 persons visiting friends and relatives. See Drug-drug Interactions between Antimalarial Drugs and ARVs

Drug-drug Interactions between Antimalarial Drugs and ARVs

Antimalarial	Indication[i]	NNRTI EFV, NVP, ETV	RPV, RAL, MVC	PI COBI (C)
Mefloquine (M) CYP 3A4	P/T	↓	→	→ M may reduce PI/C (RTV ca 35%)
Artemisinins/ **Artemether (A)**[ii] CYP 2B6, 3A4, 2A6, 2C19	T	↓ A & Dihydroartemisin; A & metabolites reduce NVP, but not EFV/ETR	→ A may reduce RPV, MVC	↑ A monitor toxicity (liver)
Lumefantrin (L) CYP 3A4	T	↓	→	↑LPV increases L 2-3x
Atovaquone (At)[iii] **Proguanil (P)**[iv] CYP 2C19	P/T	↓ ETV is increased	→	↓ At & P take with fat meal, consider dose increase
Doxycycline	P	possibly ↓	→	→
Chloroquine CYP 3A4, 2D6	T	→	→	possibly ↑
Quinine (Q) CYP 3A4	T	↓ consider dose increase	→	↑ RTV increases Q 4x: consider dose reduction, monitor toxicity (tinnitus). **CAVE:** PI & Q prolong QT
Primaquine CYP 2E1, 2B6, 1A2, 2D6, 3A4	(P)/T	possibly ↑ haemolytic metabolites	→	NA

CYP: cytochrome p450 subtypes which the drug is metabolised via

Legend

↑↓ indicate effect of antiretrovirals on antimalarial drug/key metabolite

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

ii (A) Artemether and the key metabolite, dihydroartemisinin, are active compounds

iii (At) increases ZDV levels by 35%

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

Colour legend

no clinically significant interaction expected

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

clinically relevant interaction; do not use or use with caution

Vaccination

• Vaccinate according to national guidelines for healthy population • Delay polysaccharide vaccination until CD4 ≥ 200 cells/µL • Consider repeating vaccinations performed at CD4 < 200 cells/µL (CD4% < 14) following adequate immune reconstitution • As vaccine responses may be significantly lower in HIV-positive persons, consider antibody titres to assess their effectiveness	• For attenuated live vaccines[i] (in addition to restrictions for general population): • ***Varicella, measles, mumps, rubella, yellow fever*** contraindicated if CD4 < 200 cells/µL (14%) and/or AIDS • **Oral typhoid, oral polio (OPV)** contraindicated as inactivated vaccines are available

Infection	Vaccination rationale in HIV+ persons	Comment
Influenza Virus	Higher rate of pneumonia	Yearly
Human Papilloma Virus (HPV)	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	If HPV infection is established, efficacy of vaccine is questionable
Hepatitis B Virus (HBV)	Shared risk with HIV of contracting infection. HIV accelerates liver disease progression	Vaccinate if seronegative. 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. See page 62
Hepatitis A Virus (HAV)	According to risk profile (travel, MSM, IVDU, active hepatitis B or C infection)	Vaccinate if seronegative. Check antibody titres in individuals with risk profile See page 62
Neisseria meningitidis	As general population	Use conjugated vaccine (2 doses) if available, then continue with polysaccharide vaccine
Streptococcus pneumoniae	Higher rate and severity of invasive disease	Consider conjugated 13-valent vaccine instead of PPV-23 polysaccharide vaccine if available[ii] Consider one single booster with PPV-23 after 5 years[iii]
Varicella Zoster Virus (VZV)	Higher rate and severity of both chickenpox and zoster	Vaccinate if seronegative For contraindications, see*
Yellow Fever Virus	Mandatory for travel to selected countries (provide exemption letter if no true risk of exposure)	Contraindicated if past or current haematological neoplasia or thymus resection/radiation Relatively contraindicated at age > 60 years For other contraindications, see*

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

Sexual and Reproductive Health of Women and Men Living with HIV

Screening questions about sexual and reproductive health and sexual functioning should be routinely asked in every HIV consultation.

Sexual transmission of HIV

Effective measures to reduce sexual transmission of HIV include:

Measure	Comment
Male condom or female condom use	• Effective in treated and untreated HIV-positive persons
Post-exposure prophylaxis (PEP)	• Consider after situations of unprotected anal or vaginal intercourse, if one partner has detectable HIV-VL and the other partner is seronegative • Start as soon as possible and within 72 hours post sexual exposure
ART for HIV-positive partner	• Considered effective from 6 months of fully suppressive ART if no active STIs • Consider in e.g. serodifferent couples(i)

i See page 7

STI screening and treatment

STI screening should be offered to all sexually active HIV-positive persons at the time of HIV diagnosis, annually thereafter or at any time STI symptoms are reported. Diagnosis procedures should follow local or national guidelines. More comprehensive advice can be found at www.iusti.org/regions/Europe/euroguidelines.htm

The following STIs should be universally considered in HIV-positive persons and their sexual partner(s):

	Therapy	Comment
Chlamydia infection	Consider Doxycycline (100 mg bd for 7-10 days) or Ofloxacin (200 mg bd), Erythromycin (500 mg qd for 7 days) or Azithromycin (1 g once). For *Lymphogranuloma venerum* consider Doxycycline (100 mg bd for at least 3 weeks)	• May cause therapy-resistant proctitis in HIV-positive MSM • Consider co-infections with *Neisseria gonorrhoeae*
Gonorrhoea	Therapy recommended according to geographical resistance profiles. Options: Ciprofloxacin (500 mg orally once), Levofloxacin (250 mg orally once), or Ceftriaxone (250 mg im once). Consider Azithromycin (1 g orally once) to simultaneously treat chlamydia co-infection.	• Can cause proctitis, prostatitis and epididymitis • In women often asymptomatic • Fluroquinolone resistance is extensive
HBV infection **HCV infection**	See table on HIV/HCV or HIV/HBV co-infections, page 62, 64-77	• Interruption of TDF, 3TC or FTC can lead to HBV reactivation • Clusters of acute HCV infection in HIV-positive MSM across Europe
HPV infection	Treatment of genital warts is challenging. Consider operative removal by laser surgery, infrared coagulation, cryotherapy etc. Management of both pre-invasive cervical lesions as well as peri- and intra-anal lesions should follow local or national guidelines	• Infection is mostly asymptomatic; relapse of genital warts is frequent • Cervical PAP smear test recommended in all HIV-positive women • Anal HPV screening and PAP smear should be considered in all HIV-positive persons practising anal sex • Consider high resolution anoscopy in case of suspicious cytologic findings (rectal palpation or external inspection is not sufficient)
HSV2 infection	Primary infection: Acyclovir (400–800 mg orally TID) or Valacyclovir (500 mg bd) for 5 days	• Treatment of HSV2 alone does not prevent HIV-transmission and only modestly prevents HIV disease progression.
Syphilis	**Primary/secondary syphilis:** Benzathine Penicillin G (2.4 million IU im as single dose). **Late latent syphilis and syphilis of unknown duration:** Benzathine Penicillin (2.4 mio IU im weekly on days 1, 8 and 15); alternatives such as Doxycycline (100 mg bd), or Erythromycin (2 g/day) for 2 weeks are considered less effective. **Neurosyphilis:** Penicillin G (6x3-4 million IU iv for at least 2 weeks)	• Expect atypical serology and clinical courses • Consider cerebral spinal fluid (CSF) testing in persons with neurological symptoms (evidence for intrathecally-produced specific antibodies, pleocytosis etc.) • Successful therapy clears clinical symptoms and/or decreases VDRL test by at least 2 titre levels • Serology cannot distinguish re-infection from re-activation

Reproductive health

Reproductive health issues should be preferentially discussed with both partners, particularly in serodifferent couples. RAL, RPV and NRTIs have been shown to have no interaction with oral contraceptives.

