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English

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Green text = online only at http://www.eacsociety.org and in the EACS Guidelines App. Page numbers in brackets refer to corresponding page in the online version of the Guidelines.

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Introduction to the EACS Guidelines 2016

Welcome to the EACS Guidelines!

These Guidelines were developed by the European AIDS Clinical Society (EACS), a not-for-profit organisation, whose mission is to promote excellence in standards of care, research and education in HIV infection and related co-infections, and to actively engage in the formulation of public health policy, with the aim of reducing HIV disease burden across Europe.

The EACS Guidelines were first published in 2005, and are currently available in print, online, and as a free App available for iOS and Android devices. The Guidelines are available in eight different languages, and are formally revised at least annually for the electronic version and biennially for the printed version. The electronic version can, however, be updated at any given moment if the panels consider it necessary.

The aim of the EACS Guidelines is to provide easily accessible recommendations to clinicians centrally involved in the care of HIV-positive persons.

The Guidelines consist of five main sections, including a general overview table of all major issues in HIV infection, as well as detailed recommendations on antiretroviral treatment, diagnosis, monitoring and treatment of co-morbidities, co-infections and opportunistic diseases.

Each respective section of the Guidelines is managed by a panel of experienced European HIV experts, and additional experts, where needed. All recommendations are evidence-based whenever possible, and based on expert opinions in the rare instances where adequate evidence is unavailable. It was decided not to provide formal grades of evidence in the Guidelines. The panels make decisions by consensus or by vote when necessary. Yet, it was decided not to publish results of the votes or discrepancies if any.

A list of the main references used to produce the Guidelines is provided as a separate section. Please reference the EACS Guidelines as follows: EACS Guidelines version 8.1, October 2016.

The diagnosis and management of HIV infection and related co-infections, opportunistic diseases and co-morbidities continue to require a multidisciplinary effort for which we hope the 2016 version of the EACS Guidelines will provide you with an easily accessible and updated overview.

All comments to the Guidelines are welcome, and can be directed to guidelines@eacsociety.org

Enjoy!

Manuel Battegay, Jens D. Lundgren and Lene Ryom

Oct. 2016

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Abbreviations

Antiretroviral drug (ARV) abbreviations

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
COBI	cobicistat (used as booster=/c)
d4T	stavudine
ddI	didanosine
DRV	darunavir
DTG	dolutegravir
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/c	protease inhibitors pharmacologically boosted with cobicistat
PI/r	protease inhibitors pharmacologically boosted with ritonavir
RAL	raltegravir
RPV	rilpivirine
RTV	ritonavir (used as booster=/r)
SQV	saquinavir
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
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
bid	twice daily
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
cART	combination antiretroviral treatment
CKD	chronic kidney disease
CKD-EPI	CKD epidemiology collaboration formula
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
FRAX	fracture risk assessment tool
GT	genotype
HAV	hepatitis A virus
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-c	HDL-cholesterol
HIVAN	HIV-associated nephropathy
HPV	human papillomavirus
HSR	hypersensitivity reaction
IGRA	interferon-gamma release assay
IHD	ischaemic heart disease
im	intramuscular
IRIS	immune reconstitution inflammatory syndrome
iv	intravenous
IVDU	intravenous drug use
LDL-c	LDL-cholesterol
LGV	lymphogranuloma venereum
Mg	magnesium
MSM	men who have sex with men
PAP	papanicolaou test
PEG-IFN	pegylated-interferon
PHI	primary HIV infection
po	per oral
PPD	purified protein derivative
PPI	proton pump inhibitor
PRT	proximal renal tubulopathy
PSA	prostate specific antigen
PTH	parathyroid hormone
qd	once daily
RBV	ribavirin
sc	subcutaneous
STI	sexually transmitted infection
SVR	sustained virological response
TC	total cholesterol
TDM	therapeutic drug monitoring
TG	triglycerides
tid	three times daily
TMP-SMX	trimethoprim-sulfamethoxazole
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)	+		First visit	Premature CVD: cardiovascular events in a first degree relative (male < 55, female < 65 years)	36-38, 40, 46
	• Concomitant medicines[(i)]	+	+	Every visit		
	• Past and current co-morbidities	+	+	Every visit		
	• Vaccination history	+		Annual	Measure antibody titres and offer vaccinations where indicated, see Vaccination	
Psychosocial	Current lifestyle (alcohol use, smoking, diet, exercise, drug use)	+	+	6-12 months	Adverse lifestyle habits should be addressed more frequently	35
	Employment	+	+	Every visit	Provide advice and support if needed	
	Social and welfare	+	+		Provide counselling if needed	
	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	61-63
	Safe sex	+			Risk of sexual transmission should be addressed	
	Partner status and disclosure	+			Recommend starting ART in serodifferent couples	
	Conception issues	+	+			
HIV DISEASE						
Virology	Confirmation of HIV Ab pos	+		3-6 months	More frequent monitoring of HIV-VL at start of ART	8-12
	Plasma HIV-VL	+	+		Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection	
	Genotypic resistance test and sub-type	+	+/-	At virological failure		
	R5 tropism (if available)		+/-		Screen if considering R5 antagonist in regimen	
Immunology	CD4 absolute count and % (optional: CD8 and %)	+	+	3-6 months	Annual CD4 count if stable on ART and CD4 count > 350 cells/μL[(ii)]	8-12
	HLA-B*5701 (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	61
	STI screen	+		Annual/ as indicated	Screen if at risk	
Viral Hepatitis	HAV serology	+		Annual/ as indicated	Screen at risk; vaccinate if non-immune	60, 69
	HCV screen	+			Annual screen if ongoing risk Measure HCV-RNA if HCV Ab pos or if acute infection suspected	
	HBV screen	+	+		Annual screen in susceptible persons; vaccinate if non-immune	
Tuberculosis	CXR	+		Re-screen if exposure	Consider routine CXR in persons from high TB prevalence populations. Use of PPD/IGRA depending on availability and local standard of care. IGRA should, however, be tested before PPD if both are to be used, given the potential for a false positive IGRA after PPD See Diagnosis and Treatment of TB in HIV-positive Persons	90-92, 14
	PPD if CD4 count > 400 cells/μL	+				
	IGRA in selected high-risk populations (if available)	+				
Others	Varicella zoster virus serology	+			Offer vaccination where indicated	60
	Measles/Rubella serology	+			Offer vaccination where indicated	
	Toxoplasmosis serology	+				
	CMV serology	+				
	Cryptococcus antigen	+/-			Consider screening for cryptococcus antigen in serum in persons with CD4 count < 100 cells/μL	85
	Leishmania serology	+/-			Screen according to travel history/origin	
	Tropical screen (e.g. Schistosoma serology)	+/-			Screen according to travel history/origin	
	Influenza virus	+		Annual	In all HIV-positive persons, see Vaccination	60
	Streptococcus pneumonia	+			No recommendations available regarding the need for a booster dose, see Vaccination	60

	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		35
Cardiovascular Disease	Risk assessment (Framingham score[iii])	+	+	2 years	Should be performed in all men > 40 years and women > 50 years without CVD	36
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
Hypertension	Blood pressure	+	+	Annual		37-39
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	42
Glucose	Serum glucose	+	+	Annual	Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL)	40-41
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		50-54
	ALT/AST, ALP, Bilirubin	+	+	3-12 months	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs	
	Staging of liver fibrosis			12 months	In HCV and/or HBV co-infected persons (e.g. FibroScan, serum fibrosis markers)	51-52, 73
	Hepatic ultrasound			6 months	Persons with liver cirrhosis and persons with HBV co-infection at high risk of HCC[xiii]	52, 69, 73
Renal Disease	Risk assessment[vi]	+	+	Annual	More frequent monitoring if eGFR < 90mL/min, CKD risk factors present[vi] and/or prior to starting and on treatment with nephrotoxic drugs[ix]	46-49
	eGFR (CKD-EPI)[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[viii]	
Bone Disease	Bone profile: calcium, PO_4, ALP	+	+	6-12 months		43, 45
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons (see page 43 for details)	
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons	44
Neurocognitive Impairment	Screening questionnaire	+	+	As indicated	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 68 for further assessment.	68
Depression	Questionnaire	+	+	As indicated	Screen at risk persons	64-66
Cancer	Mammography			1-3 years	Women 50-70 years	34, 52
	Cervical PAP			1-3 years	Sexually active women	
	Rectal exam and anoscopy (MSM)			1-3 years	Evidence of benefit not known	
	Ultrasound and alpha-foetoprotein			6 months	Controversial; persons with cirrhosis and persons with HBV co-infection at high risk of HCC[xiii]	
	Others				Controversial	

i Review all concomitant medicines which may potentially interact with ARVs or increase co-morbidities, see
Drug-drug Interactions between DAAs and ARVs
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 Anticoagulants/Antiplatelet Agents and ARVs
Drug-drug Interactions between Antimalarial Drugs and ARVs
Drug-drug Interactions between Corticosteroids and ARVs
Drug-drug Interactions between Contraceptives and ARVs
Drug-drug Interactions between DAAs and ARVs
and http://www.hiv-druginteractions.org

ii If stable on ART with undetectable HIV-VL and CD4 count > 350 cells/μL, suggest annual CD4 count.

iii A risk equation developed from HIV populations is available, see http://www.chip.dk/Tools Of note, if an individual receives medicines 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 http://www.hivpv.org.

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 CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated > 60 mL/min. The abbreviated modification of diet in renal disease (aMDRD) or the Cockroft-Gault (CG) equation may be used as an alternative; see http://www.chip.dk/Tools

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 Different models have been developed for calculating a 5-year CKD risk score while using different nephrotoxic ARVs, integrating HIV independent and HIV-related risk factors [4], [5]

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: http://www.shef.ac.uk/FRAX

xii A diagnosis of COPD should be considered in persons over the age of 35 years 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.

xiii Persons of Asian and Black ethnicity, family history of HCC, liver cirrhosis, NAFLD or replicating HBV infection

Part II ART of HIV-positive Persons

Assessing HIV-positive Persons' Readiness to Start and Maintain ART[x]

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's stage of readiness using WEMS[i] techniques, and start discussion with an open question/invitation: "I would like to talk about HIV medicines." <wait> "What do you think about them?" 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, individualised 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 and side effects. / Discuss integration into daily life. / Assess self-efficacy. Ask: How confident are you that you can take your medicines as we discussed (specify) once you have started? Use VAS 0-10[iii] Consider skills training: • Medicines-taking training, possibly Medication Event Monitoring System, e.g. electronic pill boxes • Directly observed therapy with educational support • Use aids: mobile phone alarm, pillboxes • Involve supportive tools/persons where appropriate
START ART	
Action: ***"I will start now."***	**'Final check': With a treatment plan established, is the person capable of taking ART and is ART available?**
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 medicines? 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

Several barriers are known to influence ART decision making and adherence to ART	
Screen for and talk about problems and facilitators	
Consider systematic assessment of: • Depression[vii], see page 64-65 • Cognitive problems[viii], see page 68 • Harmful alcohol[ix] or recreational drug use, see page 33, 35	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 the stage, and then to support/intervene accordingly. In the case of late presentation (CD4 count < 350 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 medicines: 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 PHQ-2 or PHQ-9 [4]. Meta-analysis shows a consistent relationship between depression and ART non-adherence that is not limited to those with clinical depression. Therefore, assessment and intervention aimed at reducing depressive symptom severity, even at subclinical level is important. Ask: "Over the last two weeks, how often have you been bothered by any of the following problems? 1. Little interest or pleasure in doing things; 2. Feeling down, depressed or hopeless." Answers: Not at all (0) / Several days (1) / More than half the days (2) / Nearly every day (3). If the person scores 2 or more, seven additional questions, see [5]

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?" [6].

ix FAST-alcohol use, ask: How often have you had 6 or more units if female, or 8 or more units if male, on a single occasion in the last year? Never=0, Less than monthly=1, Monthly=2, Weekly=3, Daily or almost daily=4. Stop if the answer is 0 (Never). Ask more questions if the answer is 1, 2, 3 or 4. See [7].

x Algorithm adapted from [8].

Recommendations for Initiation of ART in HIV-positive Persons with Chronic Infection without prior ART Exposure

Recommendations take into account the level of evidence, the degree of progression of HIV disease and the presence of, or high risk for, developing various types of (co-morbid) conditions.

ART is recommended in all adults with chronic HIV infection, irrespective of CD4 counts[i]

i ART should always be recommended irrespective of the CD4 count, but the lower the CD4 count, the greater the urgency to start ART immediately.

- For best timing for starting ART in persons with tuberculosis and cryptococcal meningitis, see page 14 and page 85.
- A possible exception could be elite controllers with high and stable CD4 count. Time should always be taken to prepare the person, in order to optimise 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 drug with high genetic barrier to resistance in the first-line regimen (e.g. a PI/r, PI/c or DTG). Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to obtain a baseline to assess subsequent response.
- Use of ART should also be recommended with any CD4 count in order to reduce sexual transmission, risk of AIDS event and mother-to-child transmission of HIV (before third trimester of pregnancy).

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

A) Recommended regimens (one of the following to be selected)[*,]**

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC/DTG[i, ii]	ABC/3TC/DTG 600/300/50 mg, 1 tablet qd	None	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before). DTG 50 mg bid with rifampicin.
TAF/FTC[iii] or TDF/FTC[iv, v] + DTG	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + DTG 50 mg, 1 tablet qd	None	
TAF/FTC/EVG/c[iii] or TDF/FTC/EVG/c[iv, vi]	TAF/FTC/EVG/c 10/200/150/150 mg, 1 tablet qd or TDF/FTC/EVG/c 300/200/150/150 mg, 1 tablet qd	With food	Al/Ca/Mg-containing antacids or multivitamins should be taken well separated in time (minimum 2h after or 6h before).
TAF/FTC[iii] or TDF/FTC[iv, v] + RAL	TAF/FTC 25/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Co-administration of antacids containing Al or Mg not recommended. RAL 400 or 800 mg bid with rifampicin.
2 NRTIs + NNRTI			
TAF/FTC/RPV[iii] or TDF/FTC/RPV[iv]	TAF/FTC/RPV 25/200/25 mg, 1 tablet qd or TDF/FTC/RPV 300/200/25 mg, 1 tablet qd	With food (min 390 Kcal required)	Only if CD4 count > 200 cells/µL and HIV-VL < 100,000 copies/mL. PPI contra-indicated; H2 antagonists to be taken 12h before or 4h after RPV.
2 NRTIs + PI/r or PI/c			
TAF/FTC[iii] or TDF/FTC[iv, v] + DRV/c or + DRV/r	TAF/FTC 10/200 mg, 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Monitor in persons with a known sulfonamide allergy.

B) Alternative regimens (to be used when none of the preferred regimens are feasible or available, whatever the reason)

Regimen	Dosing	Food requirement	Caution
2 NRTIs + INSTI			
ABC/3TC[i, ii] + RAL	ABC/3TC 600/300 mg, 1 tablet qd + RAL 400 mg, 1 tablet bid	None	Co-administration of antacids containing Al or Mg not recommended. RAL 400 or 800 mg bid with rifampicin.
2 NRTIs + NNRTI			
ABC/3TC[i, ii] + EFV[vii]	ABC/3TC 600/300 mg, 1 tablet qd + EFV 600 mg, 1 tablet qd	At bed time or 2 hours before dinner	Only if HIV-VL < 100,000 copies/mL
TDF/FTC/EFV[iv, vii]	TDF/FTC/EFV 300/200/600 mg, 1 tablet qd		
2 NRTIs + PI/r or PI/c			
ABC/3TC[i, ii] + ATV/c or + ATV/r[viii]	ABC/3TC 600/300 mg, 1 tablet qd + ATV/c 300/150 mg, 1 tablet qd or + ATV 300 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Only if HIV-VL < 100,000 copies/mL
TAF/FTC[iii] or TDF/FTC[iv, v] + ATV/c or ATV/r[viii]	TAF/FTC 10/200 mg 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + ATV/c 300/150 mg 1 tablet qd or + ATV 300 mg, 1 tablet qd + RTV 1 tablet 100 mg qd		
ABC/3TC[i, ii] + DRV/c or + DRV/r	ABC/3TC 600/300 mg, 1 tablet qd + DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 1 tablet 100 mg qd	With food	Monitor in persons with a known sulfonamide allergy.
TAF/FTC[iii] or TDF/FTC[iv, v] + LPV/r	TAF/FTC 10/200 mg 1 tablet qd or TDF/FTC 300/200 mg, 1 tablet qd + LPV 200 mg + RTV 50 mg, 2 tablets bid	With food	Use with caution in persons with high cardiovascular risk
Other combinations			
3TC[ii] + LPV/r	3TC 300 mg, 1 tablet qd + LPV 200 mg, 2 tablets bid + RTV 50 mg, 2 tablets bid	With food	
RAL[ii] + DRV/c or + DRV/r	RAL 400 mg, 1 tablet bid + DRV/c 800/150 mg, 1 tablet qd or + DRV 800 mg, 1 tablet qd + RTV 100 mg, 1 tablet qd	With food	Only if CD4 count > 200 cells/µL and HIV-VL < 100,000 copies/mL. Co-administration of antacids containing Al or Mg not recommended.

* 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 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 (> 20%).
ii Use this combination only if HBsAg-negative.
iii In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the concentration of the active metabolite (tenofovir disoproxil). When available, combinations containing TDF can be replaced by the same combinations containing TAF, especially in elderly HIV-positive persons or in HIV-positive persons with or at increased risk of osteoporosis or renal impairment. Note that few data are available and there are ongoing studies comparing TAF/FTC vs. TDF/FTC when third drug is other than EVG/c. Use TAF/FTC/EVG/c only if eGFR > 30mL/min. TAF is used at 10 mg when co-administered with drugs that inhibit P-gp and at 25 mg when co-administered with drugs that do not inhibit P-gp.
iv Avoid TDF if osteoporosis, renal monitoring required, see page 47
v If TDF/FTC is not available, one alternative could be TDF+3TC as separate entities.
vi TDF/FTC/EVG/c use only if eGFR ≥ 70 mL/min. It is recommended that TDF/FTC/EVG/c is not initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment.
vii EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains.
viii Co-administration of PPI is contra-indicated. If PPI co-administration is judged unavoidable, consider an alternative regimen; if given, dose increase of ATV to 400 mg qd may be considered, 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. H2 antagonists to be taken 12 hours before or 4 hours after ATV.

Primary HIV Infection (PHI)

Definition of PHI[i-iv]

- High-risk exposure within previous 6 months, and
- Detectable virus in plasma (p24 Ag and/or HIV-RNA) and/or
- Evolving anti-HIV antibody reactivity (negative or indeterminate to positive)
- With (23-92%) or without clinical symptoms.

Classification of PHI[i-iv]

- Acute infection: HIV detection (p24 Ag and/or HIV-RNA) in the absence of HIV antibody.
- Recent infection: HIV antibody detection; up to 6 months after infection.

Starting treatment[v-vi]

Treatment of PHI is recommended for all HIV-positive persons. Several circumstances indicate immediate treatment initiation.

Circumstances where immediate treatment initiation should be advised

Acute infection
Severe or prolonged symptoms
Neurological disease
Age ≥ 50 years
CD4 count < 350 cells/μL

The recommendation is based on:
- Demonstrated virological and immunological benefits and anticipated clinical benefits of early therapy[v].
- Reduced risk of transmission.
- Usually short interval between identification of PHI and a CD4 count < 500 cells/μL.
- Reduced anxiety and facilitated disclosure to contacts.

The HIV-positive person must be willing to take therapy, and counselling should promote engagement by emphasising the benefits of starting treatment early. The HIV-positive person should also be made aware of the potential disadvantages of early treatment[vi].
Asymptomatic persons with PHI with a recent infection and a preserved CD4 count who decide to defer therapy should enter follow-up according to the guidance outlined for established (chronic) infection.
Once treatment is started, it should be continued. A subsequent interruption is not recommended.

Treatment selection

- The HIV-positive person should preferably be recruited into a clinical trial or studies investigating HIV curative strategies.
- Any use of pre-exposure or post-exposure prophylaxis should be established and taken into account.
- A drug resistance test is recommended in all cases as soon as possible after diagnosis. A genotypic (rather than phenotypic) test is recommended due to increased sensitivity and wide availability.
- Where there are indications for immediate treatment (see table), therapy may have to start before the results of resistance testing become available. Whilst evidence is evolving, current guidance remains that in such cases preference should be given to starting a PI/r or PI/c in order to increase the barrier to resistance of the overall regimen. An INSTI should also be included in order to induce rapid viral load suppression. A combination of TDF or TAF, FTC, and either boosted DRV, or an INSTI should therefore be considered, and the regimen adjusted, if needed, once the resistance test becomes available and viral load suppression is achieved. Where such a regimen is not available, national epidemiological data on prevalence and patterns of transmitted drug resistance (where available and sufficiently representative) may assist with the treatment selection process.

Other considerations

- All HIV-positive persons should undergo investigations to diagnose sexually transmitted infections (e.g. syphilis, gonorrhoea, chlamydia), HBV and HCV. Antibody seroconversion can be delayed and tests to identify the viral RNA are required in order to identify a recent HCV infection.
- All HIV-positive persons should be counselled about the high risk of transmission, preventive measures, and importance of notifying partners.

i HIV-1 RNA becomes detectable in plasma around day 11 after exposure, approximately 7 days before p24 Ag and 12 days before anti-HIV antibodies.

ii Where available, Western Blot (WB) or Immunoblot patterns of reactivity can be used to stage the infection as follows [11];
- Stage I: HIV-RNA positive only (average duration 5 days). HIV-VL levels are median 2,000 copies/mL (IQR 300-20,000 copies/ml), and are < 100 copies/mL in approximately 10% of HIV-positive persons. Low HIV-VL levels should be interpreted with caution due to the risk of false positivity (e.g., due to contamination)
- Stage II: HIV-RNA and p24 Ag positive only (average duration 5.3 days). NB: HIV-VL levels are usually > 10,000 copies/mL
- Stage III: HIV-RNA, p24 Ag and anti-HIV antibody positive by immune-assay, no specific WB bands (average duration 3.2 days)
- Stage IV: as Stage III but indeterminate WB pattern (5.6 days)
- Stage V: as Stage III, but reactive WB pattern lacking p31 reactivity (average duration 69.5 days)
- Stage VI: as stage III but full WB reactivity including a p31 band (indefinite)

iii Everyone with detectable HIV-VL and negative or indeterminate serology must receive confirmation of anti-HIV antibody seroconversion in follow-up testing. The interval of testing (up to stage V) is one week.

iv Some centres may have access to sero-incidence markers (e.g., antibody avidity testing) that identify an infection acquired within the previous 3-6 months. Assay reliability varies and results should be interpreted with caution when they are the sole indicators of a recent infection.

v Potential benefits of treatment: reduce severity of acute symptoms; lower the HIV-VL set-point and size of the viral reservoir; reduce viral genetic evolution; reduce immune activation and inflammation; preserve immune function and integrity of lymphoid tissue; possibly exert neurological and gut protection; possibly enhance post-treatment control and response to future eradication strategies. These effects are more likely if treatment is started in the acute phase of PHI.

vi Potential disadvantage of treatment: firm, controlled evidence that treatment of PHI results in clinical benefit in the long-term (relative to starting therapy past the PHI stage) is currently lacking. Data supporting immediate treatment are mostly derived from persons with symptomatic PHI. Low likelihood of post-treatment control; treatment interruption usually leads to rebound of HIV-VL and inflammation markers; possible adverse consequences of long-term ART (toxicity, drug resistance). A small subset of HIV-positive persons can spontaneously control the infection without treatment (elite controllers).

