EACS
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GUIDELINES

Version 10.1
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English

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Introduction to the EACS Guidelines 2020

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 the HIV disease burden across Europe.

The EACS Guidelines were first published in 2005, and are currently available in print, online as a pdf and web-based version, and as a free App for both iOS and Android devices. The Guidelines are translated into several 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 time if the panels consider it necessary.

The aim of the EACS Guidelines is to provide easily accessible and comprehensive recommendations to clinicians involved in the care of people living with HIV (PLWH).

The EACS Guidelines cover a relatively large and diverse area geographically, with different national levels of access to care. As a natural consequence, the Guidelines aim to cover a relatively wide range of recommendations as opposed to the often more uniform national guidelines.

The 2020 version of the Guidelines includes minor updates of all sections. The most essential changes are listed in the Summary of changes from v10.0 to v10.1

Each respective section of the Guidelines is managed by a panel of experienced European HIV experts, with additional experts in other fields of expertise included where necessary. All recommendations are evidence-based whenever possible and based on expert opinions in the rare instances where adequate evidence is unavailable. The Guidelines do not provide formal grades of evidence, panels make decisions by consensus or by vote when necessary and we do not publish results of the votes or discrepancies if any occur.

The EACS Guidelines panels are overseen by a Guidelines Chair who serves a three-year term and is elected from the Governing Board. Each panel is led by a Panel Chair, supported by a Vice-Chair and a Young Scientist. The Co-Chair will take over the role of Chair after the Chair's term expires. Panel membership is reviewed annually and rotation is overseen by the Panel Leads and Guidelines Chair according to a standard operating procedure. Operational matters of the EACS Guidelines are led by a Coordinator in the Medical Secretariat, supported by the EACS Secretariat.

A list of the main references used to produce the Guidelines is provided as a separate section, see References. Please reference the EACS Guidelines as follows: EACS Guidelines version 10.1, October 2020. Video links to the EACS online course on Clinical Management of HIV are provided throughout the Guidelines, see Video links.

The diagnosis and management of HIV infection and related co-infections, opportunistic diseases and comorbidities continue to require a multidisciplinary effort for which we hope the 2020 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

We wish to warmly thank all panellists, external experts, linguists, translators, the EACS Secretariat, the Sanford team and everyone else who helped to build up and to publish the EACS Guidelines for their dedicated work.

Enjoy!

Georg Behrens and Lene Ryom

October 2020

Summary of Changes from v10.0 to v10.1

The COVID-19 situation is rapidly changing, and evidence is constantly accumulating. Therefore, we refer to the regularly updated BHIVA, DAIG, EACS, GESIDA & Polish Scientific AIDS Society Statement on risk of COVID-19 for PLWH https://www.eacsociety.org/home/covid-19-and-hiv.html

ART section

- What to start with, pages 12-13
  - New organization of treatment categories which are now divided into recommended regimens, alternative regimens and other combinations
  - Recommended regimens include unboosted INSTI (DTG, BIC or RAL) plus 2 NRTIs or 3TC/DTG
  - CD4 count restriction has been removed for 3TC/DTG
- Switch strategies for virologically suppressed persons, page 15
  - DRV/b + DTG has been included as dual therapy option supported by small trials
- Virological failure, page 16
  - Treatment recommendation wording has been changed to "New regimen will usually use at least 1 fully active PI/b (e.g. DRV/b) plus a drug remaining fully active despite resistance to other drugs from the class (e.g. INSTI, NNRTI) and/or from a class not used previously (e.g. INSTI, NNRTI, PI, CCR5 antagonist (if tropism test shows R5 virus only) assessed by genotypic testing"
- Treatment of pregnant women living with HIV or women considering pregnancy, page 17
  - TAF has been removed from table 2 Antiretroviral drugs not recommended in women who become pregnant while on ART
  - TAF/FTC+DTG has been included as a recommended regimen in table 3 Antiretroviral regimen for ART-naïve pregnant women
- Post-exposure prophylaxis (PEP), page 22
  - ZDV/3TC has been removed from alternative regimens and DRV/b included

DDI section

- All tables have been updated to include changes implemented in the HIV drug interaction website (University of Liverpool) in the past year. The most relevant changes include:
  - EFV + atorvastatin: changed to amber due to the decrease in atorvastatin exposure requiring the monitoring of lipid values, page 27
  - RPV + chloroquine, methadone or pimozide were changed to amber due to the known risk for QT interval prolongation associated with the comedication, pages 27 and 36
  - A note on the risk of DDI with ibalizumab has been added to the footnote of each DDI table
  - Ibalizumab has been added in the table for ARV administration in PLWH with swallowing difficulties as well as in the tables for ARV dose adjustment in case of renal and hepatic impairment, pages 40-43

Co-morbidity section

- Adverse Effects Table Updates, page 24
  - Increased risk of neural tube defects associated with DTG
  - The CD4-directed post-attachment inhibitor, ibalizumab is now included
- Ibalizumab has been added to all DDI tables and to the tables for dose adjustment in the case of renal or hepatic impairment, pages 67 and 74
- A PLWH-population specific reference has been included for the PCSK9 inhibitor, evolocumab, page 60
- In the Obesity section, an indication for intervention of BMI ≥ 30 kg/m^2 or ≥ 25 kg/m^2 and weight-related complications (diabetes mellitus, hypertension) has been included with expanded detail regarding exercise, dietary, behavioural and therapeutic management, page 75
- In sero-discordant couples, a recommendation that fully effective ART should be a primary goal has been included, page 80
- In those wishing to conceive, a recommendation to consider PrEP in the partner of PLWH in the absence of HIV suppression has been included, page 80
- In PLWH at high risk of STI, three-monthly STI screening is recommended, page 81
- The treatment of gonorrhoea infection has been updated to ceftriaxone 1 g im as a single dose, page 81

Viral Hepatitis Co-infections section

- The main tables on HCV treatment options and DDIs have been updated, pages 98-100
- Resistance testing guidance before re-treatment with DAAs has been modified, page 97
- The sections on HBV, HDV and HEV infections remain unchanged, page 96-103

Opportunistic Infections section

- Some minor stylistic changes were made to all OI tables
- Cidofovir was deleted from the list of drugs for secondary prophylaxis/maintenance therapy for CMV retinitis, page 111
- Rifabutin was added to the list of drugs for primary prophylaxis of Non-Tuberculous Mycobacteria, page 112
- Moxifloxacin was added to the list of drugs for treatment of MAC, page 112

EACS Guidelines are available online at http://www.eacsociety.org and in the EACS Guidelines App

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Abbreviations

Antiretroviral drug (ARV) abbreviations

3TC	lamivudine
ABC	abacavir
ATV	atazanavir
BIC	bictegravir
COBI	cobicistat (used as booster=/c)
d4T	stavudine
ddI	didanosine
DOR	doravirine
DRV	darunavir
DTG	dolutegravir
EFV	efavirenz
EVG	elvitegravir
ENF	enfuvirtide (T20)
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/b	protease inhibitors pharmacologically boosted with cobicistat or ritonavir
PI/c	protease inhibitor 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
AFP	alpha-foetoprotein
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
CAPD	continuous ambulatory peritoneal dialysis
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
DDI	drug-drug interaction
DXA	dual energy X-ray absorptiometry
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESLD	end stage liver disease
FBC	full blood count
FRAX	fracture risk assessment tool
GDR	genotypic drug resistance test
GT	genotype
HAV	hepatitis A virus
HAD	HIV-associated dementia
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HDL-c	HDL-cholesterol
HDV	hepatitis D virus
HEV	hepatitis E virus
HIVAN	HIV-associated nephropathy
HIV-VL	HIV viral load (HIV-RNA)
HPV	human papillomavirus
HRS	hepatorenal syndrome
HSR	hypersensitivity reaction
HSV	herpes simplex virus
IFN	interferon
IGRA	interferon-gamma release assay
ICS	inhaled corticosteroids
IHD	ischaemic heart disease
im	intramuscular
IRIS	immune reconstitution inflammatory syndrome
iv	intravenous
IVDU	intravenous drug use
LABA	long-acting β2-agonist
LAMA	long-acting muscarinic antagonist
LDL-c	LDL-cholesterol
LGV	lymphogranuloma venereum
LOQ	limit of quantification
MDR-TB	multidrug resistant TB
Mg	magnesium
MND	mild neurocognitive disorder
MRI	magnetic resonance imaging
MSM	men who have sex with men
MTCT	mother to child transmission
MX	methylxanthines
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NP	neuropsychological
OIs	opportunistic infections
OLTX	orthotopic liver transplantation
PAP	papanicolaou test
PD4	phosphodiesterase 4 inhibitors
PEP	post-exposure prophylaxis
PLWH	people living with HIV
PREP	pre-exposure prophylaxis
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
qid	four times daily
RAS	resistance-associated substitutions
RBV	ribavirin
RCT	randomized controlled trial
SABA	short-acting β2-agonist
SAMA	short-acting muscarinic antagonist
sc	subcutaneous
SOT	solid organ transplant
SSRI	selective serotonin-reuptake inhibitor
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
US	ultrasound
VL	viral load (HIV-RNA)
VZV	varicella-zoster virus
WB	western blot
XDR-TB	extensively drug-resistant TB
Zn	zinc

Part I Assessment of PLWH 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)	54, 55-56
	• 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	53
	Employment	+	+	Every visit	Provide advice and support if needed Provide counselling if needed	
	Social and welfare	+	+			
	Psychological morbidity	+	+			
	Partner and children	+			Test partner and children if at risk	
Sexual and Reproductive Health	Sexual history	+		6-12 months	Address issues concerning sexual dysfunction Risk of sexual transmission should be addressed	80-83
	Safe sex	+				
	Partner status and disclosure	+			Recommend starting ART in serodifferent couples	
	Conception issues	+	+			
	Hypogonadism (including menopause)	+	+	As indicated	Persons with complaints of sexual dysfunction	80, 82
POST-REPRODUCTIVE HEALTH						
Menopause		+	+	Annual/as indicated	Screen for perimenopause symptoms in women ≥ 40 years.	80
HIV DISEASE						
Virology	Confirmation of HIV Ab pos	+		3-6 months	More frequent monitoring of HIV-VL at start of ART Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection	11-13
	Plasma HIV-VL	+	+			
	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 %, CD4/CD8 ratio (optional: CD8 and %)	+	+	3-6 months	Annual CD4 count if stable on ART and CD4 count > 350 cells/μL[(ii)] CD4/CD8 ratio is a stronger predictor of serious outcomes	11-13
	HLA-B*57:01 (if available)	+	+/-		Screen before starting ABC containing ART, if not previously tested, pages 11-12, 24	
CO-INFECTIONS						
STIs	Syphilis serology	+		Annual/ as indicated	Consider more frequent screening if at risk	14, 80
	STI screen	+		Annual/ as indicated	Screen if at risk and during pregnancy	

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
Viral Hepatitis	HAV screen	+		As indicated	Screen if ongoing risk (e.g. MSM); vaccinate if non-immune	79, 95-97
	HBV screen	+	+		Annual screen if ongoing risk; vaccinate if non-immune. Use ART containing TDF or TAF in vaccine non-responders	
	HCV screen	+			Further screen based on risk behaviour and local epidemiology. Measure HCV-RNA if HCV Ab pos or if recently acquired infection suspected	
	HDV screen			As indicated	All Persons with positive HBs-Ag should also be screened for HDV co-infection	95, 103
	HEV screen			As indicated	Screen persons with symptoms consistent with acute hepatitis, unexplained flares of aminotransferases or elevated liver function tests, neuralgic amyotrophy, Guillain-Barré, encephalitis or proteinuria. Include anti-HEV IgG and IgM and NAT for HEV-RNA in blood and if possible in stool	103
Tuberculosis	CXR	+		Re-screen if exposure	Consider routine CXR in persons from high TB prevalence populations. Some national guidelines consider the ethnicity, CD4 count and ART usage to define indication for latent tuberculosis infection screening. 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 PLWH	20, 114
	PPD	+				
	IGRA in selected high-risk populations (if available)	+				
Others	Varicella zoster virus serology	+			Offer vaccination where indicated	79
	Measles/Rubella serology	+			Offer vaccination where indicated	
	Toxoplasmosis serology	+				
	CMV serology	+				79
	Cryptococcus antigen	+/-			Consider screening for cryptococcus antigen in serum in persons with CD4 count < 100 cells/µL	
	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 PLWH, see Vaccination	79
	Streptococcus pneumoniae	+			No recommendations available regarding the need for a booster dose, see Vaccination	79
	Human papilloma virus	+		As indicated	Vaccinate all PLWH with 3 doses between ages 9 and 40. If HPV infection is established, efficacy of vaccine is questionable, see Vaccination	79
CO-MORBIDITIES						
Haematology	FBC	+	+	3-12 months		
	Haemoglobinopathies	+			Screen at risk persons	
	G6PD	+			Screen at risk persons	
Body Composition	Body-mass index	+	+	Annual		53
Cardiovascular Disease	Risk assessment (Framingham score[iii])	+	+	2 years	Should be performed in all men > 40 years and women > 50 years without CVD	54
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
Hypertension	Blood pressure	+	+	Annual		55-56
Lipids	TC, HDL-c, LDL-c, TG[iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	60
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)	58-59
Pulmonary Disease	Respiratory symptoms and risk factors[xii]	+	+	Annual	If severe shortness of breath is reported with preserved spirometry, echocardiography may be performed to rule out heart failure and/or pulmonary hypertension	89
	Spirometry			As indicated	Spirometry should be performed in all symptomatic persons[xii]	
Liver Disease	Risk assessment[v]	+	+	Annual		69-72
	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)	69-72
	Hepatic ultrasound			6 months	Persons with liver cirrhosis[xiii]	69-72

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
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]	64-65
	eGFR (CKD-EPI)[vii]	+	+	3-12 months		
	Urine dipstick analysis[viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min or rapid decline in eGFR, if proteinuria ≥ 1+ and/or eGFR < 60 mL/min perform UA/C or UP/C[viii]	
Bone Disease	Bone profile: calcium, PO_4, ALP	+	+	6-12 months		61-63
	Risk assessment[x] (FRAX®[xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons (see page 61 for details)	
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons	62
Cognitive impairment	Screening questionnaire	+	+	As indicated	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 88 for further assessment.	88
Depression	Questionnaire	+	+	As indicated	Screen at risk persons	84-85
Cancer	Mammography			1-3 years	Women 50-70 years	52
	Cervical PAP or liquid based cytology			1-3 years	HIV-positive women > 21 years	
	Rectal exam and anoscopy			1-3 years	MSM and persons with HPV-associated dysplasia. 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	

If PLWH have been stable on ART for 6 months or more, with no other significant issues, clinicians could consider using alternative modalities such as email/phone/or other electronic means (Good practice point, GPP).
This form of consultation can have the same validity as a face-to-face consultation if properly instituted in a clinical protocol.
The European Union funded EmERGE project is currently looking at such interventions https://www.emergeproject.eu

i Review all concomitant medicines which may potentially interact with ARVs or increase co-morbidities, see
Drug-drug Interactions between Antidepressants and ARVs
Drug-drug Interactions between Antihypertensives and ARVs
Drug-drug Interactions between Analgesics and ARVs
Drug-drug Interactions between Anticoagulants/Antiplatelet Agents and ARVs
Drug-drug Interactions between Antimalarial Drugs and ARVs
Drug-drug Interactions between Bronchodilators (for COPD) and ARVs
Drug-drug Intercations between Immunosuppressants (for SOT) and ARVs
Drug-drug Interactions between Pulmonary Antihypertensives 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 https://www.chip.dk/Tools-Standards/Clinical-risk-scores.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 https://www.mdcalc.com/ldl-calculated

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 https://www.chip.dk/Tools-Standards/Clinical-risk-scores

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 and can be used for screening for ARV toxicity, page 64

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 [13], [14]

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 Respiratory symptoms: shortness of breath, chronic cough and sputum. Risk factors: tobacco, occupation, in- and outdoor pollution and host factors including previous PCP or TB, recurrent pneumonia and Alpha-1 antitrypsin deficiency. 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 HCC screening is indicated in all cirrhotic HBV or HCV co-infected persons (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in persons with F3 fibrosis* is uncertain, surveillance may be considered based on an individual risk assessment (https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/). In HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines. Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH, see pages 52, 71 and 95

* See table on cut-off values of non-invasive tests for the detection of significant fibrosis and cirrhosis, page 102. The combination of blood biomarkers, the combination of liver stiffness measurement and blood tests or repeated assessments may improve accuracy, see https://easl.eu/publication/easl-recommendations-treatment-of-hepatitis-c/

Part II ART of PLWH

This section provides an overview of the important aspects of the management of PLWH starting or established on ART. Recommendations are based on a range of evidence, in particular it is weighted towards randomised controlled clinical trials. Other data have been taken into account, including cohort studies, and where evidence is limited, the panel has reached a consensus around best clinical practice. The ART section is wide ranging and, with the change in starting therapy independently of CD4 count, there is an important section on readiness to start. Treatment recommendations are based on drugs licensed in Europe and range from initial therapy through to switching with or without virological failure. Two important areas of ART are highlighted: pregnancy and TB. Details on the use of PrEP, which is being rolled out across Europe, are also included.

Assessing PLWH's Readiness to Start and Maintain ART[ix]

Goal: to help persons start and/or maintain ART	
Starting ART is recommended for all PLWH regardless of CD4 count to reduce the morbidity and mortality associated with HIV infection, and to prevent HIV transmission (START and TEMPRANO trials, HPTN 052, PARTNER Study) [1-4]. Evidence is accumulating that starting ART on the same day after establishing a diagnosis of HIV infection is feasible and acceptable to PLWH. Nevertheless, assessment of the readiness to start ART is essential to enable PLWH to express their preference and not feel pressured to start ART immediately, unless clinically indicated Given the need for lifelong treatment, successful ART requires a person's readiness to start and adhere to the regimen in a sustained manner. 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] Immediate (i.e. same day) start of ART should be considered, especially in the following situations: - In the setting of primary HIV infection, especially in case of clinical signs and symptoms of meningoencephalitis (within hours). In this situation, the clinician may start ART immediately after a positive screening HIV test and before obtaining confirmatory HIV test results such as a HIV-VL - The wish of a PLWH to start ART immediately - In a setting where loss-to-follow-up is more likely if ART is not started the same day

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? 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
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[iii] 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? For a person without sufficient adherence: use mirroring techniques[iv] on problems, ask open questions to identify dysfunctional beliefs Assess: Stage of readiness and provide stage-based support Assess: Barriers and facilitators[v] 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[vi], see pages 84-85 • Cognitive problems[vii], see page 88 • Harmful alcohol[viii] or recreational drug use, see page 51	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 multi-disciplinary team approach	

i WEMS: Waiting (> 3 sec), Echoing, Mirroring, Summarising [5]

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 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?” [6]

iv 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

v Adherence to long-term therapies [7]

vi PHQ-2 or PHQ-9 [8]. 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 [9]

vii 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?” [10]

viii 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 [11]

ix Algorithm adapted from [12]

Recommendations for Initiation of ART in PLWH with Chronic Infection without prior ART Exposure[(i)]

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 adult PLWH, irrespective of CD4 counts[(i)]

i ART is recommended irrespective of the CD4 count. In certain situations (i.e lower CD4 count or pregnancy), there is a greater urgency to start ART immediately

- In persons with OIs, ART initiation may have to be deferred, see page 104, for ART initiation in the presence of specific OIs. For ART initiation in persons with TB, see page 20
- A possible exception to immediate start of ART might be HIV controllers, persons with high CD4 counts and HIV-VL < 1000 copies/mL, although even in such persons ART initiation has been shown to increase CD4 count, decrease inflammation, lower the risk of clinical events and prevent HIV transmission
- 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 select a first-line regimen with a high barrier to resistance (e.g. a PI/b, DTG or BIC combined with TDF/FTC, TAF/FTC, TDF/3TC or ABC/3TC)
- Whether rapid, possibly same-day ART start is proposed to newly diagnosed persons or postponed until complementary assessments depends on the setting and medical circumstances, medical indications to start ART more urgently and risk of loss from care. To reduce loss to follow-up between diagnosis and ART initiation, structural barriers delaying the process should be addressed

Initial Combination Regimen for ART-naïve Adult PLWH

Before selecting an ART regimen, it is critical to review:
- If a woman **wishes to conceive**: Antiretroviral drugs not recommended in women who wish to conceive
- If a woman is **pregnant**: Antiretroviral regimen for ART-naïve pregnant women
- If the person has an **opportunistic infection**: Initiation of ART regimen in persons with opportunistic infections
- If the person has **TB**: Antiretroviral regimens in TB/HIV co-infection
- If the person has potential **treatment limiting comorbidities**: Comorbidity section, dose adjustment for renal and liver impairment
- If the person is treated with **other medications**: Drug-drug interactions
- If the person has **Swallowing Difficulties:** Administration of ARVs in PLWH with swallowing difficulties

- Only drugs currently licensed for initiation of therapy by the EMA are taken into consideration (in alphabetical order)
- An increasing number of generic HIV drugs are now available, and their use can lead to large cost savings. The use of generic forms of drugs included in recommended regimens should therefore be encouraged, even if single tablet regimens are not used, as recent studies have shown similar virologic outcomes in ART-naïve PLWH receiving either a single pill or two pills qd
- Tailoring antiretroviral regimens for each individual is essential in the presence of resistance
- For a wider review of possible drug-related adverse events, please see: Adverse Effects of ARVs and Drug Classes

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, cardiovascular risk) II (Weight increase (DTG))
TAF/FTC or TDF/FTC or TDF/3TC + DTG		III (Weight increase (DTG, TAF)) IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC/BIC		II (Weight increase (BIC))
TAF/FTC or TDF/FTC or TDF/3TC + RAL qd or bid		IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) V (RAL: dosing)
1 NRTI + INSTI		
3TC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL	
Alternative regimens		
2 NRTIs + NNRTI		
TAF/FTC or TDF/FTC or TDF/3TC + DOR or TDF/3TC/DOR		IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (DOR: HIV-2)
TAF/FTC or TDF/FTC or TDF/3TC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count > 200 cells/μL HIV-VL < 100,000 copies/mL Not on proton pump inhibitor With food	IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/FTC or TDF/3TC + DRV/c or DRV/r or TAF/FTC/DRV/c	With food	IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VIII (DRV/r: cardiovascular risk)
Other combinations		
2 NRTIs + INSTI		
ABC/3TC + RAL qd or bid	HBsAg negative HLA-B*57:01 negative	I (ABC: HLA-B*57:01, cardiovascular risk) V (RAL: dosing)
TDF/FTC/EVG/c or TAF/FTC/EVG/c	With food	IV (TDF: prodrug types. Renal and bone toxicity) IX (EVG/c: use in renal impairment)
2 NRTIs + NNRTI		
ABC/3TC + EFV	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL At bed time or 2 hours before dinner	I (ABC: HLA-B*57:01, cardiovascular risk) X (EFV: neuro-psychiatric adverse events. HIV-2 or HIV-1 group 0)
TAF/FTC or TDF/FTC or TDF/3TC + EFV or TDF/FTC/EFV	At bed time or 2 hours before dinner	IV TDF: prodrug types. Renal and bone toxicity. TAF dosing) X (EFV: neuro-psychiatric adverse events. HIV-2 or HIV-1 group 0)

2 NRTIs + PI/b		
ABC/3TC + ATV/c or ATV/r	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL Not on proton pump inhibitor With food	I (ABC: HLA-B*57:01, cardiovascular risk) XI (ATV/b: renal toxicity, hyperbilirubinemia)
ABC/3TC + DRV/c or DRV/r	HLA-B*57:01 negative HBsAg negative With food	I (ABC: HLA-B*57:01, cardiovascular risk) VIII (DRV/r: cardiovascular risk)
TAF/FTC or TDF/FTC or TDF/3TC + ATV/c or ATV/r	Not on proton pump inhibitor With food	IV (TDF: prodrug types. Renal and bone toxicity. TAF dosing) XI (ATV/b: renal toxicity, hyperbilirubinemia)
1 INSTI + PI/b		
RAL 400 mg bid + DRV/c or DRV/r	HBsAg negative HIV-VL < 100,000 copies/mL CD4 > 200 cells/µL With food	VIII (DRV/r: cardiovascular risk)

Additional Guidance

I ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk (> 10%), page 54

II A pooled analysis of 8 RCT showed greater weight increase in persons initiating ART including INSTI, and in particular BIC or DTG, compared to PIs or NNRTIs [13]

III Two randomized controlled trials (performed in South Africa and Cameroon) showed that, in comparison with EFV, treatment with DTG in naïve persons was associated with increased weight increase when combined with TAF/FTC, TDF/FTC or TDF/3TC. The effect on increased weight was more important for women under treatment containing both DTG and TAF [14], [15]

IV 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). There are available generic forms of TDF, which instead of fumarate use phosphate, maleate, and succinate salts. They can be used interchangeably

When available, combinations containing TDF can be replaced by the same combinations containing TAF. TAF is used at 10 mg when coadministered with drugs that inhibit P-gp, and at 25 mg when coadministered with drugs that do not inhibit P-gp

The decision whether to use TDF or TAF depends on individual characteristics as well as availability. So far, there are only limited long-term data on TAF.

If the ART regimen does not include a booster, TAF and TDF have a similar short-term risk of renal adverse events leading to discontinuation and bone fractures.

TAF*** should be considered as a first choice**** over TDF in individuals with:

- established or high risk of CKD, see page 64;
- coadministration of medicines with nephrotoxic drugs or prior TDF toxicity, see page 65;
- osteoporosis / progressive osteopenia, high FRAX score or risk factors, see page 61;
- history of fragility fracture, see pages 61 and 63

*** There are limited data on use of TAF with eGFR < 30 mL/min

**** Expert opinion pending clinical data

V RAL can be given as RAL 400 mg bid or RAL 1200 mg (two, 600 mg tablets) qd. Note: RAL qd should not be given in presence of an inducer (i.e. TB drugs, antiepileptics) or divalent cations (i.e. calcium, magnesium, iron), in which case RAL should be used bid

VI DOR is not active against HIV-2

VII RPV is not active against HIV-2

VIII A single study has shown increase in CVD risk with cumulative use of DRV/r [16]

IX TDF/FTC/EVG/c to be used 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

X EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains

XI Potential renal toxicity with ATV/b. Hyperbilirubinemia and cholelithiasis also possible side effects

Primary HIV Infection (PHI)

Definition of PHI[i-iv]

- High-risk exposure within previous 6 weeks, and
- Detectable virus in plasma (p24 Ag and/or HIV-RNA) and/or
- Evolving anti-HIV antibody reactivity (negative or indeterminate to positive)
- With 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

Treatment of PHI is recommended for all PLWH. Several circumstances indicate immediate treatment initiation

Circumstances where immediate treatment initiation should be advised

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

The recommendation is based on:

- Improvement of clinical symptoms of PHI, when present, especially severe general symptoms and/or nerurological disease
- Benefits of early therapy:
  - virological: decrease of the HIV-VL set-point and size of the viral reservoir; reduction of viral genetic evolution
  - immunological: decrease of immune activation and inflammation; preservation of immune function and integrity of lymphoid tissue; possibly neurological and gut protection; possibly enhancement of post-treatment control and response to future eradication strategies
- Usually short interval between identification of PHI and a CD4 count < 500 cells/μL
- Potential benefits of treatment for the community: reduced risk of transmission. Most infections are transmitted by persons who are unaware of their HIV status
- Reduced anxiety and facilitated disclosure to contacts

The PLWH should be counselled on indications and benefits of starting treatment as soon as possible, despite absence of demonstrated improved long-term clinical benefits[v]

Once treatment is started, it should be continued. A subsequent interruption is not recommended

Treatment selection

- The PLWH should preferably be recruited into a clinical trial or studies investigating HIV curative strategies
- Any use of PrEP or PEP should be identified and taken into account when choosing the initial regimen
- A drug resistance test is recommended in all cases as soon as possible after diagnosis. A genotypic test is recommended
- Therapy may have to start before the results of resistance testing become available. In such cases, preference should be given to starting a PI/b or an INSTI with high barrier to resistance (DTG or BIC), in order to increase the barrier to resistance of the overall regimen. A potential advantage for selecting DTG or BIC is the faster VL suppression. The benefit of combining PI/b with INSTI has not been shown. A combination of TDF or TAF, FTC, and either DRV/b, DTG or BIC, 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 PLWH should undergo investigations to diagnose sexually transmitted infections (e.g. syphilis, gonorrhoea, chlamydia), HBV, HCV and HPV, pages 7-8. Antibody seroconversion can be delayed and tests to identify the viral RNA are required in order to identify a recent HCV infection, page 101
- All women living with HIV of reproductive age should have a pregnancy test
- All PLWH 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:
- 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 PLWH. Low HIV-VL levels should be interpreted with caution due to the risk of false positivity
- 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., anti-body 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 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

A small subset of PLWH can spontaneously control the infection without treatment (elite controllers)

vi Post-treatment controllers. A few PLWH have been able to spontaneously control HIV-infection following ART discontinuation, when ART was initiated during PHI

A small subset of PLWH can spontaneously control the infection without treatment (elite controllers)

See online video lectures When to start ART-Part 1, When to start ART-Part 2, What ART to start-Part 1 and What ART to start-Part 2 from the EACS online course on Clinical Management of HIV

Switch Strategies for Virologically Suppressed Persons

Definition of virologically suppressed

Clinical trials exploring switching strategies have generally 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, DTG), diarrhoea (PI/r) and jaundice (ATV), proximal renal tubulopathy and low bone mineral density (TDF) or weight increase (DTG, BIC), see Adverse Effects of ARVs and Drug Classes
2. **Prevention of long-term toxicity**. Example of this proactive switch: prevention of lipoatrophy in persons receiving d4T or AZT and prevention of proximal renal tubulopathy with TDF, see Adverse Effects of ARVs and Drug Classes. This may include person's concerns about safety
3. **Avoidance of drug-drug interactions,** page 26. This includes ART switch when starting HCV treatment to avoid DDIs, see Drug-drug Interactions between DAAs and ARVs
4. **Planned pregnancy or women wishing to conceive,** see Antiretroviral Drugs Not Recommended in Women who Wish to Conceive or Become Pregnant while on ART
5. **Ageing and/or comorbidity** 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, improve adherence and reduce monitoring needs
7. **Protection from HBV** infection or reactivation by including tenofovir in the regimen
8. **Regimen fortification**: Increasing the barrier to resistance of a regimen in order to prevent VF (e.g. in persons with reduced adherence)
9. **Cost reduction:** switching to the generic form of their current regimen, if available

Principles

Clinicians should always review possible adverse events or tolerability issues with current antiretroviral regimens. Just because the viremia is suppressed it should not be assumed that the PLWH is well adapted and tolerating the current regimen

1. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of comorbid conditions, and improve quality of life. 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 and historical resistance
2. The complete ARV history with HIV-VL, tolerability issue, cumulative genotypic resistance history and/or phases of viremia on previous regimens with the potential of resistance development should be evaluated prior to any drug switch
3. Switches within the same drug class (e.g. TDF/FTC -> TAF/FTC, EFV -> RPV) are usually virologically safe if equal potency and in the absence of resistance
4. Cross-class switches of single drugs with the same barrier to resistance (for example EFV to RAL) are usually virologically safe in the absence of resistance to the new compound
5. In case of prior virologic failures, with or without evidence of resistance, switches have to be planned especially carefully when they result in a lower barrier to resistance of the regimen. A PI/b may only be switched to unboosted ATV, an NNRTI, INSTIs RAL and EVG if full activity of the 2 NRTIs in the new regimen can be assumed based on resistance data, ARV history and HIV-VL results before switching (see 2.) Due to the higher barrier to resistance of DTG and BIC, it is currently unclear if a switch to DTG- or BIC-based regimens also requires full activity of 2 NRTIs in the combination
6. Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. This requires knowledge about the resistance selection profile of the switch regimen. For example, some mutations (e.g. K65R or M184I/V) might affect the activity of most currently available STRs and preclude their future use. Especially, when reducing the number of drugs in a regimen or its barrier to resistance, the chances of composing a fully suppressive regimen after potential failure following switch should be considered
7. Proviral DNA genotyping may be useful in persons with multiple virological failures, unavailable resistance history or low-level viremia at the time of switch. Results ought to be taken cautiously as proviral DNA genotype may not detect previous resistance mutations and can also detect clinically irrelevant mutations. Therefore, routine proviral DNA genotyping is currently not recommended
8. When selecting a new regimen, clinicians should carefully review the possibility of new drug-drug interactions with antiretroviral and concomitant medication leading to suboptimal drug exposure or toxicity, as well as the lag time for hepatic enzyme induction or blockade following discontinuation of the offending drug. Examples are: increased TDF toxicity with a PI/b or an increase in metformin exposure with DTG
9. If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV and HBV vaccination status. TDF or TAF should not be discontinued in persons with chronic HBV
10. PLWH should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity or tolerability issues of the new regimen
11. If a PLWH receives and tolerates a regimen that is no longer a preferred option, and none of the other reasons for change applies, there is no need to change. Example: persons tolerating EFV-containing regimens
12. See online video lecture How to Change ART from the EACS online course Clinical Management of HIV

Dual therapies

Dual therapies supported by large randomized clinical trials or meta-analyses

DTG + RPV
3TC + DTG
3TC + DRV/b
3TC + ATV/b

In clinical trials, these strategies have not been associated with more virological rebounds than triple therapy. There were a few cases of resistance development on DTG + RPV.

