



EACS
European
AIDS
Clinical
Society

GUIDELINES

Version 11.0
October 2021

English

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Introduction to the EACS Guidelines 2021

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, online as a pdf and web-based version, and as a free App for iOS and Android devices. The Guidelines are as of 2021 no longer produced as a printed booklet, but continue to be translated into several different languages. The Guidelines undergo formal minor revisions annually and major revisions every second year. Interim updates may however also be provided at any time the panels consider it necessary.

The aim of the EACS Guidelines is to provide easily accessible and comprehensive recommendations to clinicians involved in all aspects of 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 2021 version of the Guidelines includes updates of all existing sections but have also included an entirely new section on COVID-19 in PLWH and recommendations on paediatric ART developed in collaboration with Penta. The most essential changes are listed in the [Summary of changes from v10.1 to v11.0](#)

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do not provide formal grades of evidence, panels make decisions by consensus or by vote when necessary and we do not publish results of the votes or discrepancies if any occur.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.

Only the latest and key references used to produce the Guidelines are provided in a separate section, see [References](#). New in 2021 is the inclusion of a short summary of the key findings of highlighted references.

Please reference the EACS Guidelines as follows: EACS Guidelines version 11.0, October 2021.

Video links to the EACS online course on Management of HIV and Co-infections are provided throughout the Guidelines, see [Video links](#).

The diagnosis and management of HIV infection and related co-infections, opportunistic diseases and co-morbidities across all ages continue to require a multidisciplinary effort for which we hope the 2021 version of the EACS Guidelines will provide you with an easily accessible 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 2021

Summary of Changes from v10.1 to v11.0

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 13-14
 - New organization of treatment categories which are now divided into recommended regimens and alternative regimens
 - DOR has been included as a recommended drug in a triple drug tenofovir-based regimen
 - EVG and ATV-based regimens, DRV/b + RAL and ABC combinations with either EFV, DRV/b or RAL have been removed
 - New guidance for PrEP failure is included
- Switch strategies for virologically suppressed persons, page 16
 - Long-acting CAB + RPV has been included as dual therapy option
 - 3TC + ATV/b has been removed from recommended dual therapies
- Virological failure, page 17
 - Section has been updated including new wording for treatment recommendations in the presence of resistance mutations
- Treatment of pregnant women living with HIV or women considering pregnancy, page 18
 - Section has been re-organized
 - ART choice should be discussed with women wishing to conceive or pregnant. DTG to be discussed with women considering to become pregnant or if to be used in first 6 weeks of pregnancy
 - TAF has been included among recommended/alternative regimens as a drug option after 14 weeks of pregnancy
 - ATV, ZDV and LPV/r are removed from alternative regimens
- ART and TB co-infection, page 20
 - ART should be started as soon as possible (within two weeks of initiating TB treatment) regardless of CD4 count, with the exception of TB meningitis
- Pre-Exposure Prophylaxis page 23
 - Whole section has been updated including on demand PrEP for men, and indication to continue PrEP during pregnancy and breastfeeding if the risk of acquiring HIV persists

DDI section

- CAB oral, CAB/RPV LA and FTR have been added to all DDI tables.
- DDIs for ABC, 3TC and FTC are now summarized in the footnote of each DDI table
- Four novel DDI tables have been added: DDIs with anti-tuberculosis drugs; DDIs with anxiolytics; DDIs with COVID-19 therapies and DDIs with hormone replacement therapy, see pages 35, 36, 41, 42
- All tables have been updated to include changes implemented in the HIV drug interaction website (University of Liverpool) in the past year. For the most part, changes relate to the risk of QT interval prolongation with RPV, ATV/b and LPV/r
- TAF + rifampicin footnote was changed to indicate that although rifampicin decreases TAF exposure when given 25 mg qd, the intracellular tenofovir diphosphate levels are likely to be higher than those observed with TDF even without rifampicin suggesting that usage of TAF 25 mg qd with rifampicin (or rifapentine, rifabutin) may be acceptable, see page 35
- Several comedications have been added in the Antidepressants, Antihypertensives, Analgesics, Anticoagulants, Bronchodilators and Anti-malarials DDI tables, see pages 31, 32, 29, 30, 37, 34
- A summary of the differences in the risk of DDIs for oral and im CAB/RPV is provided in the introduction of part III, see page 26
- The table on the administration of ARVs in persons with swallowing difficulties has been revised to include CAB, CAB/RPV LA and FTR, see page 46
- Delafoxacin and eslicarbazepine have been added to the table of non-ARV drugs requiring dosage adjustment in renal insufficiency, see page 52