Approaches for serodifferent couples who want to have children
Screening for STIs (and treatment, if required) of both partners is mandatory. For HIV-positive female persons wishing to conceive: (1) avoid using ddI, d4T or triple NRTI, avoid EFV in first trimester; among PI/r, prefer LPV/r, SQV/r or ATV/r, already started NVP, RAL or DRV/r can be continued, see page 12; (2) consider treating the HIV-positive partner to reduce risk of HIV transmission to the HIV-negative partner

No single method is fully protective against transmission of HIV; the following list represents selected measures with increasing safety for serodifferent couples without active STIs:
- Unprotected intercourse during times of maximum fertility (determined by ovulation monitoring), if the HIV-positive partner has undetectable HIV-VL
- Vaginal syringe injection of seminal fluid during times of maximum fertility, if the male partner is HIV-negative
- Sperm washing, with or without intra-cytoplasmic sperm injection, if the male partner is HIV-positive

Sexual dysfunction

Guidelines for treatment of sexual dysfunction in the general population are available for men but not women. Refer to specialist where appropriate. See Sexual Dysfunction and Treatment of Sexual Dysfunction in HIV-positive Men

Sexual Dysfunction

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)	
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?	CVD (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, betablockers, alfablockers), 4) others (Omeprazole, Spironolactone, Metoclopramide, Finasteride, Cimetidine); 5) contribution from ARVs 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 HIV-positive Men

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 • Tadalafil also licensed for use as an everyday ongoing therapy	Consider behavioural interventions and/or psychosexual counselling, SSRIs, tricylclic antidepressants, Clomipramine and topical anaesthetics. • Use lower dose of Clomipramine and other tricyclic antidepressants if on PI/r • Dapoxetine, a short-acting SSRI, is the only drug approved for on-demand treatment of premature ejaculation in Europe. • Treatment must be maintained as recurrence is highly likely following withdrawal of medication

Depression: Screening and Diagnosis

Significance

- Higher prevalence of depression reported in HIV-positive persons (20-40% versus 7% in general population)
- Significant disability and poorer treatment outcomes 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 • Persons with history of drug addiction, psychiatric, neurologic or severe somatic co-morbidity • Use of EFV and other neurotropic - incl. recreational - drugs • As part of investigation of neurocognitive impairment if any of the 3 initial screening questions are positive, see page 61	• 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? • Specific symptoms in men: – Stressed, burn out, angry outbursts, coping through work or alcohol • Rule out organic cause (such as hypothyroidism, hypogonadism, Addison's disease, non-HIV drugs, vit B12 deficiency)	**Symptoms – evaluate regularly** **A.** At least 2 weeks of depressed mood OR **B.** Loss of interest OR **C.** 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

Depression: Management

Degree of depression	Number of symptoms (see page 57: A,B or C + 4/7)	Treatment	Consultation with expert
No	< 4	No	
Mild	4	• Problem-focused consultation • Consider antidepressant treatment(i) • Recommend physical activity	• Always if treating physician is unfamiliar with use of antidepressants • If depression not responding to treatment • If person has suicidal ideation • In case of complex situations such as drug addiction, anxiety disorders, personality disorders, dementia, acute severe life events
Intermediate	5-6	Start antidepressant treatment(i)	
Severe	> 6	Refer to expert (essential)	

i See Drug-drug Interactions between Antidepressants and ARVs

Classification, Doses, Safety and Adverse Effects of Antidepressants

Mechanisms & classification	Start dose	Standard dose	Lethality in overdose	Insomnia and agitation	Sedation	Nausea or GI effects	Sexual dysfunction	Weight gain
	mg/day							
Selective serotonin-reuptake inhibitors (SSRIs)[i]								
Paroxetine	10-20	20-40	Low	+	- / +	+	++	++
Sertraline	25-50	50-150	Low	+	- / +	+	+	+
Citalopram	10-20	20-40	Low	+	- / +	+	+	+
Escitalopram	5-10	10-20	Low	+	- / +	+	+	+
Mixed or dual-action reuptake inhibitors								
Venlafaxine	37.5-75	75-225	Moderate	++	- / +	+	+	- / +
Mixed-action newer agents								
Mirtazapine	30	30-60	Low	- / +	++	- / +	- / +	++

- none
\+ moderate
++ severe

i For many persons, SSRI induction may be associated with adverse effects (GI tract, dizziness, anxiety, panic attacks). Commencing at lower doses (i.e. 10, 25 & 10 mg for Paroxetine, Sertraline and Citalopram, respectively) and increasing to the above starting doses after 4 to 7 days if tolerated may reduce such effects.

Drug-drug Interactions between Antidepressants and ARVs

antidepressants		ATV/r	DRV/r	LPV/r	SQV/r	EFV	ETV	NVP	RPV	MVC	RAL
SSRI	citalopram	↑ [a]	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↔
	escitalopram	↑ [a]	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↔
	fluvoxamine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	fluoxetine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↓39%	↑↓?	↑↓?	↔	↔	↔	↔	↔	↔
	sertraline	↓	↓49%	↓	↓	↓39%	↓	↓	↔	↔	↔
SNRI	duloxetine	↑↓	↑↓	↑↓	↑↓	↔	↔	↔	↔	↔	↔
	venlafaxine	↑	↑	↑	↑	↓	↓	↓	↔	D	↔
TCA	amitriptyline	↑	↑	↑	↑ [b]	↔	↔	↔	↔	↔	↔
	clomipramine	↑	↑	↑	↑ [b]	↓	↓	↓	↔	↔	↔
	desipramine	↑	↑	↑5%	↑	↔	↔	↔	↔	↔	↔
	doxepin	↑	↑	↑	↑ [b]	↔	↔	↔	↔	↔	↔
	imipramine	↑ [a]	↑	↑ [a]	↑ [a]	↓	↓	↓	↔	↔	↔
	nortriptyline	↑ [a]	↑	↑ [a]	↑ [ab]	↔	↔	↔	↔	↔	↔
	trimipramine	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
TeCA	maprotiline	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔
	mianserine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔
Others	bupropion	↓	↓	↓57%	↓	↓55%	↔	↓	↔	↔	↔
	lamotrigine	↓32%	↓	↓50%	↓	↔	↔	↔	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↓	↓ E	↓	E	E	↔
	St John's wort	D	D	D	D	D	D	D	D	D	↔
	trazodone	↑	↑	↑	↑ [b]	↓	↓	↓	↔	↔	↔

Legend

↑ potential elevated exposure of the antidepressant
↓ potential decreased exposure of the antidepressant
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
a ECG monitoring is recommended
b coadministration contraindicated in the European SPC. However, US prescribing information recommends TDM for antidepressants. The charts reflect the more cautious option. Numbers refer to decreased AUC of the antidepressant as observed in drug-drug interactions studies.
SSRI selective serotonin reuptake inhibitors
SNRI serotonin and norepinephrine reuptake inhibitors
TCA tricyclic antidepressants
TeCA tetracyclic antidepressants

Colour legend

no clinically significant interaction expected.
these drugs should not be coadministered.
potential interaction which may require a dosage adjustment or close monitoring.
potential interaction predicted to be of weak intensity (< 2 fold ↑AUC or < 50% ↓AUC). A dosage adjustment is *a priori* not recommeded.

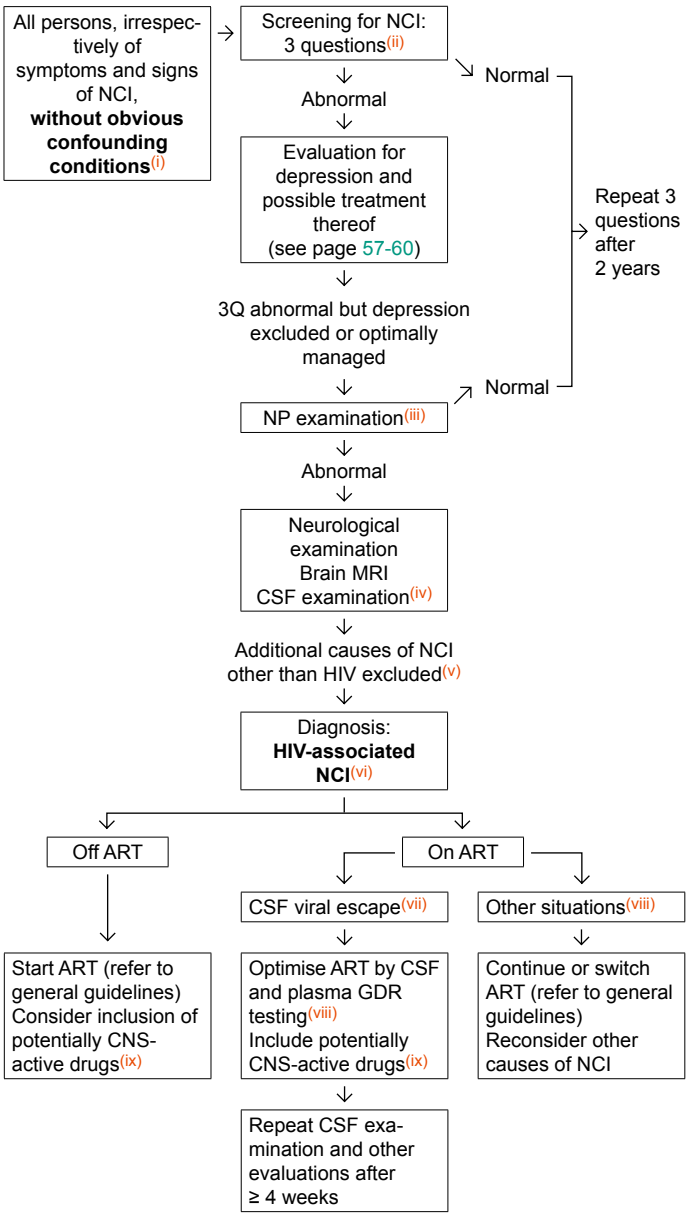
Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on www.hiv-druginteractions.org (University of Liverpool). For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, refer to the above-mentioned website.