Dual therapy options supported only by small trials:

DRV/b+ RPV
DRV/b+ DTG

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is
a) no historical resistance and
b) absence of chronic HBV co-infection

Strategies not recommended

a. Monotherapy with a PI/b
b. Monotherapy with DTG
c. Dual or triple NRTIs combinations
d. Specific two-drug combination, i.e. 1 NRTI + 1 NNRTI or 1 NRTI + 1 unboosted PI, 1 NRTI + RAL, MVC + RAL, PI/b + MVC, ATV/b + RAL
e. Intermittent therapy, sequential or prolonged treatment interruptions. In a randomized study, 4 consecutive days a week of triple therapy with DRV/b or DTG was as effective as 7 days a week, at 48 weeks in the context of close monitoring and counseling with visits every 3 months

Virological Failure

Definition	**INCOMPLETE SUPPRESSION**: HIV-VL > 200 copies/mL at 6 months[i] after starting therapy in PLWH not previously on ART **REBOUND**: confirmed HIV-VL > 50 copies/mL in PLWH with previously undetectable HIV-VL
General measures	Review expected potency of the regimen
	Evaluate adherence, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues
	Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels > 200-500 copies/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations
	Tropism testing if considering MVC
	Consider TDM
	Review ART history
	Identify treatment options, active and potentially active drugs/combinations
Management of virological failure (VF)	**If HIV-VL > 50 and < 200 copies/mL:**
	Check for adherence
	Check HIV-VL 1 to 2 months later[ii]
	If genotype not possible, consider changing regimen based on past treatment and resistance history
	If HIV-VL confirmed > 200 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) based on resistance mutations present in current and earlier genotypic analyses
	New regimen will usually use at least 1 fully active PI/b (e.g. DRV/b) plus a drug remaining fully active despite resistance to other drugs from the class (e.g. INSTI, NNRTI) and/or from a class not used previously e.g. INSTI, NNRTI, PI/b or CCR5 antagonist (if tropism test shows R5 virus only), assessed by genotypic testing. Alternatively, a regimen can be constructed with DTG (when fully active) plus 2 NRTIs, of which at least 1 NRTI is fully active
	Defer change if < 2 active drugs available, based on resistance data, except in PLWH 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*log10 reduction) by recycling
	If limited options, consider experimental and new drugs, favouring clinical trials (but avoid functional monotherapy). New drugs with promising results include humanised CD4+-binding antibody ibalizumab and attachment inhibitor fostemsavir (currently not licensed by the EMA)
	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 PLWH with very high baseline HIV-VL (> 100,000-500,000 copies/mL), achieving viral suppression may take longer than 6 months.
ii In the absence of resistance and in persons fully adherent to treatment, consider non-suppressible viremia due to cellular proliferation [17]

See online video lecture Adherence and Prevention of HIV Drug Resistance from the EACS online course Clinical Management of HIV

Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy

Scenarios for pregnant women or women who wish to conceive

1. Women planning to be pregnant or becoming pregnant while already on ART	Maintain ART, unless taking not recommended drugs (see Tables 1 and 2)
2. Women becoming pregnant while treatment-naïve	Starting ART as soon as possible is highly recommended (See Table 3)
3. Women whose follow-up starts late in the second or in the third trimester	Start ART immediately (see Table 2) and consider RAL or DTG as the preferred choice to obtain rapid HIV-VL decline and to ensure the HIV-VL is undetectable by the time of delivery
4. Women whose HIV-VL is not undetectable at third trimester	Perform resistance testing and consider changing to or adding INSTI (RAL or DTG) if not on this class to obtain rapid HIV-VL decline
5. Women whose HIV-VL is > 50 copies/mL at week 34-36 of pregnancy	Elective cesarean section to be planned at week 38, see labour and breastfeeding, page 19
6. Women diagnosed with HIV in labour	See labour and breastfeeding, page 19

Table 1. Antiretroviral drugs not recommended in women who wish to conceive

DRUG	Reason
INSTI	
DTG	Higher risk of neural tube defects if used preconception. Should be switched to another drug

Table 2. Antiretroviral drugs not recommended in women who become pregnant while on ART

DRUG	Reason
INSTI	
RAL qd	Insufficient data about safety and efficacy in pregnancy
BIC	Insufficient data about safety and efficacy in pregnancy
DTG	Higher risk of neural tube defects if used periconception
EVG/c	Lower levels during pregnancy
NNRTI	
DOR	Insufficient data about safety and efficacy in pregnancy
PI	
ATV/c	Lower levels during 2nd and 3rd trimester
DRV/c	Lower levels during 2nd and 3rd trimester
OTHER	
COBI	Low levels during 2nd and 3rd trimester of pregnancy, subtherapeutic levels of boosted drug should be expected

Table 3. Antiretroviral regimen for ART-naïve pregnant women
Pregnant women should initiate treatment as soon as possible. They should be monitored monthly or bimonthly (depending on adherence and length of virological suppression) and as close as possible to the predicted delivery date. HIV-VL should be tested every two months of pregnancy and including 36 weeks of gestation.

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens		
2 NRTIs + INSTI (PREFERRED)		
ABC/3TC + DTG or ABC/3TC/DTG	DTG not recommended in first 8 weeks of pregnancy HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, may delay starting ART) II (DTG: neural tube defects risk during periconception)
TDF/FTC or TDF/3TC or TAF/FTC + DTG	DTG not recommended in first 8 weeks of pregnancy TAF/FTC+DTG not recommended in first 14 weeks of pregnancy	II (DTG: neural tube defects risk during periconception) III (Tenofovir salts) IV (TAF & pregnancy)
TDF/FTC or TDF/3TC + RAL 400 mg bid		III (Tenofovir salts) V (RAL in pregnancy, bid dosing)
2 NRTIs + PI/r		
TDF/FTC or TDF/3TC + DRV/r 600 mg/100 mg bid	With food	III (Tenofovir salts) VI (DRV dosing) VII (COBI boosting)

Alternative regimens		
2 NRTIs + INSTI		
ABC/3TC + RAL 400 mg bid	HBsAg negative HLA-B*57:01 negative	I (ABC: HLA-B*57:01, may delay starting ART) V (RAL in pregnancy, bid dosing)
2 NRTIs + NNRTI		
ABC/3TC + EFV	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL At bed time or 2 hours before dinner	I (ABC: HLA-B*57:01, may delay starting ART) VIII (EFV HIV-2 & group O)
TDF/FTC or TDF/3TC + EFV or TDF/FTC/EFV	At bed time or 2 hours before dinner	III (Tenofovir salts) VIII (EFV HIV-2 & group O)
TDF/FTC or TDF/3TC + RPV or TDF/FTC/RPV	CD4 count > 200 cells/μL HIV-VL <100,000 copies/mL Not on proton pump inhibitor With food	II (Tenofovir salts) IX (RPV exposure during 2nd and 3rd trimester, HIV-2) X (Interactions)
2 NRTIs + PI/r		
ABC/3TC + ATV/r	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL Not on proton pump inhibitor H2 blockers timing recommended With food	I (ABC: HLA-B*57:01, may delay starting ART) VII (COBI boosting) X (Interactions) XI (maternal hyperbilirubinemia)
TDF/FTC or TDF/3TC + ATV/r	Not on proton pump inhibitor H2 blockers timing recommended With food	VII (COBI boosting) X (Interactions) XI (maternal hyperbilirubinemia)
ABC/3TC + DRV/r 600 mg/100 mg bid	HLA-B*57:01 negative and HBsAg negative With food	I (ABC: HLA-B*57:01, may delay starting ART) VI (DRV dosing) VII (COBI boosting)
Other drugs not recommended as initial therapy for PLWH but with evidence of safety during pregnancy		
AZT		XII (access) XIII (toxicity)
LPV/r	Dose increase recommended in third trimester of pregnancy	XII (access) XIV (LPV/r toxicity)

Additional guidance

I ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on HSR risk still mandatory. If testing for HLA-B*57:01 results in delay of ART initiation, consider other recommended backbone

II The last interim analysis from Tsepamo observational cohort showed that neural tube defects occurred in 2 per 1000 deliveries among women on DTG from conception, a small increase compared with all other antiretroviral exposure (1 per 1000 deliveries) [18]

III Some generic forms of TDF use phosphate, maleate, and succinate salts instead of fumarate. They may be used interchangeably. 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)

IV TAF/FTC+DTG not recommended in first 14 weeks of gestational age as the randomized study evaluating the safety and virologic efficacy of this combination recruited women only between 14-28 weeks of pregnancy [19]

V There were no reports of neural tube defects among 1991 prospective reports of RAL exposure in pregnancy, 456 of which were in the periconception period. No data on RAL 1200 mg qd: not recommended

VI DRV/r 800/100 mg qd not recommended during pregnancy due to decreased levels. DRV/c is not recommended during pregnancy due to significant lower exposures of DRV and COBI in the second and third trimester of pregnancy

VII Boosting with COBI is not recommended after the second trimester of pregnancy (insufficient drug levels)

VIII EFV not active against HIV-2 and HIV-1 group O strains

IX Lower RPV exposure during second and third trimesters; Consider monitoring VL more frequently. RPV is not active against HIV-2

X Pregnant women are often prescribed anti-H2 or proton pump inhibitors for nausea. Careful review of concomitant medicines at each visit and providing pregnant women with information on potential interactions is recommended

XI ATV/r may produce maternal hyperbilirubinemia, no evidence for neonatal hyperbilirubinemia

XII In countries with limited access to drugs listed in recommended and alternative regimens, treatment with 2 NRTIs + LPV/r or including AZT as part of the NRTI backbone are acceptable choices for pregnant women

XIII AZT may cause maternal anaemia, consider monitoring for haematological toxicity

XIV LPV/r has higher toxicity then other PIs (nausea)

Labour
Scenarios:
1) Women whose HIV-VL is > 50 copies/mL at week 34-36:
- Elective cesarean section to be planned at week 38
- iv ZDV: During labor and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery
  - Scheduled cesarean delivery: start iv ZDV 3 hours before surgery
  - Unscheduled cesarean delivery: consider administering loading dose then proceed to delivery

2) Women diagnosed with HIV during labour:
- If possible, perform caesarean section
- iv ZDV: During labor and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery. Consider administering loading dose then proceed to delivery

PEP should be given to all newborns born to mothers living with HIV according to local guidelines

Breastfeeding
- The topic of feeding intentions should be discussed with a pregnant woman as early as possible in pregnancy, together with providing education and support to the mother
- **We advise against breastfeeding**, as in high-income settings the optimal way to prevent mother-to-child transmission is to feed infants born to mothers living with HIV with formula milk
  - To reduce the potential physical and emotional discomfort associated with breast engorgement, together with the risk of covert breastfeeding, women living with HIV should be given cabergoline to suppress lactation after delivery
- **In situations where a woman chooses to breastfeed, we recommend input from an interdisciplinary team including adult HIV specialist, paediatrician and obstetrician/gynecologist**
  - We recommend monthly follow-up during the whole breastfeeding period with increased clinical and virological monitoring of both the mother and the infant. Measurement of drug concentrations in the milk could be done to inform clinical practice
  - **Maternal HIV-VL > 50 copies/mL should result in a stop of breastfeeding, providing cabergoline and support from interdisciplinary team and a nursing specialist**
  - Immediate consulting by the interdisciplinary team should be provided in case of signs and symptoms of mastitis, infant mouth or gut infections
  - Currently there is no evidence supporting PrEP recommendation for the infants who are breastfed
  - **After stopping the breastfeeding, the child should undergo routine diagnostics as recommended in HIV-exposed children**

ART in TB/HIV Co-infection

Principles

PLWH 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 PLWH

All persons with TB/HIV co-infection should start ART irrespective of CD4 count. Treatment supervision and adherence evaluation are very important. If the person is already on ART, check for potential DDIs and if these are significant, consider switching to one of the recommended regimens for TB/HIV co-infection

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 whenever possible within 2 weeks
≥ 50 cells/μL: Can be deferred up to 8 weeks of TB treatment, especially when there are difficulties with DDIs, 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 PLWH with TB co-infection [20]

* Be aware of IRIS reaction in persons starting ART at low CD4 count levels and with early initiation of ART. Prophylactic prednisone for 4 weeks at the time of ART initiation (prednisone 40 mg qd for 14 days, then 20 mg qd for 14 days) can prevent paradoxical TB-associated IRIS in persons with CD4 < 100 cells/μL receiving TB treatment [21]
Corticosteroids should be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response

Table 1. Antiretroviral regimens in TB/HIV co-infection
These recommendations are for PLWH initiating ART with susceptible Mycobacterium tuberculosis infection. When treating MDR-TB or XDR-TB, careful review of DDIs and potential toxicities is mandatory before initiating ART

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens with rifampicin		
2 NRTIs + NNRTI		
TDF/FTC or TDF/3TC + EFV or TDF/FTC/EFV	At bed time or 2 hours before dinner	I (tenofovir salts) II (EFV: suicidality. HIV2 or HIV-1 group 0)
ABC/3TC + EFV	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL At bed time or 2 hours before dinner	III (ABC: HLA-B*57:01) II (EFV: suicidality. HIV-2 or HIV-1 group 0)
Alternative regimens with rifampicin		
2 NRTIs + INSTI		
TDF/FTC or TDF/3TC + DTG bid		I (tenofovir salts) IV (DTG: dosing)
TDF/FTC or TDF/3TC + RAL bid		I (tenofovir salts) V (RAL: dosing)
ABC/3TC + RAL bid	HBsAg negative HLA-B*57:01 negative	III (ABC: HLA-B*57:01) V (RAL: dosing)
Other combinations with rifabutin		
2 NRTIs + PI/r		
TDF/FTC or TDF/3TC + DRV/r, ATV/r or LPV/r	With food	VI (rifabutin dosing)
ABC/3TC + DRV/r, ATV/r, or LPV/r	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL With food	III (ABC: HLA-B*57:01) VI (rifabutin dosing)

Additional guidance

I There are available generic forms of TDF, which instead of fumarate use phosphate, maleate, and succinate salts. They can be used interchangeably. 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 EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains
III ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on HSR risk still mandatory. ABC should be used with caution in PLWH with a high CVD risk (> 10%)
IV DTG should be dosed 50 mg bid when given with rifampicin since rifampicin lowers DTG exposure
V RAL 400 or 800 mg bid. With RAL 400 bid a large phase 3 study showed non-inferiority at week 24 but failed to show non-inferiority at week 48. With 800 mg bid only limited date from a phase 2 study with potential increases in liver toxicity [22]
VI See table 2 for guidance on antiretroviral and rifabutin dosing page 21

Table 2. Drug-drug interactions relevant to ART co-administered with rifampicin and rifabutin

	Rifampicin	Rifabutin
NRTIs		
TDF	No significant effect	No significant effect
TAF	Administer TAF bid Note: TAF qd results in intracellular levels of tenofovir diphosphate which are still higher than those achieved with TDF. Additional clinical data are needed to assess the efficacy of TAF qd in presence of rifampicin	Expected to decrease TAF. Based on TAF-rifampicin DDI study, consider administration of TAF bid
NNRTIs		
EFV 600 mg or alternative 400 mg	EFV levels by ↓ 20–30% EFV at standard dose not weight dependent Rifampicin at standard dose	Rifabutin levels ↓ by 38% Rifabutin increase dose to 450 mg daily EFV at standard dose
NVP	NVP levels ↓ 20–55% No change in rifampicin Not recommended	Use standard dose but little data so not recommended
ETR	No data available	Use standard doses but little data so not recommended
RPV	RPV levels ↓ 90% Do not use	RPV levels ↓ 50% Double dose RPV/but not recommended
DOR	DOR levels ↓ 56% with steady state rifampicin Do not use	Increase DOR to 100 mg bid. Maintain bid dosing for at least another 2 weeks following cessation of rifabutin due to persisting inducing effect
PIs		
ATV	80% ↓ level ATV Do not use	Reduce rifabutin to 150 mg 3 times per week
ATV/r	↓ level ATV Do not use	Reduce rifabutin to 150 mg qd
DRV/r	No data Do not use	Reduce rifabutin to 150 mg qd
LPV/r	75% ↓ level LPV Higher doses cause hepatotoxicity Advice not to use (If no other option use 400 mg bid RTV or double dose boosted LPV)	Reduce rifabutin to 150 mg qd
PI/c	No data Do not use	No data Do not use
INSTI		
EVG/c	EVG levels ↓ Do not use	Reduce rifabutin to 150 mg 3 times per week
RAL	RAL levels ↓ 60% 400 or 800 mg bid can be used but with caution	Use standard doses
DTG	Use 50 mg bid	Use standard doses
BIC	Decrease trough levels by 80% Do not use	Decrease by 38% Do not use
CCR5 Inhibitors		
MVC	Use with caution MVC levels ↓ Double MVC dose to 600 mg bid	Use standard doses
FI		
ENF (T20)	No interaction Use standard doses	No interaction Use standard doses

Non-rifamycin regimens

Tuberculosis can be treated with regimens that do not contain rifamycins. Their use should be contemplated only in persons with serious toxicity to rifamycins where desensitisation has failed, or in persons with rifamycin-resistant isolates. Although non-rifamycin regimens have fewer drug-drug interactions, such regimens are inferior to a rifampicin-based regimen for fully drug-sensitive TB treatment

Non-rifamycin treatment regimens used for one year when coadministered with streptomycin have shown high relapse rates of greater than 15%. Poorer outcomes have also been seen in cases where rifampicin is used for the initial two months before the regimen is switched to isoniazid and ethambutol in the continuation phase

In countries where neither DTG nor rifabutin are available, or there is no possibility to use RAL or EFV, following combinations could also represent a short-term alternative until anti-TB treatment has been completed

- 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, DOR, ETV or MVC, consultation with an HIV specialist is recommended

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 and not on PrEP or low PrEP adherence	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 and not on PrEP or low PrEP adherence	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 HBV, 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 or TAF/FTC + RAL bid or qd, or + DRV/b qd. TDF/FTC or TAF/FTC+ DTG qd or TAF/FTC/BIC may be also considered as alternatives
- Full sexual health screen in case of sexual exposure
- Emergency contraception counselling for sexual exposure
- Follow-up:
  - HIV serology + HBV and HCV, pregnancy test (women) within 48 hours of exposure and test for STIs if appropriate
  - 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)
  - HIV serology at the end of PEP and one month later
  - Discuss opportunity to start PrEP

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 STI, use of post-exposure prophylaxis or chem-sex 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 STIs 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 a week prior to starting PrEP. In case of suspicion of acute HIV-infection, an RNA test on plasma should also be performed, page 14. During PrEP, a fourth generation HIV test should be repeated at one month and then every 3 months. 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 Clinical Management and Treatment of HBV and HCV Co-infection in PLWH
- Counsel that PrEP does not prevent other types of STIs; screen for STI (syphilis, chlamydia, gonorrhoeae, HAV, HCV) when starting PrEP and regularly during use of PrEP, pages 6-8
- Counsel that PrEP may impact renal and bone health, see pages 61 and 63-65. 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

See online video lectures PrEP-Part 1 and PrEP-Part 2 from the EACS online course Clinical Management of HIV

3. PrEP regimen

- TDF/FTC 300*/200 mg 1 tablet qd. In both men and women PrEP should be taken for 7 days before the first exposure and stopped 7 days after the last exposure
- A trial with daily TAF/FTC in MSM and transgender women has shown non inferiority to daily TDF/FTC. No data are available in other high risk groups [23]
- For MSM only, 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). There are no efficacy data with on demand PrEP with TDF/FTC in women
- 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

* 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 and Drug Classes

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genito-urinary	Nervous	Body fat	Metabolic	Other
NRTIs										
ABC	Rash	Nausea* Diarrhoea*		IHD						*Systemic hypersensitivity syndrome (HLA B*57:01 dependent)
ZDV[ii]	Nail pigmen-tation	Nausea	Steatosis		Myopathy, Rhabdomy-olysis			**Lipoatrophy**	Dyslipi-daemia, Hyperlacta-taemia	Anaemia
3TC										
FTC								**↓plasma lipids**		
TDF[iii]			Hepatitis		↓ BMD, Osteoma-lacia ↑ Fractures risk	↓ **eGFR**, Fanconi syndrome				
TAF[iii]										**Weight increase**
NNRTIs										
EFV	Rash		Hepatitis				**Neuropsychi-atric events including: depression, sleep disturbance, headache**		**Dyslipi-daemia,** Gynaeco-mastia	↓ **plasma 25(OH) vitamin D**
ETV	Rash									
NVP	Rash*		Hepatitis*							*Systemic hypersensitivity (CD4 count and gender dependent)
RPV	Rash		Hepatitis			↓ eGFR[iv]	Depression, Sleep disturbance, Headache			
DOR										
PIs										
ATV[v]		**Nausea and Diarrhoea**[vii]	**Hyperbilirubinaemia,** Jaundice, Cholelithiasis			↓ eGFR, Nephrolithiasis			Dyslipi-daemia	
DRV[v]	Rash			IHD		Nephrolithiasis			Dyslipi-daemia	
LPV				IHD		↓ eGFR			**Dyslipi-daemia**	
Boosting										
RTV		**Nausea and diarrhoea**				↓ **eGFR**[iv]			**Dyslipidae-mia**	
COBI		Nausea and diarrhoea				↓ **eGFR**[iv]			Dyslipidae-mia	

FI										
ENF	Injection nodules									Hypersensitivity
INSTI										
RAL		Nausea			Myopathy, Rhabdomyolysis		Sleep disturbance, Headache			Systemic hypersensitivity syndrome[viii] **Weight increase**
DTG	Rash	Nausea				↓ eGFR[iv]	**Sleep disturbance, Headache**			Systemic hypersensitivity syndrome (< 1%) **Weight increase** **↑ risk of neural tube defects (pre-conception)**
EVG/c		**Nausea,** Diarrhoea				↓ **eGFR**[iv]	Sleep disturbance, Headache			**Weight increase**
BIC						↓ eGFR[iv]	Sleep disturbance, Headache			**Weight increase**
CCR5 inhibitor										
MVC			Hepatitis							
CD4-directed post-attachment HIV-1 inhibitor										
Ibalizumab	Rash	Nausea Diarrhoea					Dizziness			

i **"Frequent effects" (events expected in at least 10% of treated PLWH), 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 has lower tenofovir-related kidney and bone adverse effects, but long-term experience is lacking, see pages 61, 64-65
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 minor digestive problems and lipid increases (low-dose RTV more than COBI). IHD reported with ritonavir-boosted DRV only (no data with cobicistat-boosted DRV, although lipid effects lower)
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

Notes:
1. The adverse effects listed 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
2. D4T, ddI, FPV, IDV, SQV and TPR removed. Please refer to EACS v9.1 for details, http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

See online video lecture Adverse Effects and Monitoring of ART from the EACS online course Clinical Management of HIV

Part III Drug-drug Interactions and Other Presribing Issues in PLWH

ARVs are recognised to be amongst the therapeutic agents with the highest potential for drug-drug interactions (DDIs) as these drugs can be both a victim (affected by other drugs) and/or a perpetrator (affect other drugs) of DDIs. Given the life-long ART, DDIs are practically unavoidable in PLWH with comorbid conditions. Thus, the potential for DDIs should be considered systematically when selecting an ART regimen or when any new medicine is coadministered to existing ART with particular attention to adjust dosage and perform clinical monitoring when needed.

The DDIs profiles between ARVs and coadministered medicines within a therapeutic class are also presented in the corresponding Co-morbidities section and Viral Hepatitis Co-infection section.

Detailed information on DDIs can be found on the University of Liverpool DDIs websites: http://www.hiv-druginteractions.org and http://www.hep-druginteractions.org

Age-related physiological changes and co-morbidities predispose elderly PLWH to inappropriate drug use or dosing in addition to DDIs [1].

Besides highlighting the most common DDIs, this section also provides guidance on how to adjust drug dosing in case of liver or renal impairment, considerations for those with swallowing difficulties and what to consider when prescribing drugs in elderly PLWH including the top ten drug classes to avoid.

Drug-drug Interactions between ARVs and non-ARVs

	Non-ARV drugs	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
Cardiovascular drugs	atorvastatin	↑822%	↑	↑290%	↑	↑490%	↓2%	↓43%	↓37%	↓	↑4% D10%	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluvastatin	↑	↑	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	pravastatin	↑	↑	↑	↑81%	↔	↔	↓44%	↓	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	rosuvastatin	↑242%	↑213%	↑93%	↑48%	↑108%	↔	↔	↔	↔	↔	↔	↔	↔	↑38%	↔	↔	↔	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↑	↔	↓68%	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	amlodipine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	diltiazem	↑a	↑a	↑	↑	↑a	E	↓69%	↓E	↓	E	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	metoprolol	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	verapamil	↑a	↑a	↑	↑	↑a	E	↓	↓E	↓	E	E	E	↔	↑	↔	↔	↔	↔	E	E
	warfarin	↑	↑ or ↓	↑	↓	↓	↔	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔
CNS drugs	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↑?	↔	↔	↔	↔	↔	↔
	carbamazepine	↑D	↑D	↑D	↑	↑D b	D	↓27% D36%	D	↓D	D	D	D	D49%	↑ D	D b	↑	↔	↔	D	↔
	citalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔c	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	diazepam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	lamotrigine	↔	↓32%d	↔	↓	↓50%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↓1%	↔	↔	↔	↔	↔
	midazolam (oral)	↑	↑	↑	↑	↑	↓18%	↓	↓	↓	↔	↑18%	↑15%	↔	↑	↓8%	↔	↔	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔	↔	↔	↔
	phenytoin	D	↓D	D	↓D	↓D b	D	↓D	D	D	D	D	D	D	D	D b	D	↔	↔	D	↔
	pimozide	↑	↑	↑	↑	↑	↔	↑	↓	↓	↔c	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	sertraline	↑	↓	↑	↓49%	↓	↔	↓39%	↓	↓	↔	↔	↔	↔	↓7%	↔	↔	↔	↔	↔	↔
	triazolam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Anti-infectives	clarithromycin	↑Ea	↑Ea	↑E	↑	↑a	↑	↓39%	↓39% E42%	↓31% E26%	E c	E	E	↔	↑E	↔	↔	↔	↔	E	E
	fluconazole	↑?	↔	↑?	↔	↔	↑	↔	E86%	E100%	E	↔	↔	↔	↑?	↔	↔	↔	↔	E?	↔
	itraconazole	↑E	↑E	↑E	↑E	↑E	↑	↓39%	↓E	↓61%	E	E	E	↔	↑E	↔	↔	↔	↔	E	E
	rifabutin	↑D	↑	↑D	↑E50%	↑	D50%	↓38%	↓17% D37%	↑17%	D42%	e	D38%	↔	↑D	E19%	↔	↔	↔	D f	↔
	rifampicin	D	D72%	D	D57%	D75%	D82%	D26%	D	D58%	D80%	D	D75%	D54%g	D	D40%b	D	↔	↔	D f	D12%
	voriconazole	↑↓ E	↑↓ D	↑E	↓	↑↓ E	↑	↓E	↑14% E36%	↓E	E	E	E61%	↔	↑E	↔	↔	↔	↔	↔	↔
Miscellaneous	antacids	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	D	D	D	D h	↔	↔	↔	↔	↔
	PPIs	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	E	↔	↔	↔	↔	↔
	H2 blockers	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	E	↔	↔	↔	↔	↔
	alfuzosin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	beclometasone (inhaled)	↑i	↑i	↑?i	↓11%	↑i	↔	↔	↔	↔	↔	↔	↔	↔	↑i	↔	↔	↔	↔	↔	↔
	budesonide (inhaled)	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	buprenorphine	↑	↑67%j	↑	↓11%j	↑~2%	↔	↓50%	↓25%	↓9%	↔	↔	↔	↔	↑35%	↔	↔	↔	↑~5%	↔	↑~5%
	ergot derivatives	↑	↑	↑	↑	↑	E	↑	↑	↓	E	E	↔	↔	↑	↔	↔	↔	↔	↔	↔
	ethinylestradiol	↑1%k	↓19%l	↓30%	↓44%k	↓42%k	↓2%	m	↑22%	↓20%	↑14%	↓<1%	↑4%	↑3%	↓25%n	↓2%	↔	↑11%	↔	↑11%	↔
	fluticasone (inhaled)	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	methadone	↑? a	↔a	↑?	↓16%	↓53%a	↓5%	↓52%	↑6%	↓~50%	↓16%a	↔	↔	↓2%	↑7%	↔	↓	↔	↔	↔	↑~5%
	salmeterol (inhaled)	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	sildenafil (erectile dys.)	↑	↑	↑	↑	↑	↔	↓	↓37%	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	St John's wort	D	D	D	D	D	D	D	D	D	D	D	D	D o	D	D	↔	↔	↔	D	↔
	varenicline	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour legend

No clinically significant interaction expected

These drugs should not be co-administered

Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration

Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Comment

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Legend

↑ Potential elevated exposure of the non-ARV drug
↓ Potential decreased exposure of the non-ARV drug
↔ No significant effect
D Potential decreased exposure of ARV drug
E Potential elevated exposure of ARV drug
ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)
Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies.

* This table summarises the drug-drug interactions between HIV therapy and some commonly prescribed co-medicines 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)

Interactions with ZDV

Clarithromycin, rifampicin (decrease in ZDV exposure)
Fluconazole, methadone (increase in ZDV exposure)
Carbamazepine (increase in carbamazepine exposure)
Phenytoin (decrease in phenytoin exposure)

Interactions with ibalizumab

none

Comments

a ECG monitoring is recommended
b Co-administration with LPV/r 800/100 qd or RAL 1200 mg qd is not recommended. If use is unavoidable, give LPV/r 400/100 mg bid or RAL 400 mg bid, with monitoring of response
c RPV manufacturer recommends caution when co-administering with another drug susceptible to prolong QT interval
d No PK changes with unboosted ATV
e No dose adjustment for MVC in absence of PI. With PI (except TPV/r, FPV/r), give MVC 150 mg bid
f Interaction can be overcome by administering TAF 25 mg bid
g Administer DTG 50 mg bid in treatment-naïve or INSTI-naïve PLWH. Alternative to rifampicin should be used where possible for INSTI-experienced PLWH with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance
h Al, Mg containing antacids not recommended with RAL 400 mg bid or 1200 mg qd. If co-administration with an antacid is unavoidable, calcium carbonate antacids can be used but only with RAL 400 mg bid
i 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
j Concentrations of norbuprenorphine increased
k Alternative or additional contraceptive measures are recommended or, if used for hormone replacement therapy, monitor for signs of oestrogen deficiency
l Increase in ethinylestradiol with unboosted ATV
m No effect on ethinylestradiol as a combined oral contraceptive, but ethinylestradiol decreased when administered as a vaginal ring. Progestin decreased with both methods. Use with efavirenz is not recommended
n European SmPC states a hormonal contraceptive should contain at least 30 µg ethinylestradiol
o The European SmPC recommends DTG 50 mg bid in PLWH without INSTI resistance. The US Prescribing Information recommends that co-administration should be avoided as there are insufficient data to make dosing recommendations

Drug-drug Interactions between Antidepressants and ARVs

	Antidepressants	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
SSRI	citalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	escitalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluoxetine	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluvoxamine	↑	↑	↑	↑	↑	↔	↔	↔	E	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔	↔	↔	↔
	sertraline	↑	↓	↑	↓49%	↓	↔	↓39%	↓	↓	↔	↔	↔	↔	↓7%	↔	↔	↔	↔	↑9%	↔
SNRI	duloxetine	↑	↑↓	↑	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	venlafaxine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	D	↔	↔	↑	↔	↔	↔	↔	↔	↔
TCA	amitriptyline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	clomipramine	↑a	↑a	↑a	↑a	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑a	↔	↔	↔	↔	↔	↔
	desipramine	↑a	↑a	↑	↑	↑5%a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	doxepin	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	imipramine	↑a	↑a	↑a	↑a	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑a	↔	↔	↔	↔	↔	↔
	nortriptyline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	trimipramine	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
TeCA	maprotiline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	mianserine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Others	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↑?	↔	↔	↔	↔	↔	↔
	lamotrigine	↔	↓32%c	↔	↓	↓50%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↓1%	↔	↔	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↑	E	↓E	↓E	↓E	E	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	St John's wort	D	D	D	D	D	D	D	D	D	D	D	D	D d	D	D	↔	↔	↔	D	↔
	trazodone	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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
ATV/c	ATV co-formulated with COBI (300/150 mg qd)
DRV/c	DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

SSRI	selective serotonin reuptake inhibitors
SNRI	serotonin and norepinephrine reuptake inhibitors
TCA	tricyclic antidepressants
TeCA	tetracyclic antidepressants

Interactions with ZDV

No clinically relevant interactions expected with ZDV and antidepressants

Interactions with ibalizumab

none

Comments

a	ECG monitoring is recommended
b	Caution as both drugs can induce QT interval prolongation
c	No PK change with unboosted ATV
d	The European SmPC recommends DTG 50 mg bid in persons without INSTI resistance. The US Prescribing Information recommends that co-administration should be avoided as there are insufficient data to make dosing recommendations

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Antihypertensives and ARVs

Antihypertensives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
ACE inhibitors	captopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eprosartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔
	losartan	↔	↓a	↔	↓a	↓a	↔	↑b	↑b	↔	↔	↔	↔	↔	↓a	↔	↔	↔	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↑c	↔c	↑	↔	↔c	↔	↔	↔	↔	↔	↔	↑	↑	↑	↔	↔	↔	↑ E	↔	↔
	bisoprolol	↑c	↑c	↑	↑	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	carvedilol	↑c	↑↓c	↑	↑↓	↑↓c	↔	↑↓	↑↓	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	metoprolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	propranolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Calcium channel blockers	amlodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	diltiazem	↑d	↑d	↑	↑	↑e	E	↓69%	↓E	↓	E	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	felodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	lacidipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	nicardipine	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	E	E	↔	↔	↑	↔	↔	↔	↔	↔	↔
	nifedipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	nisoldipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	verapamil	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	E	E	E	↔	↑	↔	↔	↔	↔	E	E
Diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↑ E	↔	↔
	bendroflume-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chlortalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E
	hydrochloro-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indapamide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	torasemide	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
Others	doxazosin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	sacubitril	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	E	↔	↔	↔	↔	↔	↔	↔	↔	↑
	spironolactone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

Interactions with ZDV
No clinically relevant interactions expected with ZDV and anti-hypertensives

Interactions with ibalizumab
none

Comments

a	Parent drug concentrations decreased but active metabolite increased
b	Parent drug concentrations increased but active metabolite decreased
c	Risk of PR interval prolongation
d	ECG monitoring recommended
e	Use with caution as both LPV and calcium channel blockers prolong the PR interval. Clinical monitoring is recommended

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

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

Drug-drug Interactions between Analgesics and ARVs

Analgesics		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
Non-opioid analgesics	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b
	celecoxib	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b
	diclofenac	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E b
	ibuprofen	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b
	mefenamic acid	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b
	naproxen	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b
	nimesulide	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b
	paracetamol	↔	↓3%	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	piroxicam	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	b
Opioid analgesics	alfentanil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	buprenorphine	↑	↑67%c	↑	↓11%c	↑~2%	↔	↓50%	↓25%	↓9%	↔	↔	↔	↔	↑35%	↔	↔	↔	↑~5%	↔	↑~5%
	codeine	↑d	↑d	↑d	↑d	↑d	↔	↓	↓	↓	↔	↔	↔	↔	↑d	↔	↔	↔	↔	↔	↔
	dihydrocodeine	↑	↓↑	↑	↓↑	↓↑	↔	↓↑	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fentanyl	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	methadone	↑?e	↔e	↑?	↓16%	↓53%e	↓5%	↓52%	↑6%	↓~50%	↓16%e	↔	↔	↓2%	↑7%	↔	↓	↔	↔	↔	↑~5%
	morphine	↔f	↓f	↔f	↓f	↓f	↔	↑	↔f	↔	↔	↔	↔	↔	↔f	↔	↔	↔	↔	↔	↔
	oxycodone	↑	↑	↑	↑	↑160%	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	pethidine	↑	↓	↑	↓	↓	↔	↓g	↓g	↓g	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	sufentanil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	tramadol	↑d	↑d	↑d	↑d	↑d	↔	↓h	↔	↓h	↔	↔	↔	↔	↑d	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

Interactions with ZDV

Ibuprofen, naproxen (potential additive hematological toxicity)
Methadone (moderate increase in ZDV exposure, monitor for toxicity)

Interactions with ibalizumab

none

Comments

a	Clinical significance unknown. Use the lowest recommended dose particularly in individuals with risk factors for CVD, those individuals at risk of developing gastrointestinal complications, persons with hepatic or renal impairment, and in elderly persons
b	Potential risk of nephrotoxicity which is increased if NSAID is used for a long duration, if the person has a pre-existing renal dysfunction, a low body weight or receives other drugs that may increase TDF exposure. Concurrent use of NSAIDs with TDF warrants monitoring of renal function
c	Concentrations of norbuprenorphine increased
d	Potential decrease of the analgesic effect due to the reduced conversion to the active metabolite
e	Both drugs can potentially prolong the QT interval, ECG monitoring recommended
f	Inhibition of P-gp by RTV, COBI or ETV could potentiate the effect of opiate in the CNS
g	Concentrations of parent drug decreased and concentrations of neurotoxic metabolite increased
h	Concentrations of parent drug decreased but no change in concentrations of more active metabolite

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Anticoagulants/Antiplatelet Agents and ARVs