Switch Strategies for Virologically Suppressed Persons

Definition of virologically suppressed

Clinical trials exploring switching strategies have defined suppression as an HIV-VL < 50 copies/mL for at least 6 months.

Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. Examples of these reactive switches: lipoatrophy (d4T, AZT), central nervous system adverse events (EFV), diarrhoea (PI/r) and jaundice (ATV).
2. **Prevention of long-term toxicity.** Example of this proactive switch: prevention of lipoatrophy in persons receiving d4T or AZT.
3. **Avoid serious drug-drug interactions**
4. **Planned pregnancy**
5. **Ageing and/or co-morbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification:** to reduce pill burden, adjust food restrictions and improve adherence.

Principles

1. Clinicians should always review possible adverse events or tolerability issues with current antiretroviral regimens. Just because the HIV-VL is suppressed it should not be assumed that the HIV-positive person is well adapted and tolerating the current regimen.
2. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of co-morbid conditions, and improve quality of life.
3. The primary concern when switching should be to sustain and not to jeopardize virological suppression. In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy. The majority of clinical trials showing non-inferiority of the new regimen after the switch have actively excluded persons with prior virological failures.
4. A complete ARV history with HIV-VL, tolerability issues and cumulative genotypic resistance history should be analysed prior to any drug switch.
5. A PI/r or PI/c may be switched to unboosted ATV, an NNRTI, or an INSTI only if full activity of the 2 NRTIs remaining in the regimen can be guaranteed. Switches have to be planned especially carefully when they result in a decrease in the genetic barrier of the regimen in case of prior virologic failures. Clinicians should review the complete ARV history and available resistance test and HIV-VL results before switching, and ensure no drug-drug interactions may lead to suboptimal drug levels (e.g. unboosted ATV and TDF).
6. Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. For example, the development of the M184V RT mutation in HIV-positive persons who fail a 3TC-containing regimen might preclude the future use of all currently available single-tablet regimens.
7. Switches of single drugs with the same genetic barrier (for example EFV to RAL) is usually virologically safe in the absence of resistance to the new compound.
8. Clinicians should carefully review the possibility of drug-drug interactions with the new regimen.
9. If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV status (avoid discontinuation of TDF in persons with chronic HBV and assess HBV vaccination status).
10. HIV-positive persons should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity of the new regimen.
11. If a HIV-positive person receives and tolerates a regimen that is no longer a preferred option, there is no need to change. Example: persons tolerating EFV-containing regimens.

Strategies not recommended

a. Intermittent therapy, sequential or prolonged treatment interruptions
b. Specific two-drug combination, i.e. 1 NRTI + 1 NNRTI or 1 NRTI + 1 unboosted PI, 1 NRTI + RAL, 2 NRTIs, MVC + RAL, PI/r or PI/c + MVC, ATV/r or ATV/c + RAL
c. Triple NRTIs combinations

Class-sparing strategies

PI/r monotherapy and dual therapy with 3TC+ PI/r may only be given to persons without a) resistance to the PI, b) suppression of HIV-VL to < 50 copies/mL for at least the past 6 months and c) absence of chronic HBV co-infection.

Boosted PI monotherapy with DRV/r or DRV/c qd or LPV/r bid might represent an option in persons with intolerance to NRTIs or for treatment simplification or in recreational drug users with documented frequent interruption of cART. This strategy is associated with more virological rebounds than continuing triple therapy. However, resistance occurs rarely, and suppression can be regained with nucleoside reintroduction.

Dual therapy: 3TC + DRV/r or + DRV/c or + LPV/r or + ATV/r or + ATV/c.
In clinical trials this strategy has not been associated with more virological rebounds than triple therapy. It might therefore be a better option than PI/r or PI/c monotherapy.

Virological Failure

Definition	Confirmed (< 1 month) HIV-VL > 50 copies/mL 6 months[i] after starting therapy (initiation or modification) in persons on ART. Depending on the HIV-VL assay, this limit could be higher or lower.
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 ART 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 copies/mL:
	Change regimen as soon as possible. What to change will depend on the resistance testing results:
	If no resistance mutations found: re-check for adherence, perform TDM
	If resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary expert discussion advised
	Goal of new regimen: HIV-VL < 50 copies/mL within 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, and future salvage therapy

i In persons with very high baseline HIV-VL (> 100,000-500,000 copies/mL) achieving viral suppression may take longer than 6 months.

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. In such instance, risk of transmission is 0 to < 0.5%
Resistance testing	Same as for non-pregnant women, i.e. before starting ART and in case of virological failure
SCENARIO	
1. Women planning to be pregnant while already on ART	1. Maintain ART, unless taking some contra-indicated regimen during pregnancy (ddI + d4T, triple NRTI combinations)
2. Women becoming pregnant while already on ART	2. Maintain ART, unless taking some contra-indicated regimen during pregnancy (ddI + d4T, triple NRTI combinations)
3. Women becoming pregnant while treatment-naïve	3. Starting ART as soon as possible is highly recommended
4. Women whose follow-up starts after week 28 of pregnancy	4. Start ART immediately and consider INSTI as the preferred choice to obtain rapid HIV-VL decline in case of high HIV-VL
5. Women whose HIV-VL is not undetectable at third trimester	5. Perform resistance testing and consider changing to or adding INSTI to obtain rapid HIV-VL decline
Antiretroviral regimen in pregnancy	Same as non-pregnant
	NVP not to be initiated but continuation is possible if started before pregnancy
	EFV can be started if other options are not available or suitable. Continuation of EFV is possible if already started before pregnancy
	Among PI/r, prefer LPV/r or ATV/r
	If RAL, EVG/c, RPV or DRV/r: could be continued
	Limited experience with TAF and DTG in pregnancy: use with caution
Drugs contra-indicated during pregnancy	ddI + d4T, triple NRTI combinations
iv ZDV during labour	Only if HIV-VL > 50 copies/mL at week 34-36
Single dose NVP during labour	Not recommended
Caesarean section	Only if HIV-VL > 50 copies/mL at week 34-36

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 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 count

< 50 cells/μL*,** : As soon as TB treatment is tolerated and wherever possible within 2 weeks

≥ 50 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

Although a RCT showed that early ART (within 2 weeks) did not reduce mortality in TB meningitis, recommendations on ART initiations should be based on the CD4 count in HIV-positive persons with TB co-infection.

* Be aware of IRIS reaction in persons starting ART at low CD4 count 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 count, a cut-off of 100 cells/μL may be more appropriate.

Recommended 1st line ARV combination with anti-TB medicines

TDF/FTC + RAL or TDF/FTC/EFV (see table for dose adjustment with rifamycins).

Alternatives

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

- TDF/FTC + PI/r, using rifabutin instead of rifampicin (see table for dose adjustment of rifabutin). Use with caution.
- TDF/FTC + DTG bid*** with rifampicin.

In countries where neither DTG nor rifabutin are available, following combinations could also represent a short-term alternative until anti-TB treatment has been completed.

- Rifampicin plus fixed-dose combination of ABC/3TC/ZDV bid + TDF qd (if HIV-VL < 100,000 copies/mL).
- Rifampicin plus double dose LPV/r or with RTV super boosted (400 mg bid) + LPV.
- For other regimens based on 2 NRTIs plus NVP, RPV, ETV or MVC, consultation with an HIV specialist is recommended.

*** Only pharmacokinetic and not clinical data are available, 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(i)		rifampicin: standard dose of all drugs
		rifabutin: standard dose of all drugs
PI/r and PI/c		rifampicin: not recommended
PI/r	Monitor liver enzymes and, whenever possible, perform TDM for PI	rifabutin: dose as 150 mg qd(ii). PI/r at standard dose
PI/c		rifabutin: not recommended. If needed recommended dose of rifabutin: 150 mg qd(iii)
NNRTIs	EFV	rifampicin: No dose change required. EFV: standard dose ARV TDM recommended after 2 weeks
		rifabutin: 450 mg qd. 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/c	rifampicin: not recommended
		rifabutin: 150 mg qd. EVG: standard dose. Use with caution.
	RAL	rifampicin: standard dose. RAL 400 or 800 mg bid and perform TDM for RAL
		rifabutin: standard dose of both drugs
	DTG	rifampicin: standard dose. DTG 50 mg bid (use only in absence of INSTI resistance)
		rifabutin: standard dose of both drugs
Other ART	MVC	rifampicin: MVC 600 mg bid
		rifabutin: Standard dose of MVC (300 mg bid in absence of a PI, 150 mg bid in presence of a PI)

i The drug-drug interaction between TAF and rifampicin has not been evaluated in detail yet. As TAF may be susceptible to enzymatic induction, avoid its use during rifampicin-containing anti-TB treatment.

ii Initial pharmacokinetic studies in healthy volunteers showed that concentrations of rifabutin and its active metabolite were significantly increased when combined with PI/r. Thus, a reduction of rifabutin dosage to 150 mg x3/week was recommended to reduce the risk of rifabutin-related toxicity. However, more recent pharmacokinetic data derived from HIV/TB co-infected persons have shown that the co-administration of LPV/r or ATV/r with rifabutin (150 mg x3/week) resulted in rifabutin concentrations that were lower than those observed with rifabutin 300 mg x1/day without PI/r suggesting that rifabutin dosage may be inadequate. Cases of relapses with acquired rifamycin-resistant TB have been described in co-infected persons treated with rifabutin 150 mg x3/week and LPV/r or ATV/r. The US guidelines for HIV treatment recommend the administration of rifabutin at 150 mg qd with PI/r. Due to the limited safety data with this dose and combination, persons receiving rifabutin 150 mg qd with PI/r should be closely monitored for rifabutin related toxicities (i.e. uveitis or neutropenia).

iii Few data are available. Use with caution and always seek the advice of an HIV specialist. Some experts advise that, in presence of COBI a rifabutin dose of 150 mg x3/week may be used in order to reduce the risk of toxicity. If used at 150 mg qd, enhanced monitoring of rifabutin toxicity is needed.

Post-exposure Prophylaxis (PEP)

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 recent 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	Viraemic HIV-positive or serostatus unknown but presence of HIV risk factors. If source person is on ART, PEP should be started, HIV-VL should be repeated, and, if undetectable, PEP can be stopped
	Receptive oral sex with ejaculation	Viraemic 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 HIV-VL detectable
- Individualise PEP according to the source's treatment history and previous resistance tests
- For sexual exposure, if HIV-positive source has documented undetectable HIV-VL, PEP is no longer recommended.
- PEP to be started ideally < 4 hours after the exposure, and no later than 48/72 hours
- Duration of PEP: 4 weeks (unless discontinued due to lack of indication)
- PEP regimens: TDF/FTC (alternative: ZDV/3TC) + RAL bid, or + DRV/r qd or + LPV/r bid. TDF/FTC + DTG qd may be also considered as an alternative
- Clinical experience with TAF in the PEP setting is lacking, hence its use should be avoided

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

Pre-exposure Prophylaxis (PrEP)

1. PrEP should be used in adults at high-risk of acquiring HIV infection when condoms are not used consistently. Before PrEP is initiated, HBV serology status should be documented.

- Recommended in HIV-negative men who have sex with men (MSM) and transgender individuals when condoms are not used consistently with casual partners or with HIV-positive partners who are not on treatment. A recent STD, use of post-exposure prophylaxis or chemsex may be markers of increased risk for HIV acquisition.
- May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and have multiple sexual partners where some of whom are likely to have HIV infection and not being on treatment.

2. PrEP is a medical intervention that provides a high level of protection against HIV acquisition but does not protect against other STDs and should be used in combination with other preventive interventions. PrEP should be supervised by a doctor, experienced with sexual health and use of HIV medicines, possibly as part of a shared care arrangement.

   The following procedures are recommended:

- Documented negative fourth generation HIV test prior to starting PrEP. During PrEP, this test should be repeated every 3 months, and PrEP should be stopped immediately in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test and the person referred for evaluation to an HIV unit.
- Before PrEP is initiated, HBV serology status should be documented. If HBsAg positive, see Clinlical Management and Treatment of HBV and HCV Co-infection in HIV-positive Persons.
- Counsel that PrEP does not prevent other types of STDs; screen for STD (including HCV) when starting PrEP and regularly during use of PrEP.
- Counsel that PrEP may impact renal and bone health, see page 47 and 43. Check renal function before starting PrEP and check renal function and bone mineral density during PrEP according to guidelines on TDF use.
- Counsel that PrEP, like other prevention methods, only works when it is taken. Adherence counselling is recommended.
- Counsel that PrEP can be prescribed long-term but that each consecutive PrEP prescription should be for a period of maximum 3 months (90 tablets) to ensure appropriate monitoring.

3. PrEP regimen

- TDF/FTC 300*/200 mg 1 tablet qd. For MSM with high-risk sexual behavior PrEP may be dosed ‘on demand’ (double dose of TDF/FTC 2-24 hours before each sexual intercourse, followed by two single doses of TDF/FTC, 24 and 48 hours after the first drug intake). If dosed ‘on demand’, the total dose per week should not exceed 7 tablets.
- Use of generic formulations of TDF/FTC, if and where available, may help to improve the cost-effectiveness of PrEP, which is essential for its use as public health approach.
- There are not currently clinical data on the use of 3TC or TAF for PrEP.

* In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate).

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
NRTIs										
ABC	Rash*	Nausea* Diarrhoea*		IHD						*Systemic hypersensitivity syndrome (HLA B*5701 dependent)
ZDV[ii]	Nail pigmentation	Nausea	Steatosis		Myopathy, Rhabdomyolysis			**Lipoatrophy**	Dyslipidaemia, Hyperlactataemia	Anaemia
d4T[ii]		Pancreatitis	**Steatosis**				**Peripheral neuropathy**		**Dyslipidaemia,** Hyperlactataemia	
ddI[ii]			Steatosis, Liver fibrosis	IHD					Hyperlactataemia	
3TC										
FTC										
TDF[iii]					↓ BMD, Osteomalacia ↑ Fractures risk	↓ eGFR, Fanconi syndrome				
TAF[iii]										
NNRTIs										
EFV	Rash		Hepatitis				**Depression, Sleep disturbances, Headache,** Suicidal ideation		**Dyslipidaemia,** Gynaecomastia	**↓ plasma 25(OH) vitamin D,** Teratogenesis
ETV	Rash									
NVP	Rash*		Hepatitis*							*Systemic hypersensitivity (CD4 count-and gender-dependent)
RPV	Rash		Hepatitis			↓ eGFR[iv]	Depression, Sleep disturbances, Headache			
PIs										
ATV[v]		**Nausea and Diarrhoea**[vii]	**Hyperbilirubinaemia,** Jaundice, Cholelithiasis			↓ eGFR, Nephrolithiasis			Dyslipidaemia	
DRV[v]	Rash					Nephrolithiasis			Dyslipidaemia	
FPV[vi]	Rash			IHD					**Dyslipidaemia**	
IDV[vi]	**Dry skin,** Nail dystrophy		Jaundice	IHD		**Nephrolithiasis**		**↑ Abdominal fat**	**Dyslipidaemia,** Diabetes mellitus	
LPV				IHD		↓ eGFR			**Dyslipidaemia**	
SQV[vi]									Dyslipidaemia	
TPV[vi]			Hepatitis				Intracranial haemorrhage		Dyslipidaemia	
Boosting										
RTV						**↓ eGFR**[iv]				
COBI						**↓ eGFR**[iv]				

FI										
ENF	Injection nodules									Hypersensitivity
INSTI										
RAL		Nausea			Myopathy, Rhabdomy-olysis		Sleep distubances, Headache			Systemic hypersensitivity syndrome[viii]
DTG	Rash	Nausea				↓ eGFR[iv]	**Sleep disturbanes, Headache**			Systemic hypersensitivity syndrome (< 1%)
EVG/c		**Nausea,** Diarrhoea				↓ **eGFR**[iv]	Sleep disturbances, Headache			
CCR5 inhibitor										
MVC			Hepatitis	IHD						↑ Infection risk

i **"Frequent effects" (events expected in at least 10% of treated HIV-positive persons), in bold**
"Severe effects" (events that can put a person's life at risk and represent a medical emergency), in red
"Neither frequent nor severe effects", in black
ii Still available, but generally not recommended due to toxicity.
iii TDF has been the classical prodrug of tenofovir. TAF may have a lower risk of tenofovir-related kidney and bone adverse effects but long-term experience is lacking.
iv Due to inhibition of renal tubular creatinine secretion without affecting glomerular filtration itself.
v ATV can be used unboosted, or boosted with low-dose RTV or COBI. ATV-related adverse effects are more common with boosting. DRV can be used boosted with low-dose RTV or COBI. Both low-dose RTV and COBI as boosters may cause similar minor digestive problems.
vi Still available but seldom used. Requires RTV-boosting.
vii Frequency and severity differs between individual ARVs.
viii DRESS syndrome reported, but currently in only 6 cases.
* 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/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Cardiovascular drugs	atorvastatin	↑	↑	↑	↑490%	↓43%	↓37%	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	fluvastatin	↔	↑	↔	↔	↑	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	pravastatin	↔	↑	↑81%	↔	↓44%	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	rosuvastatin	↑213%	↑	↑48%	↑107%	↔	↔	↔	↔	↔	↔	↑38%	↔	↔	↔	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↓68%	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	amlodipine	↑[iii]	↑	↑	↑[iii]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[iii]	↑	↑	↑[iii]	↓69%	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑[iii]	↑	↑	↑[iii]	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑[iii]	↑	↑	↑[iii]	↓	↓E	↓	E	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	↑	↑D	↓27%D36%	D	↓D	D	D	D	D	D	↑	↔	↔	D	↔	↑[ix]
	lamotrigine	↓32%[ii]	↔	↓[ii]	↓50%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenytoin	↓D	D	↓D	↓D	↓D	D	↓D	D	D	D	D	D	D	↔	↔	D	↔	↓
Anti-infectives	clarithromycin	↑[iii]	↑	↑	↑[iii]	↓	↓E	↓	E	E	↔	↑E	↔	↔	↔	↔	E	E	D
	fluconazole	↔	↑?	↔	↔	↔	E86%	E100%	E	↔	↔	↑?	↔	↔	↔	↔	E?	↔	E74%
	itraconazole	↑E	↑E	↑E	↑E	↓	↓E	↓61%	E	E	↔	↑E	↔	↔	↔	↔	E	E	↔
	rifabutin	↑	↑D	↑E50%	↑	↓38%	D37%	↑17%	D	*	↔	↑D	↔	↔	↔	↔	D	↔	↔
	rifampicin	D72%	D	D	D	D26%	D	D58%	D80%	D	D54%[x]	D	D40%	D	↔	↔	D	↔	D47%
	voriconazole	↓	↑E	↓	↓	↓E	↑E	↓E	E	E	↔	↑E	↔	↔	↔	↔	↔	↔	↔
Miscellaneous	antacids	D	↔	↔	↔	↔	↔	↔	D	↔	D	D	D	↔	↔	↔	↔	↔	↔
	PPIs	D	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	E	↔	↔	↔	↔	↔	↔
	H2 blockers	D	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	E	↔	↔	↔	↔	↔	↔
	alfuzosin	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	beclometasone inhal.	↑[v]	↑?[v]	↓11%	↑[v]	↔	↔	↔	↔	↔	↔	↑[v]	↔	↔	↔	↔	↔	↔	↔
	buprenorphine	↑67%	↑	↑[vi]	↔	↓50%	↓25%	↔	↔	↔	↔	↑35%	↔	↔	↔	↔	↔	↔	↔
	budesonide inhal.	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	ergot derivatives	↑	↑	↑	↑	↑	↑	↓	E	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	ethinylestradiol	↓[vii]	↑	↓	↓	↔[viii]	↔	↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
	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	D	D	D	D?	↔	↔	↔	D	↔	↔
	varenicline	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Comments

i This table summarises 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 http://www.hiv-druginteractions.org (University of Liverpool).

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 RPV manufacturer recommends caution when co-administering with another drug susceptible to prolong QT interval

v increase in concentration of active metabolite observed with RTV 100 mg bid alone but without significant effect on adrenal function. Caution is still warranted, use the lowest possible corticosteroid dose and monitor for corticosteroid side effects.

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

x administer DTG at a dose of 50 mg bid in treatment-naïve or INSTI-naïve HIV-positive persons. Alternative to rifampicin should be used where possible for INSTI-experienced HIV-positive persons with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance

* no dose adjustment for MVC in absence of PI. With PI (except TPV/r; FPV/r), give MVC 150 mg bid

Colour legend

no clinically significant interaction expected.

these drugs should not be co-administered.

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 http://www.hiv-druginteractions.org.

Drug-drug Interactions between Antidepressants and ARVs

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

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 the US Prescribing Information recommends that co-administration should be avoided as there are insufficient data to make dosing recommendations.
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 co-administered.
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 http://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/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
ACE inhibitors	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↓	↔	↓	↓	↑	↑	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
	losartan	↓[a]	↔	↓[a]	↓[a]	↑[b]	↑[b]	↔	↔	↔	↔	↓[a]	↔	↔	↔	↔	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↔[d]	↔	↔	↔[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bisoprolol	↑[d]	↑	↑	↑[d]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	carvedilol	↑↓[d]	↑	↑↓	↑↓[d]	↑↓	↑↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑[d]	↑	↑	↑[d]	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	propranolol	↑[d]	↑	↑	↑[d]	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
Calcium channel blockers	amlodipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[c]	↑	↑	↑[e]	↓69%	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	felodipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	lacidipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	nicardipine	↑[c]	↑	↑	↑[e]	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	nifedipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	nisoldipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑[c]	↑	↑	↑[e]	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	E	E	↔
Diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bendroflumethiazide	?	?	?	?	?	?	?	↔	↔	↔	?	↔	↔	↔	↔	↔	↔	↔
	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
e use with caution as both LPV and calcium channel blockers prolong the PR interval. Clinical monitoring is recommended.