Algorithm for Diagnosis and Management of HIV-Associated Neurocognitive Impairment (NCI) in Persons without Obvious Confounding Conditions

Abbreviations

CSF	cerebrospinal fluid
GDR	genotypic drug resistance test
HAD	HIV-associated dementia
MND	mild neurocognitive disorder
MRI	brain magnetic resonance imaging
NP	neuropsychological



i Persons with obvious confounding conditions are not to be considered in this algorithm.

Obvious confounding conditions include:

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** [3]

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, book or movie)?

For each question, answers could be: **a)** never, **b)** hardly ever, or **c)** yes, definitely. HIV-positive persons 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 [4] plus assessment of daily functioning.

iv **Brain MRI and CSF examination**
These are required to further exclude other pathologies and to further characterize HIV-associated NCI, 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 For differential diagnosis, see www.aidsetc.org/aidsetc?page=cg-802_dementia

vi Includes **HAD and MND definitions** [4].
- 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

vii CSF escape definition: either CSF VL > 50 and plasma VL < 50 c/mL- or both CSF and plasma VL > 50 c/mL, with CSF VL > 1 $\log_{10}$ higher than plasma VL

viii Including all situations that do not fulfil the CSF escape definition

ix **Definition of 'potentially CNS-active' drugs:**
ARV drugs with either demonstrated clear CSF penetration when studied in healthy HIV-positive populations (concentration above the IC_{90} in > 90% examined persons) or with proven short-term (3-6 months) efficacy on cognitive function or CSF VL 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: IDV/r, LPV/r, DRV/r*
  - Other classes: MVC
- Drugs with proven clinical efficacy:
  - NRTIs: ZDV, d4T, ABC
  - Boosted PIs: LPV/r

* When administered twice daily. Once-daily administration of these drugs, although common in clinical practice, has not been studied extensively with regard to CNS effects/CSF penetration and may have different CNS activity.

Part IV Clinical Management and Treatment of Chronic HBV and HCV Co-infection in HIV-positive Persons

General Recommendations for Persons with Viral Hepatitis/HIV Co-infection

Screening

1. All HIV-positive persons should be screened for HCV at time of HIV diagnosis and annually hereafter. Screening should use an anti-HCV antibody test. A positive result should be followed by HCV-RNA and genotype determination. Persons 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 anti-HCV antibody test should be tested for HCV-RNA for early detection of a recent infection.
2. HIV-positive persons should be screened for HAV and HBV. Persons 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+ persons.
4. Persons with liver cirrhosis Child Pugh class A or B and Child Pugh class C awaiting liver transplantation and persons with HBV irrespectively of fibrosis stage should be screened at 6-monthly intervals with hepatic ultrasound (CT in case of nodules– alpha-foetoprotein may also be used, but value controversial) for the occurrence of hepatocellular carcinoma (HCC). Routine screening is also advised for oesophageal varices at the time of diagnosis mainly when there is evidence of portal hypertension and at 3-4-year intervals thereafter if not present initially, see page 45. Regarding HCC screening, see page 46. In the presence of a liver nodule or a liver mass, recall policy of EASL/EORTC guidelines should be followed. Management of HCC should be defined for each case with a multidisciplinary team including transplant surgeon, interventional radiologist and hepatologist. In persons treated with Sorafenib, toxicity of ARVs and Sorafenib should be strictly monitored.

Vaccination see page 53

5. Persons lacking anti-HAV IgG antibodies or anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4 cell count. The response to the HBV vaccine is influenced by the CD4 cell count and level of HIV-VL. In persons with low CD4 cell count (< 200 cells/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 IgG positive persons (HBsAg 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-positive persons vaccinated for HBV with insufficient response (anti-HBs < 10 IU/L), re-vaccination should be considered. Double-dose (40 µg) at 3-4 time points (months 0, 1, 6 and 12) may help to improve response rates to the HBV vaccine. Persons who fail to seroconvert after HBV vaccination and remain at risk for HBV should have annual serological tests for evidence of HBV infection.

ART

7. HIV-positive persons with HBV and/or HCV co-infection benefit from early ART because liver fibrosis progression is reduced with immune reconstitution and suppression of HIV-VL. Thus, ART initiation with a TDF-based regimen is recommended in all persons with HBV co-infection needing anti-HBV therapy irrespective of CD4 cell count, and in all HBsAg positive persons 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 persons with chronic HCV, ART initiation is recommended when CD4 cell counts drop below 500 cells/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 persons with hepatitis co-infection. Stopping anti-HBV containing ART should be avoided in persons with HIV/HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis.

End Stage Liver Disease (ESLD)

9. HIV-positive persons require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative persons, see page 45-47 and Diagnosis and Management of Hepatorenal Syndrome (HRS).
10. Persons with viral hepatitis/HIV co-infection suffering from ESLD warrant particular attention in the management of liver insufficiency; see Dose Adjustment of ARVs for Impaired Hepatic Function. Nevertheless, it is important to highlight that ART initiation in cirrhotic persons generally improves overall survival and is therefore strongly recommended in these persons when indicated.
11. Renal complications are frequent, see page 46 and Diagnosis and Management of Hepatorenal Syndrome (HRS)
12. Persons with HCC or a MELD-score > 15*, CD4 cell count > 100 cells/µL and options for efficacious and durable ART should be evaluated for liver transplantation (OLTX). OLTX outcomes in persons with HIV/HBV co-infection are particularly promising, whereas post-transplant survival in persons with HIV/HCV co-infection has been somewhat lower than in persons with HCV mono-infection mainly due to the complicated course of HCV re-infection after transplantation.

* MELD calculation, see page 46.

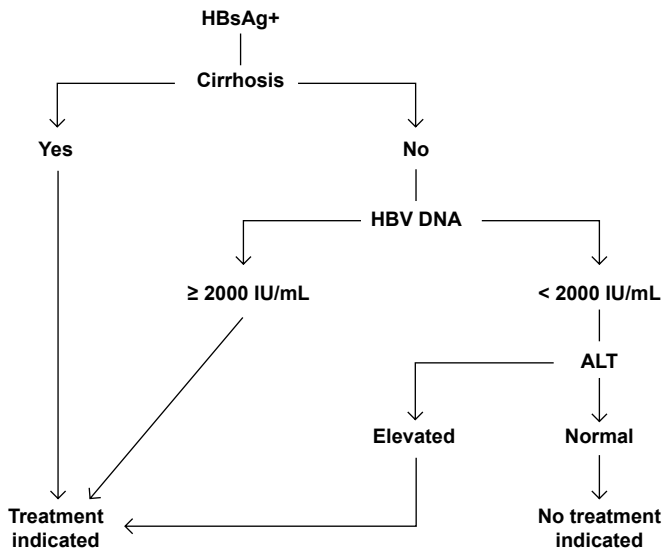
Prevention/Support

13. Psychiatric, psychological, social and medical support should be made available to persons with alcohol intake to stop drinking.
14. Substitution therapy (opioid replacement therapy) in persons 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). See Drug Dependency and Drug Addiction
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