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

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Interactions with ZDV

No clinically relevant interactions expected with ZDV and anticoagulants or platelet agents

Interactions with ibalizumab

none

Comments

a	US label suggests to use apixaban at a reduced dose (2.5 mg twice daily) if needed
b	Unboosted ATV predicted to increase the anticoagulant, monitor INR and adjust the anticoagulant dosage accordingly
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	No pharmacokinetic interaction is expected, however, abacavir has been shown to potentiate platelet activation in vitro and may reduce the pharmacodynamic effect of clopidogrel
f	Unboosted ATV predicted to increase dipyridamole exposure due to UGT1A1 inhibition
g	Reduced active metabolite, but without a significant reduction in prasugrel activity

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Bronchodilators (for COPD) and ARVs

Bronchodilators		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
LAMA	aclidinium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	glycopyrronium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tiotropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	umeclidinium bromide	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SAMA	ipratropium	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
LABA	formoterol	↔a	↔a	↔	↔	↔a	↔	↔	↔	↔	↔a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indacaterol	↑b	↑b	↑b	↑b	↑b	↔	↓	↓	↓	↔	↔	↔	↔	↑b	↔	↔	↔	↔	↔	↔
	olodaterol	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	salmeterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	vilanterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SABA	salbutamol (albuterol)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
MX	aminophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	theophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
PDE4	roflumilast	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
ICS	beclometasone	↑d	↑d	↑?d	↓11%	↑d	↔	↔	↔	↔	↔	↔	↔	↔	↑d	↔	↔	↔	↔	↔	↔
	budesonide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluticasone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑	Potential elevated exposure of the bronchodilator
↓	Potential decreased exposure of the bronchodilator
↔	No significant effect
D	Potential decreased exposure of ARV drug
E	Potential elevated exposure of ARV drug

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

ICS inhaled corticosteroids
LABA long-acting β2 agonists
LAMA long-acting muscarinic antagonists
MX methylxanthines
PD4 phosphodiesterase 4 inhibitors
SABA short-acting β2 agonists
SAMA short-acting muscarinic antagonists

Interactions with ZDV
No clinically relevant interactions expected with ZDV and bronchodilators

Interactions with ibalizumab
none

Comments

a	Caution as both drugs can induce QT interval prolongation
b	Exposure can be increased up to 2-fold however this increase does not raise any concerns based on indacaterol's safety data
c	ECG monitoring is recommended
d	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

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Contraceptives and ARVs

Contraceptives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
Es	ethinylestradiol (COC, TS, VR)	↑1%a	↓19%b	↓30%	↓44%a	↓42%a	↓2%	c	↑22%	↓20%	↑14%	↓<1%	↑4%	↑3%	↓25%d	↓2%	↔	↑11%	↔	↑11%	↔
Progestins	desogestrel (COC)	↑	↑e,b	↑	↑f	↑f	↔	↓g	↓	↓	↔	↔	↔	↔	↑d,e	↔	↔	↔	↔	↔	↔
	desogestrel (POP)	↑	↑	↑	↑	↑	↔	↓g	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	drospirenone (COC)	↑130%	↑e,b	↑58%f	↑f	↑f	↔	↓g	↓	↓	↔	↔	↔	↔	↑d,e	↔	↔	↔	↔	↔	↔
	etonogestrel (IP)	↑	↑	↑	↑	↑52%	↔	↓63%g	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	etonogestrel (VR)	↑	↑~80%h	↑	↑h	↑h	↔	↓~79%g	↓	↓	↔	↔	↔	↔	↑h	↔	↔	↔	↔	↔	↔
	gestodene (COC)	↑	↑e,b	↑	↑f	↑f	↔	↓g	↓	↓	↔	↔	↔	↔	↑d,e	↔	↔	↔	↔	↔	↔
	levonorgestrel (COC)	↓8%	↑e,b	↑	↑f	↑f	↑21%	↓g	↓	↑	↔	↓2%	↔	↔	↑	↔	↔	↔	↔	↔	↔
	levonorgestrel (IP)	↑	↑	↑	↑	↑	↔	↓57%g	↓	↑14%	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	levonorgestrel (IUD)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel (POP)	↑	↑	↑	↑	↑	↔	↓g	↓	↑	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	medroxy-progesterone (POI)	↔	↔	↔	↔	↑~70%	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	norelgestromin (TS)	↑	↑e,b	↑	↑f	↑83%f	↔	↓g	↓	↓	↔	↔	↔	↔	↑d,e	↔	↔	↔	↔	↔	↔
	norethisterone (COC)	↑	↑e,i	↑	↓14%f	↓17%f	↔	↓g	↓5%	↓19%	↓11%	↔	↔	↔	↑d,e	↔	↔	↔	↔	↔	↔
	norethisterone (POI)	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	norethisterone (POP)	↑	↑50%	↑	↑50%	↑50%	↔	↓g	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	norgestimate (COC)	↑	↑85% e,b	↑	↑f	↑f	↔	↓64%g	↓	↓	↔	↔	↑8%	↓2%	↑126% d,e	↑14%	↔	↔	↔	↔	↔
	norgestrel (COC)	↑	↑e,b	↑	↑f	↑f	↔	↓g	↓	↑	↔	↔	↔	↔	↑d,e	↔	↔	↔	↔	↔	↔
Other	levonorgestrel (EC)	↑j	↑j	↑j	↑j	↑j	↔	↓58%k	↔	↔	↔	↔	↔	↔	↑j	↔	↔	↔	↔	↔	↔
	mifepristone	↑j	↑j	↑j	↑j	↑j	E j	↓	↓	↓	E j	E j	E j	↔	↑j	↔	↔	↔	↔	↔	↔
	ulipristal	↑j	↑j	↑j	↑j	↑j	↔	↓l	↓l	↓l	↔	↔	↔	↔	↑j	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

Es estrogens
COC combined oral contraceptive
EC emergency contraception
IP implant
IUD ntrauterine device
POI progestin only injectable
POP progestin only pill
TS transdermal patch
VR vaginal ring

Interactions with ZDV
No clinically relevant interactions expected with ZDV and contraceptives

Interactions with ibalizumab
none

Comments

a Alternative or additional contraceptive measures are recommended or, if used for hormone replacement therapy, monitor for signs of oestrogen deficiency
b 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
c Depending on the contraceptive method, ethinylestradiol concentrations are either not significantly changed (COC) or significantly decreased (VR). Levels of co-administered progestin are markedly decreased. Use with EFV is not recommended as it may impair contraceptive efficacy
d European SmPC states a hormonal contraceptive should contain at least 30 µg ethinylestradiol
e When used in a combination pill, the estrogen component is reduced to a small extent
f When used in a combination pill, the estrogen component is significantly reduced, caution is recommended and additional contraceptive measures should be used
g EFV is expected to decrease the progestin exposure and thereby impair the efficacy of the contraceptive method. A reliable method of barrier contraception must be used in addition to hormonal contraceptives
h Used in combination with ethinylestradiol (0.015 mg/day) which is predicted to be decreased. Since there is no possibility to adjust ethinylestradiol, caution is recommended and additional contraceptive measures should be used
i Unboosted ATV increased ethinylestradiol AUC by 48% and norethisterone AUC by 110%. 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
j Unlikely to have clinical consequences as hormone is administered as single dose
k Use 3 mg as a single dose for emergency contraception. Of note, the doubling of the standard dose is outside the product license and there is limited evidence in relation to efficacy
l Not recommended, non-hormonal emergency contraception (Cu-IUD) should be considered

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Corticosteroids and ARVs

Corticosteroids		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
Inhaled, oral, topic and/or injected corticosteroids	beclometasone (inhalation)	↑a	↑a	↑?a	↓11%b	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↑a	↔	↔	↔	↔	↔	↔
	betamethasone	↑c	↑c	↑c	↑c	↑c	D	↓	↓	↓	D	D	D	↔	↑c	↔	↔	↔	↔	↔	↔
	budesonide (inhalation)	↑c	↑c	↑c	↑c	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑c	↔	↔	↔	↔	↔	↔
	ciclesonide (inhalation)	↑d	↑d	↑d	↑d	↑d	↔	↔	↔	↔	↔	↔	↔	↔	↑d	↔	↔	↔	↔	↔	↔
	clobetasol (topical)	↑c,e	↑c,e	↑c,e	↑c,e	↑c,e	↔	↔	↔	↔	↔	↔	↔	↔	↑c,e	↔	↔	↔	↔	↔	↔
	dexamethasone	↑c D	↑c D	↑c D	↑c D	↑c D	D	↓ D	↓ D	↓ D	D	D	D	↔	↑c D	↔	↔	↔	↔	↔	↔
	flunisolide (inhalation)	↑f	↑f	↑f	↑f	↑f	↔	↓	↓	↓	↔	↔	↔	↔	↑f	↔	↔	↔	↔	↔	↔
	fluocinolone (topical)	↑c,e	↑c,e	↑c,e	↑c,e	↑c,e	↔	↔	↔	↔	↔	↔	↔	↔	↑c,e	↔	↔	↔	↔	↔	↔
	fluticasone (inhalation)	↑c	↑c	↑c	↑c	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑c	↔	↔	↔	↔	↔	↔
	hydrocortisone (oral)	↑c	↑c	↑c	↑c	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑c	↔	↔	↔	↔	↔	↔
	hydrocortisone (topical)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	methylprednisolone	↑c	↑c	↑c	↑c	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑c	↔	↔	↔	↔	↔	↔
	mometasone (inhalation)	↑c	↑c	↑c	↑c	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑c	↔	↔	↔	↔	↔	↔
	prednisolone (oral)	↑c	↑c	↑c	↑c	↑c	↔	↓20%	↓	↓	↔	↔	↔	↔	↑c	↔	↔	↔	↔	↔	↔
	prednisone	↑c	↑c	↑c	↑c	↑c	↔	↓20%	↓	↓	↔	↔	↔	E 11%	↑c	↔	↔	↔	↔	↔	↔
	triamcinolone	↑c	↑c	↑c	↑c	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑c	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

Interactions with ZDV
No clinically relevant interactions expected with ZDV and corticosteroids

Interactions with ibalizumab
none

Comments

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 and injected corticosteroid but also for topical, inhaled or eye drops administration

d No dose adjustment required but monitor closely, especially for signs of Cushing's syndrome when using a high dose or prolonged administration

e 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

f Use the lowest possible flunisolide dose with monitoring for corticosteroid side effects

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Antimalarial Drugs and ARVs

Antimalarial drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
First line and second line drugs	amodiaquine	↑	↑	↔	↑	↑	↔	↑a	↓?	↓29% a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	artemisinin	↑	↑	↑	↑	↑	D	↓	↓D	↓D	D	D	D	↔	↑	↔	↔	↔	↔	↔	↔
	atovaquone	↔	↓10%	↔	↓ b	↓74% b	↔	↓75% b	↓E55% b	↓ b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chloroquine	↔c,d	↔c,d	↔d	↔d	↔c,d	↔	↔e	↔f	↔f	↔g	↔	↔	↔	↔d	↔	↔	↔	↔	↔	↔
	clindamycin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	doxycycline	↔	↔	↔	↔	↔	↔	↓?	↓?	↓?	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lumefantrine	↑ c	↑ c	↑	↑175%	↑382% c	↔	↓~40%	↓	↓D46%	↔g	↔	↔	↑10%	↑	↔	↔	↔	↔	↔	↔
	mefloquine	↑ c	↑ c	↑	↑	↓28%c	↔	↓	↓	↓	↔g	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	piperaquine	↑ c	↑ c	↑ c	↑ c	↑ c	E	↓	↓	↓	E g	E	E	↔	↑ c	↔	↔	↔	↔	↔	↔
	primaquine	↔	↔	↔	↔	↔	↔	↔h	↔h	↔h	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	proguanil	↔	↓41% b	↔	↓b	↓38% b	↔	↓44% b	↓E55% b	↓b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pyrimethamine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E	E	↔	↔
	quinine	↑ c	↑ c	↑	↑	↓56% c	↔	↓	↓	↓	↔ g	E	↔	↔	↑	↔	↔	↔	↔	↔	↔
	sulfadoxine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E	E	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑	Potential increased exposure of the antimalarial drug
↓	Potential decreased exposure of the antimalarial drug
↔	No significant effect
D	Potential decreased exposure of ARV drug
E	Potential elevated exposure of ARV drug

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

Interactions with ZDV
Amodiaquine, atovaquone, primaquine, pyrimethamine, sulfadoxine (potential additive hematological toxicity)

Interactions with ibalizumab
none

Comments

a	Liver toxicity
b	Take with high fat meal, consider dose increase
c	ECG monitoring is recommended
d	Chloroquine concentrations may increase, but to a moderate extent. No dose adjustment is required but monitor toxicity
e	Chloroquine concentrations may increase or decrease. No dose adjustment is required but monitor toxicity and efficacy
f	Chloroquine concentrations may decrease, but to a moderate extent. No dose adjustment is required but monitor efficacy
g	Both drugs can induce QT interval prolongation (only at supratherapeutic dose for RPV)
h	Increase of haemotoxic metabolites

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

Pulmonary anti-hypertensives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
ERA	ambrisentan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bosentan	↑a	↑a	↑a	↑a	↑a	D	↓	↓	↓b	D	D	D	D	↑a	↔	↔	↔	↔	↔	↔
	macitentan	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
PDE5	sildenafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↓3%	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	tadalafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
sGC	riociguat	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
PA	epoprostenol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	iloprost	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	treprostinil	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
IPr	selexipag	↔c	↔c	↔c	↔c	↑120%d	↔	↔	↔	↔	↔	↔	↔	↔	↔c	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑	Potential increased exposure of the pulmonary antihypertensive
↓	Potential decreased exposure of the pulmonary antihypertensive
↔	No significant effect
D	Potential decreased exposure of ARV drug
E	Potential elevated exposure of ARV drug

ATV/c	ATV co-formulated with COBI (300/150 mg qd)
DRV/c	DRV co-formulated with COBI (800/150 mg qd)

ERA	endothelin receptor antagonists
IPr	IP receptor agonists
PA	prostacyclin analogues
PDE5	phosphodiesterase type 5 inhibitors
sGC	soluble guanylate cyclase stimulators

Interactions with ZDV

No clinically relevant interactions expected with ZDV and pulmonary antihypertensives

Interactions with ibalizumab

none

Comments

- a Co-administration is not recommended in the European labels, but the US labels suggest the following dose modifications:
  When starting bosentan in individuals already on PI/r, PI/c or EVG/c use a bosentan dose of 62.5 mg qd or every other day.
  Discontinue bosentan at least 36 h prior to starting PI/r, PI/c or EVG/c and restart after at least 10 days at 62.5 mg qd or every other day
- b Potential additive liver toxicity
- c Exposure of parent drug increased but exposure of active metabolite unchanged
- d This change is unlikely to be clinically relevant

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Immunosuppressants (for SOT) and ARVs

Immunosuppressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
CS	prednisone	↑	↑	↑	↑	↑	↔	↓20%	↓	↓	↔	↔	↔	E11%	↑	↔	↔	↔	↔	↔	↔
AM	azathioprine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	mycophenolate	↔	↓a	↔	↓a	↓a	↔	↓a	↔	↓a D13%	↔	↔	↔	↔	↔	↔	↓?	↔	↔	↔	↑ Eb
CNI	cyclosporine	↑a	↑a	↑a	↑a	↑a	E	↓a	↓a	↓a	E	E	E	↔	↑a	↔	↔	↔	↔	E	Eb
	tacrolimus*	↑a	↑a	↑a	↑a	↑a	↓a	↓a	↓a	↓a	↔	↔	↔	↔	↑a	↔	↔	↔	↔	↔	↔b
mTOR	everolimus	↑	↑	↑	↑	↑	↔	↓a	↓a	↓a	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	sirolimus	↑	↑	↑	↑	↑	↓a	↓a	↓a	↓a	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔b
Other	anti-thymocyte globulin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	basiliximab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	belatacept	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑ Potential increased exposure of the immunosuppressant
↓ Potential decreased exposure of the immunosuppressant
↔ No significant effect
D Potential decreased exposure of ARV drug
E Potential elevated exposure of ARV drug

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

* available as prolonged release formulation

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

AM antimetabolite
CNI calcineurin inhibitors
CS corticosteroids
mTOR mTOR inhibitors

Interactions with ZDV
Azathioprine (potential risk of additive hematotoxicity).
Mycophenolate (potential alteration in mycophenolate level, monitor plasma concentrations)

Interactions with ibalizumab
none

Comments
a TDM of immunosuppressant is recommended
b Monitor renal function

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between DAAs and ARVs

HCV drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
DAAs	daclatasvir	↑31% a	↑110% a	↑	↑41%	↑15%	↔	↓32% b	↓	↓	↔	↔	↔	↓2% E33%	↑ a	↔	↔	↔	↔	↔	↑10% E10%
	elbasvir/ grazoprevir	↑	↑376% ↑958%	↑	↑66% ↑650%	↑271% ↑1186%	↓4% ↑7%	↓54% ↓83%	↓	↓	↑7% ↓2%	↔	↔	↓2% ↓19%	↑118% ↑436%	↓19% ↓11%	↔	↔	↔	↔	↓7% ↓14%
	glecaprevir/ pibrentasvir	↑	↑553% ↑64%	↑	↑397% -	↑338% ↑146%	↔	↓	↓	↓	E 84%	E	E	↔	↑205% ↑57% E47%	E47%	↔	↔	↔	↔	E29%
	paritaprevir/r/ ombitasvir/ dasabuvir	↑	↑94% ↓17% ↓18%c	↑	D d	↑117% ↑17% ↓7%	E	f	↓	↓E	E 225% g	E	E	↓16% ↓5% ↓2%	↑	E134%	↓18% ↓9% ↓9%	↓16% ↓1% ↓15%	↓18% ↓9% ↓9%	E	↓16% ↓1% ↓15%
	paritaprevir/r/ ombitasvir	↑	↑187% c	↑	↑ e	↑510% -	E	f	↓	↓E	E g	E	E	↔	↑	E20%	↔	↔	↔	E	↔
	simeprevir	↑	↑	↑	↑159%	↑	↔	↓71%	↓	↓	↑6% E12%	↔	↔	↔	↑	↓11% E8%	↔	↔	↔	↔	↓14% E18%
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↓6%	↔	↔	↑9%	↔	↔	↔	↔	↓5% D27%	↔	↓6%	↔	↔	↓6%
	sofosbuvir/ ledipasvir	↑ h	↑8% ↑113%h	↑ h	↑34% ↑39% h	↔ h	↑4% ↓8%	↓6% ↓34%	↔	↔	↑10% ↑8% h	E	↑7% ↓13%	↔	↑36% ↑78%h	↓5% ↓9% D~20%	↑21% ↑18% D 10%	↔	↑21% ↑18% D 6%	E32%	E h
	sofosbuvir/ velpatasvir	↔ h	↑22% ↑142%h	↔ h	↓28% ↓16% h	↓29% ↑2% h	↔	↓3% ↓53%	↓	↓	↑16% ↓1%	E	↔	↓8% ↓9%	↑ h	↑24% ↓2%	↔	↔	↔	↔	E h
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40% ↑93% ↑331%	↑ h	↓28% ↓5% ↑143%i	↑	↔	↓	↓	↓	↔	E	↑9% ↓4% ↓9%	↔	↑22% ↑16% ↑171% h	↔	↔	↔	↔	E	E h

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to decreased/increased AUC as observed in drug interactions studies.
First/second numbers refer to AUC changes for EBR/GZR or GLE/PIB or SOF/LDV or SOF/VEL.
First/second/third numbers refer to AUC changes for SOF/VEL/VOX

Interactions with ZDV
No clinically relevant interactions expected with ZDV and DAAs

Interactions with ibalizumab
none

Comments

a DCV should be reduced to 30 mg qd with ATV/c, ATV/r or EVG/c. No dose reduction with unboosted ATV
b DCV should be increased to 90 mg qd
c Study details are with unboosted ATV. Use only with unboosted ATV (ATV increased PTV exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without DSV)
d Co-administration decreased DRV trough concentration by ~50%. Although co-administration of DRV with OBV/PTV/r + DSV is not recommended in the US Prescribing Information, the European SmPC advises that DRV (dosed at 800 mg qd and administered at the same time as OBV/PTV/r + DSV) can be used in the absence of extensive HIV PI resistance and should be taken without additional RTV
e Not recommended due to increase in PTV exposure when co-administered with DRV 800 mg given with OBV, PTV, RTV (Viekirax). Of note: exposures of PTV greater than this have been evaluated in phase 2 studies and were not expected to have a clinically meaningful impact on safety
f Severe tolerability issues
g Not recommended unless benefit outweighs the risk due to potential for QT interval prolongation with higher concentrations of RPV. Co-administration should be only considered in persons without known QT prolongation and without other QT prolongation co-medicines
h Monitoring of kidney function recommended due to increase of tenofovir concentration if the regimen contains TDF
i Study details are with once daily DRV/r. Twice daily DRV has not been studied and should be used with caution as VOX concentrations may increase more than with once daily DRV (this would be of further significance in cirrhotic patients). Monitoring of kidney function recommended due to increase of tenofovir concentrations if the regimen contains TDF

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

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
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)[vii]	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]	yes		Crushing of tablets is not recommended in the product information. However based on data with the fixed-dose combination tablet (TAF/FTC/DRV/c), crushing of tablets does not impact significantly TAF/FTC pharmacokinetics (of note: TAF bioavailability is reduced by 20% (crushing) but this decrease is unlikely to be clinically significant)[viii]
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				
DOR	tablet (100 mg)	no		Tablet must be swallowed whole
TDF/3TC/DOR	tablet (300/300/100 mg)	no		Tablet must be swallowed whole
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)[v]	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	no	Do not open the capsule, swallow whole
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)	yes		Crushing of tablets is not recommended in the product information. However, based on data with the fixed-dose combination tablet (/TAF/FTC/ DRV/c), crushing of tablets does not impact significantly DRV/c pharmacokinetics[viii]
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
TAF/FTC/DRV/c	tablet (10/200/800/150 mg)[v]	yes		Crushing of tablets has no significant effect on the pharmacokinetics of the components of the tablet (of note: TAF bioavailability is reduced by 20% (crushing) but this decrease is unlikely to be clinically significant. TAF bio-availability is not changed when splitting the pill)[viii]
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
Ibalizumab	injectable	NA	NA	
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)
RPV/DTG	tablet (25/50 mg)	no		Tablets should be swallowed whole and should not be chewed, crushed or split

Drug	Formulation	Crush tablets	Open capsules	Comment
TAF/FTC/BIC	tablet (25/200/50 mg)[v]	no		Tablets should be swallowed whole and should not be chewed, crushed or split
TAF/FTC/EVG/c	tablet (10/200/150/150 mg)[v]	yes		Crushing of tablets is not recommended in the product information. However, based on data with the fixed-dose combination tablet TAF/FTC/DRV/c), crushing of tablets does not impact significantly TAF/FTC pharmacokinetics (of note: TAF bioavailability is reduced by 20% (crushing) but this decrease is unlikely to be clinically significant)[viii]. Similarly, crushing of /TDF/FTC/ EVG/c did not have a significant effect of the pharmacokinetics of EVG/c[iv]
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[vi]	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
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 VI 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 [2]. In addition, RAL drug absorption has been shown to be higher in PLWH taking RAL 400 mg bid by chewing the tablets as compared to swallowing the intact tablets [3]

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 [4]

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

vi The pharmacokinetic profiles of ABC/3TC/DTG were not modified to a clinically significant extent when the fixed-dose combination tablet (Triumeq) was crushed and administered suspended in water or in enteral nutrition (of note: crushing leads to a 26% increase in DTG exposure) [5]

vii The bioavailability of 3TC solution has been shown to be significantly reduced in a dose dependent manner by sorbitol present in other liquid formulations (e.g. ABC, NVP, cotrimoxazole) [6]

viii Crushing of tablets is not recommended in the product information, however the individual pharmacokinetic profiles of TAF/FTC/ DRV/c were not significantly modified when the fixed-dose combination tablet (Symtuza) was administered crushed or split compared to the whole tablet [7]

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: contraindicated
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: contraindicated
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
TDF/3TC/DOR	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
DOR	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data

PIs	
ATV	Child-Pugh Class A: no dose adjustment
	Child-Pugh Class B: 300 mg qd (unboosted)
	Child-Pugh Class C: not recommended
ATV/c	Child-Pugh Class A: no dosage adjustment
	Child-Pugh Class B or C: not recommended
COBI	Refer to recommendations for the primary PI
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
TAF/FTC/DRV/c	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: not recommended
LPV/r	No dosage recommendation; use with caution in persons with hepatic impairment
RTV	Refer to recommendations for the primary PI
FI	
ENF	No dosage adjustment
EI	
Ibalizumab	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
BIC	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
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
TAF/FTC/BIC	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data

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[ii] (mL/min)				Haemodialysis[iii]
	≥ 50	30-49	10-29	< 10	
NRTIs					
Individual agents					
ABC[iii]	300 mg q12h or 600 mg q24h	No dose adjustment required			
FTC[v]	200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h[iv]
3TC[v]	300 mg q24h	150 mg q24h	100 mg q24h[vi]	50-25 mg q24h[vi]	50-25 mg q24h[iv, vi]
TDF[vii]	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]
TAF[ix,x]	25[xi] mg q24h			no data	limited data
ZDV	300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8hi[iv]
Combinations					
ABC[iii]**/3TC**[v]	600/300 mg q24h	Use individual drugs			
ZDV/3TC	300/150 mg q12h				
ABC/3TC/ZDV	300/150/300 mg q12h				
TAF[ix]**/FTC**[v]	25[xi]/200 mg q24h		Use individual drugs[xv]		
TDF[vii]**/FTC**[v]	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				
NVP	200 mg q12h				
RPV	25 mg q24h				
TAF[ix]**/FTC**[v]**/RPV**	25[xi]/200/25 mg q24h		Use individual drugs[xv]		
TDF[vii]**/FTC**[v]**/RPV**	300[viii]/200/25 mg q24h	Use individual drugs			
DOR	100 mg q24h	No dose adjustment required; < 10: no PK data			
TDF[vii]**/3TC**[v]**/DOR**	300[viii]/300/100 mg q24h	Use individual drugs			
PIs[vii]					
ATV/c	300/150 mg q24h	No dose adjustment required[xiii]			
ATV/r	300/100 mg q24h	No dose adjustment required[xiii]			
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required[xiii]			
DRV/c	800/150 mg q24h	No dose adjustment required[xiii]			
TAF[ix]**/FTC**[v]**/DRV/c**	10/200/800/150 mg q24h	Use individual drugs			
LPV/r	400/100 mg q12h	No dose adjustment required[xiii]			
Other ART					
RAL	1 x 400 mg tablet q12h or 2 x 600 mg tablets q24h	No dose adjustment required[xiii]			
DTG	50 mg q24h	No dose adjustment required[xiii]			
3TC[v]**/DTG**	300/50 mg q24h	Use individual drugs			
ABC[iii]**/3TC**[v]**/DTG**	600/300/50 mg q24h	Use individual drugs[xvi]			
RPV/DTG	25/50 mg q24h	No dose adjustment required[xiii]			
TAF[ix]**/FTC**[v]**/BIC**	25/200/50 mg q24h		Not recommended (no PK data for BIC for eGFR < 15 mL/min)		
TAF[ix]**/FTC**[v]**/EVG/c**	10/200/150/150 mg q24h		Not recommended[xii]		
TDF[vii]**/FTC**[v]**/EVG/c**	300[viii]/200/150/150 mg q24h Do not initiate if eGFR < 70 mL/min	Not recommended			
MVC: co-administered without CYP3A4 inhibitors[xiv]	300 mg q12h	No dose adjustment required[xiii]			
MVC: co-administered with CYP3A4 inhibitors[xiv]	If eGFR < 80 mL/min 150 mg q24h[xiv]				
Ibalizumab	2000 mg loading dose followed by 800 mg every 2 weeks. No dose adjustment required				

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 https:// www.chip.dk/Tools-Standards/Clinical-risk-scores

ii For Continuous Ambulatory Peritoneal Dialysis (CAPD) dosing for hemodialysis may be used. However, elimination of drugs in CAPD varies depending on CAPD conditions. TDM therefore is recommended

iii Potential cardiovascular risk of ABC may increase cardiovascular risk associated with renal failure

iv After dialysis

v Large bodily accumulation in impaired renal function. Although affinity for mitochondrial DNA polymerase is low and clinical toxicity in patients with severe renal impairment is rare, long-term mitochondrial toxicity is possible and must be monitored (polyneuropathy, pancreatitis, lactate acidosis, lipodystrophy, metabolic disturbances)

vi 150 mg loading dose

vii 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

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 Limited clinical data documented limited accumulation in hemodialysis. However, there is no long-term data on residual kidney function and bone toxicity. No data for eGFR < 10 mL/min but no dialysis

x Only licenced for hepatitis B

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

xii TAF/FTC/EVG/c as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, TAF/FTC/EVG/c may be used with caution if the potential benefits are considered to outweigh potential risks. One clinlical study has demontrated safety of TAF/FTC/EVG/c for PLWH on chronic dialysis [30]

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

xiv See summary of product characteristics for specific recommendations; use with caution if eGFR ≤ 30 mL/min10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)

xv TAF/FTC and TAF/FTC/RPV single tablet regimens should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, these combinations may be used with caution if the potential benefits are considered to outweigh potential risks

xvi ABC/3TC/DTG as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic haemodialysis. A recent case series study found that use of ABC/3TC/DTG appears to be a safe and effective option in PLWH on chronic dialysis [31]

Selected Non-ARV Drugs Requiring Dosage Adjustment in Renal Insufficiency

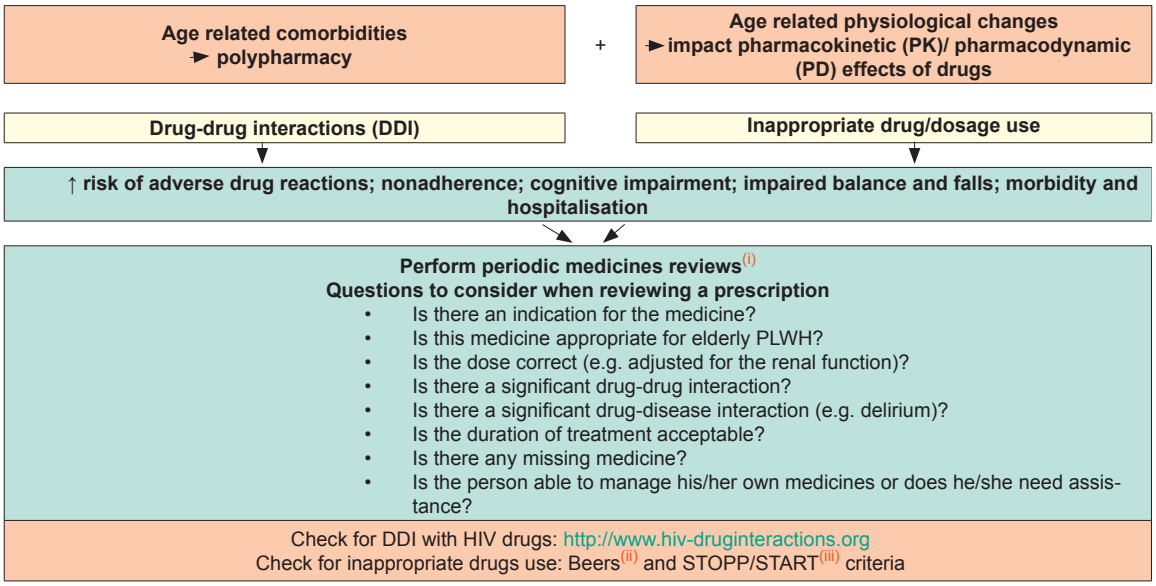
Therapeutic class and drugs	CL_{CRT} threshold for adjustment[a,b]	Additional information[c]
ANTIBACTERIALS[d]		
Fluoroquinolones		
Ciprofloxacin	≤ 60 mL/min	
Levofloxacin	≤ 50 mL/min	
Ofloxacin	≤ 50 mL/min	
Cephalosporins		
Cefpodoxime	≤ 40 mL/min	
Ceftazidime	≤ 50 mL/min	
Cefepime	≤ 50 mL/min	
Penicillins		
Amoxicillin/clavulanate	≤ 30 mL/min	
Benzylpenicillin (parenteral)	≤ 60 mL/min	
Piperacillin/tazobactam	≤ 40 mL/min	
Aminoglycosides		
Amikacin	≤ 70 mL/min	Dose dependent oto- and nephrotoxicity. Avoid in renal insufficiency if alternatives available otherwise perform TDM
Gentamicin	≤ 70 mL/min	
Tobramycin	≤ 70 mL/min	
Miscellaneous		
Nitrofurantoin		Avoid if CL_{CRT} < 60 mL/min
Trimethoprim-sulfamethoxazole	≤ 30 mL/min	
Vancomycin	≤ 50 mL/min	Dose dependent nephrotoxicity. TDM recommended
Antimycotics		
Fluconazole	≤ 50 mL/min	No adjustment in single dose therapy
Antivirals		
Ribavirin	≤ 50 mL/min	
Valaciclovir	variable	Dose adjustment depends on indication and person characteristics (< 30, < 50 or < 75 mL/min)
Antimycobacterials		
Ethambutol	≤ 30 mL/min	
Antithrombotics		
Apixaban	< 50 mL/min	Dose adjustment depends on indication and person characteristics. It may be required for CL_{CRT} < 50 mL/min. Avoid if CL_{CRT} < 15 mL/min
Dabigatran	≤ 50 mL/min	Contraindicated if CL_{CRT} < 30 mL/min
Edoxaban	≤ 50 mL/min	Avoid if CL_{CRT} < 15 mL/min
Enoxaparin	< 30 mL/min	Dose adjustment depends on indication and person characteristics.
Rivaroxaban	< 50 mL/min	Dose adjustment depends on indication and person characteristics. It may be required for CL_{CRT} < 50 mL/min. No dose adjustment if recommended dose is 10 mg qd Avoid if CL_{CRT} < 15 mL/min
BETA BLOCKERS		
Atenolol	≤ 35 mL/min	
Sotalol	≤ 60 mL/min	
ACE INHIBITORS		
Enalapril	≤ 80 mL/min	Dose adjustment for starting dose
Lisinopril	≤ 80 mL/min	Dose adjustment for starting dose
Perindopril	< 60 mL/min	
Ramipril	< 60 mL/min	
CARDIOTONIC AGENT		
Digoxin	≤ 100 mL/min	Dose adjustment for maintenance and loading dose. Avoid in renal insufficiency if alternatives
ANTIDIABETICS		
Biguanide		
Metformin	< 60 mL/min	Contraindicated if CL_{CRT} < 30 mL/min
GLP1-agonist		
Exenatide	≤ 50 mL/min	Avoid if CL_{CRT} < 30 mL/min