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 co-administered.
- 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.

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 http://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/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Non-opioid analgesics	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	h	↔
	celecoxib	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	h	↔
	diclofenac	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E[h]	↔
	ibuprofen	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E[h]	↔[b]
	mefenamic acid	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E[h]	↔
	naproxen	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E[h]	↔[b]
	nimesulide	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	h	↔
	paracetamol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	piroxicam	↔	↔	↔	↔	↑[a]	↑[a]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	h	↔
Opioid analgesics	alfentanil	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	buprenorphine	↑67%	↑	↑[c]	↔	↓50%	↓25%	↔	↔	↔	↔	↑35%	↔	↔	↔	↔	↔	↔	↔
	codeine	↑[e]	↑[e]	↑[e]	↑[e]	↓[e]	↓[e]	↓[e]	↔	↔	↔	↑[e]	↔	↔	↔	↔	↔	↔	↔
	dihydrocodeine	↓↑	↑	↓↑	↓↑	↓↑	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	fentanyl	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	methadone	↓[d]	↑?	↓16%	↓53%[d]	↓52%	↑6%	↓≈50%	↓16%[d]	↔	↔	↑7%	↔	↓	↔	↔	↔	↔	E
	morphine	↓	↔	↓	↓	↑	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	oxycodone	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	pethidine	↓[f]	↑	↓[f]	↓[f]	↓[f]	↓[f]	↓[f]	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	sufentanil	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	tramadol	↑[e]	↑[e]	↑[e]	↑[e]	↓[g]	↔	↔	↔	↔	↔	↑[e]	↔	↔	↔	↔	↔	↔	↔

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 HIV-positive persons with risk factors for cardiovascular disease, those HIV-positive persons at risk of developing gastrointestinal complications, HIV-positive persons with hepatic or renal impairment, and in elderly HIV-positive persons.
b potential additive haematological toxicity
c [parent drug] unchanged but [metabolite] increased
d both drugs can potentially prolong the QT interval, ECG monitoring recommended
e potential decrease of the analgesic effect due to the reduced conversion to the active metabolite
f [parent drug] decreased and increased [neurotoxic metabolite]
g [parent drug] decreased but no change in [more active metabolite]
h potential risk of nephrotoxicity which is increased if NSAID is used for a long duration, if the HIV-positive 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 co-administered
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 http://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 Anticoagulants/Antiplatelet agents and ARVs

		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Anticoagulants	acenocoumarol	↓	↔	↓	↓	↓	↑	↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
	apixaban	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	dabigatran	↑	↑	↑	↑?	↔	↔	↔	↑?	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	dalteparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	edoxaban	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	enoxaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fondaparinux	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	heparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenprocoumon	↑or↓[a]	↑	↑or↓	↑or↓	↓	↑or↓	↓	↔	↔	↔	↑or↓	↔	↔	↔	↔	↔	↔	↔
	rivaroxaban	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	warfarin	↑or↓[a]	↑	↓	↓	↑or↓	↑	↑or↓	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
Antiplatelet agents	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b	↔
	clopidogrel	↓[c]	↓[c]	↓[c]	↓[c]	↑[d]	↓[c]	↑[d]	↔	↔	↔	↓[c]	↔	↔	↔	↔	↔	↔	↔
	dipyridamole	↓[e]	↔	↓	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	prasugrel	↓[f]	↓[f]	↓[f]	↓[f]	↔	↔	↔	↔	↔	↔	↓[f]	↔	↔	↔	↔	↔	↔	↔
	ticagrelor	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔

Legend

↑ potential elevated exposure of the anticoagulant/antiplatelet agent
↓ potential decreased exposure of the anticoagulant/antiplatelet agent
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
a unboosted ATV predicted to increase the anticoagulant, monitor INR and adjust the anticoagulant dosage accordingly
b potential risk of nephrotoxicity, monitor renal function
c decreased conversion to active metabolite leading to non-responsiveness to clopidogrel. An alternative to clopidogrel should be considered
d increase in amount of active metabolite via induction of CYP3A4 and CYP2B6
e unboosted ATV predicted to increase dipyridamole exposure due to UGT1A1 inhibition
f reduced active metabolite, but without a significant reduction in prasugrel activity

Colour legend

no clinically significant interaction expected.
these drugs should not be co-administered.
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 http://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 Contraceptives/Hormone Therapy Replacement Treatment and ARVs

		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Estro-gens	ethinylestradiol	↓19%[a]	↑	↓44%[b]	↓42%[b]	↔[d]	↑22%	↓20%[b]	↑14%	↔	↑3%	↓25%[e]	↔	↔	↔	↔	↔	↔	↔
	estradiol	↓[f]	↑	↓[f]	↓[f]	↓[f]	↓[f]	↓[f]	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
Progestins	desogestrel	↑[g,h]	↑[g,n]	↑[g,h]	↑[g,h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[g,h]	↔	↔	↔	↔	↔	↔	↔
	drospirenone	↑[h]	↑[h,n]	↑[h]	↑[h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔	↔
	dydrogesterone	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	etonogestrel	↑[h]	↑[n]	↑[h]	↑52%[h]	↓63%[c]	↓[c]	↓[c]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔	↔
	gestodene	↑[h]	↑[n]	↑[h]	↑[h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel	↑[h]	↑[n]	↑[h]	↑[h]	↓[c]	↓[c]	↓[c]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔	↔
	medroxypro-gesterone (IM)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	medroxypro-gesterone (oral)	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	norelgestromin	↑[j]	↑[n]	↑[j]	↑83%[j]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[j]	↔	↔	↔	↔	↔	↔	↔
	norethisterone	↓[i,k]	↑[n]	↓14%[i]	↓17%[i]	↓[i]	↓5%	↓19%[i]	↓ 11%	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔	↔
	norgestimate	↑85%[h]	↑[n]	↑[h]	↑[h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑126%[h]	↑14%	↔	↔	↔	↔	↔	↔
	norgestrel	↑[h]	↑[n]	↑[h]	↑[h]	↓[i]	↓[i]	↓[i]	↔	↔	↔	↑[h]	↔	↔	↔	↔	↔	↔	↔
Other	levonorgestrel (EC)	↑	↑	↑	↑	↓58%[l]	↓[l]	↓[l]	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	mifepristone	↑	↑	↑	↑	↓	↓	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	ulipristal	↑	↑	↑	↑	↓[m]	↓[m]	↓[m]	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔

Legend

↑ potential increased exposure of the hormone
↓ potential decreased exposure of the hormone
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug

a unboosted ATV increased ethinylestradiol AUC by 48%. Use no more than 30 µg of ethinylestradiol if co-administered with unboosted ATV and at least 35 µg of ethinylestradiol if co-administered with ATV/r
b alternative or additional contraceptive measures are recommended or, if used for hormone replacement therapy, monitor for signs of oestrogen deficiency
c the use of implants or vaginal rings is not recommended in women on long-term treatment with hepatic enzyme inducing drugs
d no effect on ethinylestradiol exposure, however levels of co-administered progestin were markedly decreased. A reliable method of barrier contraception must be used in addition to oral contraception
e European SPC states a hormonal contraceptive should contain at least 30 µg ethinylestradiol
f monitor for signs of oestrogen deficiency
g increased conversion to active metabolite etonogestrel
h when used in combined tablet, oestrogen component is reduced. Given the lack of clinical data on the contraceptive efficacy, caution is recommended and additional contraceptive measures should be used
i a reliable method of barrier contraception should be used in addition to oral contraception
j norelgestromin is combined with ethinylestradiol and administered as transdermal patch. Ethinylestradiol was shown to be reduced which may compromise the contraceptive efficacy, caution is recommended and additional contraceptive measures should be used
k unboosted ATV increased norethisterone AUC by 2.1 fold
l use 3 mg as single dose for emergency contraception. Of note: the doubling of the standard dose is outside the product licence and there is limited evidence in relation to efficacy
m may reduce the efficacy of the emergency contraceptive tablet
n since no data are available to make recommendations on the use of DRV/c with combined or progestagen only oral or implanted contraceptives, alternative forms of contraception should be used.
Numbers refer to increased or decreased AUC of the non-ARV drug as observed in drug-drug interaction studies
Comment: transdermal application: first-pass metabolism avoided however hepatic metabolism still occurs and therefore there is a risk of DDI. Intrauterine administration: hormone (i.e. levonorgestrel) is released directly to the target organ before it is absorbed into the systemic circulation and therefore less likely to be affected by ARVs.

Colour legend

no clinically significant interaction expected.
these drugs should not be co-administered.
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). No *a priori* dosage adjustment is recommended.

Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on http://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 Corticosteroids and ARVs

Corticosteroids		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
Inhaled, oral, topic and/or injected corticosteroids	beclometasone (inhalation)	↑[a]	↑?[a]	↓[b]	↑[a]	↔	↔	↔	↔	↔	↔	↑[a]	↔	↔	↔	↔	↔	↔	↔
	betamethasone	↑[c]	↑[c]	↑[c]	↑[c]	↓	↓	↓	D	D	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	budenoside (inhalation)	↑[c]	↑[c]	↑[c]	↑[c]	↓	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	clobetasol (topical)	↑[c,d]	↑[c,d]	↑[c,d]	↑[c,d]	↔	↔	↔	↔	↔	↔	↑[c,d]	↔	↔	↔	↔	↔	↔	↔
	dexamethasone	↑[c] D	↑[c] D	↑[c] D	↑[c] D	↓ D	↓ D	↓ D	D	D	↔	↑[c] D	↔	↔	↔	↔	↔	↔	↔
	fluocinolone (topical)	↑[c,d]	↑[c,d]	↑[c,d]	↑[c,d]	↔	↔	↔	↔	↔	↔	↑[c,d]	↔	↔	↔	↔	↔	↔	↔
	fluticasone (inhalation)	↑[c]	↑[c]	↑[c]	↑[c]	↓	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	hydrocortisone (oral)	↑[c]	↑[c]	↑[c]	↑[c]	↓	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	hydrocortisone (topical)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	methylpredni-solone	↑[c]	↑[c]	↑[c]	↑[c]	↓	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	mometasone (inhalation)	↑[c]	↑[c]	↑[c]	↑[c]	↓	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	prednisolone (oral)	↑[c]	↑[c]	↑[c]	↑[c]	↓ 40%	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	prednisone	↑[c]	↑[c]	↑[c]	↑[c]	↓ 40%	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔
	triamcinolone	↑[c]	↑[c]	↑[c]	↑[c]	↓	↓	↓	↔	↔	↔	↑[c]	↔	↔	↔	↔	↔	↔	↔

Legend

↑ potential increased exposure of the corticosteroid
↓ potential decreased exposure of the corticosteroid
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug

a co-administration of RTV (100 mg bid) increased the concentrations of the active metabolite (beclometasone-17-monopropionate) but no significant effect on adrenal function was seen. Caution is still warranted, use the lowest possible corticosteroid dose and monitor for corticosteroid side effects

b DRV/r decreased the exposure of active metabolite (beclometasone-17-monopropionate), no significant effect on adrenal function was seen

c risk of having elevated corticosteroid levels, Cushing's syndrome and adrenal suppression. This risk is present for oral, injected but also for topical, inhaled or eye drops corticosteroid

d the extent of percutaneous absorption is determined by many factors such as degree of inflammation and alteration of the skin, duration, frequency and surface of application, use of occlusive dressings

Colour legend

no clinically significant interaction expected.
these drugs should not be co-administered.
potential interaction which may require a dosage adjustment or close monitoring.

Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on http://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

Effect of ARVs on antimalarial drugs and key metabolite

Legend:
Arrows indicate effect of antiretrovirals on antimalarial drug/key metabolite
Green no clinically significant interaction expected
Orange potential interaction (consider treatment ahead of travel and therapeutic drug monitoring)
Red clinically relevant interaction, do not use or use with caution

Mefloquine (M)		
Metabolism	**CYP 3A4**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓	No
RPV, RAL, MVC, DTG	→	No
PI, COBI	↑ M may reduce PI/c (RTV ca. 35%)	Potential

Artemisinins (A)		
Artemisinins and its key metabolite, dihydroartemisinin, are active compounds		
Metabolism	**CYP 2B6, 3A4, 2C19**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓ A & dihydroartemisinin; A & metabolites reduce NVP, but not EFV/ETV	Do not use or use with caution
RPV, RAL, MVC, DTG	→ A may reduce RPV, MVC	Potential
PI, COBI	↑ Increase A: monitor toxicity (liver)	Potential

Lumefantrin (L)		
Metabolism	**CYP 3A4**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	↑ LPV increases L 2-3x	Do not use or use with caution

Atovaquone (At), Proguanil (P)		
• Atovaquone increases ZDV levels by 35% • Synergy with atovaquone is related to proguanil, not its active metabolite; therefore presumably no net effect of induction/inhibition		
Metabolism	**CYP 2C19**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓ ETV is increased	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	↓ At & P take with fat meal, consider dose increase	Potential

Doxycycline		
Metabolism	**NA**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	possibly ↓	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	→	No

Chloroquine		
Metabolism	**CYP 3A4, 2D6**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	→	No
RPV, RAL, MVC, DTG	→	No
PI, COBI	→	No

Quinine (Q)		
Metabolism	**CYP 3A4, 2D6**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓ Consider dose increase	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	↑ RTV increases Q 4x: consider dose reduction, monitor toxicity (tinnitus). CAVE: PI & Q prolong QT	Potential

Primaquine		
Metabolism	**CYP 1A2, 2D6, 3A4**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	N/A	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	N/A	

Dose Adjustment of ARVs for Impaired Hepatic Function

NRTIs	
ABC	Child-Pugh Class A: 200 mg bid (use oral solution) Child-Pugh Class B or C: Contra-indicated
ddI	Contra-indicated If used no dosage adjustment
d4T	Contra-indicated If used no dosage adjustment
FTC	No dosage adjustment
3TC	No dosage adjustment
TAF	No dosage adjustment
TAF/FTC	No dosage adjustment
TDF	No dosage adjustment
TDF/FTC	No dosage adjustment
ZDV	Reduce dose by 50% or double the interval between doses if Child-Pugh Class C
NNRTIs	
EFV	No dosage adjustment; use with caution in persons with hepatic impairment
TDF/FTC/EFV	
ETV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
NVP	Child-Pugh Class B or C: contra-indicated
RPV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TAF/FTC/RPV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TDF/FTC/RPV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data

PIs	
ATV	Child-Pugh Class B: 300 mg qd
	Child-Pugh Class C: not recommended
	RTV boosting is not recommended in persons with hepatic impairment (Child-Pugh Class B or C)
DRV	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: not recommended
DRV/c	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: not recommended
FPV	**PI-naïve persons:**
	Child-Pugh Class A or B: 700 mg bid
	Child-Pugh Class C: 350 mg bid
	PI-experienced persons:
	Child-Pugh Class A: 700 mg bid + RTV 100 mg qd
	Child-Pugh Class B: 450 mg bid + RTV 100 mg qd
	Child-Pugh Class C: 300 mg bid + RTV 100 mg qd
IDV	Child-Pugh Class A or B: 600 mg q8h
	Child-Pugh Class C: no data
LPV/r	No dosage recommendation; use with caution in persons with hepatic impairment
RTV	Refer to recommendations for the primary PI
SQV	Child-Pugh Class A or B: use with caution
	Child-Pugh Class C: contra-indicated
TPV	Child-Pugh Class A: use with caution
	Child-Pugh Class B or C: contra-indicated
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
EVG	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
DTG	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TAF/FTC/EVG/c	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TDF/FTC/EVG/c	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
ABC/3TC/DTG	Use separate compounds and refer to those adjustments

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			
ddI[ii]	≥ 60 kg	400 mg q24h	200 mg q24h	150 mg q24h	100 mg q24h	100 mg q24h[iv]
	< 60 kg	250 mg q24h	125 mg q24h	100 mg q24h	75 mg q24h	75 mg q24h[iv]
d4T	≥ 60 kg	40 mg q12h	20 mg q12h	20 mg q24h	20 mg q24h	20 mg q24h[iv]
	< 60 kg	30 mg q12h	15 mg q12h	15 mg q24h	15 mg q24h	15 mg q24h[iv]
FTC		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h[iv]
3TC		300 mg q24h	150 mg q24h	100 mg q24h[iii]	50-25 mg q24h[iii]	50-25 mg q24h[iii], [iv]
TAF/FTC		25[ix]/200 mg q24h	25[ix]/200 mg q24h	Not recommended		
TDF[v]		300[viii] mg q24h	300[viii] mg q48h	Not recommended (300[viii] mg q72-96h, if no alternative)	Not recommended (300[viii] mg q7d, if no alternative)	300[viii] mg q7d[iv]
ZDV		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h[iv]
ABC/3TC		600/300 mg q24h	Use individual drugs			
ZDV/3TC		300/150 mg q12h				
ABC/3TC/ZDV		300/150/300 mg q12h				
TDF/FTC		300[viii]/200 mg q24h	300[viii]/200 mg 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			
TAF/FTC/EVG/c		10/200/150/150 mg q24h	Not recommended			
TAF/FTC/RPV		25/200/25 mg q24h	Not recommended			
TDF/FTC/RPV		300[viii]/200/25 mg q24h	Do not use			

	eGFR[i] (mL/min)				Haemodialysis
	≥ 50	30-49	10-29	< 10	
PIs[v]					
ATV/r	300/100 mg q24h	No dose adjustment required[vi]			
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required[vi]			
DRV/c	800/150 mg q24h	No dose adjustment required[vi]			
FPV/r	700/100 mg q12h	No dose adjustment required[vi]			
LPV/r	400/100 mg q12h	No dose adjustment required[vi]			
SQV/r	1000/100 mg q12h	No dose adjustment required[vi]			
TPV/r	500/200 mg q12h	No dose adjustment required[vi]			
Other ART					
RAL	400 mg q12h	No dose adjustment required[vi]			
DTG	50 mg q24h	No dose adjustment			No clinical data; PK data suggest safety
ABC/3TC/DTG	600/300/50 mg q24h	Use individual drugs			
TDF/FTC/EVG/c	Do not initiate if eGFR < 70 mL/min	Discontinue if eGFR < 50 mL/min			
MVC: co-administered without CYP3A4 inhibitors[vii]	300 mg q12h	No dose adjustment required			
MVC: co-administered with CYP3A4 inhibitors[vii]	If eGFR < 80 mL/min 150 mg q24h[vii] except: 150 mg q12h if co-administered with FPV/r				

i eGFR: Use CKD-EPI formula; the abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see http://www.chip.dk/Tools

ii Dose reduction if combined with TDF

iii 150 mg loading dose

iv After dialysis

v TDF and (boosted) PIs are associated with nephrotoxicity; consider alternative ART if pre-existing CKD, risk factors for CKD and/or decreasing eGFR, see ARV-associated Nephrotoxicity and Kidney Disease: Definition, Diagnosis and Management

vi Limited data available in persons with renal impairment; pharmacokinetic analysis suggests no dose adjustment required

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

viii In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)

ix 10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)

Administration of ARVs in Persons with Swallowing Difficulties

Drug	Formulation	Crush tablets	Open capsules	Comment
NRTIs				
ABC	tablet (300 mg) solution 20 mg/mL	yes		Bitter taste. Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately
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		Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately
TDF	tablet (300[i] 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%
TAF/FTC	tablet (25/200 mg and 10/200 mg)[v]	no		Tablets should be swallowed whole and should not be chewed, broken, cut or crushed
TDF/FTC	tablet (300[i]/200 mg)	yes		Better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste)
ABC/3TC	tablet (600/300 mg)	no		Use solution of individual compounds
ZDV/3TC	tablet (300/150 mg)	yes		Disperse in ≥ 15 mL water, alternative: use solution of individual compounds
ABC/3TC/ZDV	tablet (300/150/300 mg)	no		Use solution of individual compounds
NNRTIs				
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. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed.
NVP	tablet (200, 400 mg[ii]) suspension 10 mg/mL	yes[ii]		Dissolve in water
RPV	tablet (25 mg)	no		Crushing of tablets and dispersion into a liquid is not recommended. RPV is insoluble in water over a wide pH range
TDF/FTC/EFV	tablet (300[i]/200/600 mg)	no		
TAF/FTC/RPV	tablet (25/200/25 mg)	no		Tablets should be swallowed whole and should not be chewed, crushed or split
TDF/FTC/RPV	tablet (300[i]/200/25 mg)	no		Crushing of tablets and dispersion into a liquid is not recommended. RPV is insoluble in water over a wide pH range.
PIs				
ATV	capsule (150, 200, 300 mg)	no	yes	Difficult to open; take with food
ATV/c	tablet (300/150 mg)	no		Tablets should be swallowed whole and should not be chewed, broken, cut or crushed
DRV	tablet (75,150, 400, 600, 800 mg) solution 100 mg/mL	yes		Take with food. Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately
DRV/c	tablet (800/150 mg)	no		
FPV	tablet (700 mg) suspension 50 mg/mL			Bitter taste; adults take suspension on empty stomach
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
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		
Others				
DTG	tablet (50 mg)	yes		Tablets may be split or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately
MVC	tablet (150, 300 mg)	yes		While the company does not have any specific kinetic information, crushing the tablet is not expected to negatively affect the bioavailability
RAL[iii]	tablet (400 mg) chewable tablets (25, 100 mg)	yes		The bioavailability of the chewable tablet is higher: 300 mg chewable tablet (= 400 mg film-coated tablet)
TAF/FTC/EVG/c	tablet (10/200/150/150 mg)	no		Tablets should be swallowed whole and should not be chewed, broken, cut or crushed
TDF/FTC/EVG/c	tablet (300[i]/200/150/150 mg)	yes		Crushing of tablets does not significantly modify the pharmacokinetic profiles[iv]
ABC/3TC/DTG	tablet (600/300/50 mg)	yes		Tablets may be split or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately

Drug	Formulation	Crush tablets	Open capsules	Comment
Prophylaxis/treatment of opportunistic infections				
azithromycin	tablet (250, 500 mg) suspension 40 mg/mL	no		
cotrimoxazole	tablet (400/80 mg, forte 800/160 mg) solution 40/8 mg/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) solution 50 mg/mL	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	Mix with apple sauce, syrup (insoluble in water)
isoniazid	tablet (100, 150 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

For recommendations on prophylaxis/treatment of opportunistic infections, see Part V Opportunistic Infections

i In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate).