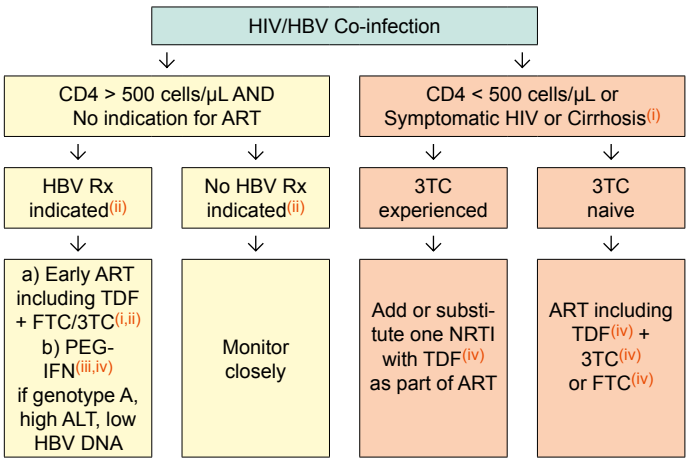
16. In persons with Delta virus co-infection and significant liver fibrosis (≥ F2), long-term (> 18 months) treatment with PEG-IFN might be considered in association with TDF-based ART. Because of its anti-HBV activity, TDF should be added to PEG-IFN in order to reduce HBV-DNA load. Treatment efficacy should be monitored with HBV-DNA and HDV-RNA measurements, when available, and with follow-up of biochemical and liver fibrosis estimates.
    Persons with anti-HCV antibodies and detectable HCV-RNA should be offered anti-HCV treatment in order to induce a sustained virologic response for HCV co-infection. 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 persons. Histological remission of liver disease is a less ambitious but more likely to be achieved goal. In persons with Delta virus and ESLD or HCC, liver transplantation should be strongly considered especially in the absence of active HCV co-infection. Transplant cures HBV and Delta virus infection.

Assessment of Treatment Indications for HBV in Persons with HBV/HIV Co-infection



Note: In persons with significant liver fibrosis (F2-F4), anti-HBV treatment might be considered even when serum HBV-DNA is below 2000 IU/mL and liver enzymes are not elevated.

Treatment of Chronic HBV in Persons with HBV/HIV Co-infection



i For management of cirrhotic persons, see page 45-48. Persons with liver cirrhosis and low CD4 cell count 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 page 63 for assessment of HBV Rx indication. Some experts strongly believe that any person with HBV infection requiring ART should receive TDF + 3TC or FTC unless history of TDF intolerance, particularly with advanced liver fibrosis (F3/F4). See (iv) for handling of intolerability to TDF. Entecavir may be used, in addition to fully supressive ART.

iii ART-naive Asian, HBeAg+, HIV-co-infected persons 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 person 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 persons 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. Recent data obtained in HBV mono-infected persons suggests that on-treatment quantification of HBsAg in persons with HBeAg-negative chronic HBV 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 persons 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+ persons who have achieved HBe-seroconversion for at least six months or after confirmed HBs-seroconversion in those who are HBeAg. In persons with liver cirrhosis, stopping 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 TDF intolerance (i.e. renal disease, see page 41), 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 persons with no prior 3TC 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 TDF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pretreated cirrhotic persons 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 TDF to Entecavir. The addition of Entecavir to TDF in persons with low persistent HBV-replication has not statistically proved to be efficient and should therefore be avoided. Results of trials are awaited.

Diagnostic Procedures for HCV in Persons with HCV/HIV Co-infection

Diagnosis of HCV
HCV-Ab (turn positive 1-6 months after infection as late seroconversions have been described, may rarely be lost due to immunosuppression)
HCV-RNA levels[i] (in particular important for the prediction of response to treatment)
Status of Liver Damage
Staging of fibrosis (e.g. FibroScan, liver biopsy, serum fibrosis markers[ii])
Hepatic synthetic function (e.g. coagulation, albumin, cholinesterase)
Ultrasound every 6 months if cirrhosis (gastroscopy upon diagnosis of cirrhosis and every 1-2 years thereafter), see page 46
Before HCV Treatment
HCV genotype (GT) and HCV-RNA
IL28b GT
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 cell count every 12 weeks
TSH every 12 weeks

i Low HCV-RNA defined as <400,000-600,000 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 Persons 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.

Treatment of HCV in Persons with HCV/HIV Co-infection

Treatment indication

1. HCV treatment offers the possibility of eradicating HCV within a defined treatment period. This is potentially advantageous for the subsequent management of the person with HIV, and every person with co-infection 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 persons with HIV/HCV co-infection and with better HCV-treatment outcome with the use of direct acting antivirals (DAAs) in these persons.
2. If chronic HCV is detected early in the course of HIV infection (before ART initiation), treatment for chronic HCV is advised.
   For persons with a CD4 cell count < 500 cells/µL, early ART initiation is recommended to optimize HCV treatment outcome.
   However, if a person with co-infection has significant immunodeficiency (CD4 cell count < 350 cells/µL), the CD4 cell count should be improved using ART prior to commencing anti-HCV treatment.
   Persons with a CD4 relative percentage > 25% are more likely to achieve SVR than those with a lower CD4 percentage. Also persons with undetectable HIV-VL are more likely to achieve SVR than persons with ongoing HIV-replication.
3. Information on liver fibrosis staging is important for making therapeutic decisions in persons with co-infection. However, a liver biopsy is no longer mandatory for considering treatment of chronic HCV.
   Current therapy is particularly recommended in persons with a high likelihood of achieving sustained virological response (SVR) such as GT 2 or 3 or GT 1 persons with an IL28B CC GT or GT 1 persons with a previous relapse under dual therapy which can now be retreated with triple therapy(i)
4. Based on 4 baseline variables (serum HCV-RNA, HCV GT, liver fibrosis staging using elastometry, and IL28B genotyping), the Prometheus index has recently been developed and can optionally be used for predicting the likelihood of SVR using PEG-IFN-RBV therapy in persons with HCV/HIV co-infection. It is freely available online www.fundacionies.com/prometheusindex.php
5. 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.
6. In case of the availability of a liver biopsy or FibroScan demonstrating lack of or minimal liver fibrosis (F0-1), regardless of HCV GT, treatment can be deferred. This may also account for persons with low chances of SVR under the current treatment options for whom improved treatment options will become available within the coming years. Indeed, Sofosbuvir, Faldaprevir and Simeprevir are expected to be licensed in Europe in 2014. All three drugs have been tested in persons with HCV co-infection and will have data available upon licensing. This is also relevant in persons with GT 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 page 69-70. In these cases, fibrosis assessment should be carried out periodically to monitor for fibrosis progression.

Treatment of chronic HCV in persons with HCV/HIV-co-infection

7. The combination of PEG-IFN alpha and RBV remains the treatment of choice for HCV GT 2, 3 and 4. The standard dose for PEG-IFN 2a is 180 µg once weekly, and for PEG-IFN 2b 1.5 µg/kg body weight once weekly. An initial weight-adapted dose of RBV of 1000 (wt ≤ 75 kg) - 1200 (wt > 75 kg) mg/day (administered bd) is recommended for all HCV GTs in the HIV setting. For the treatment paradigm for dual therapy, see page 70.
   HCV GT 4 behaves similarly to GT 1 with respect to treatment response to IFN and influence of IL28B; however, it is not sensitive to currently licensed HCV DAAs. For some of the upcoming new DAAs, anti-GT4 activity has been documented and clinical trial data in treatment of HCV GT 4 infection is currently being collected, hopefully also allowing improved treatment algorithms for treatment of GT 4 infections soon.
8. With first pilot studies in HCV treatment-naive persons with HCV/HIV co-infection demonstrating significantly higher SVR12-24 rates with triple therapy compared to dual therapy, HCV DAA-based therapy with either Boceprevir or Telaprevir is now the new standard of treatment in HCV GT 1 infection in HIV-positive persons where available. Interim results from pilot trials in treatment-experienced persons also demonstrate good early treatment responses (negative HCV-RNA after 4-week lead-in followed by 12 weeks of triple therapy was between 63 and 88%) even in more advanced fibrosis stages. Final SVR data from these trials, however, is not yet available so SVR rates cannot be provided at this time (also note that previous null-responders and cirrhotics were excluded from these trials). Telaprevir is added to PEG-IFN-RBV standard treatment for 12 weeks at 750 mg every 8 hours or 1125 mg every 12 hours. Due to drug-drug interactions, Telaprevir can currently only be safely combined with ATV/r, RTV, MVC, RPV, ETV or DFV (with EFV, Telaprevir doses need to be increased to 1125 mg every 8 hours) in combination with TDF or ABC and FTC or 3TC, see 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. 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 persons with HCV mono-infection with rapid virological response, this data so far is not available for persons with HCV/HIV co-infection. Due to drug-drug interactions Boceprevir can only be currently safely combined with RAL, RPV or ETV in combination with TDF or ABC and FTC or 3TC. The EMA has suggested considering Boceprevir with ATV/r in persons without previous HIV-treatment failure, drug resistance and suppressed HIV-RNA when starting HCV-therapy. Boceprevir is not impacted by concomitant ATV/r, whereas ATV AUC decreased significantly, but trough levels remained above the recommended IC_{90} in all persons. Considering the complex treatment issues, in particular drug-drug interactions, inclusion into clinical trials should be preferred and close monitoring for persons treated outside of trials is highly recommended.
9. 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 RBV reduction and EPO use have both been demonstrated to be effective in anaemia management while not lowering overall SVR rates. Data from persons with HCV mono-infection and cirrhosis suggest even higher anaemia rates and haemoglobin values need to be determined in such persons at least every 2 weeks after starting HCV therapy. Careful surveillance should be addressed to severe infectious complications and liver decompensation, which have been observed in 3-8% of cirrhotic persons with HCV mono-infection on triple therapy in an observational study where they caused a mortality rate > 1%. Predictive factors for hepatic decompensation are in particular serum albumin < 35 mg/dL in combination with platelets < 90,000/µL. Data in persons with HCV/HIV co-infection with more advanced fibrosis also suggests more adverse events in this special person population, but data from completed trials is still lacking.
10. During PEG-IFN-RBV therapy, ddI is contraindicated in persons with cirrhosis and should be avoided in persons with less severe liver disease. D4T and ZDV should also be avoided if possible. ABC can be safely used with concomitant HCV therapy if appropriate RBV dosages are being used.