DPP4-inhibitors		
Alogliptin	≤ 50 mL/min	
Saxagliptin	< 45 mL/min	
Sitagliptin	< 45 mL/min	
Vildagliptin	< 50 mL/min	
SGLT2-inhibitors		
Canagliflozin	< 60 mL/min	Should not be initiated if CL_{CRT} < 60 mL/min. Dose adjustment if CL_{CRT} falls below 60 mL/min during treatment, and stop if CL_{CRT} < 45 mL/min (lack of efficacy)
Dapagliflozin	-	Should not be initiated if CL_{CRT} < 60 mL/min. Stop if CL_{CRT} < 45 mL/min (lack of efficacy)
Empagliflozin	< 60 mL/min	Should not be initiated if CL_{CRT} < 60 mL/min. Dose adjustment if CL_{CRT} falls below 60 mL/min during treatment, and stop if CL_{CRT} < 45 mL/min (lack of efficacy)
GOUT MEDICATION		
Allopurinol	≤ 50 mL/min	
Colchicine	≤ 50 mL/min	Dose dependent toxicity. Routine monitoring of colchicine adverse reactions recommended
ANTIPARKINSON DRUG		
Pramipexole	≤ 50 mL/min	Dose adjustment depends on indication
ANALGESICS		
NSAIDs	-	Avoid chronic use in persons with any stage of renal insufficiency
Morphine	-	Risk of respiratory depression in persons with renal insufficiency due to accumulation of 6-morphine-glucuronide (highly active metabolite). Avoid if alternatives; or titration to adequate pain control with close monitoring for signs of overdose
Oxycodone	< 50 mL/min	Initial dosage: reduced dose at initiation and further titration to adequate pain control and close monitoring for signs of overdose
Tramadol	< 30 mL/min	Increase dosing interval to 8-12 hours. Maximum daily dose 200 mg
ANTIEPILEPTICS		
Gabapentin	< 80 mL/min	
Levetiracetam	< 80 mL/min	
Pregabalin	< 60 mL/min	
PSYCHOLEPTIC		
Lithium	< 90 mL/min	Reduced dose and slow titration. TDM recommended. Avoid if CL_{CRT} < 30 mL/min
DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)		
Methotrexate (low dose)	< 60 mL/min	Dose dependent toxicity. Contraindicated if CL_{CRT} < 30 mL/min

Legend
a Renal function estimated for dosage adjustment mostly based on Cockcroft formula (CL_{CRT}: creatinine clearance)
b For persons with creatinine clearance < 15 mL/min or persons on dialysis, a nephrologist should be consulted
c The drug package insert should be consulted for specific dose adjustments
d No dose adjustment on antibacterial loading dose

[1], [8], [9]

Prescribing in Elderly PLWH



Adapted from [10], [11], [12]

i-iii The Beers and STOPP criteria are tools established by experts in geriatric pharmacotherapy to detect and reduce the burden of inappropriate prescribing in elderly. Inappropriate medicines include, for instance, those which in elderly persons with certain diseases can lead to drug-disease interactions, are associated with a higher risk of adverse drug reactions in the elderly, medicines that predictably increase the risk of falls in the elderly or those to be avoided in case of organ dysfunction. The START criteria consist of evidence-based indicators of potential prescribing omission in elderly with specific medical conditions

Selected Top 10 Drug Classes To Avoid in Elderly PLWH

Drug class	Problems/alternatives
First generation antihistamines e.g., clemastine, diphenhydramine, doxylamine, hydroxyzine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: cetirizine, desloratadine, loratadine
Tricyclic antidepressants e.g., amitryptiline, clomipramine, doxepin, imipramine, trimipramine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: citalopram, escitalopram, mirtazapine, venlafaxine
Benzodiazepines Long and short acting benzodiazepines e.g., clonazepam, diazepam, midazolam Non-benzodiazepines hypnotics e.g., zolpidem, zopiclone	Elderly are more sensitive to their effect, risk of falls, fractures, delirium, cognitive impairment, drug dependency. Use with caution, at the lowest dose and for a short duration. Alternatives: non-pharmacological treatment of sleep disturbance/sleep hygiene.
Atypical antipsychotics e.g., clozapine, olanzapine, quetiapine	Anticholinergic adverse reactions, increased risk of stroke and mortality (all antipsychotics). Alternatives: aripiprazole, ziprasidone
Urological spasmolytic agents e.g., oxybutynin, solifenacin, tolterodine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: non-pharmacological treatment (pelvic floor exercises).
Stimulant laxatives e.g., senna, bisacodyl	Long-term use may cause bowel dysfunction. Alternatives: fibres, hydration, osmotic laxatives
NSAIDs e.g., diclofenac, indomethacin, ketorolac, naproxen	Avoid regular, long-term use of NSAIDs due to risk of gastrointestinal bleeding, renal failure, worsening of heart failure. Alternatives: paracetamol, weak opioids
Digoxin Dosage > 0.125 mg/day	Avoid doses higher than 0.125 mg/day due to risk of toxicity. Alternatives for atrial fibrillation: beta-blockers
Long acting sulfonylureas e.g., glyburide, chlorpropamide	Can cause severe prolonged hypoglycemia. Alternatives: metformin or other antidiabetic classes
Cold medications Most of these products contain antihistamines (e.g., diphenhydramine) and decongestants (e.g., phenylephrine, pseudoephedrine)	First generation antihistamines can cause central and peripheral anticholinergic adverse reactions as described above. Oral decongestants can increase blood pressure. Avoid

Legend
NSAID nonsteroidal anti-inflammatory drug

[1]

Dosage Recommendations for Hormone Therapy when Used at High Doses for Gender Transitioning

		HIV Drugs	Starting Dose	Average Dose	Maximum Dose
Estrogens	**Estradiol oral**	No predicted effect a	2 mg/day	4 mg/day	8 mg/day
		Inhibits metabolism b	1 mg/day	2 mg/day	4 mg/day
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Estradiol gel (preferred for >40 y and/or smokers)	No predicted effect a	0.75 mg bid	0.75 mg tid	1.5 mg tid
		Inhibits metabolism b	0.5 mg bid	0.5 mg tid	1 mg tid
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Estradiol patch (preferred for >40 y and/or smokers)	No predicted effect a	25 µg/day	50-100 µg/day	150 µg/day
		Inhibits metabolism b	25 µg/day*	37.5-75 µg/day	100 µg/day
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Conjugated estrogen†	No predicted effect a	1.25-2.5 mg/day	5 mg/day	10 mg/day
		Inhibits metabolism b	0.625-1.25 mg/day	2.5 mg/day	5 mg/day
		Induces metabolism c	Increase estradiol dosage as needed based on clinical effects and monitored hormone levels.		
	Ethinylestradiol	No predicted effect a	No interaction expected, but not recommended due to thrombotic risks		
		Inhibits metabolism b	Not recommended		
		Induces metabolism c	Not recommended		
Androgen Blockers ‡	**Spironolactone**	No predicted effect a	50 mg/day	150 mg/day	400 mg/day
		Inhibits metabolism d	No interaction expected. No dose adjustment required.		
		Induces metabolism e	No interaction expected. No dose adjustment required.		
	Finasteride	No predicted effect a	2.5 mg/day	2.5 mg/day	5 mg/day
		Inhibits metabolism d	Finasteride has a large safety margin. No dose adjustment required.		
		Induces metabolism e	Increase finasteride dosage as needed based on clinical effects and monitored hormone levels.		
	Cyproterone acetate	No predicted effect a	50 mg/day	150 mg/day	150 mg/day
		No predicted effect a	25 mg/day	75 mg/day	75 mg/day
		Induces metabolism e	Increase cyproterone dosage as needed based on clinical effects and monitored hormone levels.		
	Goserelin	No predicted effect a	3.6 mg/month	3.6 mg/month	3.6 mg/month
		Inhibits metabolism d	No interaction expected. No dose adjustment required.		
		Induces metabolism e	No interaction expected. No dose adjustment required.		
	Leuprorelin acetate	No predicted effect a	3.75 mg/month	3.75 mg/month	3.75 mg/month
		Inhibits metabolism d	No interaction expected. No dose adjustment required.		
		Induces metabolism e	No interaction expected. No dose adjustment required.		
	Triptorelin	No predicted effect a	3.75 mg/month	3.75 mg/month	3.75 mg/month
		Inhibits metabolism d	No interaction expected. No dose adjustment required.		
		Induces metabolism e	No interaction expected. No dose adjustment required.		
Androgens	**Testosterone topical gel 1%**	No predicted effect a	12.5-25 mg in the morning	50 mg in the morning	100 mg in the morning
		Inhibits metabolism d	12.5-25 mg in the morning	25-50 mg in the morning	50-100 mg in the morning
		Induces metabolism e	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.		
	Testosterone enanthate or cypionate	No predicted effect a	Not applicable	50-100 mg/week	Not applicable
		Inhibits metabolism d	Not applicable	25-50 mg/week	Not applicable
		Induces metabolism e	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.		
	Testosterone undecanoate	No predicted effect a	Not applicable	750 mg IM, repeat after 4 weeks and then every 10 weeks	Not applicable
		Inhibits metabolism d	Not applicable	375-500 mg IM, repeat after 4 weeks and then every 10 weeks	Not applicable
		Induces metabolism e	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.		
	Testosterone mixed esters	No predicted effect a	Not applicable	250 mg/2-3 weeks	Not applicable
		Inhibits metabolism d	Not applicable	125 mg/2-3 weeks	Not applicable
		Induces metabolism e	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.		

Comments

a ARVs with **no predicted effect**: DOR, RPV, MVC, BIC, DTG, RAL, ABC, FTC, 3TC, TAF, TDF, ZDV

b ARVs **predicted to inhibit estrogen** metabolism: ATV alone, ATV/c, DRV/c, EVG/c

c ARVs **predicted to induce estrogen** metabolism: ATV/r, DRV/r, LPV/r, EFV, ETV, NVP

d ARVs **predicted to inhibit** androgen blocker and androgen metabolism: ATV alone, ATV/c, DRV/c, EVG/c, ATV/r, DRV/r, LPV/r

e ARVs **predicted to induce** androgen blocker and androgen metabolism: EFV, ETV, NVP

* Matrix type transdermal patch can be cut in order to reduce the amount of hormone delivered/day

† Conjugated estrogen is associated with high thromboembolic risk and therefore should be avoided

‡ Androgen deprivation treatment may prolong the QT interval. Caution should be taken when using with ARVs that can potentially prolong the QT interval (i.e., ATV alone, ATV/r, ATV/c, LPV/r, RPV)

Recommendations for dose changes

- Dose changes in presence of inhibitors of estrogen metabolism are based on the assumption that the magnitude of the DDI is expected to be less pronounced for transdermal or topical applications than for oral drug administration as the first-pass metabolism is avoided
- Dose changes in presence of inhibitors of testosterone metabolism are based on the assumption that the magnitude of the DDI is expected to be less pronounced for topical and intramuscular applications than for oral drug administration as the first-pass metabolism is avoided [13] [14] [15] [16]

Part IV Prevention and Management of Co-morbidities in PLWH

Successful management of PLWH goes beyond provision of effective ART, with increasing focus attributed to the appropriate management of co-morbidities in order to ensure the best outcomes for PLWH. Recognised co-morbidities that disproportionately affect PLWH include cardiovascular, pulmonary, hepatic, metabolic, neoplastic, renal, bone, central nervous system disorders as well as sexual dysfunction. Many of these conditions significantly impact populations as they grow older. Recognising that older persons comprise a significant proportion of many populations living with HIV, the current version of the Guidelines suggests HIV-specific age cut-offs for screening for many of these co-morbidities as well as the introduction of a new section offering guidance on screening for frailty in older PLWH.

Potential contributors to co-morbidity pathogenesis include a higher prevalence of recognised risk factors, potential toxicities from ART-exposure, and HIV infection (or co-infections with CMV and HCV) contributing to immune dysfunction/dysregulation, chronic immune activation and inflammation. Taking this into consideration, particular focus should be paid to cessation of smoking, which contributes to many of the co-morbidities described.

Health care professionals other than HIV specialists, who are involved in the care of PLWH and who are not familiar with the use of ART, should consult their HIV specialist colleagues before introducing or modifying any treatments for co-morbidities. As intervals between visits to HIV clinics are increasingly extended, PLWH may need more frequent review by their primary care doctor and we would encourage establishment of formal shared-care arrangements to optimise management of co-morbidities and prevent unwanted drug-drug interactions.

Conversely, many HIV doctors 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.

In particular, as individuals with treated HIV age, some individuals may experience multiple co-morbidities, which may contribute to 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 PLWH. Suggesting for this approach are included in this version of the Guidelines. Areas that require further exploration include how co-morbidities impact on overall quality of life and appropriate approaches to mitigate this, as well as the impact of COVID-19 pandemic on the overall treatment and management of PLWH. These issues will be a focus of the Guidelines panel going forward.

Depending on future clinical research findings, these recommendations will be regularly updated as required. The online versions 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 PLWH 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 or INSTIs • EFV: ↓ up to 50% (B) and 70% (N) • ETV: ↓ 25% (B) • 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 • EVG/c, ↑ 35-42% (B&N) (BIC, DTG, RAL, RPV & LPV/r do not affect B & N metabolism)
	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 and persons with HPV-associated dysplasia[ii]	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	HIV-positive women > 21 years	PAP smear or liquid based cervical cytology test	↓ Cervical cancer mortality	1-3 years	HPV genotype testing may aid PAP/liquid based cervical screening
Colorectal cancer	Persons 50-80 years with a life expectancy > 10 years	Faecal occult blood test annually or sigmoidoscopy every 5 years or colonoscopy every 10 years	↓ Colorectal cancer mortality	1-3 years	
HepatoCellular Carcinoma (HCC)	Persons with HCV and HBV with cirrhosis & in HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines* see pages pages 7, 71 and 95[iii]	Ultrasound (and alpha-foetoprotein)	Earlier diagnosis allowing for improved ability for surgical eradication	Every 6 months	* Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH
Prostate cancer	Men > 50 years with a life expectancy >10 years	PSA[iv]	Use of PSA is controversial	2-4 years	Pros: ↑ early diagnosis and modest ↓ prostate cancer specific mortality. Cons: overtreatment, adverse effects of treatment on quality of life

i Screening recommendations derived from the general population.
These screenings should preferably be done as part of national general population-screening programmes.
Careful examination of skin should be performed regularly to detect cancers such as Kaposi's sarcoma, basal cell carcinoma and malignant melanoma

ii Includes Anal Intraepithelial Neoplasia (AIN), Penile Intraepithelial Neoplasia (PIN), Cervical Intraepithelial Neoplasia (CIN), Vaginal Intraepithelial Neoplasia (VAIN) and Vulval Intraepithelial Neoplasia (VIN)

iii HCC screening is indicated in all cirrhotic HBV or HCV co-infected persons (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in persons with F3 fibrosis is uncertain, surveillance may be con-sidered based on an individual risk assessment (https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/). In HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines. Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH, see pages 71 and 95

iv Whilst prostate cancer screening with PSA can reduce prostate cancer specific mortality, the absolute risk reduction is very small. Given limitations in the design and reporting of the randomized trials, there remain important concerns that the benefits of screening are outweighed by the potential harms to quality of life, including the substantial risks for over-diagnosis and treatment complications.
See online video lectures Epidemiology of cancers and HIV-Part 1, Epidemiology of cancers and HIV-Part 2, Clinical Management of cancers and HIV-Part 1 and Clinical Management of cancers and HIV-Part 2 from the EACS online course Clinical Management of HIV

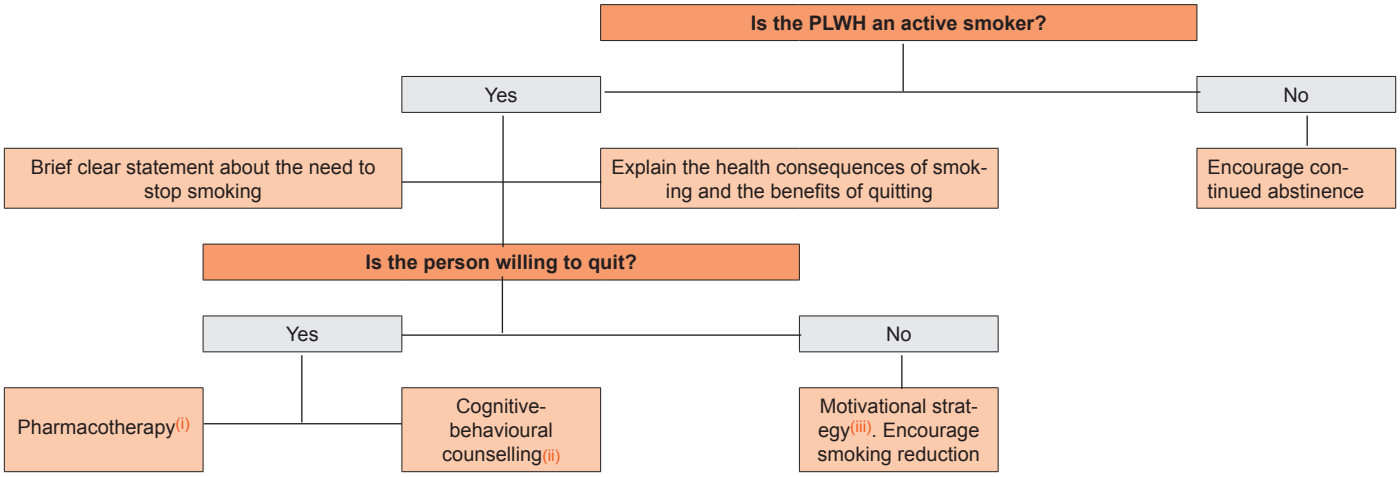
Lifestyle Interventions[i]

Dietary counselling	• Dietary intervention should not interfere with the dietary requirements necessary for appropriate absorption of ART drugs (e.g. maintaining sufficient calorie intake for RPV). • 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. Adequate intakes of sodium in adults have been estimated mostly around 1.5 g/day (corresponding to 3.8 g salt/day[ii] • 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, see NAFLD, 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
ii [1]

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:

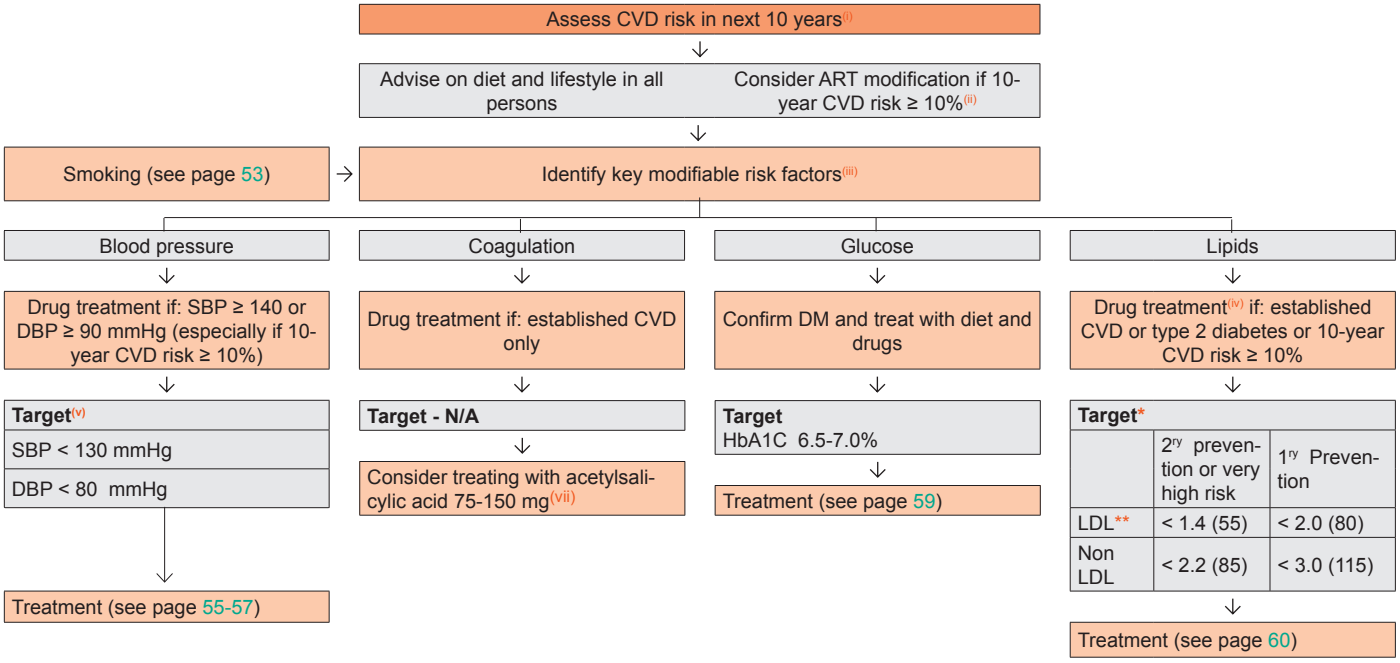


Adapted from [2] and [3]
i Pharmacotherapy: Nicotine replacement therapy: nicotine substitution (patch, chewing gum, spray), varenicline and bupropion are approved by the EMA. Bupropion is contraindicated with epilepsy and varenicline may induce depression. Bupropion may interact with PIs and NNRTIs, 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 PLWH. 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 PLWH 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 PLWH is not willing/ready enough to quit smoking

At this moment, neither EMA nor FDA approve e-cigarettes as a smoking cessation agent. In PLWH there is no data on long term outcomes and it is not possible to add any more specific recommendations. EACS follows the statement issued by the CDC in 2018 [4]
- E-cigarettes have the potential to benefit adult smokers who are not pregnant if used as a complete substitute for regular cigarettes and other smoked tobacco products
- E-cigarettes are not safe for people who do not currently use tobacco products
- E-cigarettes have the potential to benefit some people and harm others, however, whether e-cigarettes are effective for quitting smoking has not been definitively established
- E-cigarettes should not be recommended in persons who never smoked or used other tobacco products or e-cigarettes.
- E-cigarettes may have a potential benefit if used as a complete substitution for tobacco, but are not considered safe if not currently using tobacco products

Prevention of Cardiovascular Disease (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



* Fasting or non-fasting samples may be used
** and ≥ 50% reduction from baseline

i Use the Framingham equation or whatever system local National Guidance recommends; a risk equation developed from HIV populations is available: see https://www.chip.dk/Tools-Standards/Clinical-risk-scores. This assessment and the associated considerations outlined in this figure should be repeated annually in all persons under care, see page 7, 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 and/or lower CVD risks, see page 11
(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 ESC/EAC Guidelines for the Management of Dyslipidaemias EHJ September 2019 [5]

v Age 65+: Target 130-139 SBP
Age 18-65: 120-129 SBP

vi 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 measured or calculated because of high triglyceride levels, the non-HDL-c (TC minus HDL-c) target should be used. Target levels for TG are usually < 1.7 (65) but the independent contribution from TG to CVD risk is uncertain

vii In acute settings (Post-MI, ischemic, stroke or stent insertion) dual anticogulation is recommended for up to 1 year

See online video lecture CVD, CKD, Endocrinology from the EACS online course Clinical Management of HIV

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	• Lifestyle changes[i] • No BP drug intervention	• Lifestyle changes[i] for several months • Then add BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] for several weeks • Then add BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • Immediate BP drugs targeting < 130/80[ii]
1-2 risk factors	• Lifestyle changes[i] • No BP drug intervention	• Lifestyle changes[i] for several weeks • Then add BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] for several weeks • Then add BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • Immediate BP drugs targeting < 130/80[ii]
≥ 3 risk factors	• Lifestyle changes[i] • i.e. no BP drug intervention	• Lifestyle changes[i] for several weeks • Then add BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • Immediate BP drugs targeting < 130/80[ii]
Organ damage, CKD stage 3 or diabetes	• Lifestyle changes[i] • Consider blood pressure drugs targeting < 130/80[ii]	• Lifestyle changes[i] • BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • Immediate BP drugs targeting < 130/80[ii]
Symptomatic CVD, CKD stage ≥ 4 or diabetes with organ damage/risk factors	• Lifestyle changes[i] • Consider blood pressure drugs targeting < 130/80[ii]	• Lifestyle changes[i] • BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • BP drugs targeting < 130/80[ii]	• Lifestyle changes[i] • Immediate BP drugs targeting < 130/80[ii]

BP blood pressure
DBP diastolic blood pressure
SBP systolic blood pressure

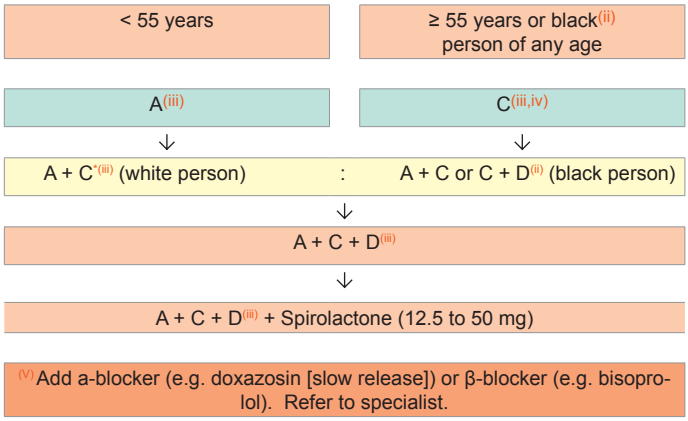
Repeated blood pressure measurements should be used for stratification

i Recommended lifestyle interventions, see page 53
ii Age 18-65: 120-129
Age 65+: Target 130-139

Table adapted from [6] and 2018 ESC/ESH guidelines for the management of arterial hypertension [7]

Hypertension: Drug Sequencing Management

Choosing drugs[i] for persons newly diagnosed with hypertension



A ACE inhibitor (e.g. perindopril, lisinopril or ramipril) or 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 as a first choice. This excludes thiazides (e.g. hydrochlorothiazide (HCTZ), bendroflumethiazide etc.). However, if thiazide-type diuretics are not available low-dose thiazides may be used as a treatment alternative

i Two antihypertensive drugs (ideally administered as single tablet combinations, where available) are increasingly recommended both as first-line therapy (A + C or A + D) and second-line therapy particularly if the initial pre-treatment SBP is ≥ 160 mmHg

ii Black persons are those of African or Caribbean descent, and not mixed race, Asian or Chinese persons. Either A+C or C+D can be used for this

iii Wait 4-6 weeks to assess whether target, see page xx, is achieved; if not, go to next step

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

v Requirement of 4-5 drugs to manage hypertension needs specialist advice

* Use A+D if C not tolerated

Drug-drug Interactions between Antihypertensives and ARVs

Antihypertensives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
ACE inhibitors	captopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eprosartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔
	losartan	↔	↓a	↔	↓a	↓a	↔	↑b	↑b	↔	↔	↔	↔	↔	↓a	↔	↔	↔	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↑c	↔c	↑	↔	↔c	↔	↔	↔	↔	↔	↔	↑	↑	↑	↔	↔	↔	↑ E	↔	↔
	bisoprolol	↑c	↑c	↑	↑	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	carvedilol	↑c	↑↓c	↑	↑↓	↑↓c	↔	↑↓	↑↓	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	metoprolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	propranolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Calcium channel blockers	amlodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	diltiazem	↑d	↑d	↑	↑	↑e	E	↓69%	↓E	↓	E	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	felodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	lacidipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	nicardipine	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	E	E	↔	↔	↑	↔	↔	↔	↔	↔	↔
	nifedipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	nisoldipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	verapamil	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	E	E	E	↔	↑	↔	↔	↔	↔	E	E
Diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↑ E	↔	↔
	bendroflume-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chlortalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E
	hydrochloro-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indapamide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	torasemide	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔
Others	doxazosin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔
	sacubitril	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	E	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑
	spironolactone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

Interactions with ZDV
No clinically relevant interactions expected with ZDV and anti-hypertensives

Interactions with ibalizumab
none

Comments

a	Parent drug concentrations decreased but active metabolite increased
b	Parent drug concentrations increased but active metabolite decreased
c	Risk of PR interval prolongation
d	ECG monitoring recommended
e	Use with caution as both LPV and calcium channel blockers prolong the PR interval. Clinical monitoring is recommended

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

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

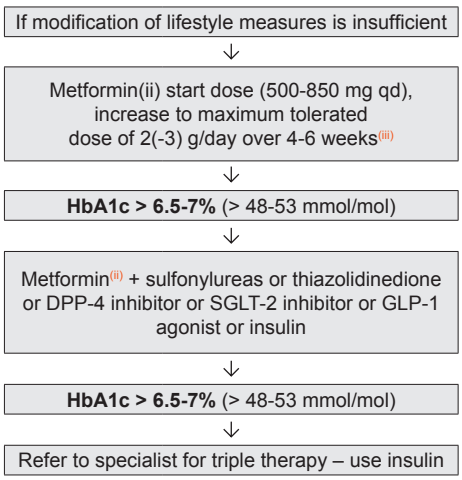
Type 2 Diabetes: Diagnosis

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, [8] and [9]
ii An abnormal finding should be repeated before confirming the diagnosis
iii Recommended in PLWH 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 PLWH, 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 60, and blood pressure < 130/80 mmHg, see page 55
- Acetylsalicylic acid (75-150 mg qd) should be considered in those with elevated underlying CVD risk, see page 54
- Nephropathy, polyneuropathy and retinopathy screening and podiatry review 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.
No data for any oral anti-diabetic agents in terms of CVD prevention in PLWH. Incretins (DDP-4 inhibitors [e.g. linagliptin, saxagliptin (reduce dose when given with a booster), sitagliptin and vildagliptin], GLP-1 agonists [liraglutide, exenatide], and SGLT-2 inhibitors [e.g. dapagliflozin, canagliflozin, empagliflozin] have not been evaluated in PLWH, but some (e.g empagliflozin, canaglifozin, dapaglifozin, liraglutide) have shown to reduce mortality from CVD; choice of drugs dependent on a variety of individual- & disease-specific factors; 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 PLWH with long-standing type 2 diabetes and evidence of CVD

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

Dyslipidaemia

Principles: Higher LDL-c levels increase risk of CVD and 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 (increase) 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 medicine, see page 54. 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. In high risk PLWH with statin intolerance, drug-drug interactions between high intensity statins and ART, or unable to reach LDL-c goals on statins and/or ezetimibe, a PCSK9 inhibitor should be considered

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		Contraindicated	
Intestinal cholesterol absorption inhibitor↓[i,viii]	ezetimibe[iv]	10 mg qd	Gastrointestinal symptoms	No known drug-drug interactions with ART	
PCSK9-inhibitor[x]	evolocumab	140 mg 2 weekly or 420 mg monthly	Nil	No drug-drug interactions anticipated	

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 54. In PLWH where LDL-c targets are difficult to achieve, consult/refer to specialist
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 PLWH 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 reducing immune activation and arterial inflammation, fewer drug-drug interactions, more HDL increase and less adverse glucose effect than other statins

x Data in PLWH available for evolocumab [10]

Bone Disease: Screening and Diagnosis

Condition	Characteristics	Risk factors	Diagnostic tests
Osteoporosis • Postmenopausal women and men age ≥ 50 years with BMD T-score ≤ -2.5 at hip, femur or lumbar spine • Premenopausal women and men age < 50 years with BMD Z-score ≤ -2 and fragility fracture	• Reduced bone mass • Increased incidence of osteoporosis and fractures in PLWH • Asymptomatic until fractures occur • Aetiology multifactorial • Loss of BMD observed with ART initiation (mainly during 1st year) • Greater loss of BMD with initiation of certain ARVs[i]	Consider classic risk factors[ii] and estimate fracture risk using FRAX in people > 40 years Consider DXA in any person with ≥ 1 risk of:[iii] 1. Postmenopausal women 2. Men ≥ 50 years 3. High risk for falls[iv] 4. Those between 40-50 years with high fracture risk (> 20% 10-year major osteoporotic fracture risk based on FRAX assessment without DXA) 5. History of low impact fracture 6. Clinical hypogonadism (symptomatic, see Sexual Dysfunction) 7. Oral glucocorticoid use (minimum 5 mg/d prednisone equivalent for > 3 months)	**DXA scan** Preferably perform DXA in those with previous risk factors prior to ART initiation Add DXA result to FRAX® to refine fracture risk prediction (http://www.shef.ac.uk/FRAX) • May underestimate risk in PLWH • Consider using HIV as a cause of secondary osteoporosis[v] **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 • Associated with vitamin D deficiency • 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 PLWH at presentation. If deficient or insufficient, check PTH levels and consider vitamin D replacement if clinically indicated, see page 62 ng/mL / nmol/L Deficiency: < 10 / < 25 Insufficiency: < 20 / < 50 **X-rays and bone biopsy can also help in the diagnosis**
Osteonecrosis	• Infarct of epiphyseal plate of long bones resulting in acute bone pain • Rare but increased prevalence in PLWH	**Risk factors:** • Low CD4 count • Glucocorticoid exposure • IVDU • Alcohol • Blood coagulation disorders	**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 is associated with less bone loss than TDF
Consider replacing TDF** by non-tenofovir drug or TAF*** if:
- Osteoporosis / progressive bone loss
- History of fragility fracture
- FRAX score for major osteoporotic fracture > 10%

* There is limited data on use of PIs and changes after their replacement.
** Expert opinion, pending clinical data
*** There is limited data on use of TAF with eGFR ≤ 30 mL/min and longer term outcomes are unknown

ii 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 trauma fracture, alcohol excess (> 3 units/day), glucocorticoid 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 3; no need for re-screening with DXA in risk groups 4 and 5 unless risk factors change and only rescreen group 6 if glucocorticoid use ongoing

iv Falls Risk Assessment Tool (FRAT), see https://www2.health.vic.gov.au/about/publications/policiesandguidelines/falls-risk-assessment-tool

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, vitamin D deficiency, hyperthyroidism, malabsorption, hypogonadism or 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 insufficiency prevalent in both HIV-positive and HIV-negative 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 vitamin D is recommended for PLWH with both vitamin D insufficiency[vi] and one of the following: • 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. However, causal association not proven for all outcomes. 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 66. 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 PLWH 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 PLWH

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 PLWH

Reducing risk of fractures **Subjects at high risk of fractures:** -Frail or sarcopenic subjects -Low BMD	• 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] • Consider screening by DXA scan[iii] • Rule out causes of secondary osteoporosis if BMD low • Where appropriate, screen for osteoporosis[iii] and refer to national/regional guidelines on treatment of osteoporosis – If no guidelines available, consider bisphosphonate[iv] – Treatment based on FRAX score (see section on Bone Disease Screening and Diagnosis). – Ensure adequate calcium and vitamin D intake – No significant interactions between bisphosphonates and antiretrovirals – If diagnosed with osteoporosis and requiring therapy, optimize vitamin D status and consider using ART that preserves or improves BMD[v] • Optimal management of frailty and sarcopenia includes optimising nutrition, exercise (aerobic and resistance training) and hormone replacement in cases of deficiency, see section on frailty, page 92 • 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 page 62 for diagnosis and management of vitamin D deficiency https://www2.health.vic.gov.au/about/publications/policiesandguidelines/falls-risk-assessment-tool

ii See page 62 for diagnosis and management of vitamin D deficiency

iii See page 61 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. Switch away from TDF can lead to increases in BMD. Consider relative risk/benefit of using these agents in persons with high fracture risk. Vitamin D supplementation can reduce bone loss with ART initiation

Kidney Disease: Definition, Diagnosis and Management

Diagnosis of kidney disease

		eGFR[i]			
		> 60 mL/min	**> 60 mL/min, but accelerated decline of eGFR***	**> 30 - ≤ 60 mL/min**	**≤ 30 mL/min**
Proteinuria (mg/mmol)[ii]	UA/C[iii] < 3	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
	UA/C[iii] 3-30	• 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			
	UA/C[iii] > 30				

* Defined as decrease in eGFR of 5 mL/min per year for ≥3 consecutive years or confirmed 25% eGFR decline from baseline