Co-morbidity section

- Updated information on adverse effects associated with new ARVs, pages 24-25
- Updated guidance on screening for cancers in PLWH, page 59
- Updated information on drug-drug interactions relevant to opiate addiction in PLWH, page 58
- Updated guidelines on the prevention and management of CVD including updated lipid targets, management of hypertension (including drug

sequencing) and primary prevention for those PLWH who are diabetic in alignment with the European Society of Cardiology, pages 62-65, 69

- The approach to management of DM in PLWH has been revised, pages 67-68
- Updated guidance on the classification, diagnosis and management of non-alcoholic fatty liver disease (NAFLD) and management of hepatorenal syndrome / acute kidney injury (HRS/AKI), page 82-83
- A major revision to provide a more comprehensive section on diagnosis and management of weight gain and obesity in PLWH has been included, page 85-86
- Inclusion of SARS-CoV-2 in the vaccination section, page 90
- More detailed information on management of menopause in PLWH, page 91
- A new section on screening, diagnosis and management of anxiety disorders in PLWH has been added, page 100-101
- The screening, diagnosis and management of frailty has undergone major revision with information on polypharmacy, screening for frailty and falls, page 108-112
- Updated information on screening and prophylaxis for PLWH undergoing solid organ transplant, page 113

Viral Hepatitis Co-infections section

- If pangenotypic regimens are foreseen, HCV genotype determination is not mandatory before starting treatment, page 117
- Treatment of recently acquired HCV infection immediately after diagnosis is recommended in PLWH with ongoing risk behavior to reduce onward transmission, page 117
- The tables on HCV treatment options and DDIs have been updated, pages 118-119
- The table "HCV treatment options if preferred treatments are not available" has been deleted
- Bulevirtide added as treatment option for HDV, page 122

Opportunistic Infections and COVID-19 section

- Section title was changed to "Opportunistic Infections and COVID-19"
- Section on management of COVID-19 in PLWH was added, page 139
- Table "When to start ART in PLWH with Opportunistic Infections", page 123 was revised
 - Column on CD4 count thresholds was removed
 - CMV end-organ disease was deleted from the table
- An alternative regimen, based on rifapentine for treatment of drug-susceptible TB was added, page 135
- Treatment recommendations for MDR-/XDR-TB were revised according to the updated WHO 2020 Guidelines, page 136
- Some minor stylistic changes were made to all OI tables

Paediatric HIV Treatment section

- First version of EACS Guidelines with integration of Penta Guidelines on first and second line ART for children living with HIV, pages 140-143
- Update of first and second line recommendations, with further emphasis on DTG as preferred option in response to extended license, new formulation and evidence of superiority from the ODYSSEY trial, pages 140-143
- Guidance on use of ABC in children less than 3 months of age, page 141
- Addition of a table and link to Penta website for dosing recommendations, pages 140, 142
- Addition of a recommendation and link to contact and refer to International Paediatric Virtual Clinic, page 140, 142
- Modification of the definition of virological failure to be in line with EACS adult Guidelines, page 143

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

Imprint

Publisher

Panel Chairs

Chair and Coordinator

Graphic Design

Layout and translations

Version, Date

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José Arribas, Catia Marzolini,

Patrick Mallon, Andri Rauch, Ole Kirk

Georg Behrens and Lene Ryom

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11.0, October 2021

EACS, 2021

Panel Members

Medical Secretariat

The EACS Medical Secretariat is responsible for the coordination and update of the EACS Guidelines based on the recommendations from the five EACS panels.