Treatment goal

11. The primary aim of HCV treatment is SVR defined as undetectable HCV-RNA 24 weeks after the end of therapy, evaluated using sensitive molecular tests. Early time points upon completion of treatment, such as SVR at week 12, still need to be examined in persons with HCV/HIV co-infection.

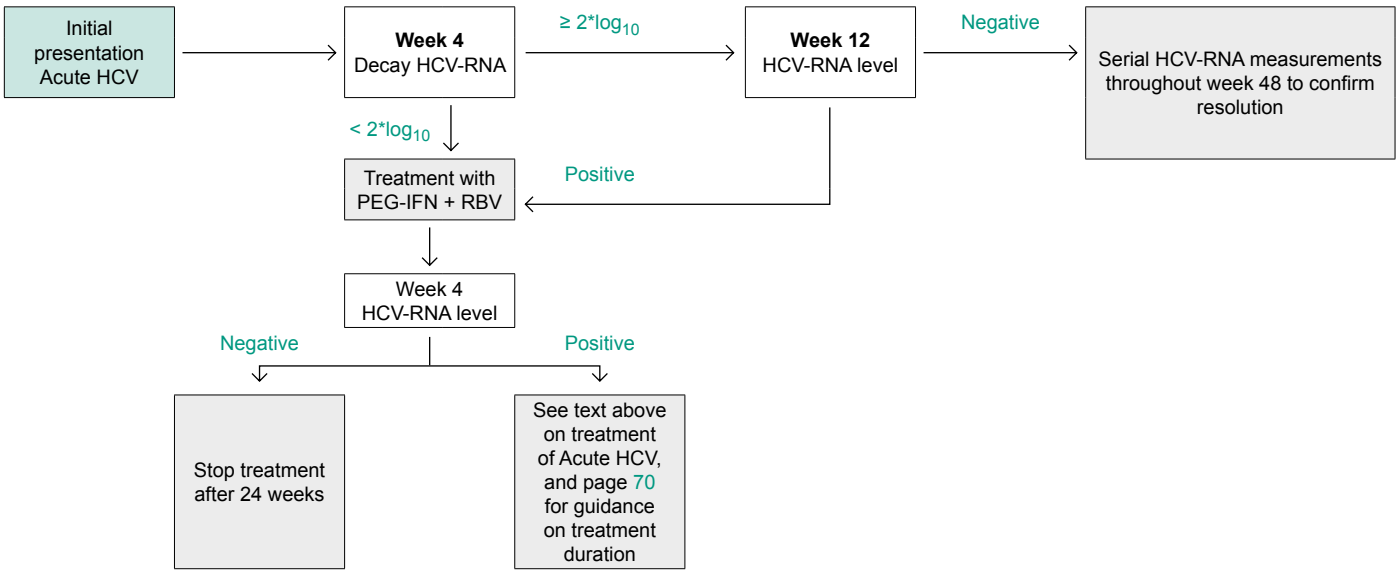
Stopping rules

12. If an early virological response (decline of at least 2*$\log_{10}$ reduction in HCV-RNA at week 12 compared to baseline) is not achieved when treating GT 2, 3 or 4 infection with dual therapy (or GT 1 when no DAAs are available), treatment should be stopped, see page 70. Different stopping rules apply when DAAs are being used and are summarized below. In case of successful Telaprevir-based HCV therapy at week 4 (HCV-RNA < 1000 IU/mL), Telaprevir should be continued until week 12, see page 72. 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. Futility rules for Boceprevir-containing HCV therapy are that in case of HCV-RNA > 100 IU/mL at week 12 or 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.

Treatment of Acute HCV

13. Identification of persons with acute HCV is important since treatment in the acute phase leads to higher SVR rates than for treatment of chronic HCV. In persons with acute HCV, HCV-RNA should be measured at initial presentation and 4 weeks later. Treatment should be offered in persons without a decrease of 2*$\log_{10}$ of HCV-RNA at 4 weeks compared with initial HCV-RNA and to persons 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 GT. Persons who do not achieve a ≥ 2*$\log_{10}$ 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 RBV in treatment of acute HCV at this point. Also, only uncontrolled data in 20 persons receiving 12 weeks of Telaprevir and PEG-IFN-RBV is available as yet. Therefore, considering the high cure rates with PEG-IFN-RBV alone in acute HCV, DAAs are currently not recommended unless there is a GT1 person with lack of virological response (at week 12 < 2*$\log_{10}$ decrease in HCV-RNA), a situation in which treatment intensification with DAAs can be discussed on an individual basis.

Algorithm for Management of Acute HCV in Persons with HCV/HIV Co-infection(i)



Management of Persons with HCV GT 1/ HIV Co-infection According to Fibrosis Stage and Prior Treatment Outcome*

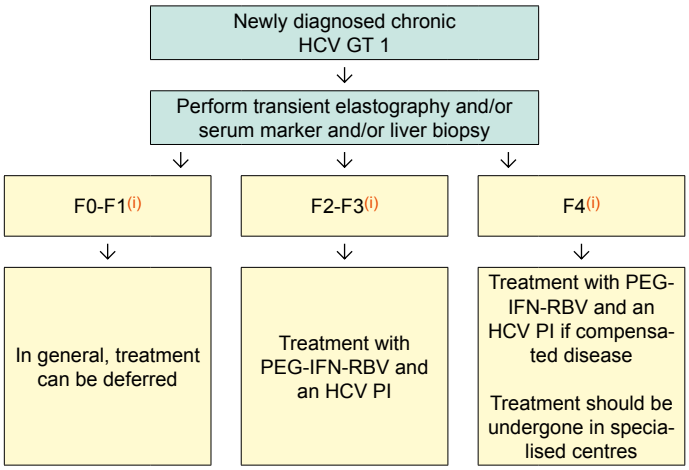
	Naive	Relapser	Non-responder
F0-F1[ii]	Individual decision	Individual decision/triple therapy	Defer[i]
F2-F3[ii]	Triple therapy	Triple therapy	Defer[i]
F4[ii]	Triple therapy	Triple therapy	Discuss Triple Therapy on a case-by-case basis

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

ii Metavir fibrosis score
F0 no fibrosis
F1 portal fibrosis, no septae
F2 portal fibrosis, few septae
F3 bridging fibrosis
F4 cirrhosis.
Monitor fibrosis stage annually, preferably with two established methods. Treat with triple therapy, if rapid progression.