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 **Consider replacing TDF** by non-tenofovir drug or TAF*** if:** • UP/C 15-50 mg/mmol (see tubulopathy section) • eGFR > 60 mL/min, but decrease in eGFR by 5 mL/min per year for at least 3 consecutive years or confirmed 25% eGFR decline from baseline • co-morbidities with a high risk of CKD (i.e. diabetes and hypertension) • body weight < 60 kg • use of a PI/r as a third agent **Replace TDF** by non-tenofovir drug or TAF*** if:** • eGFR ≤ 60 mL/min • UP/C > 50 mg/mmol • nephrotoxic comedication • previous TDF toxicity (proximal renal tubulopathy) ** Expert opinion pending clinical data ***There are limited data on use of TAF with eGFR ≤ 30 mL/min, and longer term outcomes are unknown
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 https://www.chip.dk/Tools-Standards/Clinical-risk-scores.
Definition CKD: eGFR ≤ 60 mL/min for ≥ 3 months (see https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf. If not previously known to have CKD, confirm pathological eGFR within 2 weeks. Use of DTG, RPV, COBI and RTV boosted PIs is associated with an increase in serum creatinine/reduction of eGFR (10-15 mL/min/1.73m²) 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 albumin/creatinine (UA/C) to screen for glomerular disease or protein/creatinine (UP/C) to screen for both glomerular and tubular disease, see iii and ARV-nephrotoxicity. Proteinuria is defined as persistent if confirmed on ≥ 2 occasions > 2-3 weeks apart

iii UA/C largely detects glomerular disease and can be used for screening for HIV-associated renal disease and in diabetics but is not appropriate for screening for tubular proteinuria secondary to drug nephrotoxicity (e.g. TDF), where UP/C should be used (see Indications and Tests for Proximal Renal Tubulopathy and ARV-nephrotoxicity). KDIGO screening values for UA/C are: < 3, 3-30 and > 30 mg/mmoL and for UP/C: < 15, 15-50, > 50 mg/mmol [11], [12]. UA/C and UP/C ratio are calculated as urine protein albumin (or 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 8

v See Dose Adjustment of ARVs for Impaired Renal Function

vi Joint management with a nephrologist

vii HIVAN suspected if black ethnicity & UAP/C > 30 mg/mmol & no haematuria

viii See page 60

ix See page 58-59

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 [13], [14]

See online video lecture CVD, CKD and Endocrinology from the EACS online course Clinical Management of HIV

ARV-associated Nephrotoxicity

Renal abnormality*	ARV	Management
Proximal tubulopathy with any combination of: 1. Proteinuria: urine dipstick ≥ 1, or confirmed increase in UP/C > 15 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 4. Glucosuria in non-diabetics	**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 **Replace TDF by non-tenofovir drug or TAF*** if:** • Documented tubular proteinuria and/or glucosuria • 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. Leukocyturia 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. Leukocyte 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, see page 64 **Consider stopping ARVs with potential nephrotoxicity if:** • Progressive decline in eGFR and no other cause(v)

* Use of DTG, RPV, COBI and PI/r is associated with an increase in serum creatinine/reduction of eGFR (10-15 mL/min/1.73m^2) 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 and certain PIs suggest potential reversion of renal toxicity, however, long-term experience with TAF is lacking

*** Particularly if eGFR > 30 mL/min, as there are limited data to on use of TAF with eGFR ≤ 30 mL /min, and longer term outcomes are unknown

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 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 https://www.chip.dk/Tools-Standards/Clinical-risk-scores

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 [13], [14]

Indications and Tests for Proximal Renal Tubulopathy (PRT)

Indications for proximal renal tubulopathy tests	Proximal renal tubulopathy tests[iv], including	Replace TDF by non-tenofovir drug or TAF* alternative drug 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 https://www.chip.dk/Tools-Standards/Clinical-risk-scores

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

* Particularly if eGFR > 30 mL/min, as there are limited data on use of TAF with eGFR ≤ 30 mL/min

Dose Adjustment of ARVs for Impaired Renal Function

	eGFR[ii] (mL/min)				Haemodialysis[iii]
	≥ 50	30-49	10-29	< 10	
NRTIs					
Individual agents					
ABC[iii]	300 mg q12h or 600 mg q24h	No dose adjustment required			
FTC[v]	200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h[iv]
3TC[v]	300 mg q24h	150 mg q24h	100 mg q24h[vi]	50-25 mg q24h[vi]	50-25 mg q24h[iv, vi]
TDF[vii]	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]
TAF[ix,x]	25[xi] mg q24h			no data	limited data
ZDV	300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8hi[iv]
Combinations					
ABC[iii]**/3TC**[v]	600/300 mg q24h	Use individual drugs			
ZDV/3TC	300/150 mg q12h				
ABC/3TC/ZDV	300/150/300 mg q12h				
TAF[ix]**/FTC**[v]	25[xi]/200 mg q24h		Use individual drugs[xv]		
TDF[vii]**/FTC**[v]	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				
NVP	200 mg q12h				
RPV	25 mg q24h				
TAF[ix]**/FTC**[v]**/RPV**	25[xi]/200/25 mg q24h		Use individual drugs[xv]		
TDF[vii]**/FTC**[v]**/RPV**	300[viii]/200/25 mg q24h	Use individual drugs			
DOR	100 mg q24h	No dose adjustment required; < 10: no PK data			
TDF[vii]**/3TC**[v]**/DOR**	300[viii]/300/100 mg q24h	Use individual drugs			
PIs[vii]					
ATV/c	300/150 mg q24h	No dose adjustment required[xiii]			
ATV/r	300/100 mg q24h	No dose adjustment required[xiii]			
DRV/r	800/100 mg q24h 600/100 mg q12h	No dose adjustment required[xiii]			
DRV/c	800/150 mg q24h	No dose adjustment required[xiii]			
TAF[ix]**/FTC**[v]**/DRV/c**	10/200/800/150 mg q24h	Use individual drugs			
LPV/r	400/100 mg q12h	No dose adjustment required[xiii]			
Other ART					
RAL	1 x 400 mg tablet q12h or 2 x 600 mg tablets q24h	No dose adjustment required[xiii]			
DTG	50 mg q24h	No dose adjustment required[xiii]			
3TC[v]**/DTG**	300/50 mg q24h	Use individual drugs			
ABC[iii]**/3TC**[v]**/DTG**	600/300/50 mg q24h	Use individual drugs[xvi]			
RPV/DTG	25/50 mg q24h	No dose adjustment required[xiii]			
TAF[ix]**/FTC**[v]**/BIC**	25/200/50 mg q24h		Not recommended (no PK data for BIC for eGFR < 15 mL/min)		
TAF[ix]**/FTC**[v]**/EVG/c**	10/200/150/150 mg q24h		Not recommended[xii]		
TDF[vii]**/FTC**[v]**/EVG/c**	300[viii]/200/150/150 mg q24h Do not initiate if eGFR < 70 mL/min	Not recommended			
MVC: co-administered without CYP3A4 inhibitors[xiv]	300 mg q12h	No dose adjustment required[xiii]			
MVC: co-administered with CYP3A4 inhibitors[xiv]	If eGFR < 80 mL/min 150 mg q24h[xiv]				
Ibalizumab	2000 mg loading dose followed by 800 mg every 2 weeks. No dose adjustment required				

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 https:// www.chip.dk/Tools-Standards/Clinical-risk-scores

ii For Continuous Ambulatory Peritoneal Dialysis (CAPD) dosing for hemodialysis may be used. However, elimination of drugs in CAPD varies depending on CAPD conditions. TDM therefore is recommended

iii Potential cardiovascular risk of ABC may increase cardiovascular risk associated with renal failure

iv After dialysis

v Large bodily accumulation in impaired renal function. Although affinity for mitochondrial DNA polymerase is low and clinical toxicity in patients with severe renal impairment is rare, long-term mitochondrial toxicity is possible and must be monitored (polyneuropathy, pancreatitis, lactate acidosis, lipodystrophy, metabolic disturbances)

vi 150 mg loading dose

vii 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

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 Limited clinical data documented limited accumulation in hemodialysis. However, there is no long-term data on residual kidney function and bone toxicity. No data for eGFR < 10 mL/min but no dialysis

x Only licenced for hepatitis B

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

xii TAF/FTC/EVG/c as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, TAF/FTC/EVG/c may be used with caution if the potential benefits are considered to outweigh potential risks. One clinlical study has demontrated safety of TAF/FTC/EVG/c for PLWH on chronic dialysis [30]

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

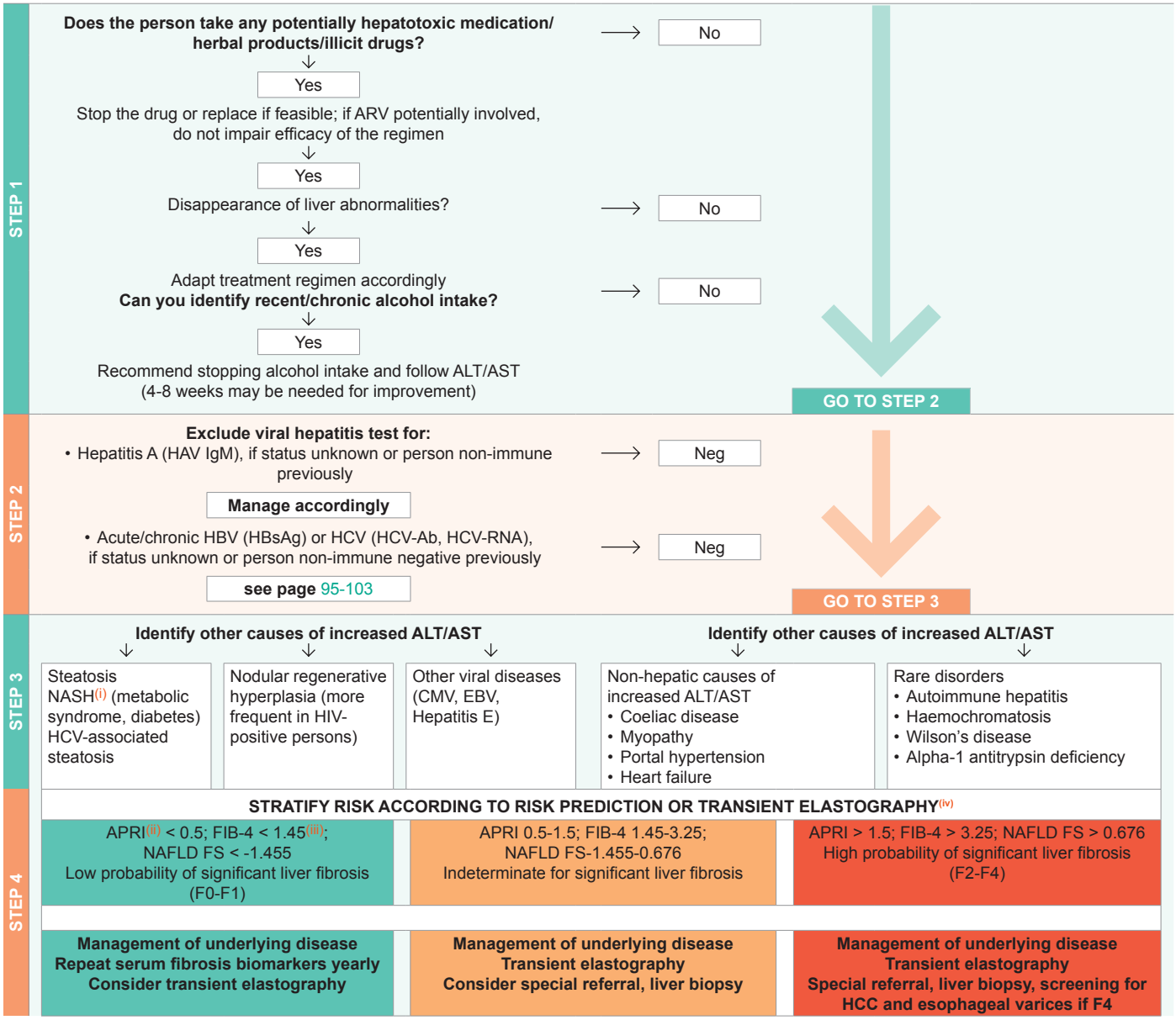
xiv See summary of product characteristics for specific recommendations; use with caution if eGFR ≤ 30 mL/min10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)

xv TAF/FTC and TAF/FTC/RPV single tablet regimens should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, these combinations may be used with caution if the potential benefits are considered to outweigh potential risks

xvi ABC/3TC/DTG as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic haemodialysis. A recent case series study found that use of ABC/3TC/DTG appears to be a safe and effective option in PLWH on chronic dialysis [31]

Work-up and Management of PLWH with Increased ALT/AST

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



See pages 70-71 and 73-74

i Non-Alcoholic Steatohepatitis, see NAFLD
ii APRI, AST to Platelet Ratio Index = (AST in IU/L) / (AST Upper Limit of Normal in IU/L)/ (Platelets in 10^9/L)
iii FIB-4 = Age ([years] x AST [U/L])/([platelet [10^9/L]) x ALT [U/L]). For NAFLD aetiology FIB4 cut offs are as follows: < 1.30 (low risk), >2.67 high risk. FIB4 cut off < 2.0 should be considered in persons aged > 65 years
iv [15]

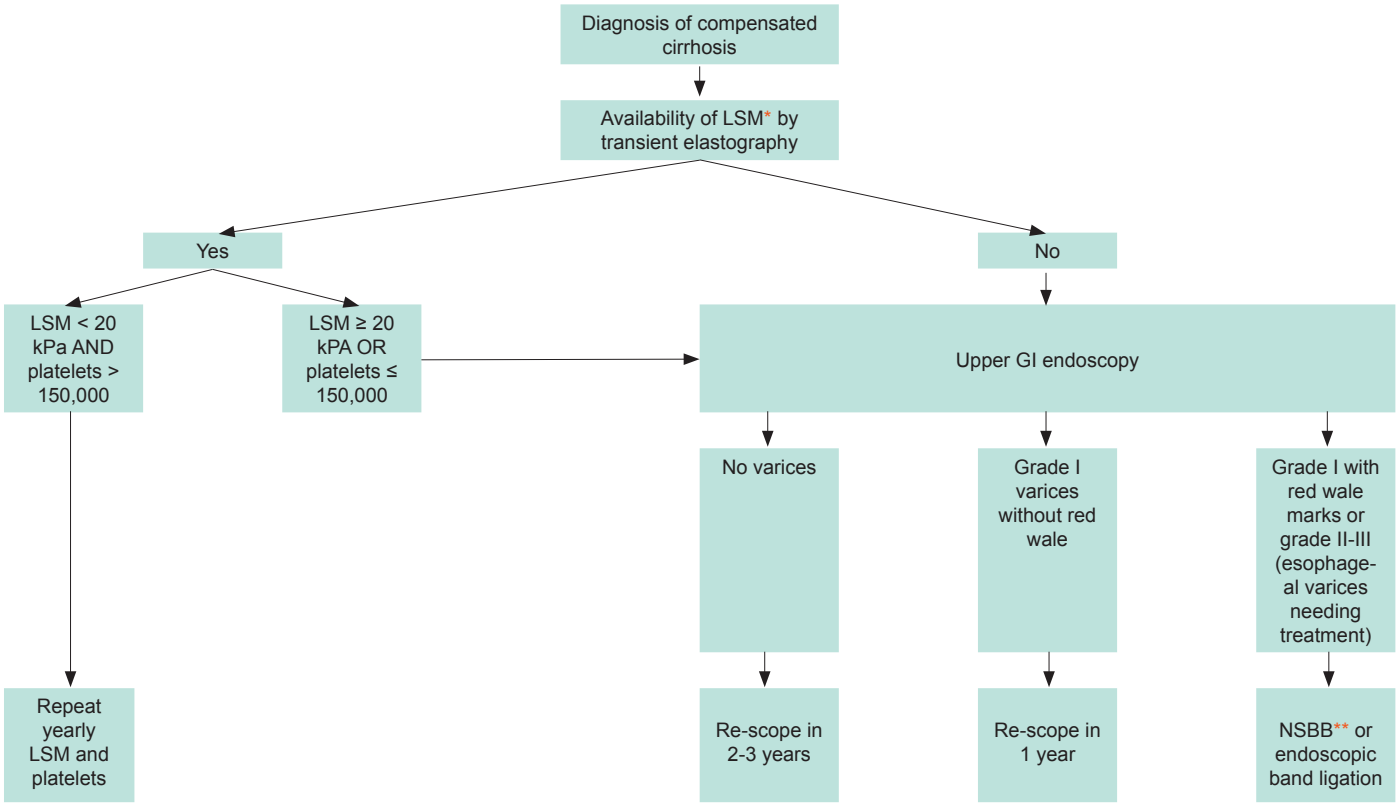
Liver Cirrhosis: Classification and Surveillance

Child-Pugh classification of the severity of cirrhosis

	Points[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



Based on Baveno VI consensus (EASL) and guideline on portal hypertension (AASLD) [16], [17]
* LSM, liver stiffness measurement;
** NSBB, non-selective beta-blocker e.g. propranolol 80-160 mg/day or carvedilol 6.25-50 mg/day
Persons with compensated cirrhosis without varices on screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence)
Hepatic Venous Pressure Gradient (HVPG) when available, allows a direct measure of portal hypertension and prognostic stratification of persons with compensated cirrhosis
HVPG<6 mmHg: no portal hypertension
HVPG 6-9 mmHg: portal hypertension non clinically significant
HVPG≥10 mmHg: clinically significant portal hypertension
In primary and secondary prophylaxis for variceal bleeding HVPG measurement allows to monitor efficacy of beta-blockers

Liver Cirrhosis: Management

Management of PLWH 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 demyelination 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 PLWH 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 PLWH 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 contra-indicated but must be used with caution in persons with pre-existing hepatic encephalopathy

Screening for HepatoCellular Carcinoma (HCC)

- HCC screening is indicated in all cirrhotic HBV or HCV co-infected PLWH (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in PLWH with F3 fibrosis is uncertain, surveillance may be considered based on an individ-ual risk assessment https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/
- In HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines. Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH; see pages 8, 52 and 95. Table on fibrosis cut-offs, page 102
- Ultrasound (US), with or without AFP, every 6 months. Alpha-foetoprotein (AFP) should not be used alone.AFP is a suboptimal surveillance tool because of low sensitivity and specificity

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
- NASH cirrhosis[ii]
- HCC

See Solid Organ Transplantation (SOT) in PLWH

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/

ii Particularly with metabolic decompensations

Non-Alcoholic Fatty Liver Disease (NAFLD)

The prevalence of NAFLD is higher in PLWH (30 - 40% in the US) than in the general population [18]. Nearly half of the PLWH who undergo evaluation for unexplained liver test abnormalities are found to have NAFLD. The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption ≥ 30 g for men and ≥ 20 g for women

Spectrum of NAFLD

Often associated with components of the metabolic syndrome:

NAFLD is defined as:
- hepatic steatosis involving > 5% of hepatocytes
- often associated with components of metabolic syndrome
- exclusion of both secondary causes and of alcoholic fatty liver disease (defined as a daily alcohol consumption ≥ 30 g for men and ≥ 20 g for women)

Non-Alcoholic SteatoHepatitis (NASH)
- Early NASH: no or mild (F0-F1) fibrosis
- Fibrotic NASH: significant (≥ F2) or advanced (≥ F3, bridging) fibrosis
- NASH-cirrhosis (F4)
- HCC (can occur in the absence of cirrhosis and histological evidence of NASH)

Most common concurrent diseases
- AFLD-alcoholic fatty liver disease
- Drug-induced fatty liver disease
- HCV-associated fatty liver (GT 3)

Consideration on ARV drugs

- Consider use of lipid neutral regimens in individuals at risk of or with NAFLD

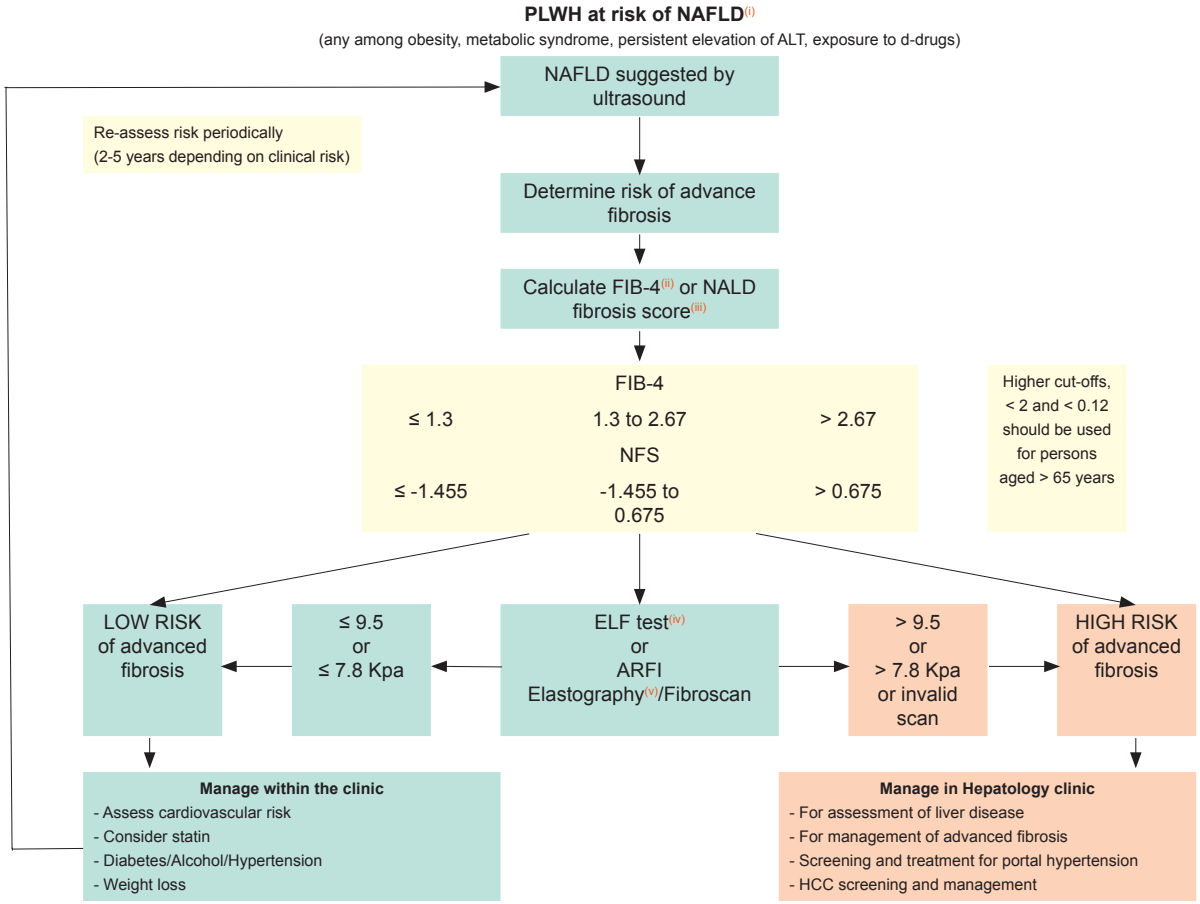
Diagnosis

- Ultrasound is the preferred first-line diagnostic procedure for imaging of NAFLD
- Whenever imaging tools are not available or feasible, serum biomarkers and scores are an acceptable alternative for the diagnosis
- Where available and in experienced centres, transient elastography with controlled attenuation parameter could be used to diagnose HIV-associated NAFLD, although no optimal cut-off has been established yet
- A quantitative estimation of liver fat can only be obtained by MRS as well as MRI-PDFF. This technique is of value in clinical trials and experimental studies, but is expensive and not recommended in the clinical setting.
- NASH has to be diagnosed by a liver biopsy showing steatosis, hepatocyte ballooning and lobular inflammation

Treatment of NAFLD

- Lifestyle modification and weight reduction is the cornerstone of treatment
- Dietary restriction **PLUS** Progressive increase in aerobic exercise/resistance training: Calorie restriction (500-1,000 /day) targeting 7-10% weight loss target in persons with central obesity and/or overweight; 150-200 min/week of moderate intensity aerobic physical activities in 3-5 sessions
- Pharmacotherapy should be reserved for individuals with NASH, particularly for those with significant fibrosis ≥ F2 and individuals with less severe disease, but at high risk of faster disease progression (i.e. with diabetes, metabolic syndrome, persistently increased ALT, high necroinflammation)
- Management and treatment of NASH should be discussed with hepatologists. Options with proven efficacy include pioglitazone, vitamin E and bariatric surgery, although no specific studies are available in the context of HIV infection
- Statins may be safely used but have demonstrated no impact on liver disease. The same is true for n-3 polyunsaturated fatty acids

Diagnostic Flow-chart to Assess and Monitor Disease Severity in Case of Suspected NAFLD and Metabolic Risk Factors



These recommendations are largely inspired by the EASL–EASD–EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease: European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity [19]

i NAFLD, Non-alcoholic fatty liver disease

ii FIB-4 = Age ([years] x AST [U/L]) / ([platelet [10^9/L]) x ALT [U/L])

iii NFS, Non-alcoholic fatty liver disease Fibrosis Score = -1.675 + 0.037 x age (years) + 0.094 x BMI (kg/m²) + 1.13 x impaired fasting glucose/diabetes mellitus(iv) (yes=1/no=0) + 0.99 x AST/ALT ratio-0.013 x platelet (x10^9)-0.66 x albumin(g/dL)

iv ELF™ test, Enhanced Liver Fibrosis Test is a blood test that provides an estimate of liver fibrosis severity by measuring Hyaluronic Acid (HA), Amino-terminal propeptide of type III procollagen (PIIINP), Tissue inhibitor of metalloproteinase 1 (TIMP-1)

v ARFI elastography, Acoustic Radiation Force Impulse

Diagnosis and Management of Hepatorenal Syndrome (HRS)

Diagnosis	Consider HRS in PLWH 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, see page 71). If person is on transplant list, MELD score should be updated daily and communicated to transplant centre, see Solid Organ Transplantation (SOT) in PLWH		
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: contraindicated
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: contraindicated
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
TDF/3TC/DOR	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
DOR	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data

PIs	
ATV	Child-Pugh Class A: no dose adjustment
	Child-Pugh Class B: 300 mg qd (unboosted)
	Child-Pugh Class C: not recommended
ATV/c	Child-Pugh Class A: no dosage adjustment
	Child-Pugh Class B or C: not recommended
COBI	Refer to recommendations for the primary PI
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
TAF/FTC/DRV/c	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: not recommended
LPV/r	No dosage recommendation; use with caution in persons with hepatic impairment
RTV	Refer to recommendations for the primary PI
FI	
ENF	No dosage adjustment
EI	
Ibalizumab	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
BIC	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
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
TAF/FTC/BIC	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data

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

Lipoatrophy and Obesity: Prevention and Management

Lipoatrophy	
Prevention • Avoid d4T and ZDV or pre-emptively switch. 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	**Management** • Modification of ART: Switch away from d4T or ZDV – Increase in total limb fat ~400-500 g/year (in the first two years) – Risk of toxicity from new drug, see Adverse Effects of ARVs & Drug Classes • Surgical intervention – Offered for cosmetic relief of (facial) lipoatrophy only

i See online video lecture CVD, CKD and Endocrinology from the EACS online course Clinical Management of HIV

Obesity

Definition:
Body mass index (BMI) > 30 kg/m^2
Also body fat > 25% (men) or > 33% (women) for persons with low muscle mass
Waist circumference is an indicator of abdominal fat and a useful predictor of cardiometabolic diseases. Cut-off points indicating higher cardiometabolic risks are > 88 cm for women and > 102 cm for men.Naturally, different ethnicities have different body builds and proportions. Asians have a naturally slimmer, petite frame and therefore the waist circumference cut off for Japanese, Chinese and South Asian people is lower than for Caucasians.
Visceral adipose tissue (VAT) area ≥ 130 cm^2 is a validated threshold for increased cardiometabolic risk
Consequences:
Not only cosmetic concern
Worse outcomes with surgery and actute infections (e.g. pneumonia, influenza)
Increased risk of diabetes mellitus, hypertension, cardiovascular disease, some cancers, obstructive sleep apnea, cholecystitis, erectile dysfunction, non-alcoholic fatty liver disease, osteoarthritis and depression
Contributing factors:
Older age
Sedentary lifestyle
Intake of excess or poor quality calories (e.g. saturated fats, processed sugars)
Excess alcohol consumption
Some medications (e.g. psychotropic drugs, steroids, anti-diabetic drugs)
Endocrine disorders (e.g. GH deficiency, hypothyroidism, Cushing's syndrome, hypogonadism)
Assessment:
Weight, waist circumference and BMI, see page 53
Fasting lipids and glucose, see pages 54, 58 and 60
Dyslipidaemia management, see page 60
Assess NAFLD, see page 72
Prevention of cardiovascular disease, see page 54
Indication for intervention:
BMI ≥ 30 kg/m^2 or ≥ 25 kg/m^2 and weight-related complications (diabetes mellitus, hypertension)
Aim:
An objective of 5% weight loss from initial weight may have a beneficial impact on obesity-related comorbidities
Management:
Preferably by a multidisciplinary team
Multifactorial, comprehensive lifestyle intervention for at least 6-12 months that includes a reduction in calorie intake, an increase in physical activity and measures to support behavioral change
Structured exercise focused on activities of daily living. The majority of guidelines recommend at least 30 minutes of moderate intensity endurance exercise five or more days a week, in combination with strength training. Dietary intervention that produces a daily energy deficit of 500-750 kcal based on personal and cultural preferences – specific composition of diet unimportant as long as it is balanced and healthy.
Consider behavioral intervention (motivational interviewing, stimulus control or cognitive re-structuring) along with self-monitoring; intensify behavioral intervention if a 2.5% weight loss is not achieved during the first month.
No data on ART switch
Treat underlying or associated conditions
There are several drugs specifically recommended for those with a BMI ≥ 30 kg/m^2 or ≥ 25 kg/m^2 and weight-related complications (diabetes mellitus, hypertension) (e.g. orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, liraglutide). Maintenance of weight loss therapies should only be considered when a person has lost 5% of initial body weight during the first 3 months or at least 2 kg during the first 4 weeks. These drugs should be prescribed by an endocrinologist or obesity expert. All of them may have adverse effects and drug-drug interactions with ART
Bariatric surgery may be considered in persons with a BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with obesity-related comorbidities refractory to serious attempts at lifestyle changes and should be coordinated through an established, specialist led obesity programme. Consider therapeutic drug monitoring and drug dose adjustment post-bariatric surgery
Surgery can be considered for localised lipomas and dorsocervical fat accumulation for cosmetic purposes only

Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management

Risk factors	Prevention/Diagnosis	Symptoms
• HCV/HBV co-infection • Use of ribavirin • Liver disease • Low CD4 count • Pregnancy • Female sex • Obesity	• 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 ARVs 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 PLWH	**1. Observe food hygiene** • Particularly important for travellers visiting friends and relatives (VFR) • Bacterial enterocolitis e.g. diarrhoeagenic *E. coli, Salmonella, Shigella, Campylobacter* • Opportunistic intestinal parasitosis Cryptosporidium, Cyclospora, Cystoisospora, Microsporidia **2. Prevent insect bites** • Repellents (DEET ≥ 30%), spray clothing with insecticide (permethrin) • Sleep under bednet • Malaria chemoprophylaxis/emergency stand-by treatment[ii] • Yellow fever, see page 79 • Leishmaniasis beware of sand flies (dogs)

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

i Higher intestinal susceptibility due to HIV-associated GALT destruction, low CD4 count. More severe malaria with CD4 count < 350 cells/µL

ii According to malaria risk at travel destination and national guidelines adherence counselling is particularly important in persons visiting friends and relatives. See Drug-drug Interactions between Antimalarial Drugs and ARVs

Drug-drug Interactions between Antimalarial Drugs and ARVs

	Antimalarial drugs	ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
First line and second line drugs	amodiaquine	↑	↑	↔	↑	↑	↔	↑a	↓?	↓29% a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	artemisinin	↑	↑	↑	↑	↑	D	↓	↓D	↓D	D	D	D	↔	↑	↔	↔	↔	↔	↔	↔
	atovaquone	↔	↓10%	↔	↓ b	↓74% b	↔	↓75% b	↓E55% b	↓ b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chloroquine	↔c,d	↔c,d	↔d	↔d	↔c,d	↔	↔e	↔f	↔f	↔g	↔	↔	↔	↔d	↔	↔	↔	↔	↔	↔
	clindamycin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	doxycycline	↔	↔	↔	↔	↔	↔	↓?	↓?	↓?	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lumefantrine	↑ c	↑ c	↑	↑175%	↑382% c	↔	↓~40%	↓	↓D46%	↔g	↔	↔	↑10%	↑	↔	↔	↔	↔	↔	↔
	mefloquine	↑ c	↑ c	↑	↑	↓28%c	↔	↓	↓	↓	↔g	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	piperaquine	↑ c	↑ c	↑ c	↑ c	↑ c	E	↓	↓	↓	E g	E	E	↔	↑ c	↔	↔	↔	↔	↔	↔
	primaquine	↔	↔	↔	↔	↔	↔	↔h	↔h	↔h	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	proguanil	↔	↓41% b	↔	↓b	↓38% b	↔	↓44% b	↓E55% b	↓b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pyrimethamine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E	E	↔	↔
	quinine	↑ c	↑ c	↑	↑	↓56% c	↔	↓	↓	↓	↔ g	E	↔	↔	↑	↔	↔	↔	↔	↔	↔
	sulfadoxine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E	E	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑	Potential increased exposure of the antimalarial drug
↓	Potential decreased exposure of the antimalarial drug
↔	No significant effect
D	Potential decreased exposure of ARV drug
E	Potential elevated exposure of ARV drug

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

Interactions with ZDV
Amodiaquine, atovaquone, primaquine, pyrimethamine, sulfadoxine (potential additive hematological toxicity)

Interactions with ibalizumab
none

Comments

a	Liver toxicity
b	Take with high fat meal, consider dose increase
c	ECG monitoring is recommended
d	Chloroquine concentrations may increase, but to a moderate extent. No dose adjustment is required but monitor toxicity
e	Chloroquine concentrations may increase or decrease. No dose adjustment is required but monitor toxicity and efficacy
f	Chloroquine concentrations may decrease, but to a moderate extent. No dose adjustment is required but monitor efficacy
g	Both drugs can induce QT interval prolongation (only at supratherapeutic dose for RPV)
h	Increase of haemotoxic metabolites

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Vaccination

- Vaccinate according to national guidelines for healthy population, preferably after having achieved suppressed viraemia and immune reconstitution (CD4 count > 200 cells/μL)
- Consider repeating vaccinations performed at CD4 count < 200 cells/μL (< 14%) or unsuppressed viraemia once adequate immune reconstitution is achieved (HIV-VL undetectable and CD4 count > 200 cells/μL)
- As vaccine responses may be significantly lower in PLWH (i.e. lower seroconversion rates, faster titer decline), do not use rapid schedules and consider antibody titers to assess their effectiveness if vaccinated at CD4 count < 200 cells/μL or unsuppressed viremia (e.g. rabies, tick-borne encephalitis, HAV, meningococci)
- Avoid polysaccharide vaccination
- For background data, 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**
    Contraindicated if CD4 count < 200 cells/μL (14%) and/or AIDS. Impaired protection after vaccination with unsuppressed viraemia
  - **Oral live typhoid**
    Contraindicated if CD4 count < 200 cells/μL (14%): give inactivated parenteral polysaccharide vaccine. Preferred if CD4 count > 200 cells/μL (> 14%)

Infection	Vaccination rationale in PLWH	Comment
Influenza Virus	Higher rate of pneumonia. Explicitly recommended in all PLWH	Yearly
Human Papilloma Virus (HPV)	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	Vaccinate all PLWH with 3 doses between ages 9 and 40 (health insurance coverage differs by country according to age, sex, sexual orientation). Use 9-valent vaccine if available. Persons treated for high grade cervical dysplasia could benefit from a full course vaccination for secondary prevention
Hepatitis B Virus (HBV)	Shared risk with HIV of contracting infection. HIV accelerates liver disease progression	Vaccinate if seronegative. Repeat doses until anti-HBs antibodies ≥ 10 IU/L / ≥ 100 IU/L according to national guidelines. In order to reach ≥ 100 IU/L in non-responders repeat 3 doses if anti-HBs < 10 IU/L, 1 dose if anti-HBs < 100 IU[ii]; consider double dose (40 μg) in particular with low CD4 count and high HIV-VL. See page 95
Hepatitis A Virus (HAV)	According to risk profile (travel, close contact with children, MSM, IVDU, active hepatitis B or C infection, chronic liver disease)	Vaccinate if seronegative. Consider checking antibody titres in PLWH with high risk. Weaker immune response expected with HAV/HBV co-vaccine. See page 95
Neisseria meningitidis	According to risk profile (travel, close contact with children, MSM)	Use conjugated[iii] 4-valent 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 PLWH	One dose of conjugated[iii] 13-valent vaccine (CPV-13) for all PLWH, also if pre-vaccinated with PPV-23 polysaccharide vaccine. No general recommendation for any booster dose. Some national guidelines consider one dose of PPV-23 at least 2 months after CPV-13 for all PLWH
Varicella Zoster Virus (VZV)	Higher rate and severity of both chickenpox and zoster	Perform serology if exposure history negative. Vaccinate if seronegative. For contraindications, see*. To prevent shingles consider adjuvant sub-unit vaccine rather than live-attenuated vaccine according to national guidelines
Yellow Fever Virus	Mandatory for travel to selected countries (provide exemption letter if no true risk of exposure)	Contraindicated if past or current haematological neoplasia or thymus affection (thymoma, resection/radiation) For other contraindications, see*. Booster q 10 years
Rabies		For PLWH with CD4 count < 200 cells/μL or unsuppressed viremia consider pre-exposure vaccination with 3 doses (0, 7, 28 days) and titer control 14 days later as well as post-exposure immunoglobulins for all non-vaccinated

i Administer live vaccines simultaneously or with an interval of 4 weeks
ii In case of non-response, ART should contain TDF or TAF
iii Conjugated vaccines are more immunogenic, induce memory cells, respond to boosting and reduce mucosal colonisation

Sexual and Reproductive Health of Women and Men Living with HIV

Screening questions about sexual and reproductive health and sexual function should be routinely asked at HIV consultation.