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

iii Crushing tablets is not recommended in the product information however absorption of RAL was not compromised when the drug was crushed, dissolved in 60 mL warm water and administered by gastrostomy tube [9]. In addition, RAL drug absorption has been shown to be higher in HIV-positive persons taking RAL 400 mg bid by chewing the tablets as compared to swallowing the intact tablets [10].

iv Crushing tablets is not recommended in the product information however the pharmacokinetic profiles of TDF/FTC/EVG/c were not significantly modified when the fixed-dose combination tablet (Stribild) was crushed and administered with food or with drip feed compared to the administration of the whole tablet [12].

v TAF is used at 10 mg when co-administered with drugs that inhibit P-gp. TAF is used at 25 mg when co-administered with drugs that do not inhibit P-gp.

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

The appropriate management of co-morbidities, which include cardiovascular, pulmonary, hepatic, metabolic, neoplastic, renal, bone, central nervous system disorders as well as sexual dysfunction, has increasingly become an integral part of the overall management of individuals living with HIV.

Potential contributors to co-morbidity pathogenesis include a higher prevalence of recognised risk factors, ART-exposure and toxicity, HIV itself as well as immune dysfunction/dysregulation and chronic immune activation/inflammation, associated with HIV or other co-infections (e.g. CMV, HCV).

Health care professionals other than HIV specialists, who are involved in the care of HIV-positive persons and who are not familiar with the use of ART, should consult their HIV specialist colleagues before introducing or modifying any type of medicines for co-morbidity. As intervals between visits to HIV-clinics are increasingly extended, HIV-positive persons can be expected to seek care more frequently with their primary care physician. In these situations, it is important to ensure some level of shared-care arrangement.

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

As individuals with treated HIV age, complex multiple co-morbidities often co-exist in the same person and may be associated with frailty and disability. Such circumstances may require a comprehensive “geriatric-type” multidimensional, multidisciplinary assessment aimed at appropriately capturing the composite of medical, psychosocial and functional capabilities and limitations of elderly HIV-positive persons.

Depending on future clinical research findings, these recommendations will be regularly updated as required. The online version at http://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%[ii] • 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 RTV or COBI 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)[iii]	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 Note that despite ETV causes a decrease in the plasma concentration of methadone, the active methadone enantiomer is in fact increased 6% by ETV.

iii 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 ± anal cytology	Unknown; advocated by some experts	1-3 years	If anal cytology abnormal, anoscopy
Breast cancer	Women 50-70 years	Mammography	↓ Breast cancer mortality	1-3 years	
Cervical cancer	Sexually active women	Liquid based cervical cytology test	↓ Cervical cancer mortality	1-3 years	Target age group should include the 25 to 64 years at least. HPV testing may aid screening
Colorectal cancer	Persons 50-75 years	Faecal occult blood test	↓ Colorectal cancer mortality	1-3 years	Flexible sigmoidscopy at 55-years is an alternative
Hepatocellular carcinoma	Persons with cirrhosis & persons with HBV co-infection at high risk of HCC[ii]	Ultrasound and alpha-foetoprotein	Earlier diagnosis allowing for improved ability for surgical eradication	Every 6 months	See pages 52 and 69
Prostate cancer	Men > 50 years	Digital rectal exam ± PSA	Use of PSA is controversial	1-3 years	Pros: ↑ early diagnosis. Cons: overtreatment; ambiguity about size of ↓ 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.

ii Persons of Asian and Black ethnicity, family history of HCC, liver cirrhosis, NAFLD or replicating HBV infection

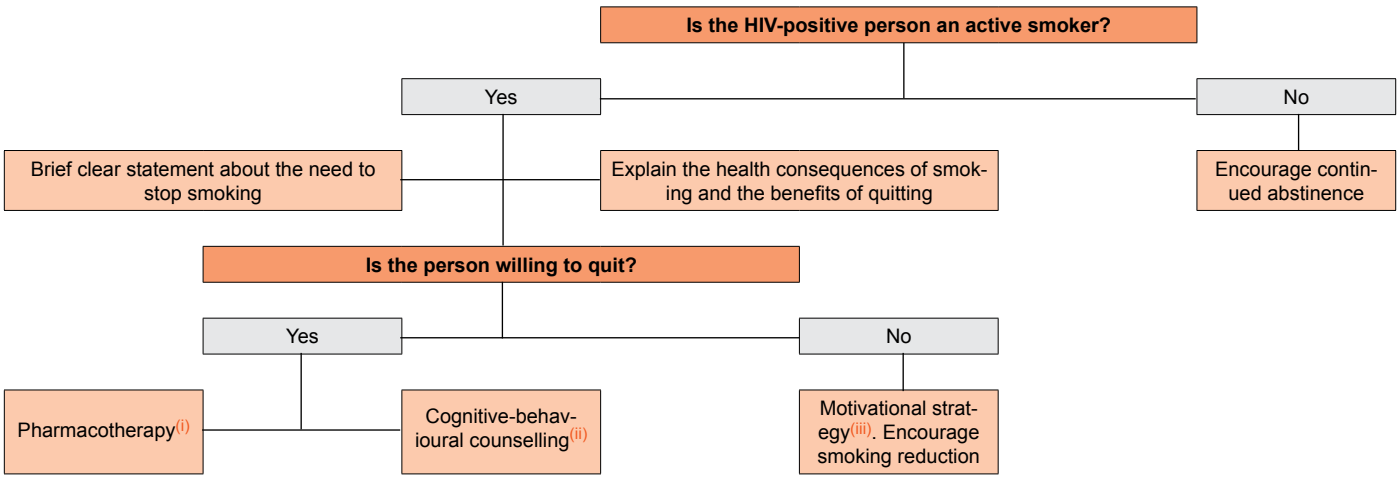
Lifestyle Interventions[i]

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 • Emphasise 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 • Emphasise 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/day). • In particular, persons with hepatic disease, adherence problems, inadequate CD4 count 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.) • Emphasise 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

Smoking cessation

HIV-positive tobacco users should be made aware of the substantial health benefits of smoking cessation which include reducing the risk of tobacco-related diseases, slowing the progression of existing tobacco related disease, and improving life expectancy by an average of 10 years.
Regularly consider the following algorithm with two major questions:



Adapted from [1] and [2]

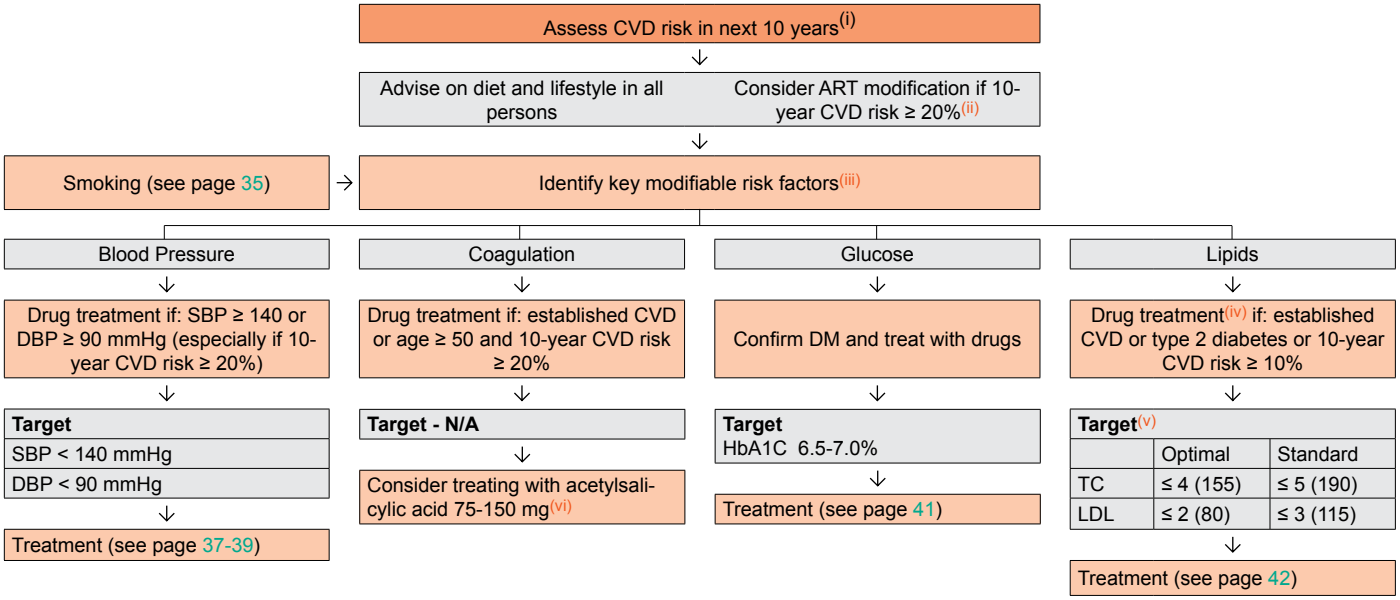
i Pharmacotherapy: Nicotine replacement therapy: Nicotine substitution (patch, chewing gum, spray), varenicline and bupropion are approved by the EMA. Buproprion is contra-indicated with epilepsy and varenicline may induce depression. Bupropion may interact with PIs and NNRTIs, see Drug-drug Interactions between ARVs and Non-ARVs

ii Cognitive-behavioral counselling: Use specific available resources. Either individual or group interventions to better suit and satisfy the HIV-positive person. The programme should consist of four or more sessions lasting 30 minutes for 3-4 months.

iii Motivational strategy: Identify potential health risks of the smoker and to stratify both acute (e.g. exacerbations of COPD) and long-term (e.g. infertility, cancer) risks. Show the HIV-positive person the personal benefits of stopping smoking. Identify the barriers or obstacles that might impede the success of a quit attempt. Smoking cessation interventions should be delivered repeatedly, as long as the HIV-positive person is not willing/ready enough to quit smoking.

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 http://www.chip.dk/Tools. This assessment and the associated considerations outlined in this figure should be repeated annually in all persons under care, see pages 5-6, to ensure that the various interventions are initiated in a timely way.

ii Options for ART modification include:
(1) Replace with NNRTI, INSTI or another PI/r known to cause less metabolic disturbances, see pages 17-18
(2) Consider replacing ZDV or ABC with TDF or use an 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 http://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 42.

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, Grading and Management

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)	Blood pressure (mmHg)	Blood pressure (mmHg)	Blood pressure (mmHg)
	High normal SBP 130-139 or DBP 85-89	Grade 1 hypertension SBP 140-159 or DBP 90-99	Grade 2 hypertension SBP 160-179 or DBP 100-109	Grade 3 hypertension SBP ≥ 180 or DBP ≥ 110
No other risk factors	• No BP intervention	• Lifestyle changes(i) for several months • Then add BP drugs targeting < 140/90	• Lifestyle changes(i) for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes(i) • Immediate BP drugs targeting < 140/90
1-2 risk factors	• Lifestyle changes(i) • No BP Intervention	• Lifestyle changes(i) for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes(i) for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes(i) • Immediate BP drugs targeting < 140/90
≥ 3 risk factors	• Lifestyle changes(i) • No BP intervention	• Lifestyle changes(i) for several weeks • Then add BP drugs targeting < 140/90	• Lifestyle changes(i) • BP drugs targeting < 140/90	• Lifestyle changes(i) • Immediate BP drugs targeting < 140/90
Organ damage, CKD stage 3 or diabetes	• Lifestyle changes(i) • No BP intervention	• Lifestyle changes(i) • BP drugs targeting < 140/90	• Lifestyle changes(i) • BP drugs targeting < 140/90	• Lifestyle changes(i) • Immediate BP drugs targeting < 140/90
Symptomatic CVD, CKD stage ≥ 4 or diabetes with organ damage/risk factors	• Lifestyle changes(i) • No BP intervention	• Lifestyle changes(i) • BP drugs targeting < 140/90	• Lifestyle changes(i) • BP drugs targeting < 140/90	• Lifestyle changes(i) • Immediate BP drugs targeting < 140/90

BP blood pressure
DBP diastolic blood pressure:
SBP systolic blood pressure

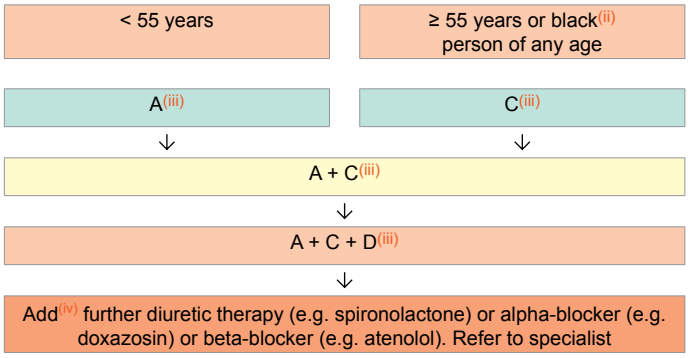
Repeated blood pressure measurements should be used for stratification

i Recommended lifestyle interventions, see page 35

Table adapted from [3].

Hypertension: Drug Sequencing 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 4-6 weeks to assess whether target, see page 36, 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. hydrochlorothiazide (HCTZ), bendroflumethiazide etc.)

Drug-drug Interactions between Antihypertensives and ARVs

Antihypertensives		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
ACE inhibitors	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↓	↔	↓	↓	↑	↑	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
	losartan	↓[a]	↔	↓[a]	↓[a]	↑[b]	↑[b]	↔	↔	↔	↔	↓[a]	↔	↔	↔	↔	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↔[d]	↔	↔	↔[d]	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bisoprolol	↑[d]	↑	↑	↑[d]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	carvedilol	↑↓[d]	↑	↑↓	↑↓[d]	↑↓	↑↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑[d]	↑	↑	↑[d]	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	propranolol	↑[d]	↑	↑	↑[d]	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
Calcium channel blockers	amlodipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	diltiazem	↑[c]	↑	↑	↑[e]	↓69%	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	felodipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	lacidipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	nicardipine	↑[c]	↑	↑	↑[e]	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	↔	↔	↔
	nifedipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	nisoldipine	↑[c]	↑	↑	↑[e]	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	verapamil	↑[c]	↑	↑	↑[e]	↓	↓E	↓	E	E	↔	↑	↔	↔	↔	↔	E	E	↔
Diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bendroflumethiazide	?	?	?	?	?	?	?	↔	↔	↔	?	↔	↔	↔	↔	↔	↔	↔
	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
e use with caution as both LPV and calcium channel blockers prolong the PR interval. Clinical monitoring is recommended.

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 co-administered.
- 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.

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 http://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 AND (100-125)	< 7.8 (140)	

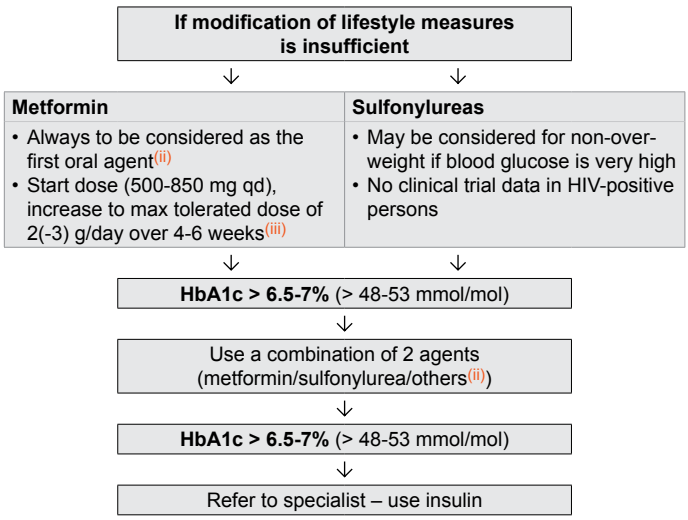
i As defined by WHO and [4]

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-positive 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 36, and blood pressure < 130/80 mmHg, see page 37.
- Acetylsalicylic acid (75-150 mg qd) considered in diabetics with elevated underlying CVD risk, see page 36.
- 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 Metformin may worsen lipoatrophy. Very limited data for any oral antidiabetic agents in terms of CVD prevention, and no data in HIV-positive persons. Incretins (DDP-IV inhibitors [e.g. linagliptin, saxagliptin (reduce doze when given with a booster), sitagliptin and vildagliptin] and GLP-1 agonists [e.g. liraglutide & exenatide]) are currently being evaluated in several major morbidity/mortality studies (neutral results to date); no clinically significant drug-drug interaction or adverse effects on CD4 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.

iii Consider lower dose in individuals with mild to moderate CKD or individuals receiving DTG.

Dyslipidaemia

Principles: Higher LDL-c levels increase risk of CVD, hence reduction diminishes 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) increase risk of pancreatitis.

Less calories, more exercise, reducing bodyweight, and stopping smoking tend to improve HDL. Eating fish, reducing calories, saturated fat and alcohol intake reduce triglyceride levels. Reducing dietary saturated fat intake improves LDL-levels; if not effective, consider change of ART, then consider lipid-lowering medication, see page 36. 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 NNRTIs
Statin[i,ix]	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		Contra-indicated	
Intestinal cholesterol absorption inhibitor↓[i,viii]	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 36. 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

viii This agent can be used for HIV-positive persons intolerant of statins or added to a statin when LDL reduction is inadequate despite maximally tolerated statin

ix Pitavastatin has as yet no morbidity/mortality trial data to support its use but may have advantages of fewer drug-drug interactions, more HDL increase and less adverse glucose effect than other statins

Bone Disease: Screening and Diagnosis

Condition	Characteristics	Risk factors	Diagnostic tests
Osteopenia • Postmenopausal women and men aged ≥ 50 years with BMD T-score -1 to -2.5 **Osteoporosis** • Postmenopausal women and men aged ≥ 50 years with BMD T-score ≤ -2.5 • Premenopausal women and men aged < 50 years with BMD Z-score ≤ -2 and fragility fracture	• Reduced bone mass • Increased incidence of fractures in HIV-positive persons • 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 risk 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/qd 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 (http://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 low**[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 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 and in the general population	• 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 44
Osteonecrosis	• Infarct of epiphyseal plate of long bones resulting in acute bone pain • Rare but increased prevalence in HIV	**Risk factors:** • Low CD4 count • 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. TAF has shown lower tenofovir-related bone adverse effects due to lower systemic tenofovir exposure. Switch studies from TDF to TAF suggest potential reversion of bone toxicity However, long-term experience with TAF is lacking.

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 trauma fracture, alcohol excess (> 3 units/day), steroid exposure (minimum prednisone 5 mg/qd or equivalent for > 3 months)

iii If T-score normal, repeat after 3-5 years in risk groups 1, 2 and 5; no need for re-screening with DXA in risk groups 3 and 4 unless risk factors change and only rescreen group 6 if steroid use ongoing.

iv Falls Risk Assessment Tool (FRAT), see https://www2.health.vic.gov.au/ageing-and-aged-care/wellbeing-and-participation/healthy-ageing/falls-prevention/falls-prevention-tools

v If including BMD within FRAX, entering yes in the secondary cause box will not be considered in the FRAX algorithms, as it is assumed that secondary osteoporosis affects fracture risk solely through BMD. However, if the contribution of HIV infection to fracture risk is partially independent of BMD, fracture probability may be underestimated by FRAX.

vi Causes of secondary osteoporosis include hyperparathyroidism, hyperthyroidism, malabsorption, hypogonadism/amenorrhoea, diabetes mellitus, and 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)	Serum 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 800-2,000 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 re-testing 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 48. 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 not completely 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 naïve, consider options for ART that preserve BMD(v) – If diagnosed with osteoporosis and requiring therapy, consider optimising ART to preserve or improve BMD • 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 https://www2.health.vic.gov.au/ageing-and-aged-care/wellbeing-and-participation/healthy-ageing/falls-prevention/falls-prevention-tools

ii See page 44 for diagnosis and management of vitamin D deficiency.

iii See page 43 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 po once a month 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.

Kidney Disease: Definition, 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 medicines 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[x] and nephrotoxic medicines including ART[iv, x] • 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[v]	CKD and proteinuria are independent risk factors for CVD

i For eGFR: Use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated > 60 mL/min. The abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see http://www.chip.dk/Tools.
Definition CKD: eGFR < 60 ml/min for > 3 months (see http://kdigo.org/home/guidelines/ckd-evaluation-management). If not previously known to have CKD, confirm pathological eGFR within 2 weeks. Use of DTG, COBI and RTV boosted 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 [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 6

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 42

ix See page 40-42

x Different models have been developed for calculating a 5-years CKD risk score while using different nephrotoxic ARVs integrating HIV-independent and HIV-related risk factors [5], [6]

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, DXA **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) 4. Leucocyte casts	**IDV** **ATV**	**Assessment:** • Renal ultrasound • Refer to nephrologist **Consider stopping IDV/ATV if:** • Progressive decline in eGFR and no other cause
Progressive decline in eGFR, but none of the above(v)	**TDF**** **PI/r**	**Complete assessment:** • Risk factors for CKD(v) (see Kidney Disease: Definition, Diagnosis and Management) • PRT, UA/C, UP/C (see Kidney Disease: Definition, Diagnosis and Mangement and Indications and Tests for Proximal Renal Tubulopathy (PRT) • Renal tract ultrasound **Consider stopping ARVs with potential nephrotoxicity if:** • Progressive decline in eGFR and no other cause(v)

* Use of COBI, DTG, RPV, but also PI/r 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

** TAF has shown lower tenofovir-related renal adverse effects due to lower systemic tenofovir exposure. Switch-studies from TDF to TAF suggest potential reversion of renal toxicity, however, long-term experience with TAF is lacking.