* Adapted from [2]

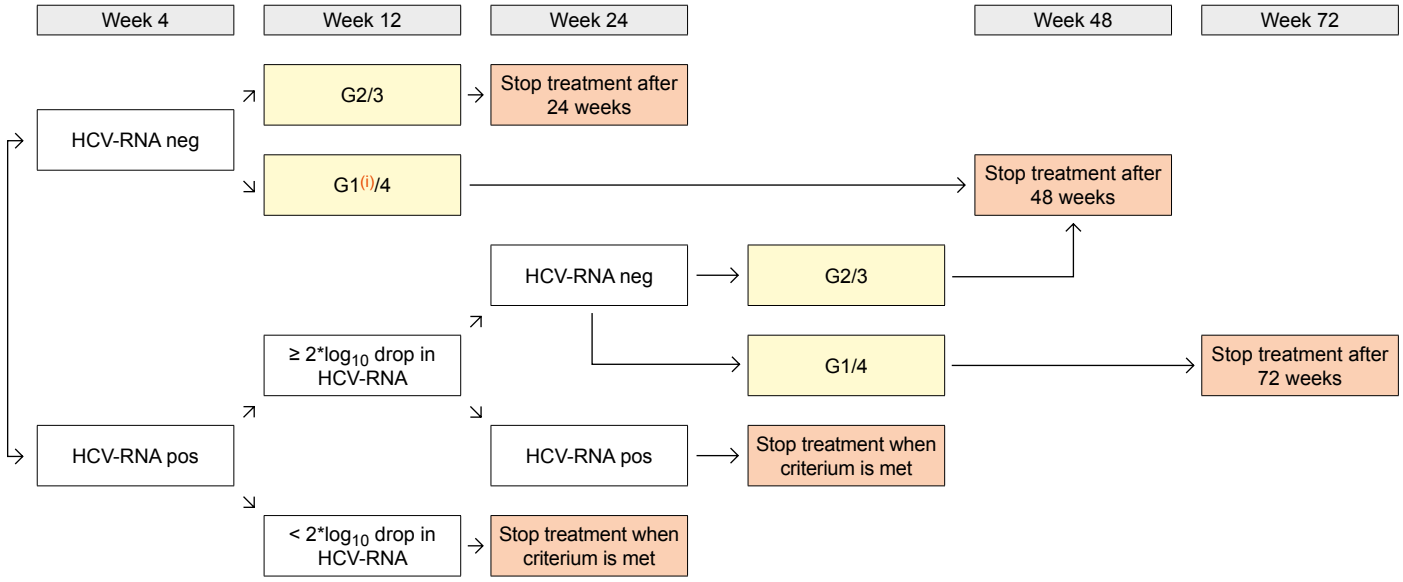
Management of Persons with Newly Diagnosed HCV GT 1/ HIV Co-infection*



i Metavir fibrosis score
F0 no fibrosis
F1 portal fibrosis, no septae
F2 portal fibrosis, few septae
F3 bridging fibrosis
F4 cirrhosis.
Monitor fibrosis stage annually, preferably with two established methods.
Treat with triple therapy, if rapid progression.

* Adapted from [2]

Proposed Optimal Duration of Dual HCV Therapy in Persons with Chronic HCV/HIV Co-infection Not Eligible for Triple Therapy Including DAAs against HCV



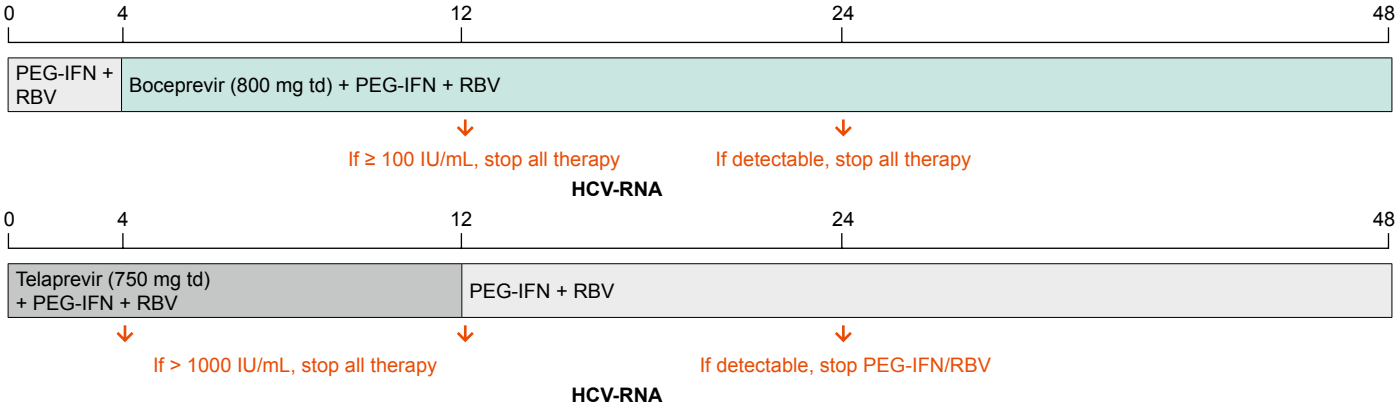
i Where no access to DAAs available or high chances of cure even with dual therapy (favourable IL28B GT, low HCV-RNA and no advanced fibrosis)

Definition of Treatment Response of PEG-IFN and RBV

	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*$\log_{10}$ decrease from baseline but not undetectable
Null Response (NR)	Week 12 on treatment	< 2*$\log_{10}$ decrease from baseline
Partial Non-Response (PR)	Week 12 and week 24 on treatment	> 2*$\log_{10}$ 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 treatment

Adapted from [3]
See www.easl.eu/assets/application/files/4a7bd873f9cccbf_file.pdf

Use of Boceprevir and Telaprevir in Persons with HIV/HCV Co-infection



Therapy should be stopped if there is a confirmed increase in HCV-RNA by 1*$\log_{10}$ following a decline at any stage.

Classification of and Interventions for HCV GT 2, 3 or 4 in non-responders/ relapsers to Prior IFN-based Therapies with HCV/HIV Co-infection

Category	Subgroup	Suggested Intervention
Suboptimal treatment	Suboptimal schedule IFN (monotherapy or with RBV) Low RBV dose Short length of therapy	Re-treatment using combination therapy with PEG-IFN plus weight-based RBV 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 persons with mild fibrosis, wait and monitor. If rapid progression or > moderate fibrosis, re-treatment using combination therapy with PEG-IFN plus weight-based RBV dosing (consider longer treatment duration)
	Non response (no undetectable HCV-RNA during treatment)	Wait for new DAAs with activity against non-GT1

i Data on the use of haematopoietic growth factors in HCV/HIV co-infection 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.

Part V Opportunistic Infections

Prevention and Treatment of Opportunistic Infections in HIV-positive Persons

Primary Prophylaxis

Disease	Drug	Dose	Evidence	Comments
Pneumocystis jirovecii (carinii) (PcP) and *Toxoplasma gondii*				**Indication:** CD4 < 200 cells/µL **Stop** if CD4 > 200 cells/µL over 3 months or CD4 100-200 cells/µL and HIV-VL undetectable for 3 months
Positive or Negative Serology for Toxoplasmosis	**TMP-SMX**	1 double-strength (ds) (160/800 mg) 3x/week or 1 single strength daily	BI	
Negative Serology for Toxoplasmosis	**Pentamidine**	300 mg in 6 mL Aqua	BI	
		1 x Inhalation/month		
Negative Serology for Toxoplasmosis	**Dapsone**	1 x 100 mg po/d	BI	Check for G6PD-deficiency
Negative or Positive Serology for Toxoplasmosis	**Atovaquone** suspension	1 x 1500 mg po/d (with food)	BI	
Positive Serology for Toxoplasmosis	**Dapsone**	200 mg po 1x/week	BI	Check for G6PD-deficiency
	+ Pyrimethamine	75 mg po 1x/week		
	+ Leucovorin	25 mg 1x/week		
Mycobacteria (Other than *M. tuberculosis*)				
	Azithromycin	1200 mg po 1x/week	AI	**Indication:** CD4 < 50 cells/µL **Stop** if CD4 > 100 cells/µL over 3 months
	or			
	Clarithromycin	2 x 500 mg/d po	AI	
Latent Tuberculosis Infection (see Diagnosis and Treatment of Resistant and Latent TB in HIV-positive Persons)				
	Isoniazid (INH)	5 mg/kg/d (max 300 mg) po	AII	**Indication:** TST > 5 mm or positive IGRA or close contacts to open tuberculosis.
	+ Pyridoxine (Vit. B6)	40 mg/d		**9 months**