Effective Measures to Reduce Sexual transmission of HIV	
Measure	**Comment**
Male condom or female condom use	• Effective in treated and untreated PLWH
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 situations, 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. sero-different couples(i)

Undetectable = untransmittable U=U [20], [21]. The evidence is now clear that people living with HIV with an undetectable VL do not transmit HIV sexually. Large studies of sexual HIV transmission among thousands of sero-different couples, one partner of which was living with HIV and the other was not, were undertaken in recent years. In those studies, there was not a single case of linked sexual transmission of HIV from a virally suppressed PLWH to their HIV-negative partner. However, a person can only know whether he or she is virally suppressed by taking a VL test

i see page 11

Reproductive health

Ensuring that women and men living with HIV are asked about their reproductive goals at HIV diagnosis and in follow-up and receive appropriate and ongoing reproductive counselling is crucial. Providing contraception and family planning counselling to women living with HIV is essential if pregnancy is not currently desired

Conception:
Reproductive health issues should be preferentially discussed with both partners, particularly in sero-different couples. See Drug-drug Interactions between Contraceptives and ARVs

Approaches for sero-different couples who want to have children:

Start ART in partner living with HIV if naïve. Ensuring the HIV-positive partner is on fully suppressive ART should be a primary goal for couples who wish to conceive.
Screening for STIs (and treatment, if required) of both partners is mandatory.

For ART of women living with HIV wishing to conceive, see pages 17-18

No single method is fully protective against transmission of HIV; the following list represents selected measures with increasing safety for sero-different couples without active STIs:

- Unprotected intercourse during times of maximum fertility (determined by ovulation monitoring), if the partner living with HIV has undetectable HIV-VL
- PrEP in the absence of HIV viral suppression e.g. during the first 6 months of ART or if uncertainty about HIV-positive partner's adherence (data on safety and efficacy are limited; [22] see Pre-exposure Prophylaxis (PrEP)
- 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, is no longer necessary because of effectiveness of ART in avoiding HIV transmission at conception in male PLWH with undetectable HIV-VL

Contraception

Women living with HIV of childbearing age should be offered contraception counselling. If hormonal contraceptives are preferred options, EFV should be avoided as it can impair the efficacy of the contraceptive method. Boosted regimens can be used with some contraceptive methods, see Drug-Drug Interactions between Contraceptives and ARVs. Otherwise intra-uterine device should be offered as the preferred option due to its high effectiveness, well established safety and no DDIs. STI and HIV transmission risk should be carefully discussed along with contraception counseling

Post-reproductive sexual health

Screen for perimenopause symptoms in women ≥ 40 years, at HIV diagnosis and prior to starting ART. Follow up annually as indicated

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 Men Living with HIV

STI screening and treatment

STI screening should be offered to all sexually active PLWH at the time of HIV diagnosis, annually thereafter or at any time STI symptoms are reported and during pregnancy. More frequent screening at three-month intervals is warranted for PLWH at particularly high risk of STIs, including those with multiple or anonymous partners. Frequent HIV screening is also essential for those on PrEP [23], see Pre-exposure Prophylaxis (PrEP).
Diagnosis procedures should follow local or national guidelines. More comprehensive advice can be found at https://iusti.org/treatment-guidelines/

The following STIs should be universally considered in PLWH and their sexual partner(s):

	Therapy	Comment
Chlamydia infection	Consider doxycycline (100 mg po bid 7-10 days, contraindicated in pregnancy) for urethritis and cervicitis [i] Preferred if rectal infection Or alternatively: azithromycin 1 g po as a single dose If rectal infection a test of cure (TOC) should be performed For *Lymphogranuloma venereum (LGV) doxycycline* (100 mg po bid for 21 days) **Alternatives**: erythromycin (500 mg po qid[ii]) or levofloxacin (500 mg/day po) for 7 days (or erythromycin 500 mg po qid[ii] for 21 days in case of LGV)	• May cause therapy-resistant proctitis in HIV-positive MSM • Screening recommended at genital, rectal and pharyngeal sites according to exposure • Rectal and pharyngeal infections are usually asymptomatic • Consider co-infections with *Neisseria gonorrhoeae* • Avoid sexual activity for 7 days post treatment initiation • Individuals should only resume having sex after symptoms have resolved and sex partners have been treated • The same treatment for LGV is recommended for asymptomatic individuals and contacts of individuals with LGV
Gonorrhoea	Ceftriaxone (1 g im as a single dose) [i]	• Can cause proctitis, prostatitis and epididymitis • Screening recommended at genital, rectal and pharyngeal sites according to exposure • Rectal and pharyngeal infections are usually asymptomatic • Often asymptomatic in women • Avoid sexual activity for 7 days post treatment initiation • Individuals should only resume having sex after symptoms have resolved and sex partners have been treated • Fluoroquinolone resistance is highly prevalent in all regions • Note ceftriaxone 1 g im as a single dose is based on recent BHIVA recommendations, https://www.bhiva.org/guidelines. IUSTI Guidelines recommend 500 mg im with azithromycin 2 g as a single dose, however these recommendations have not been updated in several years, https://iusti.org/regions/guidelines/
HBV infection **HCV infection**	See detailed information on HIV/HCV or HIV/HBV co-infections, pages 96-97	• Interruption of TDF, 3TC or FTC can lead to HBV reactivation • Clusters of acute HAV and HCV infection in HIV-positive MSM across Europe • See Vaccination
HPV infection	There are several treatment modalities for the management of genital warts with no evidence to suggest one approach is better than another approach. 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 PLWH practicing anal sex • Consider high resolution anoscopy in case of suspicious cytological findings (rectal palpation or external inspection is not sufficient) • See Vaccination
HSV infection	**Primary infection**: aciclovir (400-800 mg po tid), famciclovir (250-500 mg po tid) or valaciclovir (1000 mg po bid) for 7-10 days **Recurrent episodes**: aciclovir (400 mg po tid) or valaciclovir (500 mg po bid) for 5-10 days **Suppressive management**: Chronic suppressive therapy is usually offered to persons who experience six or more clinical episodes per year or who experience significant anxiety or distress related to their clinical recurrences. Chronic suppression: aciclovir (400-800 mg bid or tid) or famciclovir 500 mg bid or valaciclovir 500 mg po bid	• Treatment of HSV2 alone does not prevent HIV-transmission and only modestly prevents HIV disease progression
Syphilis	Penicillin is the gold standard for the treatment of syphilis in both pregnant and non-pregnant individuals. **Primary/secondary syphilis**: benzathine penicillin G (2.4 million IU im as single dose). In early syphilis adjunctive treatment with prednisolone (20-60 mg po daily for 3 days) prevents optic neuritis, uveitis and Jarisch–Herxheimer reaction Alternative regimen include doxyycline (100 mg po bid for 14 days) **Late latent syphilis and syphilis of unknown duration**: benzathine penicillin (2.4 million IU im weekly on days 1, 8 and 15); the alternative doxycycline (100 mg po bid for 4 weeks) is considered less effective **Neurosyphilis**: penicillin G (6 x 3 - 4 million IU iv for at least 2 weeks) There is no evidence to give a general recommendation on prednisolone use in this condition Alternative regimen: ceftriaxone (2 g iv daily for 10 to 14 days) if the person can be safely treated with other beta-lactam drugs. Doxycycline (200 mg po bid) for 21 days is also an alternative approach, but should be reserved for exceptional circumstances. This regimen has very limited supporting data[i]	• Expect atypical serology and clinical courses • Consider cerebrospinal fluid (CSF) testing in persons with neurological symptoms (evidence for intrathecally-produced specific antibodies, pleocytosis, etc.) or late latent syphilis • Successful therapy clears clinical symptoms and decreases VDRL test four-fold within 6-12 months

i Refer to local guidelines
ii Rarely used

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 MEN; i.e. erectile dysfunction; lack or impaired nocturnal erections MEN; difficulties lubricating WOMEN; 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)	
	Self-assessment of sexual function (questionnaires):	**Men** International Index of Erectile Function, see http://files.sld.cu/urologia/files/2011/08/iief.pdf **Women** Female Sexual Function Index (FSFI), see http://www.fsfiquestionnaire.com	
Check for endocrine causes:	Signs of hypogonadism	**Men** - Look for signs of testosterone insufficiency (main: decreased or absent nocturnal erections, decrease in testes size, decreased volume of ejaculate, hot flushes, sweats, reduction of body hair and beard; others: reduced sexual arousal and libido, decreased frequency of sexual thoughts and fantasies, decreased genital sensitivity, erectile dysfunction, loss of vitality; fatigue; loss of muscle mass and muscle strength) - If signs or symptoms of hypogonadism are present ask for hormonal assessment: lutropin hormone (LH), follicle stimulating hormone (FSH), total testosterone; sex hormone-binding globulin evaluation to calculate free testosterone, see http://www.issam.ch/freetesto.htm	If hypogonadism is present (total testosterone < 300 ng/dl or calculated free testosterone below normal): refer to endocrinologist or andrologist If hypogonadism is not present: check for other causes
		Women - Look for signs of estradiol insufficiency/menopause (amenorrhoea or missed menstrual periods, vaginal dryness, hot flashes, night sweats, sleep disturbances, emotional lability, fatigue, recurrent urogenital infections) - If symptoms of menopause are present ask for hormonal assessment: LH, FSH, estradiol	If symptoms of menopause are present: refer to endocrinologist or gynaecologist If hypogonadism is not present: check for other causes
Check for other causes:	Psychological or sociological problems	Stigma, body image alteration, depression, fear of infecting an HIV-negative partner, anxiety, awareness of a chronic disease, condom use	Refer to clinical psychologist
	Infections	**Men** - Urogenital infections (note: if complete sexual response possible, e.g. with another partner, with masturbation or nocturnal erections-then no major somatic factors are involved)	Refer to urologist, andrologist, cardiologist
		Women - Urogenital infections	Refer to gynaecologist
	Relevant medicines, drugs, lifestyle factors	Drugs associated with sexual dysfunction: 1) Psychotropics – Men and Women (antidepressants, antiepileptics, antipsychotics, benzodiazepines), 2) Lipid-lowering drugs - Men (statins, fibrates), 3) Antihypertensives - Men (ACE-inhibitors, betablockers, alfablockers), 4) Others - Men and Women (omeprazole, spironolactone, metoclopramide, finasteride, cimetidine); 5) Men and Women - contribution from ART is controversial and benefit from switching studies is not proven	Consider therapy changes

Treatment of Sexual Dysfunction in Men Living with HIV

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/b - 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 **Cave:** Poppers have a synergistic effect with PD5-blockers which can lead to profound hypotension thus concurrent use is not recommended • 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

- A higher prevalence of depression is reported in PLWH described in 20-40% versus 7% in general population
- Significant disability and poorer HIV treatment outcomes are associated with depression
- Depressive disorders are often associated with a significant anxiety and poor overall wellbeing

Screening and diagnosis of depression

Who?	How to screen?	How to diagnose?
Screening of all PLWH recommended in view of the high prevalence of depression **Populations at particularly 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 88	• 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 84: 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 doctor 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[ii]	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 PLWH, 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

ii Insomnia is associated with DTG and other INSTI containing ART regimens and with the use of some antidepressants. Clinicians should be aware when prescribing DTG and INSTI and antidepressants together

Drug-drug Interactions between Antidepressants and ARVs

Antidepressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
SSRI	citalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	escitalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluoxetine	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluvoxamine	↑	↑	↑	↑	↑	↔	↔	↔	E	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔	↔	↔	↔
	sertraline	↑	↓	↑	↓49%	↓	↔	↓39%	↓	↓	↔	↔	↔	↔	↓7%	↔	↔	↔	↔	↑9%	↔
SNRI	duloxetine	↑	↑↓	↑	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	venlafaxine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	D	↔	↔	↑	↔	↔	↔	↔	↔	↔
TCA	amitriptyline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	clomipramine	↑a	↑a	↑a	↑a	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑a	↔	↔	↔	↔	↔	↔
	desipramine	↑a	↑a	↑	↑	↑5%a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	doxepin	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	imipramine	↑a	↑a	↑a	↑a	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑a	↔	↔	↔	↔	↔	↔
	nortriptyline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	trimipramine	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
TeCA	maprotiline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	mianserine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	mirtazapine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
Others	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↑?	↔	↔	↔	↔	↔	↔
	lamotrigine	↔	↓32%c	↔	↓	↓50%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↓1%	↔	↔	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↑	E	↓E	↓E	↓E	E	E	E	↔	↑	↔	↔	↔	↔	↔	↔
	St John's wort	D	D	D	D	D	D	D	D	D	D	D	D	D d	D	D	↔	↔	↔	D	↔
	trazodone	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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
ATV/c	ATV co-formulated with COBI (300/150 mg qd)
DRV/c	DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

SSRI	selective serotonin reuptake inhibitors
SNRI	serotonin and norepinephrine reuptake inhibitors
TCA	tricyclic antidepressants
TeCA	tetracyclic antidepressants

Interactions with ZDV

No clinically relevant interactions expected with ZDV and antidepressants

Interactions with ibalizumab

none

Comments

- a ECG monitoring is recommended
- b Caution as both drugs can induce QT interval prolongation
- c No PK change with unboosted ATV
- d The European SmPC recommends DTG 50 mg bid in persons without INSTI resistance. The US Prescribing Information recommends that co-administration should be avoided as there are insufficient data to make dosing recommendations

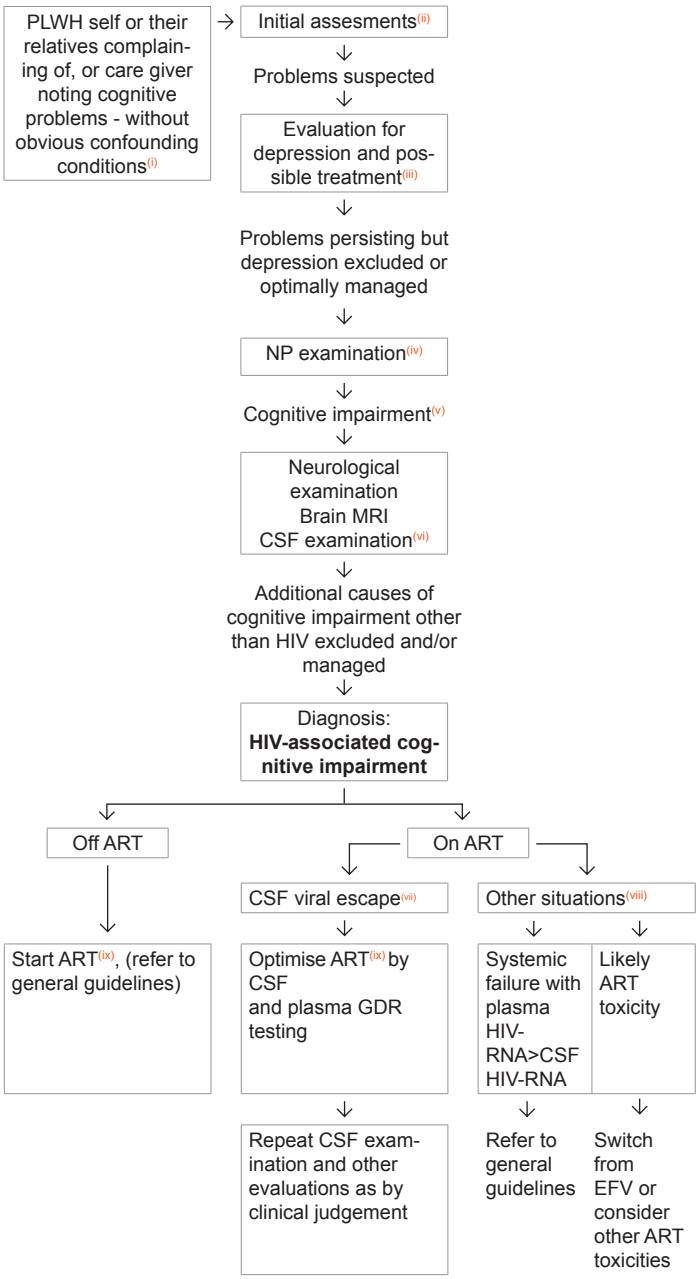
Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Algorithm for Diagnosis and Management of Cognitive Impairment in PLWH without Obvious Confounding Conditions

Abbreviations

CSF	cerebrospinal fluid
GDR	genotypic drug resistance test
HAD	HIV-associated dementia
LOQ	Limit of quantification
MND	mild neurocognitive disorder
MRI	brain magnetic resonance imaging
NP	neuropsychological
OIs	opportunistic infections
RCT	randomized controlled trial



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 questions may be used to guide doctor 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 major difficulties paying attention (e.g. to a conversation, book or film)?

Answering "yes" to one or more of these questions may suggest the presence of cognitive disorders, although not necessarily linked to HIV.

iii See Depression: Screening and Diagnosis

iv **NP examination** should 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 **Cognitive impairment** is defined by impairment in cognitive function on the above neuro-psychological test where performance is compared to age and education-matched appropriate controls and is considered clinically significant

vi **Neurological examination, brain MRI and CSF examination** are required to exclude other pathologies (consultation with neurologist specialist may be required) and to further characterise possible HIV-associated cognitve impairment by including assessment of CSF HIV-RNA level and, where appropriate, evidence for genotypic drug resistance (GDR) in a paired CSF and plasma sample

vii **CSF escape definition:**
Either CSF HIV-RNA above LOQ and plasma HIV-RNA below LOQ; or HIV-RNA above LOQ in both CSF and plasma, with CSF HIV-RNA greater than plasma HIV-RNA.
In CSF escape:
- *Avoid dual ART therapies*
- *Avoid ATV (boosted or unboosted) due to association with CSF escape in retrospective cohorts*
- *Avoid RAL 1200 mg qd and COBI as boosting due to lack of evidence in CSF escape*

viii Including situations that do not fulfill the CSF escape definition, but can benefit from ART optimisation

ix Avoid EFV because of its detrimental effects on cognitive function in a RCT and potentially confounding CNS effects due to neuropsychiatric effects

Chronic Lung Disease in PLWH

Screen for chronic lung disease:
1. Are you 40 years or older?
2. Have you smoked more than 10 pack years in your entire lifetime?

Then check for respiratory symptoms:
3. Do you have ANY of the following on a regular basis: a) shortness of breath when walking up a slight hill or hurrying on flat ground; b) cough and/or sputum; c) wheezing

"Yes" to all three questions

Assess for airflow limitation with spirometry

Post-bronchodilator $FEV_1/FVC < 0.70$

Diagnose COPD

Post-bronchodilator $FEV_1/FVC > 0.70$, *but reduced lung volumes and/or altered CO diffusion capacity test*

Consider chest CT for structural changes and/or referral to respiratory specialist[iii]

Assessment of symptoms/risk of exacerbations[i]

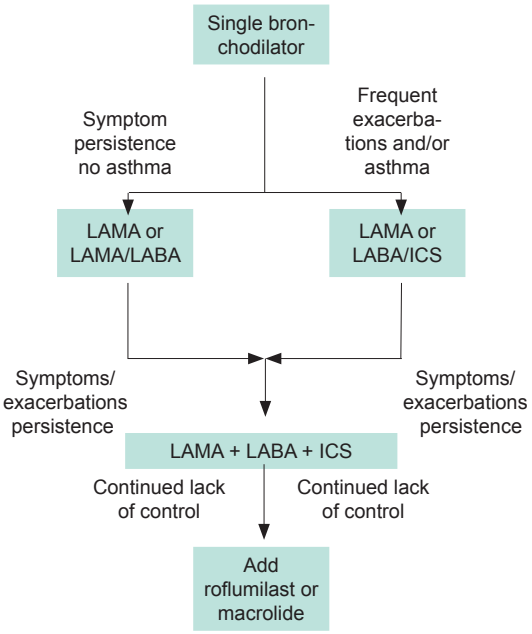
Assessment of concomitant chronic diseases[ii]

"Yes" to "shortness of breath on light exercise or at rest"

Make comprehensive assessment particularly for the risk of concomitant CVD including pulmonary hypertension

"No"
Repeat questions anually

Treatment of COPD[iv]



LABA: long-acting β2-agonist
LAMA: long-acting muscarinic antagonist
ICS: inhaled corticosteroid

Reassess and adjust regularly according to the response to treatment in terms of dyspnea and/or acute exacerbations

There are 3 life saving interventions:
1. Smoking cessation
2. Chronic oxygen when stable (non-exacerbated) resting $SpO_2 \leq 88\%$ (or $PaO_2 \leq 55$ mmHg)
3. Non-invasive ventilation (NIV) in individuals with persistent hypercapnic respiratory failure after an acute exacerbation

i Assessment of either dyspnoea using mMRC, see https://www.verywell.com/guidelines-for-the-mmrc-dyspnea-scale-914740 or symptoms using CAT™, see http://www.catestonline.org/ and history of exacerbations (including prior hospitalisations)
ii COPD itself has significant extra-pulmonary (systemic) effects including weight loss, nutritional abnormalities and skeletal muscle dysfunction
iii Based on expert opinion
iv Each pharmacological treatment should be individualised and guided by the severity of symptoms, risk of exacerbations, adverse effects, co-morbidities, drug availability and cost, and the individual's response, preference and ability to use various drug delivery devices. Inhaler technique needs to be assessed regularly. Long-term use of oral glucocorticoids has no evidence of benefits in COPD and increase the risk of pneumonia. The addition of ICS to LAMA or LABA/LAMA is recommended in individuals with history of frequent exacerbations and/or asthma and/or eosinophilia (> 3%), or anyway in individuals not adequately controlled by LAMA/LABA combination. ICS should be avoided in subjects with eosinopenia (< 1%)

Do not use inhaled glucocorticoids with boosted ART regimens, see Drug-drug Interactions between Corticosteroids and ARVs.
Influenza and pneumococcal vaccination decrease rates of lower respiratory tract infections, see Vaccination

Drug-drug Interactions between Bronchodilators (for COPD) and ARVs

Bronchodilators		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
LAMA	aclidinium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	glycopyrronium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tiotropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	umeclidinium bromide	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SAMA	ipratropium	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
LABA	formoterol	↔a	↔a	↔	↔	↔a	↔	↔	↔	↔	↔a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indacaterol	↑b	↑b	↑b	↑b	↑b	↔	↓	↓	↓	↔	↔	↔	↔	↑b	↔	↔	↔	↔	↔	↔
	olodaterol	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	salmeterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	vilanterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SABA	salbutamol (albuterol)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
MX	aminophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	theophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
PDE4	roflumilast	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
ICS	beclometasone	↑d	↑d	↑?d	↓11%	↑d	↔	↔	↔	↔	↔	↔	↔	↔	↑d	↔	↔	↔	↔	↔	↔
	budesonide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	fluticasone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑	Potential elevated exposure of the bronchodilator
↓	Potential decreased exposure of the bronchodilator
↔	No significant effect
D	Potential decreased exposure of ARV drug
E	Potential elevated exposure of ARV drug

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

ICS inhaled corticosteroids
LABA long-acting β2 agonists
LAMA long-acting muscarinic antagonists
MX methylxanthines
PD4 phosphodiesterase 4 inhibitors
SABA short-acting β2 agonists
SAMA short-acting muscarinic antagonists

Interactions with ZDV
No clinically relevant interactions expected with ZDV and bronchodilators

Interactions with ibalizumab
none

Comments

a	Caution as both drugs can induce QT interval prolongation
b	Exposure can be increased up to 2-fold however this increase does not raise any concerns based on indacaterol's safety data
c	ECG monitoring is recommended
d	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

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

Pulmonary anti-hypertensives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
ERA	ambrisentan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bosentan	↑a	↑a	↑a	↑a	↑a	D	↓	↓	↓b	D	D	D	D	↑a	↔	↔	↔	↔	↔	↔
	macitentan	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
PDE5	sildenafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↓3%	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	tadalafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
sGC	riociguat	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
PA	epoprostenol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	iloprost	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	treprostinil	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
IPr	selexipag	↔c	↔c	↔c	↔c	↑120%d	↔	↔	↔	↔	↔	↔	↔	↔	↔c	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑	Potential increased exposure of the pulmonary antihypertensive
↓	Potential decreased exposure of the pulmonary antihypertensive
↔	No significant effect
D	Potential decreased exposure of ARV drug
E	Potential elevated exposure of ARV drug

ATV/c	ATV co-formulated with COBI (300/150 mg qd)
DRV/c	DRV co-formulated with COBI (800/150 mg qd)

ERA	endothelin receptor antagonists
IPr	IP receptor agonists
PA	prostacyclin analogues
PDE5	phosphodiesterase type 5 inhibitors
sGC	soluble guanylate cyclase stimulators

Interactions with ZDV

No clinically relevant interactions expected with ZDV and pulmonary antihypertensives

Interactions with ibalizumab

none

Comments

a	Co-administration is not recommended in the European labels, but the US labels suggest the following dose modifications: When starting bosentan in individuals already on PI/r, PI/c or EVG/c use a bosentan dose of 62.5 mg qd or every other day. Discontinue bosentan at least 36 h prior to starting PI/r, PI/c or EVG/c and restart after at least 10 days at 62.5 mg qd or every other day
b	Potential additive liver toxicity
c	Exposure of parent drug increased but exposure of active metabolite unchanged
d	This change is unlikely to be clinically relevant

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Frailty in the Context of Ageing

Frailty defines age-related exhaustion of homeostatic reserves. An individual with frailty is exposed to enhanced vulnerability to stressors, and associated risk of negative health-related outcomes. This geriatric syndrome, comprising biological, psychological and social issues is more prevalent than expected in PLWH compared to HIV-negative matched controls [24].The most common instruments to measure frailty include the Frailty Phenotype [25] and Frailty Index [26]

Feature	Frailty Phenotype	Frailty Index
Clinical definition	Based on presence of signs, symptoms (pre-disability syndrome)	Based on presence of diseases, disabilities (accumulation of deficits)
How to assess	Assessed by five specific features [25]: 1. self-reported weight loss (a) 2. self-reported exhaustion (b) 3. low levels of physical activity as measured by Minnesota Leisure physical activity questionnaire (c) 4. measured 4 m walk speed time (d) 5. measured grip strength (e)	A frailty index is calculated based on the number of health deficits out of > 30 assessed health deficits [26] Health variables, including signs and symptoms of disease, laboratory measures, and self-reported data Data routinely collected in medical records can be included if they characterise age-related, acquired health deficits which cover a range of physiologic systems
How to interpret	Categorical variables Total score of 5 items: 0 deficits = fit 1-2 deficits = pre-frail 3 + deficits = frail	Continuous variables Index ranges from 0 to 1: > 0.25 = fit 0.25 - 0.4 = frail > 0.4 = most frail
How to address frailty [27]	Promote Comprehensive Geriatric Assessment (CGA), aimed at personalising interventions according to benefits/priorities for a given person through a multidisciplinary diagnostic and treatment process, that identifies medical, psychosocial, and functional limitations aimed at maximising overall health with ageing and the improvement of quality of life	
Recommendations [28], [29]	In PLWH who are frail: 1. Sustain and recover physical function impairment and sarcopenia prescribing physical activity with a resistance training component 2. Address polypharmacy by reducing or deprescribing any inappropriate/superfluous medications, see Prescribing in Elderly PLWH 3. Screen for, and address modifiable causes of fatigue 4. For PLWH exhibiting unintentional weight loss, screen for reversible causes and consider food fortification and protein/caloric supplementation 5. Prescribe vitamin D for individuals deficient in vitamin D, see page 62	

(a) Self-reported unintentional weight loss was considered present if exceeding 4.5 kg in the last year or 2.3 kg in the last 6 months

(b) Exhaustion is present if the participant answers ''occasionally'' or ''most of the time'' to either one of the following statements: During the last week, how often have you felt that (i) everything you did was an effort, or (ii) you could not 'get going'

(c) Low physical activity was considered present if participant answered 'yes, limited a lot' when asked whether their health limits vigorous activities such as running, lifting heavy objects, participating in strenuous sports

(d) Walk speed time, is measured by a 4-meter walking test in usual pace, one trial) A deficit is assigned according to the following gender-specific criteria
- Men: height ≤ 173 cm and speed ≤ 0.6531 m/s; height > 173 cm and speed ≤ 0.762 m/s
- Women: height ≤ 159 cm and speed ≤ 0.6531 m/s; height > 159 cm and speed ≤ 0.762 m/s

(e) Maximum grip strength can be assessed using a handheld dynamometer the mean value of three consecutive measurements of the dominant hand (adjusted by sex and BMI quartile based on CHS population [26]):
- Men: BMI ≤ 24 kg and strength < 29 kg; BMI 24.1–26 and strength < 30 kg; BMI 26.1–28 and strength < 30 kg; BMI > 28 and strength < 32 kg
- Women: BMI ≤ 23 and strength < 17 kg; BMI 23.1–26 and strength < 17.3 kg; BMI 26.1–29 and strength < 18 kg; BMI > 29 and strength < 21 kg

Solid Organ Transplantation (SOT) in PLWH

General features

- HIV infection is not a contraindication for transplantation consideration.
- Experts in HIV medicine should preferably be members of the multi-disciplinary team, responsible for the pre-transplant evaluation, and take primary responsibility for the management of the HIV infection and the prevention and treatment of OIs

Organ criteria for SOT

- PLWH should be considered for organ transplantation using the same indications as used in HIV-negative persons. PLWH with HCC can be evaluated for liver transplantation if they fulfill the Milan criteria[i]

Organ donation

- PLWH can receive organs from living (renal) and deceased (all types of SOT) HIV-negative donors
- In some European countries the use of organs from HIV-positive donors is allowed but the efficacy and safety of this approach is currently being evaluated in the context of research studies

HIV-infection criteria for SOT

According to most international guidelines, PLWH should fulfill the following criteria to be considered for SOT

1. **Clinical criteria.** No active OIs or HIV-related cancers. Individuals with PML, chronic crypto/microsporidiosis, multi-drug resistant fungal or mycobacterial infections, NHL and visceral KS to be excluded. For non-HIV-related cancers same criteria apply as in the general HIV-negative population
2. **Immunological criteria.** CD4 > 200 cells/μL for all SOT except for liver transplantation where CD4 > 100 cells/μL. Persons with previous opportunistic infections should have a CD4 > 200 cells/μL
3. **Virological criteria.** Full control of HIV replication prior to and after transplantation should be confirmed/predicted in all cases
4. **Drug abuse.** Abstinence period: alcohol = 6 months; heroin/cocaine = 2 years. Former IVDUs can be in methadone programme

Preparing PLWH for transplantation

Antiretroviral therapy

- Choice of ART components should avoid drugs known to cause organ dysfunction or drugs with a high potential for drug-drug interactions if at all possible, see Drug-drug Interactions between Immunosuppressants (for SOT) and ARVs
- Using a pharmacological booster (RTV or COBI) and some of the NNRTIs are best avoided, see Drug-drug Interactions between Immunosuppressants (for SOT) and ARVs
- For individuals nearing indication for transplantation, ART should be modified to ensure this if at all possible
- RAL (and probably DTG) plus 2 NRTIs is the preferred regimen
- If the individual has not yet started ART and transplantation is considered, ART should be commenced as soon as possible and preferably before the transplantation is started

Viral hepatitis co-infection

In liver transplant candidates, every effort should be made to treat the underlying viral hepatitis independently of MELD score, see pages 95-101. Use of DAAs in persons with HCV co-infection may improve their liver function, and possibly lead to them being removed from the transplant waiting list

Prevention of infections

- While screening and treatment for latent TB is recommended in all PLWH, see page 116, it is particularly important in persons pre-and post-transplantation due to the additional use of immunosuppressants. Immunisation regimens and pre-transplant diagnostic protocols are the same as in HIV-negative SOT recipients

Follow-up after transplantation

Antiretroviral therapy

- Same recommendations in individuals under preparation for transplantation
- Additionally, ARVs may exacerbate immunosuppressive agents' adverse drug effects (kidney impairment, bone marrow suppression, drug-induced liver injury, etc.). Therefore, careful consideration of which drugs to use is essential see Adverse Effects of ARVs & Drug Classes
- TAF is preferred to TDF, when available, to reduce additive nephrotoxicity to immunosuppressant agents

Primary and secondary disease-specific chemoprophylaxis

- Transplant recipients living with HIV should receive the same surveillance, prophylaxis and immunisation regimens for OIs as HIV-negative SOT recipients
- Screening and treatment for latent TB is a priority, see page 116

Viral hepatitis co-infection

- The efficacy and safety of DAAs in liver transplant recipients living with HIV with HCV recurrence is the same as in HIV-negative recipients
- Anti HBV treatment should follow the same schedules of HIV-negative persons