Guidelines Chair: Georg Behrens
Guidelines Coordinator: Lene Ryom

Hannover, Germany
Copenhagen, Denmark

SVilen Konov
Karine Lacombe
Stefan Mauss
Luís Mendão
Lars Peters
Massimo Puoti
Jürgen K. Rockstroh

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HIV Treatment

Chair: José Arribas
Vice-Chair: Jean-Michel Molina
Young scientist: Rosa De Miguel Buckley
Andrea Antinori
Margherita Bracchi
Alexandra Calmy
Nikos Dedes
Andrzej Horban
Christine Katlama
Inga Latysheva
Jens D. Lundgren
Sheena McCormack
Cristina Mussini
Anton Pozniak
Federico Pulido
François Raffi
Hans-Jürgen Stellbrink
Marc van der Valk
Marta Vasylyev

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Drug-drug Interactions

Chair: Catia Marzolini
Vice-Chair: Giovanni Guaraldi
Sara Gibbons
Françoise Livio

Basel, Switzerland
Modena, Italy
Liverpool, United Kingdom
Lausanne, Switzerland

Co-morbidities

Chair: Patrick Mallon
Vice-Chair: Alan Winston
Young scientist: Aoife Cotter
Georg Behrens
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Paola Cinque
Simon Collins
Juliet Compston
Susanne Dam Nielsen
Stéphane De Wit
Leonardo M. Fabbri
Christoph A. Fux
Magnus Gisslen
Giovanni Guaraldi
Esteban Martínez
Catia Marzolini
José M. Miro
Eugenia Negredo
Peter Reiss
Lene Ryom
Giada Sebastiani

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Acknowledgement:
Alessia Dalla Pria

London, United Kingdom

Viral Hepatitis Co-infections

Chair: Andri Rauch
Vice-Chair: Christoph Boesecke
Young scientist: Charles Béguelin
Juan Berenguer
Sanjay Bhagani
Raffaele Bruno

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Opportunistic Infections and COVID-19

Chair: Ole Kirk
Vice-Chair: Paola Cinque
Young scientist: Daria Podlekareva
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Paediatric HIV Treatment

Chair: Alasdair Bamford
Co-chair: Steven B Welch
Young Scientist: Hylke Waalewijn
Stefania Bernardi
David Burger
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Wave representative:
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Warsaw, Poland

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Abbreviations

Antiretroviral drug (ARV) abbreviations

3TC	lamivudine	NNRTI	non-nucleoside reverse transcriptase inhibitors
ABC	abacavir	NVP	nevirapine
ATV	atazanavir	PI	protease inhibitors
BIC	bictegravir	PI/b	protease inhibitors pharmacologically boosted with cobicistat or ritonavir
CAB	cabotegravir	PI/c	protease inhibitor pharmacologically boosted with cobicistat
COBI	cobicistat (used as booster=/c)	PI/r	protease inhibitors pharmacologically boosted with ritonavir
d4T	stavudine	RAL	raltegravir
ddI	didanosine	RPV	rilpivirine
DOR	doravirine	RTV	ritonavir (used as booster=/r)
DRV	darunavir	SQV	saquinavir
DTG	dolutegravir	TAF	tenofovir alafenamide
EFV	efavirenz	TDF	tenofovir disoproxil fumarate
EVG	elvitegravir	TPV	tipranavir
ENF	enfuvirtide (T20)	ZDV	zidovudine
ETV	etravirine	XTC	3TC or FTC
FI	fusion inhibitor		
FPV	fosamprenavir		
FTC	emtricitabine		
FTR	fostemsavir		
IDV	indinavir		
INSTI	integrase strand transfer inhibitor		
LPV	lopinavir		
MVC	maraviroc		
NRTI	nucleos(t)ide reverse transcriptase inhibitors		