Secondary Prophylaxis

Disease	Drug	Dose	Evidence	Comments
Pneumocystits jirovecii (carinii) Pneumonia (PcP)				**Stop** if CD4 > 200 cells/µL over 3 months
Negative or Positive Serology for Toxoplasmosis	**TMP-SMX**	1 double-strength (ds) (160/800 mg) 3x/week	BI	
Negative Serology for Toxoplasmosis	**Pentamidine**	300 mg in 6 mL Aqua First month: 2 x inhalations, Then 1 x inhalation/month	BI	
Negative Serology for Toxoplasmosis	**Dapsone**	1 x 100 mg/d po	BI	Check for G6PD-deficiency
Negative or Positive Serology for Toxoplasmosis	**Atovaquone** suspension	1 x 1500 mg/d po (with food)	BI	
Positive Serology for Toxoplasmosis	**Dapsone**	1 x 200 mg/week po	BI	Check for G6PD-deficiency
	+ Pyrimethamine	1 x 75 mg/week po		
	+ Leucovorin	1 x 25 mg/week po		

Secondary Prophylaxis

Disease	Drug	Dose	Evidence	Comments
Toxoplasma gondii Encephalitis				
	Sulfadiazine	2-3 g/d po (in 2-4 doses)	AI	**Stop** if CD4 > 200 cells/µL over 3 months
	+ Pyrimethamine	1 x 50 mg/d po		
	+ Leucovorin	1 x 10-25 mg/d po		
	or			
	Clindamycin	3 x 600 mg/d po	BI	Additional PCP prophylaxis is necessary
	+ Pyrimethamine	1 x 50 mg/d po		
	+Leucovorin	1 x 10-25 mg/d po		
	or			
	Dapsone	1 x 200 mg/week po	BII	Check for G6PD-deficiency
	+ Pyrimethamine	1 x 75 mg/week po		
	+ Leucovorin	1 x 25 mg/week po		
	or			
	Atovaquone suspension	1 x 1500 mg/d (with food)	BII	
	+ Pyrimethamine	1 x 25 mg/d po		
	+ Leucovorin	1 x 10 mg/d po		
Cryptococcal Meningitis				
	Fluconazole	1 x 200 mg/d po	AI	At least 12 months Stop to discuss if CD4 > 200 cells/µL
Cytomegalovirus (CMV) Retinitis Sight-threatening Lesions				
	Valganciclovir	1 x 900 mg/d po (with food)	AI	**Stop** if CD4 > 200 cells/µL over 3 months
	+ Ganciclovir ocular implant			
	or **Ganciclovir**	5 mg/kg iv 5x/week	AI	Ganciclovir implants should be replaced every 6-8 weeks until sustained immune recovery
	or **Foscarnet**	100 mg/kg iv 5x/week	AI	
	or **Cidofovir** + NaCl + Probenecid	5 mg/kg iv every 2 weeks	BI	
Small Peripheral Retinal Lesions	**Valganciclovir**	1 x 900 mg/d po (with food)	AI	
Mycobacterium avium (MAC) Infection				
	Clarythromycin	2 x 500 mg/d po	AI	**Stop** if CD4 > 100 cells/µL over 6 months and after MAC treatment for 12 months
	+ Ethambutol	1 x 15 mg/kg/d po		
	or **Azithomycin**	1 x 500 mg/d po	AII	
	+ Ethambutol	1 x 15 mg/kg/d po		

Treatment of Opportunistic Infections

Disease	Drug	Dose	Evidence	Comments
Pneumocystis jirovecii (carinii) Pneumonia (PcP)				
Preferred Therapy	**TMP-SMX**	3 x 5 mg/kg/d TMP iv/po + 3 x 25 mg/kg/d SMX iv/po	AI	**21 days, then secondary prophylaxis** until CD4 cell counts > 200 cells/µL for > 3 months
	+ Prednisone (if PaO2 < 10 kPa or < 70 mmHg, 15-30 min. before TMP-SMX)	2 x 40 mg/d po 5 days 1 x 40 mg/d po 5 days 1 x 20 mg/d po 10 days	AI	Benefit of corticosteroids if started before 72 hours
Alternative Therapy for *Moderate to Severe* PcP	**Pentamidine**	1 x 4 mg/kg/d iv (infused over 60 min.)	AI	
	or **Primaquine**	1 x 30 mg (base)/d po	AI	Check for G6PD deficiency
	+ Clindamycin	3 x 600-900 mg iv		
Alternative Therapy for *Mild to Moderate* PcP	**Primaquine**	1 x 30 mg (base)/d po	BI	Check for G6PD deficiency
	+ Clindamycin	3 x 600 mg/d po		
	or **Atovaquone suspension**	2 x 750 mg/d po (with food)	BI	
	or **Dapsone**	1 x 100 mg/d po	BI	Check for G6PD deficiency In case of rash: reduce dose of TMP (50%), antihistaminics
	+ Trimethoprim	3 x 5 mg/kg/d po		
Toxoplasma gondii Encephalitis				
Preferred Therapy	**Pyrimethamine**	Day 1: 200 mg po, **then** • If ≥ 60 kg; 1 x 75 mg po • If < 60 kg: 1 x 50 mg po	AI	**6 weeks, then secondary prophylaxis** until CD4 cell counts > 200 cells/µL for > 3 months
	+ Sulfadiazine	• If ≥ 60 kg: 2x 3000 mg/d po/iv • If < 60 kg: 2 x 2000 mg/d po/iv		
	+ Leucovorin	1 x 10-25 mg/d po		
Alternatives:	**Pyrimethamine**	Day 1: 200 mg po, **then** • If ≥ 60 kg: 1 x 75 mg po • If < 60 kg: 1 x 50 mg po	AI	Additional PcP prophylaxis is necessary
	+ Clindamycin	4 x 600-900 mg/d p.o/iv		
	+ Leucovorin	2 x 5-10 mg/d po		
	or **TMP-SMX**	2 x 5 mg TMP /kg po 2 x 25 mg SMX /kg po	BI	
	or **Pyrimethamine**	Day 1: 200 mg po, **then** If ≥ 60 kg; 1 x 75 mg po If < 60 kg: 1 x 50 mg po	BII	
	+ Atovaquone	2 x 1500 mg (with food)		
	+ Leucovorin	2 x 5-10 mg/d po		
	or **Sulfadiazine**	• If ≥ 60 kg: 4 x 1500 mg/d po/iv • If < 60 kg: 4 x 1000 mg/d po/iv	BII	
	+ Atovaquone	2 x 1500 mg (with food)		
	or **Pyrimethamine**	Day 1: 200 mg po, **then** • If ≥ 60 kg; 1 x 75 mg po • If < 60 kg: 1 x 50 mg po	BII	
	+ Azithromycin	1 x 900-1200 mg/d		
	+ Leucovorin	3 x 5-10 mg/d po		

Treatment of Opportunistic Infections

Disease	Drug	Dose	Evidence	Comments
Cryptococcal Meningitis				
Induction Therapy	**Liposomal AmphoB**	4 mg/kg/d iv	AI	**14 days** Then perform LP: if CSF culture sterile → switch to oral regimen. Adjust Flucytosin dosage to renal function to reduce bone marrow toxicity
	+ Flucytosine	4 x 25 mg/kg po		
Consolidation Therapy	**Fluconazole**	1 x 400 mg/d po (loading dose 800 mg day 1)	AI	**8 Weeks** (or until CSF culture sterile), **then secondary prophylaxis** Repeated LP until opening pressure < 20 cm H_2O or 50% of initial value
Candidiasis				
Oropharyngeal	**Fluconazole**	150-200 mg po	AI	Once or until improvement (5-7 days)
	or **Itraconazole**	1-2 x 100-200 mg/d po (oral solution fasting)	AI	7-14 days. Be aware of interactions with ARVs, see Drug-drug Interactions Between ARVs and Non-ARVs
	or **Amphotericin B**	3-6 lozenges at 10 mg/d		7-14 days
Oesophagitis	**Fluconazole**	400 mg po	AI	3 d
		or 400 mg loading dose, then 200 mg/d po		10-14 days
	or **Itraconazole**	1-2 x 200 mg/d po (oral solution fasting)	AI	10-14 days
Herpes simplex virus (HSV) Infections				
Initial Genital HSV	**Valacyclovir**	2 x 1000 mg/d po	AI	7-10 days
	or **Famciclovir**	2 x 500 mg/d po	AI	7-10 days
	or **Acyclovir**	3 x 400 mg/d po	AI	7-10 days
Recurrent Genital HSV (> 6 episodes/year)	**Valacyclovir**	2 x 500 mg/d po	AI	Chronic suppressive therapy
Severe Mucocutaneous Lesions	**Acyclovir**	3 x 5 mg/kg/d iv	AIII	3-4 weeks, after lesions begin to regress switch to oral treatment
Encephalitis	**Acyclovir**	3 x 10 mg/kg/d iv	AI	14-21 days
Varicella zoster virus (VZV) Infections				
Primary Varicella Infection (Chickenpox)	**Valacyclovir**	3 x 1000 mg/d po	AII	5-7 days
Herpes Zoster (Shingles): Not Disseminated	**Valacyclovir**	3 x 1000 mg/d po	AII	10 days
	or **Famciclovir**	3 x 500 mg/d po	AII	10 days
	or **Acyclovir**	3 x 5 mg/kg/d iv	AIII	10 days
Herpes Zoster: Disseminated	**Acyclovir**	3 x 10 mg/kg/d iv	AII	10-14 days