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 For eGFR: use CKD-EPI formula. The abbreviated MDRD (Modification of Diet in Renal Disease) or the Cockcroft-Gault (CG) equation may be used as an alternative, see http://www.chip.dk/Tools

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

iv Microscopic haematuria is usually present.

v Different models have been developed for calculating a 5-years CKD risk score while using different nephrotoxic ARVs integrating HIV-independent and HIV-related risk factors [5], [6]

Indications and Tests for Proximal Renal Tubulopathy (PRT)

Indications for proximal renal tubulopathy tests	Proximal renal tubulopathy tests[iv], including	Consider stopping TDF/switching to TAF 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 For eGFR: use CKD-EPI formula. The abbreviated MDRD (Modification of Diet in Renal Disease) or the Cockcroft-Gault (CG) equation may be used as an alternative, see http://www.chip.dk/Tools

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, urine 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

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			
ddI[ii]	≥ 60 kg	400 mg q24h	200 mg q24h	150 mg q24h	100 mg q24h	100 mg q24h[iv]
	< 60 kg	250 mg q24h	125 mg q24h	100 mg q24h	75 mg q24h	75 mg q24h[iv]
d4T	≥ 60 kg	40 mg q12h	20 mg q12h	20 mg q24h	20 mg q24h	20 mg q24h[iv]
	< 60 kg	30 mg q12h	15 mg q12h	15 mg q24h	15 mg q24h	15 mg q24h[iv]
FTC		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h[iv]
3TC		300 mg q24h	150 mg q24h	100 mg q24h[iii]	50-25 mg q24h[iii]	50-25 mg q24h[iii], [iv]
TAF/FTC		25[ix]/200 mg q24h	25[ix]/200 mg q24h	Not recommended		
TDF[v]		300[viii] mg q24h	300[viii] mg q48h	Not recommended (300[viii] mg q72-96h, if no alternative)	Not recommended (300[viii] mg q7d, if no alternative)	300[viii] mg q7d[iv]
ZDV		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h[iv]
ABC/3TC		600/300 mg q24h	Use individual drugs			
ZDV/3TC		300/150 mg q12h				
ABC/3TC/ZDV		300/150/300 mg q12h				
TDF/FTC		300[viii]/200 mg q24h	300[viii]/200 mg 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			
TAF/FTC/EVG/c		10/200/150/150 mg q24h	Not recommended			
TAF/FTC/RPV		25/200/25 mg q24h	Not recommended			
TDF/FTC/RPV		300[viii]/200/25 mg q24h	Do not use			

	eGFR[i] (mL/min)				Haemodialysis
	≥ 50	30-49	10-29	< 10	
PIs[v]					
ATV/r	300/100 mg q24h	No dose adjustment required[vi]			
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required[vi]			
DRV/c	800/150 mg q24h	No dose adjustment required[vi]			
FPV/r	700/100 mg q12h	No dose adjustment required[vi]			
LPV/r	400/100 mg q12h	No dose adjustment required[vi]			
SQV/r	1000/100 mg q12h	No dose adjustment required[vi]			
TPV/r	500/200 mg q12h	No dose adjustment required[vi]			
Other ART					
RAL	400 mg q12h	No dose adjustment required[vi]			
DTG	50 mg q24h	No dose adjustment			No clinical data; PK data suggest safety
ABC/3TC/DTG	600/300/50 mg q24h	Use individual drugs			
TDF/FTC/EVG/c	Do not initiate if eGFR < 70 mL/min	Discontinue if eGFR < 50 mL/min			
MVC: co-administered without CYP3A4 inhibitors[vii]	300 mg q12h	No dose adjustment required			
MVC: co-administered with CYP3A4 inhibitors[vii]	If eGFR < 80 mL/min 150 mg q24h[vii] except: 150 mg q12h if co-administered with FPV/r				

i eGFR: Use CKD-EPI formula; the abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see http://www.chip.dk/Tools

ii Dose reduction if combined with TDF

iii 150 mg loading dose

iv After dialysis

v TDF and (boosted) PIs are associated with nephrotoxicity; consider alternative ART if pre-existing CKD, risk factors for CKD and/or decreasing eGFR, see ARV-associated Nephrotoxicity and Kidney Disease: Definition, Diagnosis and Management

vi Limited data available in persons with renal impairment; pharmacokinetic analysis suggests no dose adjustment required

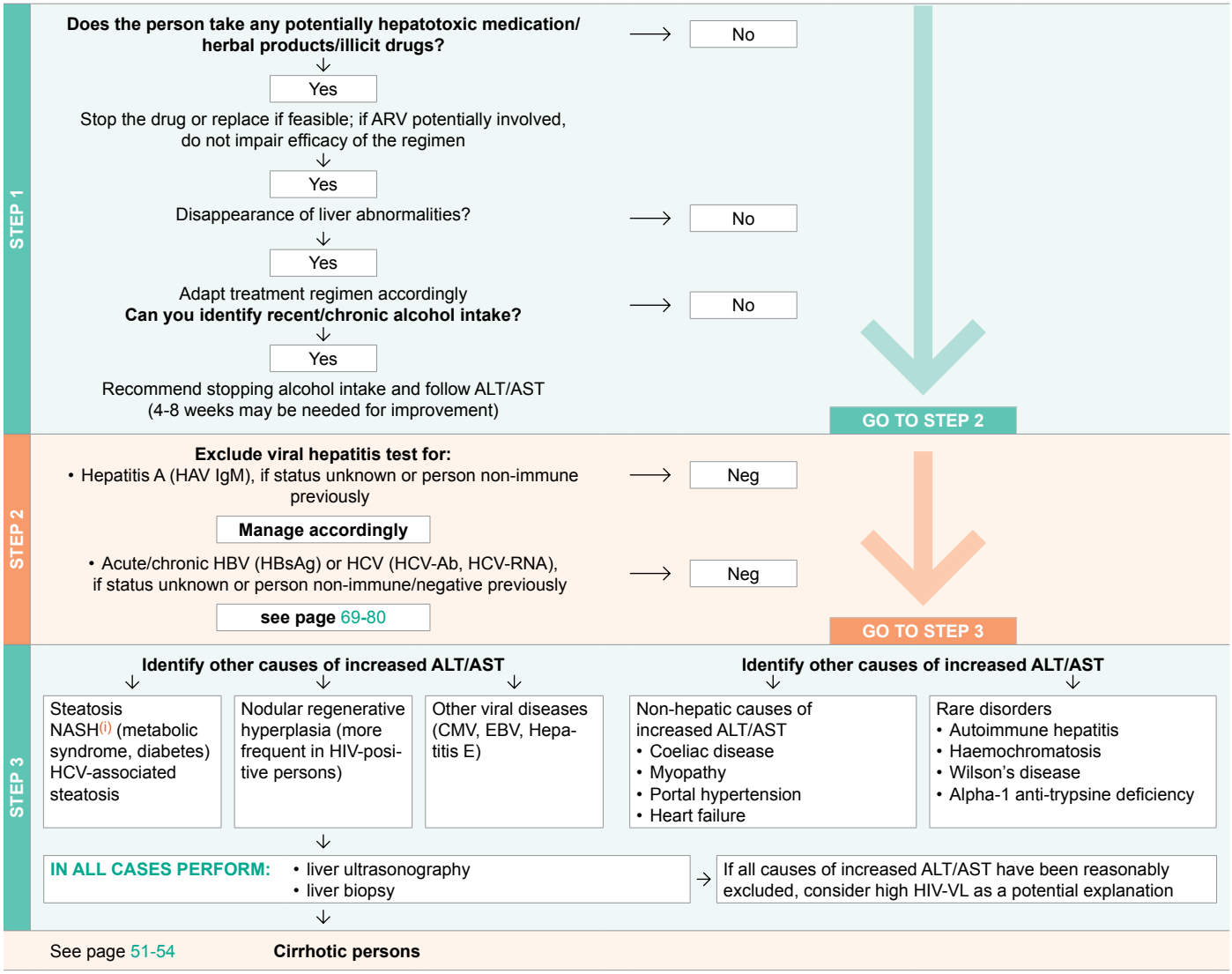
vii See summary of product characteristics for specific recommendations; use with caution if eGFR < 30 mL/min

viii In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)

ix 10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)

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

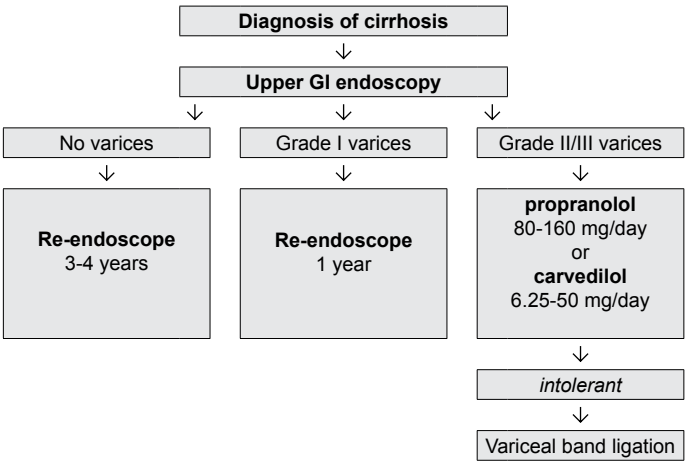
Liver Cirrhosis: Classification and Surveillance

Child-Pugh classification of the severity of cirrhosis

	Point(i)		
	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	1.7-2.20	> 2.20
Ascites	None	Mild/Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I-II (or suppressed with medicine)	Grade III-IV (or refractory)

i 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 po every 1-2h until bowel evacuation, then adjust to a dosage resulting in 2-3 formed bowel movements per day (usually 15-30 cm³ po bid) Lactulose enemas (300 cm³ in 1L of water) in persons who are unable to take it po. 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 po, 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. Liberalise if restriction results in poor food intake • Large volume paracentesis as initial therapy only in persons with tense ascites • Administer iv albumin (= 6-8 g/L 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 parenteral 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(i) 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 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 http://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 µg sc tid → Goal to increase mean arterial pressure by 15 mmHg
		+ midodrine	5-15 mg po tid
		or terlipressin	0.5-2.0 mg iv every 4-6 hours
	and iv albumin (both for at least 7 days)		50-100 g iv qd

Dose Adjustment of ARVs for Impaired Hepatic Function

NRTIs	
ABC	Child-Pugh Class A: 200 mg bid (use oral solution) Child-Pugh Class B or C: Contra-indicated
ddI	Contra-indicated If used no dosage adjustment
d4T	Contra-indicated If used no dosage adjustment
FTC	No dosage adjustment
3TC	No dosage adjustment
TAF	No dosage adjustment
TAF/FTC	No dosage adjustment
TDF	No dosage adjustment
TDF/FTC	No dosage adjustment
ZDV	Reduce dose by 50% or double the interval between doses if Child-Pugh Class C
NNRTIs	
EFV	No dosage adjustment; use with caution in persons with hepatic impairment
TDF/FTC/EFV	
ETV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
NVP	Child-Pugh Class B or C: contra-indicated
RPV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TAF/FTC/RPV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TDF/FTC/RPV	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data

PIs	
ATV	Child-Pugh Class B: 300 mg qd
	Child-Pugh Class C: not recommended
	RTV boosting is not recommended in persons with hepatic impairment (Child-Pugh Class B or C)
DRV	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: not recommended
DRV/c	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: not recommended
FPV	**PI-naïve persons:**
	Child-Pugh Class A or B: 700 mg bid
	Child-Pugh Class C: 350 mg bid
	PI-experienced persons:
	Child-Pugh Class A: 700 mg bid + RTV 100 mg qd
	Child-Pugh Class B: 450 mg bid + RTV 100 mg qd
	Child-Pugh Class C: 300 mg bid + RTV 100 mg qd
IDV	Child-Pugh Class A or B: 600 mg q8h
	Child-Pugh Class C: no data
LPV/r	No dosage recommendation; use with caution in persons with hepatic impairment
RTV	Refer to recommendations for the primary PI
SQV	Child-Pugh Class A or B: use with caution
	Child-Pugh Class C: contra-indicated
TPV	Child-Pugh Class A: use with caution
	Child-Pugh Class B or C: contra-indicated
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
EVG	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
DTG	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TAF/FTC/EVG/c	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
TDF/FTC/EVG/c	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
ABC/3TC/DTG	Use separate compounds and refer to those adjustments

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[i]
Prevention • Avoid d4T and ZDV or pre-emptively switch away from them. No evidence of benefit by switching other antiretrovirals. • Avoid excessive weight loss due to diet and exercise. • In ART-naïve persons, limb fat usually increases with initiation of ART not containing d4T or ZDV, reflecting "return-to-health" type of response	**Prevention** • No proven strategy • No current antiretroviral drug has been specifically associated with increased visceral adiposity • An excess of visceral fat has been reported in HIV vs. non-HIV non-obese persons for the same body mass index • Weight reduction or avoidance of weight gain may decrease visceral fat • Avoid inhaled fluticasone (and potentially other inhaled corticosteroids) with RTV or COBI-boosted PIs as it may cause Cushing syndrome or adrenal insufficiency (see Drug-Drug Interactions between ARVs and Corticosteroids)
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 cosmetic 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 (not approved for this indication in Europe) — Decreases visceral adipose tissue — May worsen subcutaneous lipoatrophy and insulin resistance • Tesamorelin (not approved in Europe; approved for this indication by FDA)[ii] • Metformin (not approved for this indication in Europe) — 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 Lipohypertrohy may occur as localised lipomas in the subcutaneous region or as increased visceral adiposity, both intraabdominally and/or in the the epicardium

ii Tesamorelin (growth hormone releasing factor) was shown to reduce visceral adipose tissue volume but this effect was lost on discontinuation

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 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 standardised 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 bid, riboflavin 20 mg bid, thiamine 100 mg bid; L-carnitine 1000 mg bid), although benefit is not proven.

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 medicines/syringes • Carry antiretrovirals split between suitcase and hand luggage • Beware of fake drugs
ART	• Maintain hours of medicines (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. diarrhoeagenic *E. coli, Salmonella, Shigella, Campylobacter* • Opportunistic intestinal parasitosis Cryptosporidium, Cyclospora, Isospora, Microsporidia **2. Prevent insect bites** • Repellents (DEET ≥ 30%), spray clothing with insecticide (permethrin) • Malaria chemoprophylaxis/emergency standby treatment[ii] • Yellow fever, see page 60 • Leishmaniasis Beware of sand flies (dogs)

Advice on travel restrictions – see http://www.hivtravel.org

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

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

Effect of ARVs on antimalarial drugs and key metabolite

Legend:
Arrows indicate effect of antiretrovirals on antimalarial drug/key metabolite
Green no clinically significant interaction expected
Orange potential interaction (consider treatment ahead of travel and therapeutic drug monitoring)
Red clinically relevant interaction, do not use or use with caution

Mefloquine (M)		
Metabolism	**CYP 3A4**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓	No
RPV, RAL, MVC, DTG	→	No
PI, COBI	↑ M may reduce PI/c (RTV ca. 35%)	Potential

Artemisinins (A)		
Artemisinins and its key metabolite, dihydroartemisinin, are active compounds		
Metabolism	**CYP 2B6, 3A4, 2C19**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓ A & dihydroartemisinin; A & metabolites reduce NVP, but not EFV/ETV	Do not use or use with caution
RPV, RAL, MVC, DTG	→ A may reduce RPV, MVC	Potential
PI, COBI	↑ Increase A: monitor toxicity (liver)	Potential

Lumefantrin (L)		
Metabolism	**CYP 3A4**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	↑ LPV increases L 2-3x	Do not use or use with caution

Atovaquone (At), Proguanil (P)		
• Atovaquone increases ZDV levels by 35% • Synergy with atovaquone is related to proguanil, not its active metabolite; therefore presumably no net effect of induction/inhibition		
Metabolism	**CYP 2C19**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓ ETV is increased	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	↓ At & P take with fat meal, consider dose increase	Potential

Doxycycline		
Metabolism	**NA**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	possibly ↓	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	→	No

Chloroquine		
Metabolism	**CYP 3A4, 2D6**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	→	No
RPV, RAL, MVC, DTG	→	No
PI, COBI	→	No

Quinine (Q)		
Metabolism	**CYP 3A4, 2D6**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	↓ Consider dose increase	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	↑ RTV increases Q 4x: consider dose reduction, monitor toxicity (tinnitus). CAVE: PI & Q prolong QT	Potential

Primaquine		
Metabolism	**CYP 1A2, 2D6, 3A4**	
ARVs	**Effect on antimalarial drugs and key metabolite**	**Relevance**
NNRTI (EFV, NVP, ETV)	N/A	Potential
RPV, RAL, MVC, DTG	→	No
PI, COBI	N/A	

Vaccination

- Vaccinate according to national guidelines for healthy population, preferably after having achieved suppressed viremia and immune reconstitution (CD4 count > 200 cells/μL)
- Consider repeating vaccinations performed at CD4 count < 200 cells/μL (< 14%) following adequate immune reconstitution (HIV-VL undetectable and CD4 count > 200 cells/μL)
- As vaccine responses may be significantly lower in HIV-positive persons, consider antibody titers to assess their effectiveness
- Avoid polysaccharide vaccination
- For additional details, see http://www.bhiva.org/vaccination-guidelines.aspx

- For attenuated live vaccines[i]
  (in addition to restrictions for general population):
  - ***Varicella, measles, mumps, rubella, yellow fever**
    Contra-indicated if CD4 count < 200 cells/μL (14%) and/or AIDS
  - **Oral live typhoid**
    Contra-indicated if CD4 count < 200 cells/μL (14%): give inactivated parenteral polysaccharide vaccine. Preferred if CD4 count > 200 cells/μL (> 14%).

Infection	Vaccination rationale in HIV-positive persons	Comment
Influenza Virus	Higher rate of pneumonia. Explicitly recommended in all HIV-positive persons	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) in non-responders, in particular with low CD4 count and high HIV-VL. Repeat doses until HBs antibodies ≥ 10 IU/L / ≥ 100 IU/L according to national guidelines. See page 69
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 69
Neisseria meningitidis	As general population	Use conjugated[ii] vaccine (2 doses 1-2 months apart) if available. Booster every five years if exposure continues. Polysaccharide vaccine not recommended anymore.
Streptococcus pneumoniae	Higher rate and severity of invasive disease. Vaccine explicitly recommended for all HIV-positive persons	Use conjugated[ii] 13-valent vaccine instead of PPV-23 polysaccharide vaccine if available. No recommendations yet about the need for a booster dose.
Varicella Zoster Virus (VZV)	Higher rate and severity of both chickenpox and zoster	Perform serology if exposure history negative. Vaccinate if seronegative. For contra-indications, see*
Yellow Fever Virus	Mandatory for travel to selected countries (provide exemption letter if no true risk of exposure)	Contra-indicated if past or current haematological neoplasia or thymus affection (thymoma, resection/radiation) For other contra-indications, see*

i Administer live vaccines simultaneously or with an interval of 4 weeks
ii Conjugated vaccines are more immunogenic, induce memory cells, respond to boosting and reduce mucosal colonisation

Sexual and Reproductive Health of HIV-positive Women and Men

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 48/72 hours post sexual exposure See Post-exposure prophylaxis (PEP)
Pre-exposure prophylaxis (PrEP)	• Effective in HIV-negative persons with high risk sexual behavior, See Pre-exposure prophylaxis (PrEP)
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 8

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 http://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 bid for 7-10 days) or ofloxacin (200 mg bid), erythromycin (500 mg qd for 7 days) or azithromycin (1 g once). For *Lymphogranuloma venereum* consider doxycycline (100 mg bid 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. Ceftriaxone 500 mg im as a single dose together with azithromycin 2 g as a single dose po.	• 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, pages 70-80	• 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 cytology should be considered in all HIV-positive persons practising anal sex • Consider high resolution anoscopy in case of suspicious cytological findings (rectal palpation or external inspection is not sufficient)
HSV2 infection	Primary infection: aciclovir (400–800 mg po tid) or valaciclovir (500 mg bid) for 5 days, see page 86	• 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 million IU im weekly on days 1, 8 and 15); alternatives such as doxycycline (100 mg bid), or erythromycin (2 g/day) for 2 weeks are considered less effective. **Neurosyphilis:** penicillin G (6 x 3 - 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. See Drug-drug Interactions between Contraceptives/Hormone Therapy Replacement Treatment and ARVs

Approaches for serodifferent couples who want to have children
Screening for STIs (and treatment, if required) of both partners is mandatory. For HIV-positive women wishing to conceive: (1) avoid using ddI, d4T or triple NRTIs, 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 13; (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 medicines, 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 arousal 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-inhibitors (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 medicine

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?**
Screening of all HIV-positive persons recommended in view of the high prevalence of depression **Populations at particular high risk** • 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 • Use of neurotropic and recreational drugs • As part of investigation of neurocognitive impairment, see page 68	• 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, vitamin 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(i)

i EFV has been associated with a higher risk of suicidal ideation

Depression: Management

Degree of depression	Number of symptoms (see page 64: 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

If a person is diagnosed with depression switching off EFV to another third ARV drug according to switch rules is recommended

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

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 the US Prescribing Information recommends that co-administration should be avoided as there are insufficient data to make dosing recommendations.
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 co-administered.
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.

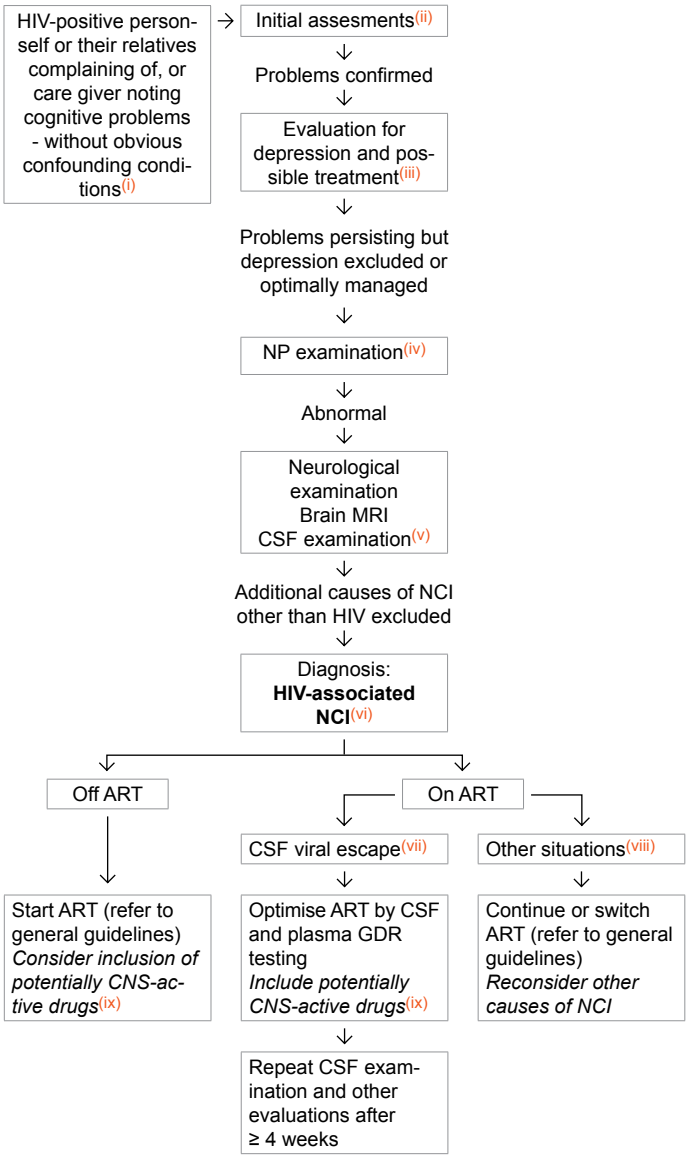
Comment

The symbol (red, amber, green) used to rank the clinical significance of the drug interaction is based on http://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
OIs	opportunistic infections



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

ii **The following 3 questions may be used to guide physician assessment**
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 See Depression: Screening and Diagnosis

iv **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 plus assessment of daily functioning

v **Neurological examination, brain MRI and CSF examination** are required to exclude other pathologies and to further characterise HIV-associated NCI, by including assessment of CSF HIV-VL level and, where appropriate, evidence for genotypic drug resistance (GDR) in a paired CSF and plasma sample.

vi **NCI includes**
1) marked 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) interference in daily functioning;
3) no evidence of another pre-existing cause for the dementia

vii **CSF escape definition**: either CSF VL > 50 and plasma HIV-VL < 50 copies/mL or both CSF and plasma HIV-VL > 50 copies/mL, with CSF HIV-VL > 0.5 $\log_{10}$ higher than plasma HIV-VL.

viii **Including all situations that do not fulfill the CSF escape definition**

ix **Definition of potentially CNS-active drug**

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

- Drugs with demonstrated clear CSF penetration:
  - —NRTIs: ZDV, ABC*
  - —NNRTIs: EFV**, NVP
  - —PI/r: IDV/r, LPV/r, DRV/r*
  - —INSTI: DTG
  - —Other classes: MVC
- Drugs with proven clinical efficacy:
  - —NRTIs: ZDV, ABC
  - —PI/r: LPV/r

* When administered bid. 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.