Immunosuppressive regimens

- Same as in HIV-negative transplant recipients. The risk of acute rejection is however double of that of HIV-negative SOT recipients and, therefore, requires close monitoring
- Special attention to interaction with ART, see Drug-drug Interactions between Immunosuppressants (for SOT) and ARVs
- Using a pharmacological booster (RTV or COBI) and some of the NNRTIs should be used with caution and requiring close monitoring of immunosuppressive drugs, see Drug-drug Interactions between Immunosuppressants (for SOT) and ARVs

i Milan criteria: solitary tumor smaller than 5 cm or 2 - 3 tumors of < 3 cm in the absence of macrovascular tumor invasion and extrahepatic metastases

Drug-drug Interactions between Immunosuppressants (for SOT) and ARVs

Immunosuppressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
CS	prednisone	↑	↑	↑	↑	↑	↔	↓20%	↓	↓	↔	↔	↔	E11%	↑	↔	↔	↔	↔	↔	↔
AM	azathioprine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	mycophenolate	↔	↓a	↔	↓a	↓a	↔	↓a	↔	↓a D13%	↔	↔	↔	↔	↔	↔	↓?	↔	↔	↔	↑ Eb
CNI	cyclosporine	↑a	↑a	↑a	↑a	↑a	E	↓a	↓a	↓a	E	E	E	↔	↑a	↔	↔	↔	↔	E	Eb
	tacrolimus*	↑a	↑a	↑a	↑a	↑a	↓a	↓a	↓a	↓a	↔	↔	↔	↔	↑a	↔	↔	↔	↔	↔	↔b
mTOR	everolimus	↑	↑	↑	↑	↑	↔	↓a	↓a	↓a	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	sirolimus	↑	↑	↑	↑	↑	↓a	↓a	↓a	↓a	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔b
Other	anti-thymocyte globulin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	basiliximab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	belatacept	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

Legend

↑ Potential increased exposure of the immunosuppressant
↓ Potential decreased exposure of the immunosuppressant
↔ No significant effect
D Potential decreased exposure of ARV drug
E Potential elevated exposure of ARV drug

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

* available as prolonged release formulation

Numbers refer to increased or decreased AUC as observed in drug-drug interaction studies

AM antimetabolite
CNI calcineurin inhibitors
CS corticosteroids
mTOR mTOR inhibitors

Interactions with ZDV
Azathioprine (potential risk of additive hematotoxicity).
Mycophenolate (potential alteration in mycophenolate level, monitor plasma concentrations)

Interactions with ibalizumab
none

Comments
a TDM of immunosuppressant is recommended
b Monitor renal function

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Part V Clinical Management and Treatment of Viral Hepatitis Co-infections in PLWH

Every person with HCV/HIV co-infection should receive DAA therapy to eradicate HCV, regardless of liver fibrosis stage. Cure of HCV infection substantially reduces the risk for hepatic and extrahepatic complications and eliminates onward HCV transmission. DAAs achieve similar cure rates and tolerability in HCV/HIV co-infected compared to HCV mono-infected persons. Therefore, treatment indication and regimens are the same as in HCV mono-infected persons. All persons with HBV/HIV co-infection should receive ART including TDF or TAF, unless history of tenofovir intolerance. All HBsAg-positive persons should be screened for Hepatitis Delta (HDV)

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

Screening at baseline

1. PLWH should be screened for HCV at time of HIV diagnosis and annually thereafter[i]. Screening should use an anti-HCV antibody test[ii]
   A positive result should be followed by HCV-RNA[iii] and genotype determination. Alternatively, HCV core-antigen testing can be performed to establish chronic HCV infection. PLWH engaging in activities associated with increased risk of HCV transmission[iv] should be tested for HCV infection every 3 to 6 months. PLWH suspected of recently acquired primary HCV infection with a negative anti-HCV antibody test should be tested for HCV-RNA. HCV-RNA or HCV core-antigen testing is also recommended in PLWH with ongoing risk behavior for HCV re-infection after successful treatment or spontaneous clearance at 3 to 6-monthly intervals
2. PLWH should be screened for HAV and HBV. PLWH 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. HDV antibodies should be screened for in all HBsAg positive persons.
4. PLWH with viral hepatitis co-infection should be assessed for concurrent causes of liver disease such as alcohol consumption, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases (e.g. genetic haemochromatosis, diabetes mellitus or obesity) and drug-induced hepatotoxicity
5. Status of liver damage should be assessed in all PLWH with viral hepatitis co-infection with a complete blood count, ALT, AST, GGT, ALP, hepatic synthetic function (e.g. coagulation, albumin, cholinesterase) and staging of fibrosis (e.g. FibroScan, liver biopsy, serum fibrosis markers[v], see Table on cut-off values of non-invasive tests for the detection of significant fibrosis and cirrhosis

Screening for complications

6. HCC screening is indicated in all cirrhotic HBV or HCV co-infected PLWH (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in persons with F3 fibrosis is uncertain, surveillance may be considered based on an individual risk assessment, see page 52. In HBV-positive non-cirrhotics, HCC screening should follow current HCC EASL guidelines (https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/). Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV co-infection and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH, see pages 8, 52 and 71
7. Screening for oesophageal varices upon diagnosis of cirrhosis in co-infected persons is also indicated (every 2-3 years thereafter according to presence of ongoing liver disease if negative for oesophageal varices at initial screening), see page 70

End Stage Liver Disease (ESLD)

8. PLWH with liver cirrhosis require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative persons, see page 70-71 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. ART in cirrhotic PLWH improves overall survival
10. PLWH with HCC or a MELD-score > 15[vi], CD4 count > 100 cells/µL and options for efficacious and durable ART should be evaluated for liver transplantation (OLTX), see Solid Organ Transplantation (SOT) in PLWH
11. Renal complications are frequent, see page 64 and Diagnosis and Management of Hepatorenal Syndrome (HRS)

Vaccination, see page 79

12. PLWH 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 PLWH 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 recommended in this population. However, if anti-HBc results are not available, HBV vaccination is recommended in all HBs-Ag negative persons
13. In PLWH 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 and ART including TDF or TAF is recommended

Prevention/Support

14. Psychiatric, psychological, social and medical support should be made available to persons with alcohol intake to stop drinking
15. 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 programs) reduces the risk of re-infection including parenteral viral transmission (harm reduction strategy), see Drug Dependency and Drug Addiction
16. 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 ongoing IDU, “chemsex” (sex under the influence of recreational drugs taken predominantly intravenously immediately before and/or during sexual contacts)[iv], should be provided and risk reduction should be discussed
17. In women of childbearing age, HCV treatment should be initiated prior to conception because of limited safety data in pregnancy, and to reduce the risk of MTCT of HCV

i Screening intervals to detect recently acquired HCV infection should be adapted to individual risk assessments and local epidemiology as described in the European AIDS Treatment Network (NEAT) consensus conference statement, www.neat-id.org

ii Anti HCV-Antibodies: turn positive 1-6 months after infection; late seroconversions have been described; may rarely be lost due to immunosuppression

iii 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

iv Risk for percutaneous HCV transmission by sharing equipment for injection drug use; risk for mucosal HCV transmission including fisting, receptive condomless anal intercourse, sharing equipment during nasally administered drug use, sharing sex toys, sharing anal douching equipment, and engaging in sexual intercourse causing rectal trauma with bleeding; the presence of ulcerative sexually transmitted infections (STIs) increases the risk of HCV transmission

v Serum fibrosis markers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices. The combination of blood biomarkers, of liver stiffness measurement and blood tests or repeated assessments may improve accuracy (https://easl.eu/publication/easl-recommendations-treatment-of-hepatitis-c/) and page 102. For HCC, see General Recommendation for Persons with Viral Hepatitis/HIV Co-infection, Cancer: Screening Methods and Liver Cirrhosis: Management

vi MELD calculation, see page 71

Treatment and Monitoring of Persons with HBV/HIV Co-infection

Treatment indication

1. All PLWH with HBV/HIV co-infection should receive ART that includes TDF or TAF unless history of tenofovir intolerance
2. Stopping anti-HBV active 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

Treatment selection

3. If TDF or TAF is strictly contraindicated, entecavir may be prescribed in PLWH with no prior 3TC exposure and together with fully active ART
4. PLWH 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 (for management of cirrhotic PLWH, see pages 70-74). Please note that diagnosis of cirrhosis may be difficult in persons already on HBV treatment
5. Caution is warranted to switch from a TDF/TAF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pre-treated cirrhotic PLWH 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
6. Prior to ART simplification with a regimen without TDF/TAF, HBV status should be re-checked
7. For HBV/HIV co-infected persons with BMD changes or CKD, see recommendations for Dose Adjustment of ARVs for Impaired Renal Function and pages 61-66

Treatment goal

8. The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy. In those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously in non-cirrhotic HBeAg-positive PLWH who have achieved HBe-seroconversion for at least one year or after confirmed HBs-seroconversion in those who are HBeAg-negative. In PLWH with liver cirrhosis, stopping of effective anti-HBV treatment is not recommended, in order to avoid liver decompensation due to flares of liver enzymes

Treatment monitoring

9. Liver blood tests should be performed every 3 months during the first year and every 6-12 months thereafter
10. HBV-DNA should be determined every 3-6 months during the first year and every 12 months thereafter
11. HBsAg should be checked at 12 months intervals at least until loss of HBsAg

HBV reactivation

12. In HBs-Ag negative, anti-HBc positive PLWH undergoing immunosuppression:
    - Those treated with severe immunosuppressive therapy (chemotherapy for lymphoma/leukaemia or stem-cell or solid-organ transplantation) should receive TDF/TAF therapy to prevent HBV reactivation. For persons with other markers of possible HBV exposure including isolated anti-HBs positivity (without a history of vaccination) careful monitoring for HBV reactivation is required
    - In PLWH treated with B-cell-depleting agents (rituximab, ofatumumab, natalizumab, alemtuzumab, ibritumomab) TDF/TAF should be part of the ART. If TDF/TAF is contraindicated, second line options include 3TC and FTC. However, cases of reactivation due to 3TC resistance have been described
    - In those not treated with HBV-active ART who receive other immunosuppressive therapy (e.g. TNF alpha inhibitor), careful monitoring with HBV-DNA and HBsAg is required for HBV reactivation. If this is not possible, addition of TDF/TAF is recommended

Treatment and Monitoring of Persons with HCV/HIV Co-infection

Treatment indication

1. Every person with HCV/HIV co-infection must be considered for DAA-based (IFN- and preferably also RBV-free) anti-HCV treatment regardless of liver fibrosis stage
2. Due to similar HCV cure rates and tolerability in HCV/HIV co-infected persons as in HCV mono-infected persons under DAA therapy, treatment indication and regimens are to be the same as in HCV mono-infection

Treatment selection

3 IFN- and preferably also RBV-free DAA combinations are now standard of care for chronic HCV see Tables HCV Treatment Options in HCV/HIV Co-infected Persons. IFN-containing HCV regimens are no longer recommended. For diagnostics and management of IFN-containing HCV regimens please refer to previous versions of these Guidelines, available online at http://www.eacsociety.org/files/guidelines_8.2-english.pdf

4. Selection of DAA combinations is based upon HCV GT(i), stage of liver fibrosis, pre-treatment history and resistance-associated substitutions (RAS) if tested
5. Use of older, first generation HCV PIs (boceprevir and telaprevir) are no longer recommended because of increased toxicities
6. Due to drug-drug interactions in particular with 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
7. Resistance testing, if available, should be considered before re-treatment of persons who failed after a PI-and/or NS5A inhibitor-containing agent. The triple combination of SOF/VEL/VOX for 12 weeks is the treatment of choice for re-treatment, especially if resistance testing is not available. In persons with complex mutations patterns SOF+GLE/PIB + RBV for 12-16 weeks can also be considered. In case of unavailability of SOF/VEL/VOX or SOF + GLE/PIB other regimens with at least two active DAAs could be combined with the preferential use of one drug with high genetic barrier to resistance and with extended treatment durations and potentially addition of RBV. In patients with decompensated cirrhosis SOF/VEL + RBV for 24 weeks is the only available option for re-treatment in case of contraindication to liver transplantation

Treatment goal

8. The primary aim of HCV treatment is SVR_{12} defined as undetectable HCV-RNA 12 weeks after the end of therapy (evaluated using sensitive molecular tests) or HCV core antigen levels where HCV- RNA assays are not available or not affordable. SVR_{12} corresponds to a definitive cure of HCV infection in the vast majority of cases

i If the PLWH is a candidate for pangenotypic drugs, HCV GT determination is not mandatory before starting anti-HCV treatment. Re-testing 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 reinfection of 'super-infection' for whom the GT/sub-type should be performed on most recent available specimen

See online video lectures HCV/HIV Co-infection-Part 1, HCV/HIV Co-infection-Part 2 and HCV/HIV Co-infection-Part 3 from the EACS online course Clinical Management of HIV

Treatment monitoring

9. In PLW with advanced fibrosis (≥ F3) differential blood count, creatinine, liver enzymes, bilirubin, albumin and INR measurement after 2-4 weeks of therapy is recommended. In HBsAg negative PLWH with positive anti-HBc, monitoring of ALT and HBV-DNA in case of ALT elevation is recommended
10. In PLWH with impaired renal function undergoing SOF based treatment creatinine should also be monitored
11. HCV-RNA measurement during therapy should only be performed in order to assess compliance and/or break-through in PLWH experienced to oral DAAs; HCV-RNA should be measured at end-of-treatment and at week 12 or 24 after treatment cessation (to assess SVR). In PLWH receiving all oral DAA therapy, no association between viral load at any given time-point during therapy and SVR has yet been found. If HCV-RNA determination is not available SVR can be identified by a negative HCV core antigen 24 weeks after treatment end
12. HIV-VL every 12 weeks

Post-Treatment monitoring

13. Surveillance for HCC and for oesophageal varices should be continued if the respective indications were present pre-treatment, despite achieving SVR, see pages 8, 52, 70 and 71
14. All PLWH with concurrent causes of liver disease should undergo periodical clinical assessments
15. Increase in body weight and changes in lipid and glucose metabolism have been described after SVR. Thus, surveillance, counseling and treatment for obesity and metabolic alterations should be enforced after SVR, see page 75

Treatment of recently acquired HCV infection

16. IFN-containing HCV regimens are no longer recommended. For diagnostics and management of IFN-containing HCV regimens please see online EACS Guidelines v8.2 at http://www.eacsociety.org/files/ guidelines_8.2-english.pdf
17. After diagnosis of recently acquired HCV infection, HCV-RNA should be re-measured 4 weeks later. Treatment is recommended in PLWH without a decrease of 2*log of HCV-RNA at 4 weeks compared with initial HCV-RNA, due to the very low probability of spontaneous clearance, and in persons with persistent serum HCV-RNA 12 weeks after diagnosis of recently acquired HCV, see Algorithm for Management of Recently aquired HCV in Persons with HIV Co-infection. HCV treatment immediately after diagnosis is recommended in PLWH with ongoing risk behavior to reduce onward transmission. IFN-free treatment with DAAs is recommended as in treatment naïve persons without cirrhosis (except for those with pre-existing cirrhosis), see pages 98-99
18. For more detailed information on the management of recently acquired HCV infection we refer to the European AIDS Treatment Network (NEAT) consensus conference guideline, www.neat-id.org

HCV Treatment Options in HCV/HIV Co-infected Persons

Preferred DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors)				
HCV GT	**Treatment regimen**	**Treatment duration & RBV usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 4	**EBR/GZR**	**12 weeks**[i]		Not recommended
	GLE/PIB	**8 weeks**	**12 weeks**	Not recommended
	SOF/VEL	**12 weeks**		**12 weeks with RBV**[viii]
	SOF/LDV +/- RBV	**8-12 weeks without RBV**[ii]	**12 weeks with RBV**[iii]	**12 weeks with RBV**[viii]
2	**GLE/PIB**	**8 weeks**	**12 weeks**	Not recommended
	SOF/VEL	**12 weeks**		**12 weeks with RBV**[viii]
3	**GLE/PIB**	**8 weeks**[iv]	**12 weeks**[iv]	Not recommended
	SOF/VEL +/- RBV	**12 weeks**[v]	**12 weeks with RBV**[vi]	**12 weeks with RBV**[viii]
	SOF/VEL/VOX	**-**	**12 weeks**	Not recommended
5 & 6	**GLE/PIB**	**8 weeks**	**12 weeks**	Not recommended
	SOF/LDV +/- RBV	**12 weeks +/- RBV**[vii]	**12 weeks with RBV**[iii]	**12 weeks with RBV**[viii]
	SOF/VEL	**12 weeks**		**12 weeks with RBV**[viii]

EBR = elbasvir
GLE = glecaprevir
GZR = grazoprevir
LDV = ledipasvir
PIB = pibrentasvir
RBV = ribavirin
SOF = sofosbuvir
VEL = velpatasvir
VOX = voxilaprevir
RAS = resistance associated substitutions

i In PLWH with GT1a with baseline HCV-RNA < 800.000 IU/mL and/or absence of NS5A RASs, as well as in treatment-naïve PLWH with GT4 with HCV-RNA <800.000 IU/mL. In GT 1b treatment-naïve PLWH with F0-F2 fibrosis 8 weeks can be considered
ii 8 weeks treatment without RBV only in treatment-naïve PLWH with F <3 and baseline HCV-RNA <6 million IU/mL
iii RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS. In persons intolerant to RBV, treatment may be prolonged to 24 weeks
iv Treatment duration in HCV GT3 who failed previous treatment with IFN and RBV +/- SOF or SOF and RBV should be 16 weeks
v In treatment experienced PLWH RBV should be added unless NS5A RASs are excluded; if these persons are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV
vi If RAS testing is available and demonstrates absence of NS5A RAS Y93H, RBV can be omitted in treatment naive PLWH with compensated cirrhosis
vii In treatment experienced (exposure to IFN/RBV/SOF) PLWH add RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV
viii In persons intolerant to RBV, treatment may be prolonged to 24 weeks

DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors) to be used if preferred option is not available				
HCV GT	**Treatment regimen**	**Treatment duration & RBV usage**		
		Non-cirrhotic	**Compensated cirrhotic**	**Decompensated cirrhotics CTP class B/C**
1 & 4	OBV/PTV/r + DSV	8[i]-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
	SOF + DCV +/- RBV	12 weeks +/- RBV[ii]	12 weeks with RBV[iii]	
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended
3	SOF + DCV +/- RBV	12 weeks +/- RBV[v] or 24 weeks without RBV	24 weeks with RBV	
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended
5 & 6	SOF + DCV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV[vi]	12 weeks with RBV[iii]	
	SOF/VEL/VOX	8 weeks[iv]	12 weeks	Not recommended

DCV = daclatasvir
DSV = dasabuvir
OBV = ombitasvir
PTV/r = paritaprevir/RTV
RBV = ribavirin
SOF = sofosbuvir
VEL = velpatasvir
VOX = voxilaprevir
RAS = resistance associated substitutions

i 8 weeks treatment without RBV only in PLWH without cirrhosis
ii Addition of RBV in GT1a treatment experienced PLWH, but not in PLWH without NS5A RASs, if RASs testing is available
iii In PLWH intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS
iv Extension of treatment to 12 weeks in DAA treatment experienced PLWH
v Addition of RBV only in treatment experienced persons with baseline NS5A RASs, if RAS testing available; if these PLWH are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV
vi In treatment experienced (exposure to IFN/RBV/SOF) PLWH RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV

Drug-drug Interactions between DAAs and ARVs

HCV drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
DAAs	daclatasvir	↑31% a	↑110% a	↑	↑41%	↑15%	↔	↓32% b	↓	↓	↔	↔	↔	↓2% E33%	↑ a	↔	↔	↔	↔	↔	↑10% E10%
	elbasvir/ grazoprevir	↑	↑376% ↑958%	↑	↑66% ↑650%	↑271% ↑1186%	↓4% ↑7%	↓54% ↓83%	↓	↓	↑7% ↓2%	↔	↔	↓2% ↓19%	↑118% ↑436%	↓19% ↓11%	↔	↔	↔	↔	↓7% ↓14%
	glecaprevir/ pibrentasvir	↑	↑553% ↑64%	↑	↑397% -	↑338% ↑146%	↔	↓	↓	↓	E 84%	E	E	↔	↑205% ↑57% E47%	E47%	↔	↔	↔	↔	E29%
	paritaprevir/r/ ombitasvir/ dasabuvir	↑	↑94% ↓17% ↓18% c	↑	D d	↑117% ↑17% ↓7%	E	f	↓	↓E	E 225% g	E	E	↓16% ↓5% ↓2%	↑	E134%	↓18% ↓9% ↓9%	↓16% ↓1% ↓15%	↓18% ↓9% ↓9%	E	↓16% ↓1% ↓15%
	paritaprevir/r/ ombitasvir	↑	↑187% c	↑	↑ e	↑510% -	E	f	↓	↓E	E g	E	E	↔	↑	E20%	↔	↔	↔	E	↔
	simeprevir	↑	↑	↑	↑159%	↑	↔	↓71%	↓	↓	↑6% E12%	↔	↔	↔	↑	↓11% E8%	↔	↔	↔	↔	↓14% E18%
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↓6%	↔	↔	↑9%	↔	↔	↔	↔	↓5% D27%	↔	↓6%	↔	↔	↓6%
	sofosbuvir/ ledipasvir	↑ h	↑8% ↑113% h	↑ h	↑34% ↑39% h	↔ h	↑4% ↓8%	↓6% ↓34%	↔	↔	↑10% ↑8% h	E	↑7% ↓13%	↔	↑36% ↑78% h	↓5% ↓9% D~20%	↑21% ↑18% D 10%	↔	↑21% ↑18% D 6%	E32%	E h
	sofosbuvir/ velpatasvir	↔ h	↑22% ↑142% h	↔ h	↓28% ↓16% h	↓29% ↑2% h	↔	↓3% ↓53%	↓	↓	↑16% ↓1%	E	↔	↓8% ↓9%	↑ h	↑24% ↓2%	↔	↔	↔	↔	E h
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40% ↑93% ↑331%	↑ h	↓28% ↓5% ↑143% i	↑	↔	↓	↓	↓	↔	E	↑9% ↓4% ↓9%	↔	↑22% ↑16% ↑171% h	↔	↔	↔	↔	E	E h

Colour legend

- No clinically significant interaction expected
- These drugs should not be co-administered
- Potential clinically significant interaction that is likely to require additional monitoring, alteration of drug dosage or timing of administration
- Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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

ATV/c ATV co-formulated with COBI (300/150 mg qd)
DRV/c DRV co-formulated with COBI (800/150 mg qd)

Numbers refer to decreased/increased AUC as observed in drug interactions studies.
First/second numbers refer to AUC changes for EBR/GZR or GLE/PIB or SOF/LDV or SOF/VEL.
First/second/third numbers refer to AUC changes for SOF/VEL/VOX

Interactions with ZDV
No clinically relevant interactions expected with ZDV and DAAs

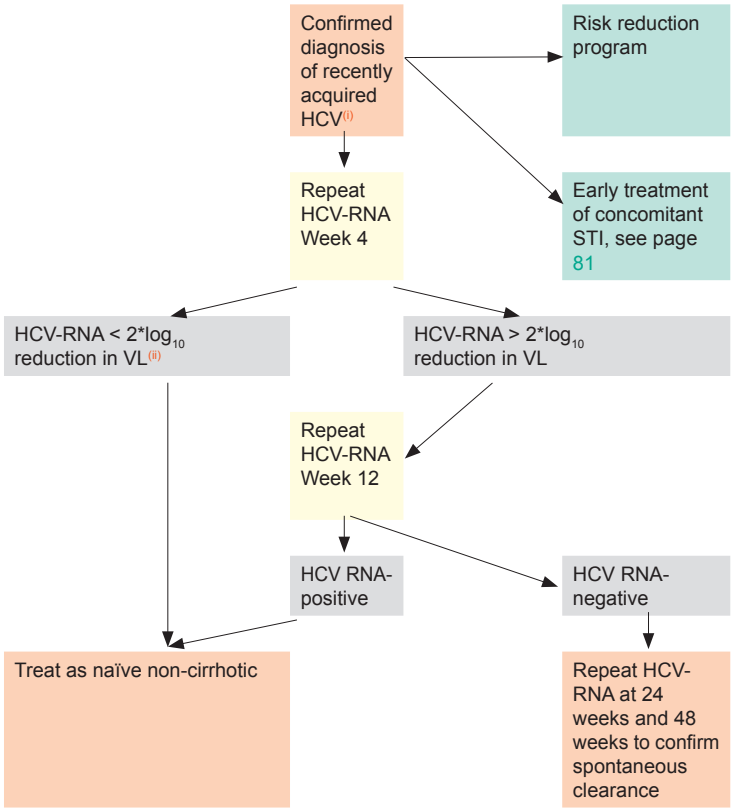
Interactions with ibalizumab
none

Comments

a DCV should be reduced to 30 mg qd with ATV/c, ATV/r or EVG/c. No dose reduction with unboosted ATV
b DCV should be increased to 90 mg qd
c Study details are with unboosted ATV. Use only with unboosted ATV (ATV increased PTV exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without DSV)
d Co-administration decreased DRV trough concentration by ~50%. Although co-administration of DRV with OBV/PTV/r + DSV is not recommended in the US Prescribing Information, the European SmPC advises that DRV (dosed at 800 mg qd and administered at the same time as OBV/PTV/r + DSV) can be used in the absence of extensive HIV PI resistance and should be taken without additional RTV
e Not recommended due to increase in PTV exposure when co-administered with DRV 800 mg given with OBV, PTV, RTV (Viekirax). Of note: exposures of PTV greater than this have been evaluated in phase 2 studies and were not expected to have a clinically meaningful impact on safety
f Severe tolerability issues
g Not recommended unless benefit outweighs the risk due to potential for QT interval prolongation with higher concentrations of RPV. Co-administration should be only considered in persons without known QT prolongation and without other QT prolongation co-medicines
h Monitoring of kidney function recommended due to increase of tenofovir concentration if the regimen contains TDF
i Study details are with once daily DRV/r. Twice daily DRV has not been studied and should be used with caution as VOX concentrations may increase more than with once daily DRV (this would be of further significance in cirrhotic patients). Monitoring of kidney function recommended due to increase of tenofovir concentrations if the regimen contains TDF

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to http://www.hiv-druginteractions.org (University of Liverpool)

Algorithm for Management of Recently Acquired HCV Infection in PLWH



i Where available initiate DAA-based treatment immediately in persons with risk of onward transmission

ii HCV-RNA < 2*$\log_{10}$ reduction at week 4 is considered as early chronic HCV infection (eg: 2*$\log_{10}$ reduction = reduction from 100 000 to 1000 IU/mL)

Cut-off Values of Non-invasive Tests for the Detection of Advanced Fibrosis and Cirrhosis

HIV/Hepatitis C co-infection (according to EASL recommendations on Treatment of Hepatitis C 2018 [1])

Test	Stage of fibrosis	Cut off	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Fibroscan	F3*	10 kPa	72	80	62	89
	F4*	13 kPa	72-77	85-90	42-56	95-98
APRI	F4	2	48	94	n.a.	n.a.
		1	77	75	n.a.	n.a.
Fib-4	F4	3.25	55	92	n.a.	n.a.
		1.45	90	58	n.a.	n.a.

These cut-offs were derived from different studies and the optimal values might vary between populations and must be interpreted together with the individual clinical assessment
*The distinction between F3 and F4 is often imprecise and must be interpreted in the individual clinical context

HIV/Hepatitis B co-infection [2], [3], [4]

Test	Stage of fibrosis	Cut off	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Fibroscan	F3	7.6 kPa	85	87	77	92
	F4	9.4 kPa	92	94	79	98
APRI	F4	2	35	89	26	92
		1	65	75	22	95

Hepatitis D and E in PLWH

Hepatitis Delta Virus (HDV)

1. HDV antibodies should be screened for in all HBsAg positive PLWH
2. In PLWH with positive HDV antibodies, HDV-RNA should be measured in order to assess activity of the disease
3. In PLWH with chronic HDV co-infection and significant liver fibrosis (≥ F2), long-term (at least 12 months) treatment with PEG-IFN might be considered in association with TDF-based ART
4. Non-invasive fibrosis markers (transient elastography and serum markers) should be used with caution in PLWH with chronic HDV infection as there are no well-established thresholds
5. Because of its anti-HBV activity, TDF/TAF should be added to PEG-IFN in order to reduce HBV-DNA load
6. PLWH without response to PEG-IFN treatment should be referred to university centers and if possible enrolled in trials on new drugs active against HDV
7. Treatment efficacy should be monitored with HBV-DNA and HDV-RNA measurements, when available, and with follow-up of biochemical and liver fibrosis estimates
8. Persistent off-treatment HDV-RNA negativity and anti-HBs seroconversion are the ideal goals of antiviral treatment for HDV even if they can only be obtained in a minority of PLWH. Histological remission of liver disease is a less ambitious but more likely achievable goal
9. In PLWH with HDV and ESLD or HCC, liver transplantation from HBsAg negative donors should be strongly considered. Transplant with anti-HBV prophylaxis post-OLTX cures HBV and HDV infection

Hepatitis E Virus (HEV)

10. Screening for HEV infection is warranted in PLWH with symptoms consistent with acute hepatitis, unexplained flares of aminotransferases (even if suspected drug induced liver injury), unexplained elevated liver function tests, neuralgic amyotrophy, Guillain-Barrè, encephalitis or proteinuria
11. Screening should include anti-HEV IgG and IgM and HEV-RNA in blood and if possible in stool
12. Treatment with RBV (600 mg daily) may be considered in cases of severe acute HEV, acute-on-chronic liver failure, extrahepatic HEV related disease or in persons with persisting HEV replication three months after first detection of HEV-RNA. RBV should be given for a duration of 12 weeks followed by HEV-RNA measurements in serum and stool. If HEV-RNA is undetectable in both, RBV can be stopped. In PLWH in whom HEV-RNA is still detectable in serum and/or stool, RBV may be continued for an additional three months. In the setting of chronic HEV infection in immunosuppressed persons, reduction in immunosuppression should be considered

Part VI Opportunistic Infections

This section provides:
- Recommendations for timing on ART initiation in PLWH with OIs without prior ART exposure
- Overview of IRIS and recommendations on its management
- Overview of the most important aspects in management of the most frequent OIs occurring in PLWH in Europe

For more detailed discussion, we refer to national guidelines

See online video lectures HIV and the Management of IRIS-Part 1, HIV and the Management of IRIS-Part 2, HIV and Pulmonary Infections-Part 1, HIV and Pulmonary Infections-Part 2, HIV and Pulmonary Infections-Part 3, CNS and HIV-related opportunistic infections-Part 1, CNS and HIV-related opportunistic infections-Part 2, Tuberculosis and HIV Co-infection-Part 1 and Tuberculosis and HIV Co-infection-Part 2 from the EACS online course Clinical Management of HIV

When to start ART in PLWH with Opportunistic Infections (OIs)

	CD4 count	Initiation of ART	Comments
General recommendation	Any	As soon as possible and within 2 weeks after starting treatment for the opportunistic infection	
Tuberculosis	< 50 cells/μL > 50 cells/μL	As soon as possible and within 2 weeks after starting TB treatment Can be delayed up to 8 weeks after starting TB treatment, especially if difficulties with adherence, drug-drug-interactions or toxicity	A threshold of 100 cells/μL may be more appropriate due to variability in CD4 count assessments CD4 thresholds also apply for TB meningitis – with close monitoring due to increased risk of adverse effects For details, see ART in TB/HIV Co-infection section, page 20
Cryptococcal meningitis	Any	Defer initiation of ART for at least 4 weeks (some specialists recommend a delay of 6-10 weeks in severe cryptococcal meningitis)	
CMV end organ disease	Any	A delay of a maximum of 2 weeks might be considered	Especially for persons with chorioretinitis and encephalitis due to risk of IRIS

Immune Reconstitution Inflammatory Syndrome (IRIS)

Definition	
Paradoxical IRIS	**Paradoxical worsening** symptoms during the ART-induced immune-reconstitution period in association with inflammatory signs (by physical exam, imaging or tissue biopsy), after exclusion of the expected course of a treated/untreated OI or drug toxicities [1]
Unmasking IRIS	**New onset** of symptoms during the ART-induced immune-reconstitution period in association with inflammatory signs (by physical exam, imaging or tissue biopsy), after exclusion of the expected course of a treated/untreated OI or drug toxicities [1]
Prevention	
Cryptococcal meningitis:	
paradoxical IRIS	Start therapy with **amphotericin B plus flucytosine** and defer start of ART for at least 4 weeks.
unmasking IRIS	Determine serum cryptococcal antigen in newly diagnosed PLWH with CD4 counts < 100 cells/μL. If cryptococcal antigen is detected, exclude active cryptococcal disease, and, in particular, examine CSF to rule out cryptococcal meningitis. If meningitis is ruled out, start pre-emptive therapy. For details, see below the specific section on cryptococcal disease
Tuberculosis	
paradoxical IRIS	Simultaneous initiation of ART and prophylactic prednisone in persons with CD4 cell count < 100 cells/μL, who started anti-TB treatment within 30 days prior to ART, may reduce risk of TB-IRIS by 30%. **Prednisone** dose: 40 mg qd po for 2 weeks, followed by 20 mg qd po for 2 weeks [2]
Treatment	
In general, OI-IRIS resolve within a few weeks with continuation of specific treatment for the OI, without discontinuing ART and without anti-inflammatory treatment In cases where anti-inflammatory treatment is contemplated by the physician, corticosteroids or non-steroidal anti-inflammatory agents can be used. However, little or no data support their use or specific administration schedules in the specific conditions	
TB-IRIS	Start of systemic corticosteroids is recommended (e.g., prednisone 1.5 mg/kg/day po for 2 weeks, then 0.75 mg/kg/day for 2 weeks) [3]
Life-threatening CNS-IRIS:	
TB-meningitis	**Prednisone** (1.5 mg/kg/day po for 2 weeks, then tapering) [4]
PML	**Methylprednisolone** (1 g/day iv for 3-5 days or dexamethasone 0.3 mg/kg/day iv for 3-5 days), then oral tapering

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* infection **Stop:** if CD4 count > 100 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	**trimethoprim-sulfamethoxazole (TMP-SMX)**	800/160 mg x 3/week po or 400/80 mg qd po or 800/160 mg qd po	
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL sterile water x 1 inhalation/month	Does not prevent the rare extrapulmonary manifestations of *P. jirovecii*
Negative serology for toxoplasmosis	**dapsone**	100 mg qd po	Check for G6PD-deficiency
Negative serology for toxoplasmosis	**atovaquone suspension**	1500 mg qd (with food)	
Positive serology for toxoplasmosis	**dapsone** **+ pyrimethamine** **+ folinic acid**	200/mg week po 75/mg week po 25-30/mg week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	**atovaquone suspension** **+/- pyrimethamine** **+ folinic acid**	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	
CD4 count < 50 cells/µL			
Prophylaxis against Non-Tuberculous Mycobacteria (NTM) *(M. avium* complex, *M. genavense, M. kansasii)* Prophylaxis is not recommended if ART is started Prophylaxis may be considered for persons with CD4 counts < 50 cells/µL who remain viraemic on ART (drug resistant HIV with no option to achieve virologic control); exclude disseminated MAC disease before starting			
Regimens listed are alternatives	**azithromycin**	1200-1250 mg/week po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
	or **clarithromycin**	500 mg bid po	
	or **rifabutin**	300 mg qd po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs Active TB should be ruled out before starting **rifabutin**