Treatment of Opportunistic Infections

Disease	Drug	Dose	Evidence	Comments
Cytomegalovirus (CMV) Disease				
Retinitis	**Ganciclovir**	2 x 5 mg/kg/d iv	AI	**3 weeks, then secondary prophylaxis**
For Immediate Sight-threatening Lesions	or **Ganciclovir** intraocular implant		AII	
	+ Valganciclovir	2 x 900 mg po		
For Small Peripheral Retinal Lesions	or **Valganciclovir**	2 x 900 mg po	AI	
	or **Foscarnet**	2 x 90 mg/kg iv	AI	
	or **Cidofovir** + Probenecid + Hydration 1x/week	5 mg/kg iv	BI	
Esophagitis/Colitis	**Ganciclovir**	2 x 5 mg/kg/d iv	BI	3 weeks
	or **Foscarnet**	2 x 90 mg/kg iv	BI	3 weeks
	or **Valganciclovir**	2 x 900 mg po	BII	In milder disease if oral treatment tolerated
Encephalitis/Myelitis	**Ganciclovir**	2x 5 mg/kg/d iv	BII	3-6 weeks
	or **Foscarnet**	2 x 90 mg/kg iv	CIII	
Bacillary angiomatosis (Bartonella henselae, Bartonella quintana)				
	Doxycycline	2 x 100 mg/d po	AII	Until improvement (until 2 months)
	or **Clarithromycin**	2 x 500 mg/d po	BIII	
Mycobacterium tuberculosis (see ART in TB/HIV Co-infection)				
	Rifampicin **+ Isoniazid** **+ Pyrizinamide** **+ Ethambutol**	Weight based	AI	Initial phase (Rifampicin+Isoniazid+Pyrizinamide+Ethambutol) for **2 months**, **then consolidation phase** (Rifampicin+Isoniazid) **for 4 months** see Diagnosis and Treatment of Resistant and Latent TB in HIV-positive Persons
Alternative	or **Rifabutin** **+ Isoniazid** **+ Pyrizinamide** **+ Ethambutol**	Weight based	AI	
Mycobacterium avium-intracellulare complex (MAC)				
	Clarithromycin	2 x 500 mg/d po	AI	12 months, then secondary prophylaxis until CD4 > 100 cells/µL for 6 months
	+ Ethambutol	1 x 15 mg/kg/d po	AI	
	Ev. + Rifabutin	450 mg/d po	CI	Rifabutin if resistance suspected, severe immunodeficiency (CD4 < 50 cells/µL), high bacterial load (> 2 L of CFU/mL of blood), no cART
	Ev. + Levofloxacin	1 x 500 mg/d po	CIII	4th drug to consider for disseminated disease
	or **Azithromycin**	1 x 500 mg/d po	AII	
	+ Ethambutol	1 x 15 mg/kg/d po give dosage 500-600 mg/d		
Mycobacterium kansasii				
	Rifampicin	600 mg/d po	AI	15-18 months
	+ Isoniazid	1 x 300 mg/d po		
	+ Ethambutol	20 mg/kg/d po		
	or			
	Rifampicin	600 mg/d po	BI	15-18 months
	+ Clarythromycin	2 x 500 mg po		
	+ Ethambuthol	15-20 mg/kg/d po		

Diagnosis and Treatment of Resistant and Latent TB in HIV-positive Persons

Treatment of TB in HIV-positive persons

For standard treatment of TB in HIV-positive persons, including appropriate choice of ARVs, see ART in TB/HIV Co-infection

Diagnosis of Multi-drug Resistant TB (MDRTB) / Extended-Drug Resistant TB (XDRTB)

MDRTB/XDRTB should be suspected in case of:

- Previous TB treatment
- Contact with MDR/XDR index case
- Birth, travel or work in an area endemic for MDRTB
- History of poor adherence
- No clinical improvement on standard therapy and/or sputum smear positive after 2 months; TB therapy or culture positive at 3 months
- Homelessness/hostel living and in some countries recent/current incarceration

Rapid Detection

Gene Xpert or similar technology has the advantage of rapid detection of drug resistance. Drug susceptibility testing is important in optimizing treatment.
Some countries/regions have neither of the above and have to use an empirical approach.

Treatment

Each dose of MDR/XDR regimen should be given as DOT throughout the whole treatment.

Treatment regimens should consist of at least four active drugs based on:

1. Susceptibility testing for Isoniazid, Rifampicin, fluoroquinolones, and injectable agents
2. Treatment history
3. Local surveillance data
4. Drug not been part of regimens used in the area

More than four drugs should be started if the susceptibility pattern is unknown or the effectiveness of one or more agents is questionable.

Drug Choices

Regimens often contain five to seven drugs

Include drugs from groups 1-5 (see below) in hierarchical order based on potency

1. Use any of the first-line oral agents (group 1) that are likely to be effective
2. Use an effective aminoglycoside or polypeptide by injection (group 2)
3. Use a fluoroquinolone (group 3)
4. Use the remaining group 4 drugs to complete a regimen of at least four effective drugs
5. For regimens with fewer than four effective drugs, consider adding two group 5 drugs

The regimen should be reassessed and modified if needed once drug sensitivity results become available.

Group 1: First-line oral agents	• Pyrazinamide (Z) • Ethambutol (E) • Rifabutin (RFB)
Group 2: Injectable agents	• Kanamycin (Km) • Amikacin (Am) • Capreomycin (CM) • Streptomycin (S)
Group 3: Fluoroquinolones	• Levofloxacin (LFX) • Moxifloxacin (MFX) • Olfoxacin (OFX) • Gatifloxacin (G)
Group 4: Oral bacteriostatic second-line agents	• Para-aminosalicylic acid (PAS) • Cycloserine (CS) • Terizidone (TRD) • Ethionamide (ETO) • Protionamide (PTO)
Group 5: Agents with unclear role in treatment of drug resistant-TB	• Clofazimine (CFZ) • Linezolid (LZD) • Amoxicillin/Clavulanate (Amx/CLV) • Thioacetazone (THZ) • Imipenem/Cilastatin (IPM/CLN) • High-dose Isoniazid (high-dose H-16–20 mg/kg/day) • Clarithromycin (CLR)

Duration of MDR/XDR Treatment

8 months of intensive phase using 5 or more drugs,
followed by 12 months of 3 drugs depending on response
e.g . 8 months of Z, Km, OFX, PTO and CS, followed by 12 months of OFX, PTO and CS.

Drug interactions with ART and MDR/XDR regimens

Unless RBT is being used, use normal doses but with caution as few data available on potential drug interactions, see ART in TB/HIV Co-infection

Treatment of Latent TB

Persons who are at a priori high risk of latent TB (evaluation based on geographic origin, +/- ART and CD4 level) and Mantoux skin test (or IGRA) positive may have the most benefit of chemopreventative therapy.

Treatment regimens for latent TB include

Drug	Duration
Rifinah	Daily 3 months
Isoniazid	Daily 6 months
Rifampicin	Daily 4 months
Rifapentine with Isoniazid	Weekly 3 months
Rifampin with Isoniazid	Twice weekly 3 months

Be aware of drug-drug interaction with ARVs, see ART in TB/HIV Co-infection

References

Green colour refers to specific references used in each section
Black colour refers to general references used in each section

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Please see references for Part III

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