** EFV should be used cautiously in HIV-positive persons with NCI because of its detrimental effects on neurocognitive function in a RCT and potentially confounding CNS effects.

Part IV Clinical Management and Treatment of 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 iv administration of recreational drugs ("chem sex"), 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. HCV-RNA testing is also recommended in persons with high risk factors for HCV re-infection after successful treatment or spontaneous clearance.
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 positive persons.
4. HCV co-infected persons with liver cirrhosis and HBV co-infected persons with high risk for hepatocellular carcinoma (HCC) i.e. Asian, Black, family history of HCC, liver cirrhosis, NAFLD, replicating HBV infection- 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 an 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 51. Regarding HCC screening, see page 52. 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 60

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 count. The response to the HBV vaccine is influenced by the CD4 count and level of HIV-VL. In persons with low CD4 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 immunisation 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 are available from current trials.
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. TDF based cART has been associated with prevention of HBV infection in these persons.

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 (HBsAg-positive) irrespective of CD4 count. In persons with chronic HCV, ART initiation is also recommended irrespective of CD4 count. Stopping ART has been associated with enhanced risk for AIDS and non-AIDS related events; indeed, the risk for non-AIDS events was particularly increased 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)

8. 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 51-52 and Diagnosis and Management of Hepatorenal Syndrome (HRS).
9. 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.
10. Persons with HCC or a MELD-score > 15[i], CD4 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. An improvement in survival in HIV/HCV co-infected persons is expected in the next years due to the possibility to eradicate HCV pre- or post- transplant with direct acting antiviral drug (DAA)-based therapy.
11. Renal complications are frequent, see page 52 and Diagnosis and Management of Hepatorenal Syndrome (HRS)

i MELD calculation, see page 52.

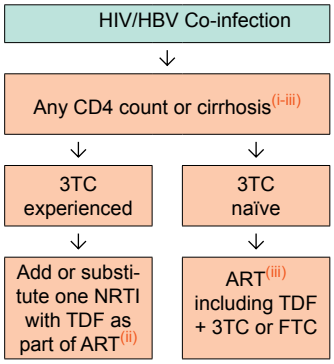
Prevention/Support

12. Psychiatric, psychological, social and medical support should be made available to persons with alcohol intake to stop drinking.
13. Substitution therapy (opioid replacement therapy) in persons with active drug use 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
14. 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 or iv administration of recreational drugs ("chem sex") should be provided and risk reduction should be discussed.

Delta Virus

15. 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 from HBsAg negative donor should be strongly considered especially in the absence of active HCV co-infection. Transplant with anti-HBV post-OLTX prophylaxis cures HBV and Delta virus infection.

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



i For management of cirrhotic persons, see pages 51-54. Persons with liver cirrhosis and low CD4 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 All persons with HBV/HIV co-infection should receive ART including TDF (or TAF) + 3TC or FTC unless history of TDF intolerance. In HBV/HIV co-infected persons with bone mineral density changes or chronic kidney disease, see recommendations for Dose Adjustment of ARVs for Impaired Renal Function and page 47. If TDF or TAF 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.

iii 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. In those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously in HBeAg positive persons who have achieved HBe-seroconversion for at least six months or after confirmed HBs-seroconversion in those who are HBeAg negative. 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.

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 IFN 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 2-3 years thereafter if negative for oesophageal varices), see page 51
Before HCV treatment
HCV genotype (GT)[iii], HCV-RNA, renal and liver function tests
Autoantibodies (ANA, LKM1)[iv]
TSH, thyroid autoantibodies (risk of hyperthyroidism under IFN-based therapy)
Monitoring of HCV treatment
Differential blood count, creatinine, liver enzymes and, in persons with advanced fibrosis, bilirubin, albumin and INR every 2-4 weeks. In persons treated with IFN-free regimens HCV-RNA at 2-4 weeks and whenever needed in order to assess compliance and or breakthrough in persons experienced to oral DAAs.
HCV-RNA at week 4 (to evaluate rapid virological response (RVR) under IFN-based HCV regimens) and under all treatments at end-of-treatment and at week 12 and 24 after treatment cessation (to assess SVR). In persons receiving all oral DAA therapy no association between viral load at any given time-point under therapy and SVR has yet been found.
CD4 count and HIV-VL every 12 weeks
TSH and non-organ specific autoantibodies every 12 weeks under IFN-based therapy

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 Re-test for GT and sub-type should be performed in persons with tests carried out before second-generation tests were available (second-generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection' for whom the GT/sub-type should be performed on most recent available specimen.

iv 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 IFN-based treatment. Other concurrent causes of liver disease should be identified by blood tests and liver biopsy if needed.

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 which translates into HCV cure. 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 including pre- or post-liver transplantation. This also needs to be seen in the context of faster liver fibrosis progression in persons with HCV/HIV co-infection (particularly in persons with low CD4 counts (< 200 cells/µL)) and with better HCV-treatment outcome with the use of DAAs in these persons. Furthermore, achieving SVR has also been associated with an improved survival even in lower fibrosis stages (F2) suggesting benefits of HCV therapy beyond cure of HCV and prevention of further liver disease progression. Thus HIV co-infection gives a high priority to anti-HCV treatment already at lower liver fibrosis stages (F0/F1). Similar HCV cure rates and tolerability in HCV/HIV co-infected persons as in HCV mono-infected persons under DAA therapy have further questioned the separation of HIV co-infected persons as a separate patient group and have claimed treatment indication and regimens to be the same as in HCV mono-infection.
2. If chronic HCV and HIV infection are newly diagnosed at the same time with a CD4 count > 500 cells/µL treatment of HCV in presence of immediate HCV treatment indication (≥ F2 fibrosis) can be considered prior to ART initiation to avoid potential drug-drug interactions between ART and HCV DAAs, see Drug-drug Interactions between DAAs and ARVs.
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.
4. 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 in countries where no or only limited DAAs have become available so far or where cost reimbursement issues still have not been clarified. In these cases, fibrosis assessment should be carried out every 12 months to monitor for fibrosis progression, see page 73.
5. Re-test for GT and sub-type should be performed in persons with tests carried out before second-generation tests were available (second-generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection' for whom the GT/sub-type should be performed on most recent available specimen.

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

6. With multiple studies in HCV treatment-naïve and treatment experienced persons with HCV/HIV co-infection demonstrating significantly higher SVR 12-24 rates with DAA based therapy, IFN-free DAA combinations should be considered standard of care for chronic HCV, in particular in advanced fibrosis. IFN-containing HCV regimens are no longer recommended. For IFN-containing HCV regimens see IFN-containing Treatment of HCV Co-infection in HIV-positive Persons
7. The combination of sofosbuvir 400 mg qd and a weight-adapted dose of RBV of 1000 (weight ≤ 75 kg) - 1200 (weight > 75 kg) mg/day (administered bid) for 12 weeks has become standard therapy for HCV GT2 infected persons. Persons with cirrhosis can be treated for an extended duration of 16 weeks. However, recent cohort data have shown response rates below 90% for treating GT2 with sofosbuvir and RBV asking for more active treatment regimen e. g. sofosbuvir/velpatasvir.
   In particular for GT1 and 4 the approval of further DAAs have offered the opportunity of IFN- and partially also RBV-free DAA combination regimens which because of significantly improved tolerability and higher HCV cure rates should now be considered as new gold standard in HCV therapy. In particular, combination of sofosbuvir and simeprevir (GT1 and 4), a fixed-dose combination of sofosbuvir/ledipasvir (GT 1 and 4), elbasvir/grazoprevir (GT 1 and 4), sofosbuvir/velpatasvir (GT 1-6), sofosbuvir plus daclatasvir (GT1, 2, 3 and 4) or a combination of ombitasvir/paritaprevir/r and dasabuvir (GT 1 and 4 without dasabuvir) are recommended, see HCV Treatment Options in HCV/HIV Co-infected Persons. Addition of RBV may be considered to reduce relapse rate and shorten treatment duration for some of the DAA combinations. Also RBV should be added to the ombitasvir/paritaprevir/r and dasabuvir combination when treating GT1a and ombitasvir/paritaprevir/r when treating GT 4. For GT3, sofosbuvir plus RBV for 24 weeks achieves SVR12 in 80-90% of non-cirrhotic persons with lower response rates in persons with liver cirrhosis (60-70%) and is considered suboptimal. Alternative treatment strategies are sofosbuvir plus daclatasvir +/- RBV for 12-24 weeks or sofosbuvir/velpatasvir achieving higher SVR rates in particular in persons with liver cirrhosis.
8. Use of older, first generation HCV PIs (boceprevir and telaprevir; only indicated in GT1) are no longer recommended because of increased toxicities. The second generation PI simeprevir can cause hyperbilirubinaemia and skin reactions/photosensibility.
9. Due to drug-drug interactions in particular HIV and HCV PIs careful checking for interactions is urgently recommended prior to starting HCV therapy, see Drug-drug Interactions between DAAs and ARVs or http://www.hep-druginteractions.org. During PEG-IFN-RBV therapy, ddI is contra-indicated in persons with cirrhosis and should be avoided in persons with less severe liver disease. Use of d4T and ZDV should also be avoided if possible.
10. In persons failing a first course with DAAs, current re-treatment strategies should include at least 2 active drug classes according to resistance testing results with a preferential use of one drug with high genetic barrier to resistance and with extended treatment durations and addition of RBV. Otherwise new treatment options should be awaited if deferred treatment can be justified and in presence of relevant resistance-associated substitutions (RASs) at failure. In order to facilitate the best choice of HCV therapy before starting re-treatment, HCV resistance testing should be repeated (only in the gene with previous RASs) and should be based on population sequencing.

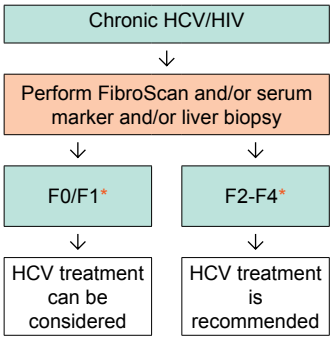
Treatment goal

11. The primary aim of HCV treatment is SVR defined as undetectable HCV-RNA 12-24 weeks after the end of therapy (evaluated using sensitive molecular tests).

Treatment of acute HCV

12. In the absence of approved DAAs in the setting of acute HCV co-infection, treatment with PEG-IFN and RBV should be based on an individual decision weighing the known toxicities and longer treatment duration under dual therapy against a potentially strong wish from the co-infected person for early HCV cure, particularly in HIV-positive MSM with a higher risk of HCV transmission and in countries where DAAs will only be reimbursed in chronic HCV with ≥F3 fibrosis. After diagnosis of acute HCV, HCV-RNA should be measured 4 weeks later. Treatment can be discussed in persons without a decrease of $2*\log_{10}$ of HCV-RNA at 4 weeks compared with initial HCV-RNA and in persons with persistent serum HCV-RNA 12 weeks after diagnosis of acute HCV, see Algorithm for Management of Acute HCV in Persons with HCV/HIV Co-infection. Early discontinuation of dual therapy is justified in persons experiencing significant side effects of PEG-IFN and/or RBV. Enrollment of persons with acute HCV co-infection in ongoing trials using IFN-free DAA combination therapy is strongly encouraged. In countries with access to DAAs and potentially individual cost reimbursement for DAAs in the setting of acute HCV, sofosbuvir/ledipasvir for 6-8 weeks has been proven to be successful. Treatment should be prolonged to 8-12 weeks in persons with high baseline HCV-RNA (≥ $6\log_{10}$ IU/mL).

Management of Persons with Chronic HCV/HIV Co-infection



* Metavir fibrosis score: F0=no fibrosis; F1=portal fibrosis, no septae; F2= portal fibrosis, few septae, F3=bridging fibrosis, F4=cirrhosis.
FibroScan®: F0-F1 < 7.1 kPa; F2 7-10 kPa; F3/F4 > 10 kPa
Treatment must be considered independently from liver fibrosis in persons with low CD4 count (< 200 cells/μL), ongoing HIV replication, HBV co-infection, debilitating fatigue, extrahepatic manifestations, high risk of HCV transmission (IVDU, prisoners, MSM with high risk behavior, fertile women who want to be pregnant).

HCV Treatment Options in HCV/HIV Co-infected Persons

IFN-free HCV Treatment Options				
HCV GT	**Treatment regimen**	**Treatment duration & ribavirin usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 4	SOF + SMP +/- RBV	GT 4 only: 12 weeks with RBV or 24 weeks without RBV[i]		Not recommended
	SOF/LDV +/- RBV	8 weeks without RBV[ii] or 12 weeks +/- RBV[iii]	12 weeks +/- RBV or 24 weeks without RBV[iv]	
	SOF + DCV +/- RBV	12 weeks +/- RBV[iii]	12 weeks +/- RBV or 24 weeks without RBV[iv]	
	SOF + VEL	12 weeks		12 weeks with RBV
	OBV/PTV/r + DSV	8[v]-12 weeks in GT 1b	12 weeks in GT 1b	Not recommended
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4		Not recommended
	EBR + GZR	12 weeks[vi]		Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF + VEL	12 weeks		12 weeks with RBV
3	SOF + DCV +/- RBV	12 weeks +/- RBV[vii] or 24 weeks without RBV	24 weeks with RBV	
	SOF + VEL +/- RBV	12 weeks +/- RBV[vii] or 24 weeks without RBV		24 weeks with RBV
5 & 6	SOF/LDV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[i]	12 weeks with RBV or 24 weeks without RBV[i]	12 weeks with RBV or 24 weeks without RBV
	SOF + DCV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[i]	12 weeks with RBV or 24 weeks without RBV[i]	12 weeks with RBV or 24 weeks without RBV
	SOF + VEL	12 weeks		12 weeks with RBV

DCV = daclatasvir
DSV = dasabuvir
EBR = elbasvir
GZR = grazoprevir
LDV = ledipasvir
OBV = ombitasvir
PTV/r = paritaprevir/RTV
RBV = ribavirin
SMP = simeprevir
SOF = sofosbuvir
VEL = velpatasvir
RAS = Resistance Associated Substitutions

i In treatment experienced persons RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV
ii 8 weeks treatment without RBV only in treatment-naïve persons with F< 3 and baseline HCV-RNA < 6 million IU/mL
iii Addition of RBV in GT1a treatment experienced persons, but not in persons without NS5A RASs, if RASs testing is available
iv RBV can be avoided in GT1b, GT4 treatment-naïve, GT1a treatment-naïve and in GT1a experienced persons without NS5A RASs, if RASs testing is available; in persons intolerant to RBV, treatment may be prolonged to 24 weeks
v 8 weeks treatment without RBV only in persons without cirrhosis
vi Extension of treatment to 16 weeks and addition of RBV in persons with GT1a with baseline HCV-RNA > 800.000 IU/mL and NS5A RASs and in HCV GT4 experienced persons with HCV-RNA > 800.000 IU/mL
vii Addition of RBV only in treatment experienced persons with baseline NS5A RASs, if RAS testing available; if these persons are intolerant to RBV treatment may be prolonged to 24 weeks without RBV

Drug-drug Interactions between DAAs and ARVs

HCV drugs		ATV/r	DRV/c	DRV/r	LPV/r	EFV	ETV	NVP	RPV	MVC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF	ZDV
DAAs	boceprevir	D35%	↓D	↓32% D44%	↓45% D34%	↓19% E20%	↑10% D23%	↓E	↓6% E39%	E	↔	↓D	↔	↔	↔	↔	D[x]	↔	↔[i]
	daclatasvir	↑110%[ii]	↑	↑41%	↑15%	↓32%[iii]	↓	↓	↔	↔	E33%	↑[ii]	↔	↔	↔	↔	↔	↑10% E10%	↔
	elbasvir/ grazoprevir	↑	↑	↑	↑	↓54/83%	↓	↓	↔	↔	↔	↑	E43%	↔	↔	↔	E	↓7/14% E34%	↔
	parita-previr/r/ ombitasvir/ dasabuvir	↑94%[iv]	↑	D[v]	↑	[vii]	↓E?	↓E?	E[viii]	E	↔	↑	E134%	↔	↔	↔	E	↔	↔
	paritaprev-ir/r/ombi-tasvir	↑[iv]	↑	↑[vi]	↑	[vii]	↓E?	↓E?	E[viii]	E	↔	↑	E20%	↔	↔	↔	E	↔	↔
	simeprevir	↑	↑	↑	↑	↓71%	↓	↓	↑6% E12%	↔	↔	↑	↓11% E8%	↔	↔	↔	↔	↓14% E18%	↔
	sofosbuvir/ ledipasvir	↑8/113%[ix]	↑E[ix]	↑34/ 39%[ix]	↔[ix]	↓-/34%	↔	↔	↔[ix]	E?	↔	↑36/ 78%E[ix]	D≈20%	↔	↔	↔	E32%	E[ix]	↔
	sofosbuvir/ velpatasvir	↑-/142%[ix]	↔[ix]	↓28%/-[ix]	↓29%/-[ix]	↓-/53%	↓	↓	↔	E?	↔	↔	↔	↔	↔	↔	↔	E[ix]	↔
	sofosbuvir	↔	↑	↑34%	↔	↓6% D4%	↔	↔	↑9% E6%	↔	↔	↔	↓5%D 27%	↔	↓6%	↔	↔	↓6%	↔
	telaprevir	↓20% E17%	↓D	↓35% D40%	↓54%	↓26% D7%	↓16%	↓?	↓5%E	E	E25%	↑13% D16%	E31%	↔	↔	↔	D[x]	E30%[ix]	↔[i]

Legend

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

Numbers refer to decreased/increased AUC of DAAs and ARVs as observed in drug interactions studies. Sofosbuvir/ledipasvir: first/second numbers refer to changes AUC sofosbuvir/ledipasvir.

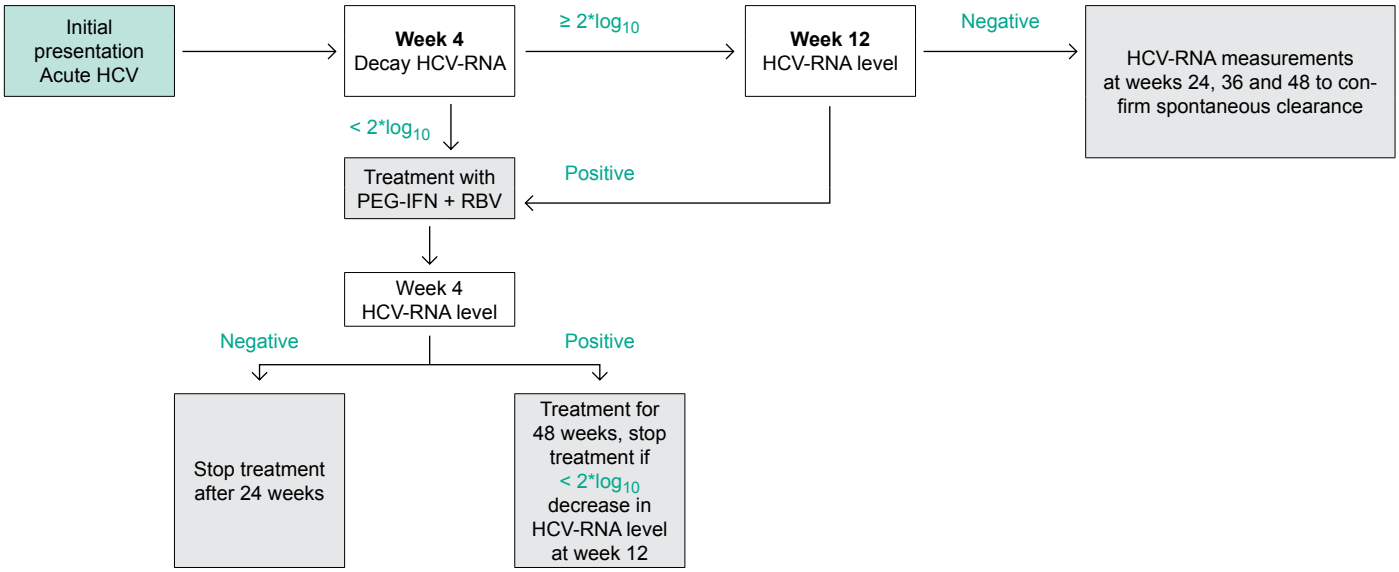
i Potential hematological toxicity
ii Daclatasvir should be reduced to 30 mg qd with ATV/r or EVG/c. No dose reduction with unboosted ATV
iii Daclatasvir should be increased to 90 mg qd
iv Use only with unboosted ATV and in persons without significant HIV PI mutations (ATV increased paritaprevir exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without dasabuvir)
v Co-administration decreased DRV trough concentration by approximately 50%. Although co-administration of DRV with ombitasvir/paritaprevir/r + dasabuvir is not recommended in the US Prescribing Information, the European SPC advises that DRV (dosed at 800 mg qd and administered at the same time as ombitasvir/paritaprevir/r + dasabuvir) can be used in the absence of extensive HIV PI resistance and should be taken without additional RTV
vi Not recommended due to increase in paritaprevir exposure when co-administered with DRV 800 mg given with ombitasvir, paritaprevir, ritonavir (Viekirax). Of note: exposures of paritaprevir greater than this have been evaluated in phase 2 studies and were not expected to have a clinically meaningful impact on safety
vii Severe tolerability issues
viii Not recommended unless benefit outweights the risk due to potential for QT interval prolongation with higher concentrations of rilpivirine, co-administration should only be considered in persons without known QT prolongation and without other QT prolongation co-medications
ix Frequent monitoring of kidney function due to increase of TDF if contained in the regimen
x The DAA can affect the intracellular activation of TAF

Colour legend

no clinically significant interaction expected.
these drugs should not be co-administered.
potential interaction which may require a dosage adjustment or close monitoring.