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 Primary Prophylaxis of OIs **Stop:** if CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months			
	Drug	**Dose**	**Comments**
Negative or positive serology for toxoplasmosis	**TMP-SMX**	800/160 mg x 3/week po or 400/80 mg qd po or 800/160 mg qd po	
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL sterile water x 1 inhalation/month	Does not prevent the rare extrapulmonary manifestations of *P. jirovecii*
Negative serology for toxoplasmosis	**dapsone**	100 mg qd po	Check for G6PD-deficiency
Negative serology for toxoplasmosis	**atovaquone suspension**	1500 mg qd po (with food)	
Positive serology for toxoplasmosis	**dapsone**	200 mg/week po	Check for G6PD-deficiency
	+ pyrimethamine	75 mg/week po	
	+ folinic acid	25-30 mg/week po	
Positive serology for toxoplasmosis	**atovaquone suspension** **+/- pyrimethamine** **+ folinic acid**	1500 mg qd po (with food) 75 mg/week po 25-30 mg/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 dyspnoea on exertion AND microorganism identification by cytology / histopathology of induced sputum (sensitivity up to 80%), broncho-alveolar lavage (sensitivity > 95%) or bronchoscopic tissue biopsy (sensitivity > 95%) **Presumptive diagnosis:** CD4 count < 200 cells/ µL AND dyspnoea / 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**	5 mg/kg tid TMP iv/po + 25 mg/kg tid 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 treatment	40 mg bid po 5 days 40 mg qd po 5 days 20 mg qd po 10 days	Benefit of corticosteroids if started within 72 hours after start of treatment
Alternative therapy for *moderate to severe* PcP	**primaquine**	30 mg (base) qd po	Check for G6PD deficiency
	+ clindamycin	600-900 mg tid iv/po	
	or **pentamidine**	4 mg/kg qd 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 or other echinocandins** to standard treatment in persons with severe PcP (requiring intensive care unit admission)	40 mg bid po 5 days 40 mg qd po 5 days 20 mg qd po 10 days **Caspofungin** 70 mg qd iv day 1, then 50 mg qd iv	Benefit of corticosteroids if started within 72 hours after start of treatment
Alternative therapy for *mild to moderate* PcP	**primaquine**	30 mg (base) qd po	Check for G6PD deficiency
	+ clindamycin	600-900 mg tid po	
	or		
	atovaquone suspension	750 mg bid po (with food)	
	or		
	dapsone	100 mg qd po	Check for G6PD deficiency In case of rash: reduce dose of TMP (50%), use antihistamines
	+ trimethoprim	5 mg/kg tid po	

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**	800/160 mg x 3/week po or 400/80 mg qd po	
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL sterile water x 1 inhalation/month	Not to use in the rare case of extrapulmonary manifestations of *P. jirovecii*
Negative serology for toxoplasmosis	**dapsone**	100 mg qd po	Check for G6PD-deficiency
Negative serology for toxoplasmosis	**atovaquone suspension**	1500 mg qd po (with food)	
Positive serology for toxoplasmosis	**dapsone** **+ pyrimethamine** **+ folinic acid**	200 mg/week po 75 mg/week po 25-30 mg/week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	**atovaquone suspension** **+/- pyrimethamine** **+ folinic acid**	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	

Toxoplasma gondii Encephalitis

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 > 100 cells/µL and HIV-VL undetectable over 3 months			
	Drug	**Dose**	**Comments**
Preferred prophylaxis	**TMP-SMX**	800/160 mg x 3/week po or 400/80 mg qd po or 800/160 mg qd po	All regimens are also effective against PcP
Alternative prophylaxis	**atovaquone suspension**	1500 mg qd po (with food)	
	dapsone **+ pyrimethamine** **+ folinic acid**	200 mg/week po 75 mg/week po 25-30 mg/week po	Check for G6PD-deficiency
	atovaquone suspension **+ pyrimethamine** **+ folinic acid**	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	
Treatment			
Treat 6 weeks, then secondary prophylaxis until CD4 count > 200 cells/µL and HIV-VL undetectable over 6 months **Diagnosis:** **Definitive diagnosis:** clinical symptoms, typical neuroradiology AND cytological / histological detection of organism in tissue **Presumptive diagnosis:** clinical symptoms, typical neuroradiology 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 qd po, **then** • If ≥ 60 kg; 75 mg qd po • If < 60 kg: 50 mg qd po • If ≥ 60 kg: 3000 mg bid po/iv • If < 60 kg: 2000 mg bid po/iv 10-15 mg qd 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 qd po, **then** • If ≥ 60 kg: 75 mg qd po • If < 60 kg: 50 mg qd po 600-900 mg qid po/iv 10-15 mg qd po	Monitor for myelotoxicity of **pyrimethamine**, mostly neutropenia Additional PcP prophylaxis is necessary, where required
	or **TMP-SMX**	5 mg TMP/kg bid iv/po 25 mg SMX/kg bid iv/po	Preferred intravenous regimen if oral route not possible
	or **pyrimethamine** **+ atovaquone** **+ folinic acid**	Day 1: 200 mg qd po, **then** If ≥ 60 kg; 75 mg qd po If < 60 kg: 50 mg qd po 1500 mg bid po (with food) 10-15 mg qd po	Monitor for myelotoxicity of **pyrimethamine**, mostly neutropenia
	or **sulfadiazine** **+ atovaquone**	• If ≥ 60 kg: 3000 mg bid po/iv • If < 60 kg: 2000 mg bid po/iv 1500 mg bid 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 qd po, then • If ≥ 60 kg; 75 mg qd po • If < 60 kg: 50 mg qd po 900-1200 mg qd po 10-15 mg qd 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			
	Drug	**Dosage**	**Comments**
Regimens listed are alternatives	**sulfadiazine** **+ pyrimethamine** **+ folinic acid**	2000-3000 mg bid - qid po 25-50 mg qd po 10-15 mg qd po	
	or **clindamycin** **+ pyrimethamine** **+ folinic acid**	600 mg tid po 25-50 mg qd po 10-15 mg qd po	Additional PcP prophylaxis is necessary
	or **atovaquone suspension** **+ pyrimethamine** **+ folinic acid**	750-1500 mg bid po (with food) 25-50 mg qd po 10-15 mg qd po	
	or **atovaquone suspension**	750-1500 mg bid po (with food)	
	or **TMP-SMX**	800/160 mg bid po	

Cryptococcosis – disease caused by *Cryptococcus neoformans*

Treatment

Cryptococcal meningitis is the most frequent manifestation of cryptococcosis. 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

Primary prophylaxis: One large RCT in Africa (the REALITY trial [5] showed that an enhanced infection prophylaxis in severely immunosuppressed persons (< 50 CD4 cells/µL) including isoniazid 12 weeks, fluconazole 100 mg/day for 12 weeks, azithromycin 500 mg/day for 5 days and albendazole 400 mg single dose may decrease overall opportunistic infections (including cryptococcal meningitis) and mortality. Due to the different epidemiology of opportunistic infections in Africa and in Europe these results may not be extrapolated to European countries

Diagnosis: positive microscopy, OR detection of antigen in serum or CSF OR culture from CSF, blood or urine. Serum cryptococcal antigen should be performed in all newly diagnosed PLWH with CD4 counts < 100 cells/µL. See Pre-emptive therapy below

Treatment (Cryptococcal meningitis and disseminated cryptococcosis)
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

	Drug	**Dose**	**Comments**
Pre-emptive therapy	**fluconazole**	800 mg qd po for 2 weeks followed by 400 mg qd po for 8 weeks	In case of: - positive cryptococcal serum antigen - asymptomatic individual with CD4 < 100 cells/µL - cryptococcal meningitis, pulmonary or other site infection ruled out
Induction therapy	**liposomal amphotericin B** **+ flucytosine**	3 mg/kg qd iv 25 mg/kg qid po	**14 days** - Perform repeated lumbar puncture (LP), until opening pressure is < 20 cm H_20: - if CSF culture is sterile, switch to oral regimen - 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 contraindicated - **Flucytosine** dosage must be adapted to renal function - Defer start of ART for at least 4 weeks, since early initiation of ART is associated with decreased survival - Due to substantial nephrotoxicity **amphotericin B deoxycholate** should only be used, if **liposomal amphotericin B** is not available. - **Flucytosine** may not be available in all European countries. Consider replacing it by **fluconazole** 800 mg qd during the induction phase - In resource-limited settings, a large RCT suggested that one week of **amphotericin B + flucytosine** or two weeks of **fluconazole** 1200 mg qd plus flucytosine may be acceptable induction regimens [6]
	or **amphotericin B deoxycholate** **+ flucytosine**	0.7 mg/kg qd iv 25 mg/kg qid po	
Consolidation therapy	**fluconazole**	400 mg qd po (single loading dose of 800 mg on 1st day)	8 weeks. See Drug-drug Interactions between ARVs and Non-ARVs

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	200 mg qd po	See Drug-drug Interactions between ARVs and Non-ARVs

Candidiasis

Oropharyngeal Candidiasis			
Diagnosis: typical clinical appearance, see Drug-drug Interactions Between ARVs and Non-ARVs, for all azole therapies			
	Drug	**Dose**	**Comments**
Preferred alternatives	**fluconazole**	150-200 mg qd po	Once or until improvement (5-7 days)
	nystatin	3-6 lozenges at 400000 units (aprox. 4-6 mL of oral suspension)/day	7-14 days
	or **amphotericin B**	oral suspension 1-2 g bid - qid	
Oesophagitis			
Definitive diagnosis: macroscopic inspection at endoscopy, OR histology of biopsy, OR cytology of specimen from the mucosal surface **Presumptive diagnosis:** if recent onset of dysphagia AND oropharyngeal candidiasis			
	Drug	**Dose**	**Comments**
Preferred alternatives	**fluconazole**	400 mg qd or 400 mg loading dose, then 200 mg qd po	3 days 10-14 days
	consider **posaconazole** or **voriconazole** or **caspofungin** and other **echinocandins**	400 mg bid po 200 mg bid po 70 mg iv qd day 1, then 50 mg qd	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			
In high endemic regions (French Guiana), histoplasmosis is the most prevalent OI **Diagnosis:** antigen detection in blood, urine or broncho-alveolar fluid, OR positive microscopy, OR mycological culture of blood, urine, broncho-alveolar fluid, CSF or tissue biopsy, OR PCR in blood or other clinical samples. *Aspergillus* galactomannan assays may be helpful to diagnose disseminated infections as cross reactivity occurs. **Note:** CSF, which shows typically a lymphatic pleocytosis, is usually microscopy and culture negative. Detection of histoplasma antigen or antibody is more sensitive. Though, a clinical diagnosis is possible, if disseminated histoplasmosis is present and CNS infection is not explained by another cause. **Fluconazole** should not be used for treatment of histoplasmosis. Little clinical evidence is available for the use of **voriconazole** or **posaconazole**. **Be aware of interactions of azoles with ARVs**, see Drug-drug Interactions Between ARVs and Non-ARVs. Measurement of plasma concentration of **itraconazole** is advised to guide optimal treatment, and **itraconazole** oral suspension should be preferred due to better bioavailability. Serum itraconazole concentration should be at least 1 mcg/mL if measured by high-performance liquid chromatography (HPLC).			
	Drug	**Dose**	**Comments**
Severe disseminated histoplasmosis	**Induction therapy:** **liposomal amphotericin B** **Consolidation therapy:** **itraconazole**	3 mg/kg qd iv 200 mg tid po for 3 days, then 200 mg bid po	For 2 weeks or until clinical improvement For at least 12 months
Moderate disseminated histoplasmosis	**itraconazole**	200 mg tid po for 3 days, then 200 mg bid po	For at least 12 months
Histoplasma meningitis	**Induction therapy:** **liposomal amphotericin B** **Consolidation therapy:** **itraconazole**	5 mg/kg qd iv 200 mg bid - tid po	For 4-6 weeks For at least 12 months and until resolution of abnormal CSF findings
Secondary prophylaxis / Maintenance therapy			
Stop: if CD4 count > 150 cells/µL and HIV-VL undetectable over 6 months, negative fungal blood cultures, histoplasma serum antigen < 2 µg/L or negative PCR, if available, and > 1 year treatment **Consider long-term suppressive** therapy in severe cases of meningitis and in cases of relapse despite adequate treatment			
	itraconazole	200 mg qd po	

Talaromycosis (*Talaromyces* (former *Penicillium marneffei*))

Treatment [7]			
Consider diagnosis in PLWH who lived in Asia. **Diagnosis:** antigen detection in blood, urine or broncho-alveolar fluid, OR positive microscopy, OR mycological culture of blood, urine, broncho-alveolar fluid, CSF or tissue biopsy or PCR in blood OR other clinical samples. *Aspergillus* galactomanan assays may be helpful to diagnose disseminated infections as cross reactivity occurs.			
	Drug	**Dose**	**Comments**
Severe disseminated talaromycosis	**Induction therapy:** **liposomal amphotericin B** **Consolidation therapy:** **itraconazole**	3 mg/kg qd iv 200 mg tid po for 3 days, then 200 mg bid po	For 2 weeks or until clinical improvement For at least 10 weeks (followed by secondary prophylaxis)
Moderate talaromycosis	**itraconazole**	200 mg tid po for 3 days, then 200 mg bid po	For 8 weeks (followed by secondary prophylaxis)
Secondary prophylaxis / Maintenance therapy			
Secondary prophylaxis: itraconazole 200 mg qd po **Stop:** if CD4 count > 100 cells/µL and HIV-VL undetectable over 6 months, negative fungal blood cultures or negative PCR/ negative antigen			

Herpes simplex virus (HSV) infections

Treatment			
Diagnosis: antigen testing / PCR / culture of swab / CSF / biopsy. Clinical appearance of skin lesions not reliable **During treatment:** monitor renal function, adjust drug dose in renal impairment			
	Drug	**Dose**	**Comments**
Initial and recurrent genital / mucocutaneous HSV			See Sexual and Reproductive Health of Women and Men Living with HIV section, page 81
Severe mucocutaneous lesions	**aciclovir**	5 mg/kg tid iv	After lesions begin to regress, switch to oral treatment until lesions have healed
Encephalitis	**aciclovir**	10 mg/kg tid iv	14-21 days
Aciclovir resistant mucocutaneous HSV infection	**foscarnet**	90 mg/kg bid 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 **During treatment:** monitor renal function, adjust drug dose in renal impairment			
	Drug	**Dose**	**Comments**
Primary Varicella infection (Chickenpox) and Herpes Zoster (Shingles): Not disseminated	**valaciclovir**	1000 mg tid po	Chickenpox: 5-7 days, Shingles: 7-10 days
	or **famciclovir** or **aciclovir**	500 mg tid po 800 mg x 5/day po	
Herpes Zoster: Disseminated	**aciclovir**	10 mg/kg tid iv	10-14 days (or until clinical improvement)
Encephalitis (including vasculitis), retinitis	**aciclovir**	10-15 mg/kg tid iv	14-21 days If retinitis, consult ophthalmologist

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 AND other pathology excluded. Antibody testing and PCR in blood not useful for diagnosis of end-organ disease **During treatment:** monitor renal function, adjust drug dose in renal impairment			
	Drug	**Dose**	**Comments**
Retinitis, immediate sight-threatening lesions	**ganciclovir**	5 mg/kg bid iv	3 weeks, then secondary prophylaxis
	or **foscarnet**	90 mg/kg bid iv	**Foscarnet** used as alternative therapy if toxicity or resistance to **ganciclovir**. Some experts would add intravitreal injections of **ganciclovir** (2 mg) or **foscarnet** (2.4 mg) for 1-4 doses over 7-10 days in combination with systemic CMV treatment
Retinitis, small peripheral retinal lesions	**valganciclovir**	900 mg bid po (with food)	2-3 weeks, then secondary prophylaxis
	or **foscarnet**	90 mg/kg bid iv	
Oesophagitis/Colitis	**ganciclovir**	5 mg/kg bid iv	3-6 weeks, until symptoms resolved, then secondary prophylaxis
	or **foscarnet**	90 mg/kg bid iv	
	or **valganciclovir**	900 mg bid po (with food)	In milder disease if oral treatment tolerated
Encephalitis/Myelitis	**ganciclovir** **foscarnet**	5 mg/kg bid iv 90 mg/kg bid iv	Treat until symptoms resolved and CMV replication in CSF has cleared (negative PCR DNA-CMV in CSF) Treatment is individualised according to clinical symptoms and response to treatment. Some guidelines recommend **ganciclovir** combined with **foscarnet**
Secondary Prophylaxis / Maintenance therapy: Cytomegalovirus (CMV) Retinitis			
Stop: if CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months			
Regimens listed are alternatives	**valganciclovir**	900 mg qd po (with food)	
	or **ganciclovir**	5 mg/kg qd (x 5 days/ week) iv	
	or **foscarnet**	90-120 mg/kg qd (x 5 days/ week) iv	

Progressive Multifocal Leukoencephalopathy (PML)

Treatment	
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. JCV-DNA in plasma may complement PML diagnosis, particularly if CSF not available. May also be a marker of disease progression [8]	
Person off-ART	Initiate ART immediately (following general guidelines for treatment, see Initial Combination Regimen for ART-naïve Adult PLWH, INSTI may reasonably be preferred, given the importance of rapid immune reconstitution in PML. Attention should be made to development of IRIS, see IRIS section
Person on-ART, HIV-VL failure	Optimise ART (following general guidelines for treatment, see Virological Failure), INSTI may reasonably be preferred, given the importance of rapid immune reconstitution in PML. Attention should be made to development of IRIS, see IRIS section
Person on-ART, treated for weeks-months or on effective ART	Continue current ART
	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 IRIS section, cytarabine, iv immunoglobulins, mefloquine, mirtazapine. Newer immune-based approaches have shown some efficacy, including Interleukin-7, infusion of polyomavirus-specific HLA-matched T-cells, anti-PD1 inhibitors, but no conclusive data are currently supporting their recommendation for clinical use

Bacillary Angiomatosis *(Bartonella henselae, Bartonella quintana)*

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

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

Primary prophylaxis			
Primary prophylaxis Prophylaxis is not recommended if ART is started Prophylaxis may be considered for persons with CD4 counts < 50 cells/µL who remain viraemic on ART (drug resistant HIV with no option to achieve virologic control); exclude disseminated MAC disease before starting			
	Drug	**Dose**	**Comments**
Regimens listed are alternatives	**azithromycin**	1200-1250 mg/week po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
	or **clarithromycin**	500 mg bid po	
	or **rifabutin**	300 mg qd po	Check for interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs. Active TB should be ruled out before starting **rifabutin**
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 **Active TB should be ruled out before starting anti-TB drugs (rifampicin, rifabutin, ethambutol, isoniazid)**			
***Mycobacterium avium-intracellulare* complex (MAC)**			
Preferred therapy	**clarithromycin** **+ ethambutol** **+/- rifabutin**	500 mg bid po 15-20 mg/kg qd po 300 mg qd po (or 150 mg qd if PI/b)	12 months, then secondary prophylaxis **rifabutin** especially indicated in case of severe disease, if resistance to macrolides or **ethambutol** is suspected or severe immunodeficiency (CD4 count < 50 cells/µL), high bacterial load (> 2*log of CFU/mL of blood), no ART
	rifabutin can be replaced by: **+ levofloxacin/moxifloxacin** or **+ amikacin**	 500 mg qd po/400 mg qd po 10-15 mg/kg qd iv	 **levofloxacin/moxifloxacin** or **amikacin** can be considered as a 4th drug for disseminated or severe/refractory disease (no data on additional clinical benefit)
	azithromycin **+ ethambutol**	500 mg qd po 15-20 mg/kg qd po	Consider additional drugs as above
Mycobacterium kansasii			
	rifampicin **+ isoniazid** **+ ethambutol**	600 mg qd po (or rifabutin 300 mg qd po) 300 mg qd po 15-20 mg/kg qd po	12 months after negative culture
	or **rifampicin** **+ clarithromycin** **+ ethambutol**	 600 mg qd po (or rifabutin 300 mg qd po) 500 mg bid po 15 -20 mg qd po	12 months after negative culture
Secondary prophylaxis / Maintenance therapy for MAC			
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**	500 mg bid po 15-20 mg/kg qd po	
	or **azithromycin** **+ ethambutol**	 500 mg qd po 15-20 mg/kg qd po	

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

Treatment			
Diagnosis of cryptosporidiosis is made in PLWH with chronic diarrhea, mostly in cases with CD4 count < 100 cells/µL by immunofluorescence, acid fast stain, cryptosporidium antigen or PCR of stools or tissue. If the diarrhea lasts > 4 weeks, the diagnosis of cryptosporidiosis is an AIDS defining illness Mainstay of therapy is the induction of ART to restore immune competence with CD4 count > 100 cells/µL. Additional measures are symptomatic treatment, rehydration and electrolyte management The following antiprotozoal therapies can be used additively to ART in severe cases, but are not sufficient to achieve protozoal eradication without immune restoration			
	Drug	**Dose**	**Comments**
	nitazoxanide	500-1000 mg bid po	14 days
	or **paromomycin**	 500 mg qid po	 14-21 days

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

Treatment			
Diagnosis of cystoisosporiasis is made in persons with chronic, mostly watery diarrhoea by UV fluorescence or microscopy of stools, duodenal aspirates or intestinal tissue biopsy. If the diarrhea lasts > 4 weeks, the diagnosis of cystoisosporiasis is an AIDS defining illness Besides antiprotozoal treatment, additional measures are symptomatic treatment, rehydration and electrolyte management			
	Drug	**Dose**	**Comments**
Preferred therapy	**TMP-SMX**	1600/320 mg bid po or 800/160 mg bid 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 tablet/day, if symptoms worsen or persist
Alternative therapy, if TMP-SMX is not tolerated	**pyrimethamine** **+ folinic acid** or **ciprofloxacin**	50-75 mg qd po 10-15 mg qd po 500 mg bid po	10 days Monitor for myelotoxicity, mostly neutropenia, for **pyrimethamine** 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**	800/160 mg three times weekly po or 800/160 mg qd po or 1600/320 mg three times weekly po	
Alternative therapy, if TMP-SMX is not tolerated	**pyrimethamine** **+ folinic acid**	25 mg qd po 10-15 mg qd po	Monitor for myelotoxicity, mostly neutropenia, for **pyrimethamine**

Leishmaniasis

Treatment			
Diagnosis: microscopy or PCR in smears, body fluids or tissue			
	Drug	**Dose**	**Comments**
Preferred treatment	**liposomal amphotericin B**	2-4 mg/kg qd iv for 10 consecutive days	Then secondary prophylaxis
	or **liposomal amphotericin B**	4 mg/kg qd iv on day 1-5, 10, 17, 24, 31 and 38	
Alternative therapy	**lipid complex amphotericin B**	3 mg/kg qd iv	10 days
	or **amphotericin B deoxycholate**	0.5-1 mg/kg qd iv (total dose 1.5-2 g)	
	or **pentavalent antimonium salt (Glucantime®)**	20 mg/kg qd iv or im	4 weeks
	or **miltefosine**	100 mg/kg qd 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 **lipid complex amphotericin B**	3 mg/kg every 3 weeks iv	
Alternative therapy	**pentavalent antimonium salts (Glucantime®)**	20 mg/kg every 4 weeks iv/im	
	or **miltefosine**	100 mg qd po	
	or **pentamidine**	300 mg every 3 to 4 weeks iv	

Diagnosis and Treatment of TB in PLWH

Treatment of TB in PLWH
For standard treatment of TB in PLWH, including appropriate choice of ARVs, see table below and ART in TB/HIV Co-infection See online video lectures TB and HIV Co-infection-Part 1 and TB and HIV Co-infection Part 2 from the EACS online course Clinical Management of HIV

Disease	Drug	Dose[i]	Comments*
Susceptible *Mycobacterium tuberculosis* [9]			
Initial phase	**rifampicin** **+ isoniazid** **+ pyrazinamide** **+ ethambutol**	Weight based	**Initial phase** 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 Preventive steroid therapy may be considered to avoid IRIS
Alternative	**rifabutin** **+ isoniazid** **+ pyrazinamide** **+ ethambutol**	Weight based	**Initial phase** for 2 months, then **Continuation phase** 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**	Weight based	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 and in other sites: 6-9 months

* Intermittent regimens (2 or 3 times per week) are contraindicated in PLWH. Missed doses can lead to treatment failure, relapse or acquired drug resistance [10]

i For dose details, please see separate table TB drug doses, page 117

Diagnosis of Multidrug Resistant TB (MDR-TB) / Extensively Drug-Resistant TB (XDR-TB)

MDR/XDR-TB 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 MDR-TB
- 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 MDR/XDR-TB prevalence

MDR-TB: Resistance to **isoniazid** AND **rifampicin**
XDR-TB: Resistance to **isoniazid** AND **rifampicin** AND **fluoroquinolones** AND at least one of the following injectable drugs:
kanamycin, **capreomycin** or **amikacin**

Rapid detection

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

Treatment of resistant TB

Isoniazid-resistant TB [11]

- **rifampicin/rifabutin** + **pyrazinamide** + **ethambutol** for 2 months and **rifampicin/rifabutin** + **ethambutol** for 10 months
- **rifampicin/rifabutin** + **pyrazinamide** + **ethambutol** + **fluoroquinolone** for 6 months

Some experts recommend to add a **fluoroquinolone** in the intensive phase and replace **ethambutol** by the **fluoroquinolone** in the maintenance phase

Rifampicin-resistant TB and MDR/XDR-TB

Treatment of MDR/XDR-TB is a specialist area. WHO has recently published new guidelines [12]. Other specialists may have different views and practice may vary
Initial therapy should include 4 likely effective TB drugs, and treatment should include at least 3 active drugs after **bedaquiline** is stopped.
Treatment compliance is crucial. If needed, each dose of MDR/XDR-TB regimen should be given as DOT throughout the whole treatment period

Surgery

Surgical resection may be part of the management for selected persons with focal pulmonary MDR-/XDR-TB

Drug choices

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

Group A: Include all three medicines	• **levofloxacin** or **moxifloxacin** • **bedaquiline** • **linezolid**
Group B: Add one or both medicines	• **clofazimine** • **cycloserine** or **terizidone**
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	• **ethambutol** • **delamanide** • **pyrazinamide** • **amikacin** (or **streptomycin** – only if susceptible) • **imipenem–cilastatin** or **meropenem** with **amoxicillin/clavulanic acid** • **ethionamide** or **prothionamide** • **para-aminosalicylic acid**

Duration of MDR/XDR treatment

6 months of intensive phase using 4 or more drugs, followed by 12-14 months of 3 drugs depending on response
In persons with **rifampicin-resistant** or MDR-TB who have not previously been treated with second-line drugs and in whom resistance to **fluoroquinolones** and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9-12 months may be used instead of a conventional regimen [13,14]
For XDR-TB, a 3-drug combination of **pretomanid, bedaquiline, and linezolid** during 6 months (3 additional months if culture positive at 4th month) show promising results [15]

Drug interactions with ART and MDR/XDR regimens

When treating MDR-TB or XDR-TB, careful review of DDIs and potential toxicities is mandatory before initiating ART

Latent tuberculosis	
Indication: TST > 5 mm or positive IGRA or close contacts to persons with sputum smear positive tuberculosis. See Assessment of PLWH at Initial & Subsequent Visits Some national guidelines consider the ethnicity, CD4 count and ART usage to define indication for latent tuberculosis treatment	
Regimen*	**Comments**
isoniazid 5 mg/kg qd (max 300 mg) po + **pyridoxine** (Vit B6) 25 mg qd po	6-9 months Consider 9-month duration in high-prevalent TB countries
rifampicin 600 mg qd po or **rifabutin**** po (dose according to current ART)	4 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs and table on Drug-drug interactions relevant ART co-administered with **rifampicin** and **rifabutin**, page 20
rifampicin 600 mg qd po or **rifabutin**** po (dose according to current ART) + **isoniazid** 5 mg/kg qd (max 300 mg qd) po + **pyridoxine** (Vit B6) 25 mg qd po	3 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs and table on Drug-drug interactions relevant ART co-administered with **rifampicin** and **rifabutin**, page 20
rifampicin 600 mg x 2/week po + **isoniazid** 900 mg x 2/week po + **pyridoxine** (Vit B6) 300 mg x 1/ week po	3 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs
rifapentine*** 900 mg x 1 /week po + **isoniazid** 900 mg x 1/week po	3 months, **rifapentine** is not yet available in Europe
rifapentine 450 mg (< 45 kg) or 600 mg (> 45 kg) qd po + **isoniazid** 300 mg qd po + **pyridoxine** (Vit B6) 25 mg qd po [16]	4 weeks, **rifapentine** is not yet available in Europe

* Other preventive regimens may be considered if high risk of latent infection with MDR/XDR-TB
** **Rifabutin** is not a WHO recommended regimen
*** **Rifapentine** is not approved by EMA

TB Drug Doses [12,17]

Drug name	Dose	Comments
First line drugs		
Isoniazid	5 mg/kg qd (usual dose 300 mg)	Max 375 mg qd Caution: neurotoxicity, add **pyridoxine** 20 mg qd
Rifampicin	10 mg/kg qd (usual dose 600 mg)	**Rifampicin** is not recommended in persons receiving PIs, ETR, RPV, EVG/c or TAF, see Drug-drug Interactions between ARVs and Non-ARVs and table on Drug-drug interactions relevant for ART co-administered with **rifampicin** and **rifabutin**, page 20
Rifabutin without PIs, EFV, RPV with PIs with EFV with TAF or EVG/c	 5 mg/kg qd (usual dose 300 mg) 150 mg qd 450-600 mg qd Not recommended	
Pyrazinamide 40-55 kg 56-75 kg 76-90 kg > 90 kg	 1000 mg qd 1500 mg qd 2000 mg qd 2000 mg qd	
Ethambutol 40-55 kg 56-75 kg > 75 kg	 800 mg qd 1200 mg qd 1200 mg qd	Max 1600 mg qd Caution: optic neuritis Baseline colour vision should be tested
Other drugs		
Levofloxacin 30-46 kg > 46 kg	 750 mg qd 1000 mg qd	Max 1500 mg qd
Moxifloxacin	400 mg qd	Max 800 mg qd (used in the standardized shorter MDR-TB regimen) Monitor ECG in respect of QT prolongation
Bedaquiline	400 mg qd for 2 weeks 200 mg qd three times weekly for 22 weeks	EFV, ETV: potential reduction of **bedaquiline** exposure and activity. Not recommended Boosted regimens: increase in **bedaquiline** exposure. Potential risk of QT interval prolongation, ECG monitoring recommended. Avoid coadministration > 14 days
Linezolid	600 mg qd	Max 1200 mg qd Caution: hematological side effects and neurotoxicity, including optic neuropathy
Clofazimine	100 mg qd	Alternative: 200 mg for 2 months then 100 mg qd Caution: skin toxicity Monitor ECG in respect of QT prolongation
Cycloserine or terizidone 30-46 kg > 46 kg	 500 mg qd 750 mg qd	Max 1000 mg qd Caution: neurotoxicity; add **pyridoxine**, up to 50 mg/250 mg **cycloserine**
Delamanid	100 mg bid for 24 weeks	Monitor ECG in respect of QT prolongation
Imipenem/cilastatin	1000/1000 mg bid iv	
Meropenem	1000 mg tid iv	
Amoxicillin/clavulanic acid	500/125 mg tid	Only to be used with carbapenems (**imipenem/meropenem**)
Amikacin 30-35 kg 36-45 kg 46-55 kg > 55 kg	 625 mg qd iv 750 mg qd iv 750-1000 mg qd iv 1000 mg qd iv	After initial period can be reduced to trice weekly Baseline audiometry should be performed Caution: monitor renal function, audiometry and drug levels
Streptomycin	12-18 mg/kg qd iv	Max 1000 mg qd iv
Ethionamide or prothionamide 30-45 kg 46-70 kg > 70 kg	 500 mg qd 750 mg qd 1000 mg qd	Caution: gastrointestinal toxicity; add **pyridoxine**, up to 50 mg/250 mg **prothionamide**
Para-aminosalycilic acid	4000 mg bid	In weight > 70 kg can be increased to 4000-6000 mg bid Caution: gastrointestinal toxicity

Video links

EACS Guidelines	Video lectures	Link to video lecture
Primary HIV Infection	When to Start ART Part 1	https://vimeo.com/197164442/93941a8e75
	When to Start ART Part 2	https://vimeo.com/197167665/3f00ac2634
	What ART to Start Part 1	https://vimeo.com/197374541/32232bd037
	What ART to Start Part 2	https://vimeo.com/197378793/215317ddab
Switch Strategies for Virologically Suppressed Persons	How to Change ART	https://vimeo.com/197161843/ae0c46e0be
Virological Failure	Adherence and Prevention of HIV Drug Resistance	https://vimeo.com/197381327/d7e972c0d5
Pre-exposure Prophylaxis	PrEP Part 1	https://vimeo.com/196714648/6a196a71a4
	PrEP Part 2	https://vimeo.com/196716750/a12a32989b
Adverse Effects of ARVs and Drug Classes	Adverse Effects and Monitoring	https://vimeo.com/197275138/3df1c99e55
Cancer: Screening Methods	Clinical Management of Cancers and HIV Part 1	https://vimeo.com/197398883/6cbeebb66e
	Clinical Management of Cancers and HIV Part 2	https://vimeo.com/197748761/68cc01229a
	Epidemiology of Cancers Part 1	https://vimeo.com/197749519/afea560124
	Epidemiology of Cancers Part 2	https://vimeo.com/197749948/e7e5062f2d
Prevention of CVD	HIV and CVD, CKD, Endocrinology	https://vimeo.com/197488153/396253a733
Kidney Disease: Definition, Diagnosis and Management	HIV and CVD, CKD, Endocrinology	https://vimeo.com/197488153/396253a733
Lipodystrophy: Prevention and Management	HIV and CVD, CKD, Endocrinology	https://vimeo.com/197488153/396253a733
Diagnostic Procedures for HCV in Persons with HCV/ HIV Co-infection	Hepatitis C and HIV Co-infection Part 1	https://vimeo.com/197259934/bc5cac91d1
	Hepatitis C and HIV Co-infection Part 2	https://vimeo.com/197261826/0462d2df0e
	Hepatitis C and HIV Co-infection Part 3	https://vimeo.com/197262690/a323b6cd72
Introduction to OIs	HIV and the Management of IRIS Part 1	https://vimeo.com/197762901/a147257ffc
	HIV and the Management of IRIS Part 2	https://vimeo.com/197765956/9b61e5d15d
	Pulmonary Infections Part 1	https://vimeo.com/197388161/dc24235ab6
	Pulmonary Infections Part 2	https://vimeo.com/197389876/7c26fb8551
	Pulmonary Infections Part 3	https://vimeo.com/197392161/f90020ae21
	CNS and HIV-related Opportunistic Infections Part 1	https://vimeo.com/197752868/34462456dd
	CNS and HIV-related Opportunistic Infections Part 2	https://vimeo.com/197758431/6b2939c62a
Diagnosis and Treatment of TB in PLWH	Tuberculosis and HIV Co-infection Part 1	https://vimeo.com/196723861/7a067d0254
	Tuberculosis and HIV Co-infection Part 2	https://vimeo.com/197161188/4e881b687c

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

Part I Assessment of PLWH at Initial & Subsequent Visits

Please see references for Part IV

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