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

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



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

IFN-containing treatment of chronic HCV in persons with HCV/HIV co-infection

1. In countries where no sofosbuvir is available PEG-IFN and RBV combination treatment for 24 weeks (if RVR i.e. negative HCV-RNA at week 4 after starting HCV therapy) or 48 weeks represents an alternative treatment choice for HCV GT2. 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.
2. In case of limited DAA availability or reimbursement issues sofosbuvir in combination with PEG-IFN and RBV would be the next best treatment option (for GT1, 3-6), see IFN-containing HCV Treatment Options For Fibrosis Stages up to CHILD A. Simeprevir in combination with PEG-INF and RBV can also be an alternative (for GT1 or 4; but with longer treatment duration for IFN), however absence of the Q80K mutation should be demonstrated prior to treatment initiation.
3. Use of older, first generation HCV PIs (boceprevir and telaprevir; only indicated in GT1) are only recommended where other DAAs are not currently available and for some future time.
4. Use of HCV PIs is associated with additional toxicities: boceprevir causes anaemia, teleprevir skin rash and simeprevir hyperbilirubinaemia and skin reactions/photosensibility.
5. Due to drug-drug interactions in particular HIV and HCV PIs, careful checking for interactions is urgently recommended prior to starting HCV therapy, see http://www.hep-druginteractions.org or Drug-drug Interactions Between ARVs and DAAs. During PEG-IFN-RBV therapy, ddI is contra-indicated in persons with cirrhosis and should be avoided in persons with less severe liver disease. d4T and ZDV should also be avoided if possible.

Treatment goal

6. The primary aim of HCV treatment is SVR defined as undetectable HCV-RNA 12-24 weeks after the end of therapy, evaluated using sensitive molecular tests.

Stopping rules

7. 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 HCV infection with PEG-IFN and RBV, treatment should be stopped, see page 78. Different stopping rules apply when DAAs are being used in combination with PEG-IFN and RBV and are summarised, see page 79. Futility rules with simeprevir in combination with PEG-IFN and RBV are that HCV-RNA > 25 IU/mL after 4,12 or 24 weeks of HCV therapy should be discontinued. 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 79. 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. In PEG-IFN and sofosbuvir or IFN-free based therapies reasons to stop treatment may be non-adherence or toxicities on an individual basis.

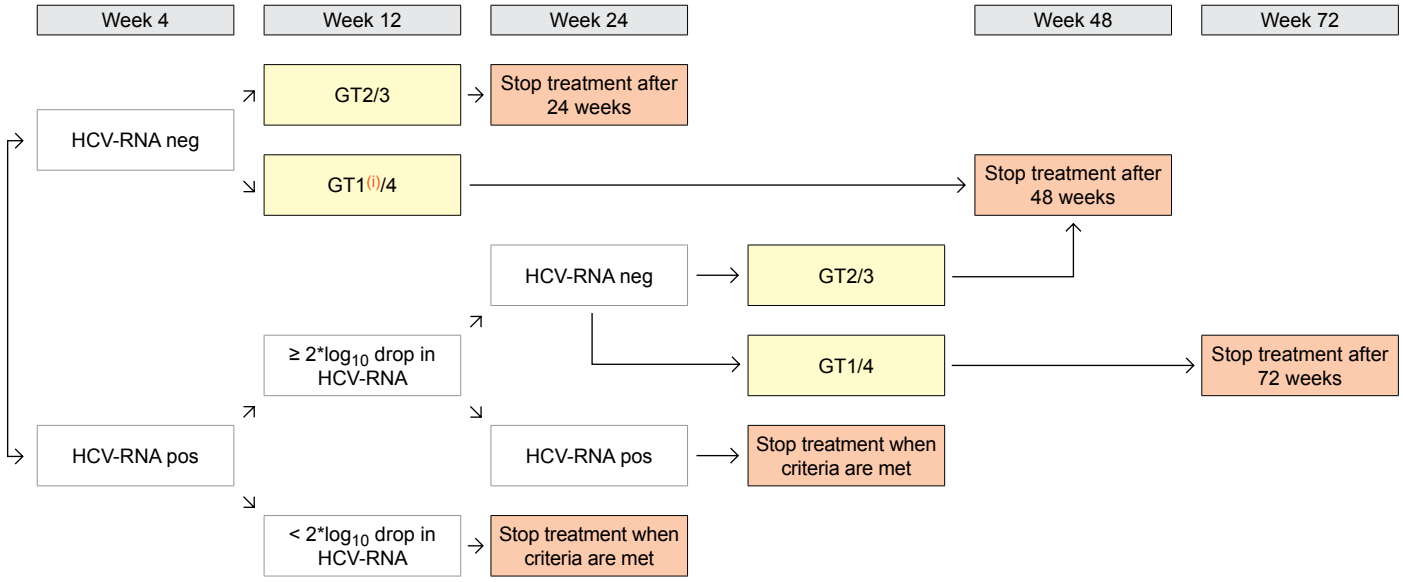
IFN-containing HCV treatment options (For fibrosis stages up to CHILD A)

HCV GT	Treatment	Treatment duration
1 & 4	SOF + PEG-IFN/RBV	12 weeks (possible extension up to 24 weeks in cirrhotics)
	SMP* + PEG-IFN/RBV	24 weeks** (48 weeks in cirrhotics and treatment-experienced)
	DCV + PEG-IFN/RBV***	24 weeks if RVR, 48 weeks if non-RVR
2	PEG-IFN/RBV	IFN-free treatment recommended. If SOF not available: PR 24 weeks if RVR, 48 weeks if non-RVR
3	SOF + PEG-IFN/RBV	12 weeks (possible extension up to 24 weeks in cirrhotics)
5 & 6	In the absence of clinical data on DAAs in HCV GT 5 and 6 infection persons should be treated similar to HCV GT 1 and 4 infection	

DCV daclatasvir
PEG-IFN/RBV pegylated-interferon + ribavirin
RBV ribavirin
SMP simeprevir
SOF sofosbuvir

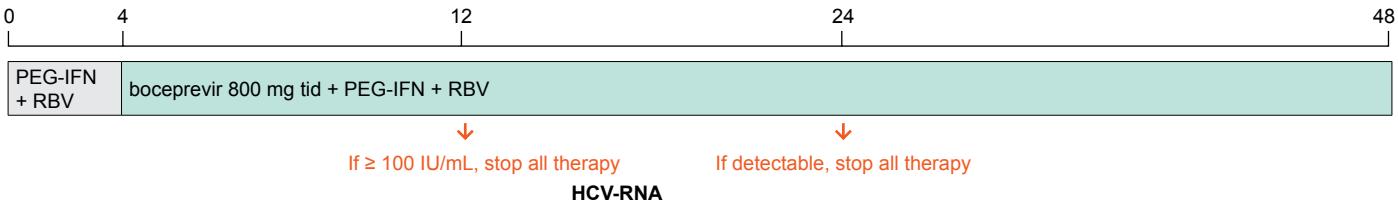
* SMP for 12 weeks only
** also in relapsers
*** GT4 only, DCV for 24 weeks only

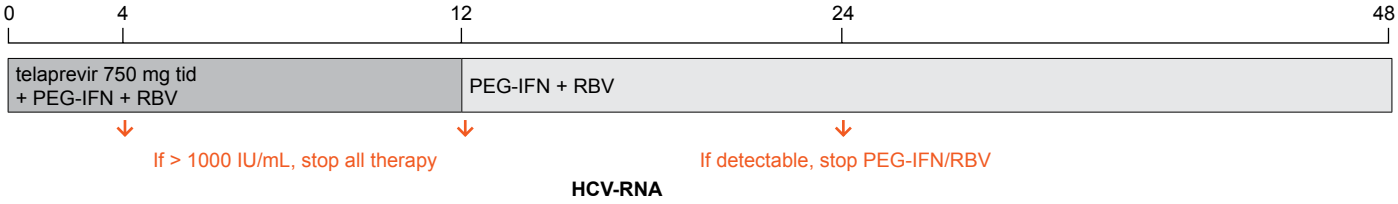
Proposed Optimal Duration of Dual HCV Therapy in Persons with Chronic HCV/HIV Co-infection Not Eligible for Triple Therapy Including DAAs against HCV

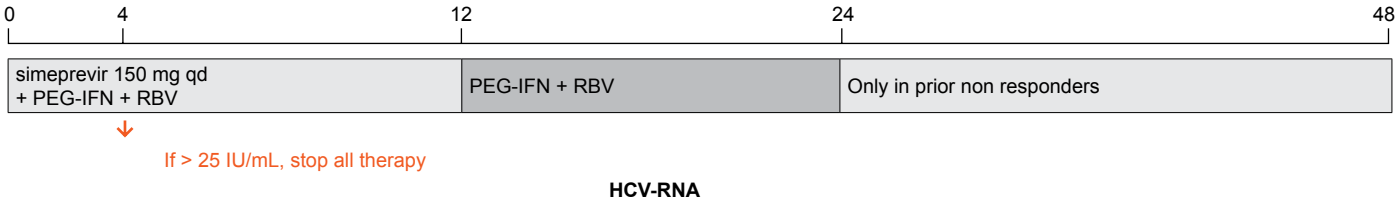


i Where no access to DAAs available or high chances of cure even with dual therapy (favourable IL28B GT, low HCV-RNA and no advanced fibrosis)

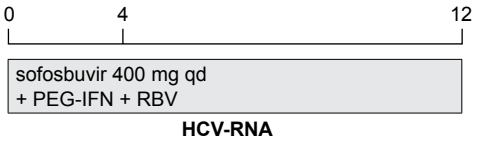
Use of Boceprevir, Telaprevir, Simeprevir or Sofosbuvir with PEG-IFN + RBV in Persons with HIV/HCV Co-infection







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



No stopping rules apply: Fixed duration of 12 weeks regardless of HCV-RNA decline.

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 [1]

Part V Opportunistic Infections

Prevention and Treatment of Opportunistic Infections (OIs) in HIV-positive Persons

This chapter provides an overview of the most important aspects in management of the most frequent OIs occurring in HIV-positive persons in Europe. For more detailed discussion, we refer to national guidelines [1-6]

Primary Prophylaxis of OIs according to stage of immunodeficiency

CD4 count threshold/indication			
CD4 count < 200 cells/µL, CD4 percentage < 14%, recurrent oral thrush, or relevant concomitant immunosuppression*			
Prophylaxis against Pneumocystis jirovecii Pneumonia (PcP) & Toxoplasma gondii **Stop:** if CD4 count > 200 cells/µL over 3 months or CD4 count 100-200 cells/µL and HIV-VL undetectable over 3 months * e.g. use of corticosteroids > 20 mg prednisone equivalent per day for > 2 weeks, cancer chemotherapy, biological agents such as rituximab and others. Decisions on installation and discontinuation in these situations have to be taken individually.			
	Drug	**Dose**	**Comments**
Positive or negative serology for toxoplasmosis	**TMP-SMX**	1 double-strength tablet (ds) (800/160 mg) 3 x/week po or 1 single-strength tablet (ss) (400/80 mg) 1 x/day po or 1 ds tablet 1 x/day po	
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL aqua 1 x inhalation/month	Does not prevent the rare extrapulmonary manifestations of P. jirovecii
Negative serology for toxoplasmosis	**dapsone**	1 x 100 mg/day po	Check for G6PD-deficiency
Positive or negative serology for toxoplasmosis	**atovaquone suspension**	1 x 1500 mg/day po (with food)	
Positive serology for toxoplasmosis	**dapsone** **+ pyrimethamine** **+ folinic acid**	200 mg 1 x/week po 75 mg 1 x/week po 25-30 mg 1 x/week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	**atovaquone suspension** **+ pyrimethamine** **+ folinic acid**	1 x 1500 mg/day po (with food) 75 mg 1 x/week po 25-30 mg 1 x/week po	
CD4 count < 50 cells/µL			
Prophylaxis against Non-Tuberculous Mycobacteria *(NTM) (M. avium complex, M. genavense, M. kansasii)* **Only consider prophylaxis if no clinical suspicion of disseminated *NTM*. Prophylaxis can be withheld if cART started within four weeks.** **Stop:** if CD4 count > 100 cells/µL over 3 months and person on effective ART (and HIV-VL undetectable in the opinion of some experts)			
Regimens listed are alternatives	**azithromycin**	1 x 1200-1250 mg/week po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
	or **clarithromycin**	2 x 500 mg/day po	
	or **rifabutin**	1 x 300 mg/day po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs

Primary Prophylaxis, Treatment and Secondary Prophylaxis/Maintenance Treatment of Individual OIs

Pneumocystis jirovecii Pneumonia (PcP)

Primary prophylaxis			
Start: if CD4 count < 200 cells/µL, CD4 percentage < 14%, oral thrush or relevant concomitant immunosuppression (see above) **Stop:** if CD4 count > 200 cells/µL over 3 months or CD4 count 100-200 cells/µL and HIV-VL undetectable over 3 months			
	Drug	**Dose**	**Comments**
Negative or positive serology for toxoplasmosis	**TMP-SMX**	1 double-strength tablet (ds) (800/160 mg) 3 x/week po or 1 single-strength tablet (ss) (400/80 mg) 1 x/day po or 1 ds tablet /1 x/day po	
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL aqua 1 x inhalation/month	Does not prevent the rare extrapulmonary manifestations of P. jirovecii
Negative serology for toxoplasmosis	**dapsone**	1 x 100 mg/day po	Check for G6PD-deficiency
Negative or positive serology for toxoplasmosis	**atovaquone suspension**	1 x 1500 mg/day po (with food)	
Positive serology for toxoplasmosis	**dapsone** **+ pyrimethamine** **+ folinic acid**	200 mg 1 x/week po 75 mg 1 x/week po 25-30 mg 1 x/week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	**atovaquone suspension** **+ pyrimethamine** **+ folinic acid**	1 x 1500 mg/day po (with food) 75 mg 1 x/week po 25-30 mg 1 x/week po	
Treatment			
Treat at least 21 days, then secondary prophylaxis until CD4 count > 200 cells/µL and HIV-VL undetectable over 3 months. **Diagnosis:** - **Definitive diagnosis**: Cough and dyspnea on exertion AND diagnosis by cytology / histopathology of induced sputum (sensitivity up to 80%), bronchoalveolar lavage (sensitivity > 95%) or bronchoscopic tissue biopsy (sensitivity > 95%) - **Presumptive diagnosis**: CD4 count < 200 cells/ µL AND dyspnea / desaturation on exertion and cough AND radiology compatible with PcP AND no evidence for bacterial pneumonia AND response to PcP treatment			
	Drug	**Dose**	**Comments**
Preferred therapy	**TMP-SMX**	3 x 5 mg/kg/day TMP iv/po + 3 x 25 mg/kg/day SMX iv/po	
	+ prednisone if PaO_2 < 10 kPa or < 70 mmHg, or alveolar/arterial O_2 gradient > 35 mmHg. Start prednisone preferentially 15-30 min before TMP/SMX	2 x 40 mg/day po 5 days 1 x 40 mg/day po 5 days 1 x 20 mg/day po 10 days	Benefit of corticosteroids if started within 72 hours after start of treatment
Alternative therapy for *moderate to severe PcP*	**primaquine** **+ clindamycin**	1 x 30 mg (base)/day po 3 x 600-900 mg/day iv/po	Check for G6PD deficiency
	or **pentamidine**	1 x 4 mg/kg/day iv (infused over 60 min.)	
	For each regimen: **+ prednisone,** if PaO_2 < 10 kPa or < 70 mmHg, or alveolar/arterial O_2 gradient > 35 mmHg. Start prednisone preferentially 15-30 min before TMP/SMX. Some experts recommend adding **caspofungin** to standard treatment in persons with severe PcP (requiring intensive care unit admission)	2 x 40 mg/day po 5 days 1 x 40 mg/day po 5 days 1 x 20 mg/day po 10 days 1 x 70 mg iv day 1, then 1 x 50 mg/day iv	Benefit of corticosteroids if started within 72 hours after start of treatment
Alternative therapy for *mild to moderate PcP*	**primaquine** **+ clindamycin**	1 x 30 mg (base)/day po 3 x 600-900 mg/day po	Check for G6PD deficiency
	or **atovaquone suspension**	2 x 750 mg/day po (with food)	
	or **dapsone** **+ trimethoprim**	1 x 100 mg/day po 3 x 5 mg/kg/day po	Check for G6PD deficiency In case of rash: reduce dose of TMP (50%), antihistamines

Secondary prophylaxis / Maintenance treatment			
Stop: if CD4 count > 200 cells/µL and HIV-VL undetectable over 3 months			
	Drug	**Dose**	**Comments**
Negative or positive serology for toxoplasmosis	**TMP-SMX**	1 ds tablet (800/160 mg) 3 x/week po or 1 ss tablet (400/80) mg 1 x/ day po or 1 ds tablet 1 x/day po	
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL aqua 1 x inhalation/month	Not to use in the rare case of extrapulmonary manifestations of P. jirovecii
Negative serology for toxoplasmosis	**dapsone**	1 x 100 mg/day po	Check for G6PD-deficiency
Negative or positive serology for toxoplasmosis	**atovaquone suspension**	1 x 1500 mg/day po (with food)	
Positive serology for toxoplasmosis	**dapsone** **+ pyrimethamine** **+ folinic acid**	200 mg 1 x/week po 75 mg 1 x/week po 25-30 mg 1 x/week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	**atovaquone suspension** **+ pyrimethamine** **+ folinic acid**	1 x 1500 mg/day po (with food) 75 mg 1 x/week po 25-30 mg 1 x/week po	

Primary prophylaxis			
Start: if CD4 count < 200 cells/µL, or CD4 percentage < 14%, oral thrush, or relevant concomitant immunosuppression (see above) **Stop:** if CD4 count > 200 cells/µL over 3 months or CD4 count 100-200 cells/µL and HIV-VL undetectable over 3 months			
	Drug	**Dose**	**Comments**
Preferred prophylaxis	**TMP-SMX**	1 double-strength tablet (ds) (800/160 mg) 3 x/week po or 1 single-strength tablet (ss) (400/80 mg) 1 x/day po or 1 ds tablet 1 x/day po	All regimens are also effective against PcP
Alternative prophylaxis	**atovaquone suspension**	1 x 1500 mg/day po (with food)	
	dapsone **+ pyrimethamine** **+ folinic acid**	200 mg 1 x/week po 75 mg 1 x/week po 25-30 mg 1 x/week po	Check for G6PD-deficiency
	atovaquone suspension **+ pyrimethamine** **+ folinic acid**	1 x 1500 mg/day po (with food) 75 mg 1 x/week po 25-30 mg 1 x/week po	
Treatment			
Treat 6 weeks, then secondary prophylaxis until CD4 count > 200 cells/µL over 6 months **Diagnosis:** - **Definitive diagnosis:** clinical symptoms, typical radiology of the cerebrum AND cytological / histological detection of organism - **Presumptive diagnosis:** clinical symptoms, typical radiology AND response to empirical treatment. It is the standard in most clinical settings.			
	Drug	**Dose**	**Comments**
Preferred therapy	**pyrimethamine** **+ sulfadiazine** **+ folinic acid**	Day 1: 200 mg po, **then** • If ≥ 60 kg; 1 x 75 mg/day po • If < 60 kg: 1 x 50 mg/day po • If ≥ 60 kg: 2 x 3000 mg/day po/iv • If < 60 kg: 2 x 2000 mg/day po/iv 1 x 10-15 mg/day po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia Sulfadiazine is associated with crystalluria and may lead to renal failure and urolithiasis. Good hydration is essential. Check renal function and urine sediment for microhematuria and crystalluria
Alternative therapy	**pyrimethamine** **+ clindamycin** **+ folinic acid**	Day 1: 200 mg/day po, **then** • If ≥ 60 kg: 1 x 75 mg/day po • If < 60 kg: 1 x 50 mg/day po 4 x 600-900 mg/day po/iv 1 x 10-15 mg/day po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia Additional PcP prophylaxis is necessary
	or **TMP-SMX**	2 x 5 mg TMP/kg/day po/iv 2 x 25 mg SMX/kg/day po	
	or **pyrimethamine** + **atovaquone** + **folinic acid**	Day 1: 200 mg po, **then** If ≥ 60 kg; 1 x 75 mg/day po If < 60 kg: 1 x 50 mg/day po 2 x 1500 mg/day po (with food) 1 x 10-15 mg/day po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia
	or **sulfadiazine** **+ atovaquone**	• If ≥ 60 kg: 2 x 3000 mg/day po/iv • If < 60 kg: 2 x 2000 mg/day po/iv 2 x 1500 mg/day po (with food)	Sulfadiazine is associated with crystalluria and may lead to renal failure and urolithiasis. Good hydration is essential. Check renal function and urine sediment for microhematuria and crystalluria
	or **pyrimethamine** **+ azithromycin** **+ folinic acid**	Day 1: 200 mg po, then • If ≥ 60 kg; 1 x 75 mg/day po • If < 60 kg: 1 x 50 mg/day po 1 x 900-1200 mg/day po 1 x 10-15 mg/day po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia
Secondary prophylaxis / Maintenance therapy			
Stop: if CD4 count > 200 cells/µL and HIV-VL undetectable over 6 months			
Regimens listed are alternatives	**sulfadiazine** **+ pyrimethamine** **+ folinic acid**	2-3 g/day po (in 2-4 doses) 1 x 25-50 mg/day po 1 x 10-15 mg/day po	
	or **clindamycin** **+ pyrimethamine** **+ folinic acid**	3 x 600 mg/day po 1 x 25-50 mg/day po 1 x 10-15 mg/day po	Additional PCP prophylaxis is necessary
	or **atovaquone suspension** **+ pyrimethamine** **+ folinic acid**	2 x 750-1500 mg/day po (with food) 1 x 25-50 mg/day po 1 x 10-15 mg/day po	
	or **atovaquone suspension**	2 x 750-1500 mg/day po (with food)	
	or **TMP-SMX**	1 ds tablet (800/160 mg) 2 x/day po	

Cryptococcal meningitis

Treatment			
14 days induction therapy, then 8 weeks consolidation therapy, then secondary prophylaxis for at least 12 months. Stop, if CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months **Diagnosis:** positive microscopy, OR detection of antigen, OR culture from CSF **Other organ manifestations:** Cryptococcal infection can also cause a pneumonitis which may be difficult to distinguish from Pneumocystis pneumonia. Infection may also involve other organs or may be disseminated. **Pre-emptive therapy:** Early stages of disseminated cryptocccal infections may be oligosymptomatic. Newer data from mainly resource limited settings support determination of serum cryptococcal antigen in all newly diagnosed HIV-positive persons with CD4 counts < 100 cells/µL. If cryptococcal antigen is detected, CSF should be examined to rule out cryptococcal meningitis. If meningitis is ruled out, pre-emptive therapy with fluconazole 800mg/day po for two weeks is recommended before starting cART to reduce the risk of unmasking IRIS.			
	Drug	**Dose**	**Comments**
Pre-emptive therapy	**flucanozole**	1 x 800 mg/day po for 2 weeks followed by 1 x 400 mg/day po for 8 weeks	In case of: - positive cryptococcal serum antigen - asymptomatic individual - cryptococcal meningitis ruled out by CSF examination
Induction therapy	**liposomal amphotericin B + flucytosine**	3 mg/kg/day iv 4 x 25 mg/kg/day po	**14 days** - Then perform lumbar puncture (LP): if CSF culture is sterile, switch to oral regimen - Opening pressure should always be measured, when LP is performed - Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure which is associated with better survival - Corticosteroids have no effect in reducing increased intracranial pressure, could be detrimental and are contra-indicated - Flucytosine dosage must be adapted to renal function - Defer start of cART for at least 4 weeks - Amphotericin B deoxycholate may not be available in all European countries
	or **amphotericin B deoxycholate + flucytosine**	0.7 mg/kg/day iv 4 x 25 mg/kg/day po	
Consolidation therapy	**fluconazole**	1 x 400 mg/day po (loading dose 1 x 800 mg 1st day)	8 weeks. Repeated LP until opening pressure < 20 cm H_20 or 50% of initial value
Secondary prophylaxis / Maintenance therapy			
At least 12 months **Consider to stop:** if CD4 count >100 cells/µL and HIV-VL undetectable over 3 months			
	Drug	**Dose**	**Comments**
	fluconazole	1 x 200 mg/day po	

Candidiasis

Oropharyngeal Candidiasis			
Diagnosis: typical clinical appearance			
	Drug	**Dose**	**Comments**
	fluconazole	1 x 150-200 mg/day po	Once or until improvement (5-7 days)
	or **itraconazole**	1-2 x 100-200 mg/day po (oral solution fasting)	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/day or oral suspension 1-2 g/day (in 2-4 doses)	7-14 days
Oesophagitis			
Definitive diagnosis: macroscopic inspection at endoscopy, OR histology of biopsy, OR cytology of specimen from the mucosal surface **Presumptive diagnosis:** if 1. Recent onset of dysphagia AND 2. Oropharyngeal candidiasis			
	Drug	**Dose**	**Comments**
	fluconazole	1 x 400 mg/day or 400 mg loading dose, then 200 mg/day po	3 days 10-14 days
	consider **itraconazole** **or** **posaconazole** **or** **voriconazole** **or** **caspofungin**	1-2 x 100-200 mg/day po (oral solution fasting) 2 x 400 mg/day po 2 x 200 mg/day po 1 x 70 mg iv/day, then 1 x 50 mg/day iv	10-14 days. Be aware of interactions with ARVs, see Drug-drug Interactions Between ARVs and Non-ARVs In cases of refractory disease, treat according to resistance testing. Adapt posaconazole and voriconazole dose according to MIC's of candida and drug trough levels.

Histoplasmosis (Histoplasma capsulatum)

Treatment			
Diagnosis: antigen detection in blood, urine or broncho-alveolar fluid, OR by positive microscopy, OR mycological culture of blood, urine, broncho-alveolar fluid, CSF or tissue biopsy. **Note:** CSF, which shows typically a lymphatic pleocytosis, is usually microscopic and culture negative. Detection of Histoplasma antigen or antibody is more sensitive. Though, a clinical diagnosis is possible in case of negative Histoplasma antigen or antibody in CSF, if dissiminated histoplasmosis is present and CNS infection is not explained by another cause. Seek expert advice for the use of fluconazole, voriconazole or posaconazole, if itraconazole is not tolerated. **Be aware of interactions of azoles with ARVs,** see Drug-drug Interactions Between ARVs and Non-ARVs**.** Measurement of plasma concentration of itraconazole and voriconazole is advised to guide optimal treatment.			
	Drug	**Dose**	**Comments**
Severe disseminated histoplasmosis	**Induction therapy:** **liposomal amphotericin B** **Consolidation therapy:** **itraconazole**	 3 mg/kg/day iv 3 x 200 mg/day po for 3 days, then 2 x 200 mg/day po	 For 2 weeks or until clinical improvement For at least 12 months
Moderate disseminated histoplamosis	**itraconazole**	3 x 200 mg/day po for 3 days, then 2 x 200mg/day po	For at least 12 months
Histoplasma meningitis	**Induction therapy:** **liposomal amphotericin B** **Consolidation therapy:** **itraconazole**	 5 mg/kg/day iv 2 x or 3 x 200 mg/day po	 For 4-6 weeks For at least 12 months and until resolution of abnormal CSF findings. Measure plasma concentration of itraconazole.
Secondary prophylaxis / Maintenance therapy			
Stop: if CD4 count > 150 cells/µL, cART and HIV-VL undetectable over 6 months, negative fungal blood cultures, Histoplasma antigen < 2 µg/L and > 1 year treatment **Consider long-term suppressive** therapy in severe cases of meningitis and in cases of relapse despite adequate treatment			
	itraconazole	1 x 200 mg/day po	
	or **fluconazole**	1 x 400 mg/day po	

Herpes simplex virus (HSV) infections

Treatment			
Diagnosis: antigen testing / PCR / culture of swab / CSF / biopsy. Clinical appearance of skin lesions not reliable			
	Drug	**Dose**	**Comments**
Initial genital / mucocutaneous HSV	**valaciclovir**	2 x 1000 mg/day po	7-10 days or until lesions healed
	or **famciclovir**	2 x 500 mg/day po	7-10 days or until lesions healed
	or **aciclovir**	3 x 400-800 mg/day po	7-10 days or until lesions healed
Recurrent genital / mucocutaneous HSV (> 6 episodes/year)	**valaciclovir**	2 x 500 mg/day po	Chronic suppressive therapy. Alternatively start early treatment as above if recurrences occur
Severe mucocutaneous lesions	**aciclovir**	3 x 5 mg/kg/day iv	After lesions begin to regress, switch to oral treatment until lesions have healed
Encephalitis	**aciclovir**	3 x 10 mg/kg/day iv	14-21 days
Aciclovir resistant mucocutaneous HSV infection	**foscarnet**	2-3 x 80-120 mg/kg/day iv	Until clinical response

Varicella zoster virus (VZV) infections

Treatment			
Diagnosis: typical clinical appearance with/without antibody testing, OR antigen testing / PCR / culture of swab / CSF / biopsy			
	Drug	**Dose**	**Comments**
Primary Varicella infection (Chickenpox)	**valaciclovir**	3 x 1000 mg/day po	5-7 days
Herpes Zoster (Shingles): Not disseminated	**valaciclovir**	3 x 1000 mg/day po	10 days
	or **famciclovir**	3 x 500 mg/day po	10 days
	or **aciclovir**	3 x 5 mg/kg/day iv	10 days
Herpes Zoster: Disseminated	**aciclovir**	3 x 10 mg/kg/day iv	10-14 days
Encephalitis (including vasculitis)	**aciclovir**	3 x 10-15mg/kg/day	14-21 days

Cytomegalovirus (CMV) infections

Treatment			
Diagnosis of retinitis: clinical appearance of typical retinal lesions AND response to therapy. PCR of aqueous and vitreous humor optional **Diagnosis of esophagitis / colitis:** endoscopic presence of ulcerations AND typical histopathological picture (cellular / nuclear inclusion bodies) **Diagnosis of encephalitis / myelitis:** clinical appearance AND positive PCR in CSF Antibody testing and PCR in blood not useful for diagnosis of end-organ disease			
	Drug	**Dose**	**Comments**
Retinitis, immediate sight-threatening lesions	**ganciclovir**	2 x 5 mg/kg/day iv	21 days, then secondary prophylaxis
	or **foscarnet**	2 x 90 mg/kg/day iv	
Retinitis, small peripheral retinal lesions	**valganciclovir**	2 x 900 mg/day po (with food)	14-21 days, then secondary prophylaxis
	or **foscarnet**	2 x 90 mg/kg/day iv	
	or **cidofovir** **+ probenecid** **+ NaCl 0.9% hydration**	1 x 5 mg/kg/week iv	2 weeks then every 2 weeks. Cidofovir may not be available in all European countries
Oesophagitis/Colitis	**ganciclovir**	2 x 5 mg/kg/day iv	Treat 3-6 weeks, respectively until symptoms resolved
	or **foscarnet**	2 x 90 mg/kg/day iv	
	or **valganciclovir**	2 x 900 mg/day po (with food)	In milder disease if oral treatment tolerated
Encephalitis/Myelitis	**ganciclovir and / or** **foscarnet**	2 x 5 mg/kg/day iv 2 x 90 mg/kg/day iv	Treat until symptoms resolved and CMV replication in CSF has cleared (negative PCR in CSF) Treatment is individualised according to clinical symptoms and response to treatment
Secondary prophylaxis / Maintenance therapy: Cytomegalovirus (CMV) Retinitis			
Stop: if CD4 count > 200 cells/µL and HIV-VL undetectable over 3 months			
Regimens listed are alternatives	**valganciclovir**	1 x 900 mg/day po (with food)	
	or **ganciclovir**	1 x 5 mg/kg/day (x 5 days/ week) iv	
	or **foscarnet**	1 x 90-120 mg/kg/day (x 5 days/ week) iv	
	or **cidofovir** **+ probenecid** **+ NaCL 0.9% hydration**	1 x 5 mg/kg every 2 weeks iv	Cidofovir may not be available in all European countries

Progressive Multifocal Leukoencephalopathy (PML)

Treatment PML	
Definitive diagnosis (laboratory): evidence of JCV-DNA in CSF AND presence of compatible clinical-radiological picture **Definitive diagnosis (histology):** typical histological findings with in situ evidence of JCV-DNA antigen or JCV-DNA AND presence of compatible clinical-radiological picture **Presumptive diagnosis:** compatible clinical-radiological picture if JCV-DNA in CSF negative or not performed	
Person off-ART	Initiate cART immediately (following general guidelines for treatment, see Initial Combination Regimen for ART-naïve Adult HIV-positive Persons), INSTI may reasonably be preferred, given the importance of rapid immune reconstituion in PML. Attention should be made to development of IRIS (see below)
Person on-ART, HIV-VL failure	Optimise cART (following general guidelines for treatment, see Virological Failure), INSTI may reasonably be preferred, given the importance of rapid immune reconstituion in PML. Attention should be made to development of IRIS (see below)
Person on-ART, treated for weeks-months or on effective cART	Continue current cART
	Note: There is no specific treatment for JCV infection that proved to be effective in PML outside of anecdotal case reports, therefore there is no recommendation to use the following drugs which previously or occasionally were used in PML: Alpha-IFN, cidofovir, corticosteroids (except for treatment of IRIS-PML, see below), cytarabine, iv immunoglobulins, mefloquine, mirtazapine and topotecan
Treatment Immune Reconstitution Syndrome (IRIS) – PML	
Diagnosis: **- Paradoxical IRIS-PML:** paradoxical worsening of PML symptoms in the context of cART-induced immune-reconstitution AND in association with inflammation at MRI (oedema, mass effect and/or contrast enhancement) or in brain biopsy **- Unmasking IRIS-PML:** onset of PML in the context of cART-induced immune-reconstitution AND in association with inflammation at MRI (oedema, mass effect, and/or contrast enhancement) or at brain biopsy	
Treatment: - Corticosteroids, e.g. high dose iv methylprednisolone (e.g.1 g/day for 3-5 days) or iv dexamethasone (e.g.0.3 mg/kg/day for 3-5 days), followed by oral tapering (e.g starting with 1 mg/kg/day and taper over 1-6 weeks) **Note:** Use of corticosteroids is not justified in persons without signs of inflammation. There are no other treatments that proved to be effective in IRIS-PML outside of anecdotal case reports	

Bacillary Angiomatosis *(Bartonella henselae, Bartonella quintana)*

Treatment			
Diagnosis: typical histology			
	Drug	**Dose**	**Comments**
	doxycycline	2 x 100 mg/day po	Until improvement (until 2 months) Possible interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
	or **clarithromycin**	2 x 500 mg/day po	

Infections with Non-Tuberculous Mycobacteria *(NTM) (M. avium complex, M. genavense, M. kansasii)*

Primary prophylaxis			
Only consider prophylaxis if no clinical suspicion of disseminated *NTM*. Prophylaxis can be withheld if cART started within four weeks **Stop:** if CD4 count > 100 cells/µL over 3 months and person on effective ART (and HIV-VL undetectable in the opinion of some experts)			
Regimens listed are alternatives	**azithromycin**	1 x 1200-1250 mg/week po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
	or **clarithromycin**	2 x 500 mg/day po	
	or **rifabutin**	1 x 300 mg/day po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
Treatment			
Diagnosis: clinical appearance and cultures of blood, lymph nodes, bone marrow or other usually sterile specimen. For any treatment regimen, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs			
***Mycobacterium avium-intracellulare* complex (MAC)**			
	clarithromycin **+ ethambutol** **Ev. + rifabutin** **Ev. + levofloxacin** **Ev. + amikacin**	2 x 500 mg/day po 1 x 15 mg/kg/day po 1 x 300 mg/day po 1 x 500 mg/day po 1 x 10-15 mg/kg/day iv	12 months, then secondary prophylaxis Consider rifabutin if resistance to macrolides or ethambutol is suspected, severe immunodeficiency (CD4 count < 50 cells/µL), high bacterial load (> 2*log of CFU/mL of blood), no cART 4th drug to consider for disseminated disease 4th drug to consider for disseminated disease
	or **azithromycin** **+ ethambutol**	 1 x 500 mg/day po 1 x 15 mg/kg/day po	Consider additional drugs as above
Mycobacterium kansasii			
	rifampicin **+ isoniazid** **+ ethambutol**	1 x 600 mg/day po (or rifabutin 1 x 300 mg/day po) 1 x 300 mg/day po 1 x 15 mg/kg/day po	12 months after negative culture
	or **rifampicin** **+ clarithromycin** **+ ethambutol**	 1 x 600 mg/day po (or rifabutin 1 x 300 mg/day po) 2 x 500 mg po 1 x 15 mg/day po	12 months after negative culture
Secondary prophylaxis / Maintenance therapy for MAC infection			
Stop: if CD4 count > 100 cells/µL and HIV-VL undetectable over 6 months and MAC treatment for at least 12 months			
Mycobacterium avium (MAC) infection **Regimens listed are alternatives**	**clarithromycin** **+ ethambutol**	2 x 500 mg/day po 1 x 15 mg/kg/day po	
	or **azithromycin** **+ ethambutol**	 1 x 500 mg/day po 1 x 15 mg/kg/day po	

Cryptosporidiosis *(C. parvum, C. hominis)*

Treatment			
Diagnosis of AIDS-defining cryptosporidiosis can be made only in cases of severe immunodeficiency (CD4 count < 100 cells/µL) AND chronic diarrhoea (over 4 weeks) by immunofluorescence or acid fast stain of stools or tissue. Mainstay of therapy is the induction of ART to restore immune competence with CD4 count > 100 cells/µL. Additional measurements are symptomatic treatment, rehydration and electrolyte management. All antiprotozoal therapies can be used additively to cART in severe cases, but are not sufficient to achieve protozoal eradication without immune restoration.			
	Drug	**Dose**	**Comments**
	nitazoxanide	2 x 500-1000 mg/day po	14 days
	or **paromomycin**	4 x 500 mg/day po	14-21 days

Cystoisosporiasis *(Cystoisospora belli,* formerly *Isospora belli)*

Treatment			
Diagnosis of AIDS-defining cystoisosporiasis can be made only in cases of chronic diarrhoea (over 4 weeks) by UV fluorescence or microscopy of stools, duodenal aspirates or intestinal tissue biopsy. Besides antiprotozoal treatment, additional measurements are symptomatic treatment, rehydration and electrolyte management.			
	Drug	**Dose**	**Comments**
Preferred therapy	**TMP-SMX**	2 x 2 double-strength tablet (ds) (800/160 mg)/day po or 2 x 1 double-strength tablet (ds) (800/160 mg) /day po	Treat minimally 10 days, increase duration to 3-4 weeks if symptoms worsen or persist Treat minimally 10 days, increase dose to 2 x 2 ds tablet/day, if symptoms worsen or persist
Alternative therapy, if TMP-SMX is not tolerated	**pyrimethamin** **+ leucovorin** or **ciprofloxacin**	1 x 50-75 mg//day po 1 x 10-15 mg//day po 2 x 500 mg/day po	10 days Monitor for myelotoxicity, mostly neutropenia, for pyrimethamin 7 days
Secondary prophylaxis / Maintenance therapy			
Stop: if CD4 count > 200 cells/µL and HIV-VL undetectable over 6 months and no signs of persistent cystoisosporiasis			
Preferred therapy	**TMP-SMX**	1 double-strength tablet (ds) (800/160 mg) 3 x /week po or 1 ds tablet/day po or 2 ds tablet 3 x/week po	
Alternative therapy, if TMP-SMX is not tolerated	**pyrimethamin** **+ leucovorin**	1 x 25 mg/day po 1 x 10-15 mg/day po	Monitor for myelotoxicity, mostly neutropenia, for pyrimethamin

Leishmaniasis

Treatment			
Diagnosis: microscopy or PCR in smears, body fluids or tissue			
	Drug	**Dose**	**Comments**
Preferred treatment	**liposomal amphotericin B**	1 x 2-4 mg/kg/day iv for 10 consecutive days	Then secondary prophylaxis
	or **liposomal amphotericin B**	1 x 4 mg/kg/day iv on day 1-5, 10, 17, 24, 31 and 38	
Alternative therapy	**lipidcomplex amphotericin B**	1 x 3 mg/kg/day iv	10 days
	or **amphotericin B deoxycholate**	1 x 0.5-1 mg/kg/day iv (total dose 1.5-2 g)	amphotericin B deoxycholate may not be available in all European countries
	or **pentavalent antimonium salt (Glucantine®)**	1 x 20 mg/kg/day iv or im	4 weeks
	or **miltefosine**	1 x 100 mg/kg/day po	4 weeks
Secondary prophylaxis / Maintenance therapy			
Consider stopping: if CD4 count > 200-350 cells/µL and HIV-VL undetectable over 3 months, no relapse for at least 6 months and negative PCR in blood or negative urinary antigen			
Preferred treatment	**liposomal amphotericin B**	4 mg/kg every 2-4 weeks iv	
	or **lipidcomplex amphotericin B**	3 mg/kg every 3 weeks iv	
Alternative therapy	**pentavalent antimonium salts (Glucantine®)**	20 mg/kg every 4 weeks iv/im	
	or **miltefosine**	1 x 100 mg/day po	
	or **pentamidine**	300 mg every 3 to 4 weeks iv	

Diagnosis and Treatment of 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 below table and ART in TB/HIV Co-infection

Disease	Drug	Dose	Comments
Susceptible *Mycobacterium tuberculosis*			
Initial phase	**rifampicin** **+ isoniazid** **+ pyrizinamide** **+ ethambutol**	Weight based	**Initial phase** (rifampicin+isoniazid+pyrizinamide+ethambutol) for 2 months, then **Continuation phase** (rifampicin+isoniazid) according to TB type (see below) Possibility to omit ethambutol, if *M. tuberculosis* is known to be fully drug sensitive
Alternative	**rifabutin** **+ isoniazid** **+ pyrizinamide** **+ ethambutol**	Weight based	**Initial phase** (rifabutin+isoniazid+pyrizinamide+ethambutol) for 2 months, then **Continuation phase** (rifabutin + isoniazid) according to TB type (see below) Possibility to omit ethambutol, if *M. tuberculosis* is known to be fully drug sensitive
Continuation phase	**rifampicin/rifabutin** **+ isoniazid** according to TB type		Total duration of therapy: 1. Pulmonary, drug susceptible TB: 6 months 2. Pulmonary TB & positive culture at 8 weeks of TB treatment: 9 months 3. Extrapulmonary TB with CNS involvement or disseminated TB: 9-12 months 4. Extrapulmonary TB with bone/joint involvement: 9 months 5. Extrapulmonary TB in other sites: 6-9 months

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 TB 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 of TB therapy or culture positive at 3 months
- Homelessness/hostel living and in some countries recent/current incarceration
- In areas with very high MDRTB/XDRTB prevalence

MDRTB: Resistance to isoniazid and rifampicin.
XDRTB: Resistance to isoniazid and rifampicin and quinolones and at last one at the following injectable drugs: kanamycin, capreomycin or amikacin

Rapid detection

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

Treatment of resistant TB

INH-resistant TB
- RIF or RFB + EMB + PZA for 7 months

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

Treatment regimens should consist of at least four active drugs based on:
- Susceptibility testing for isoniazid, rifampicin, rifabutin, floroquinolones, injectable agents and other drugs if available
- Treatment history
- Local surveillance data
- Local availability of tuberculostatic drugs and locally established treatment regimens

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
6. Consider bedaquiline and seek expert advice therefore,
   a. when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide cannot be designed
   b. when there is documented evidence of resistance to any fluoroquinolone

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) • rifampicin (RIF) • rifabutin (RFB) • isoniazid (INH)
Group 2: Injectable agents	• kanamycin (Km) • amikacin (Am) • capreomycin (CM) • streptomycin (S)
Group 3: Fluoroquinolones	• levofloxacin (LFX) • moxifloxacin (MFX) • ofloxacin (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) /tedizolid (TZD) • amoxicillin/clavulanate (Amx/CLV) • thioacetazone (THZ) • imipenem/cilastatin (IPM/CLN) • high-dose isoniazid (high-dose H-16–20 mg/kg/day) • clarithromycin (CLR) • consider bedaquiline, delamanid and new anti-TB agents for MDR/XDR TB

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

Latent tuberculosis	
Indication: TST > 5 mm or positive IGRA or close contacts to persons with sputum smear positive tuberculosis	
Regimen	**Comments**
isoniazid 5 mg/kg/day (max 300 mg) po + **pyridoxin** (Vit B6) 25 mg/day po	6-9 months
rifampicin 600 mg/day po or **rifabutin** po (dose according to current cART)	4 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
rifampicin 600 mg/day po or **rifabutin** po (dose according to current cART) + **isoniazid** 5 mg/kg/day (max 300 mg) po + **pyridoxin** (Vit B6) 25 mg/day po	3 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
rifampicin 600 mg 2 x/week po + **isoniazid** 900 mg 2 x/week po + **pyridoxin** (Vit B6) 300 mg 1 x/ week po	3 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
rifapentine 900 mg 1 x/week po + **isoniazid** 900 mg 1 x/week po	3 months, check interactions with ARVs, see Drug-drug interactions between ARVs and non-ARVs Rifapentine is not yet available in Europe.

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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