Other abbreviations

ACEi	angiotensin converting enzyme inhibitor	CSF	cerebrospinal fluid
AFP	alpha-fetoprotein	CTC	computed tomography colonoscopy
ALP	alkaline phosphatase	CVD	cardiovascular disease
ALT	alanine aminotransferase	CXR	chest X-ray
aMDD	abbreviated modification of diet in renal disease formula	DAA	direct acting antiviral drug
ARB	angiotensin receptor blocker	DDI	drug-drug interaction
ART	antiretroviral therapy	DPP-4i	dipeptidyl peptidase 4 inhibitor
AST	aspartate	DRESS	drug rash with eosinophilia and systemic symptoms
ASCVD	aminotransferase atherosclerotic cardiovascular disease	DXA	dual energy X-ray absorptiometry
B	buprenorphine	ECG	electrocardiogram
bid	twice daily	eGFR	estimated glomerular filtration rate
BMD	bone mineral density	ESLD	end stage liver disease
BMI	body mass index	FBC	full blood count
BP	blood pressure	FH	familial hypercholesterolaemia
CABG	coronary artery bypass grafting	FIT	faecal immunochemistry test
CAPD	continuous ambulatory peritoneal dialysis	FRAX®	fracture risk assessment tool
CAD	coronary artery disease	FRAT	falls risk assessment tool
cART	combination antiretroviral treatment	FS	frailty scale
CBT	cognitive behavioural therapy	GAD-2	generalized anxiety disorder 2-item screening tool
CCB	calcium channel blocker	GDR	genotypic drug resistance test
CGA	comprehensive geriatric assessment	GLP1RA	glucagon like peptide 1 receptor agonist
CKD	chronic kidney disease	GT	genotype
CKD-EPI	CKD epidemiology collaboration formula	HAV	Hepatitis A virus
CMV	Cytomegalovirus	HAD	HIV-associated dementia
CNS	central nervous system	HBV	Hepatitis B virus
COVD	chronic obstructive pulmonary disease	HCC	hepatocellular carcinoma
COVID-19	Coronavirus disease 2019	HCV	Hepatitis C virus

HDL-c	HDL-cholesterol	qd	once daily
HDV	Hepatitis D virus	qid	four times daily
HEV	Hepatitis E virus	RAS	resistance-associated substitutions
HF	heart failure	RBV	ribavirin
HIVAN	HIV-associated nephropathy	RCT	randomized controlled trial
HIV-VL	HIV viral load (HIV-RNA)	RIG	Rabies Immunoglobulin
HMOD	hypertension-mediated organ disease	SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
HPV	Human papillomavirus	SABA	short-acting β 2-agonist
HRS	hepatorenal syndrome	SAMA	short-acting muscarinic antagonist
HSR	hypersensitivity reaction	sc	subcutaneous
HSV	Herpes simplex virus	SCORE	systemic coronary risk estimation
ICS	Inhaled corticosteroid	SGLT-2i	sodium/glucose co-transporter 2 inhibitor
IFG	Impaired Fasting Glucose	SOT	solid organ transplant
IFN	interferon	SPPB	short physical performance battery
IGRA	interferon-gamma release assay	SSRI	selective serotonin-reuptake inhibitor
IGT	impaired glucose tolerance	STI	sexually transmitted infection
IHD	ischaemic heart disease	SU	sulfonylurea
im	intramuscular	SVR	sustained virological response
IRIS	immune reconstitution inflammatory syndrome	TBS	trabecular bone score
iv	intravenous	TC	total cholesterol
IVDU	intravenous drug use	TDM	therapeutic drug monitoring
LA	long-acting	TG	triglycerides
LABA	long-acting β 2-agonist	TIA	transient ischaemic attack
LAMA	long-acting muscarinic antagonist	tid	three times daily
LDL-c	LDL-cholesterol	TMP-SMX	trimethoprim-sulfamethoxazole
LGV	lymphogranuloma venereum	TZD	thiazolidinediones
LOQ	limit of quantification	UA/C	urine albumin/creatinine ratio
MDR-TB	multidrug resistant TB	UP/C	urine protein/creatinine ratio
Mg	magnesium	US	ultrasound
MND	mild neurocognitive disorder	VL	viral load (HIV-RNA)
MRI	magnetic resonance imaging	VZV	varicella-zoster virus
MSM	men who have sex with men	WB	western blot
MTCT	mother to child transmission	XDR-TB	extensively drug-resistant TB
MT	multitarget	Zn	zinc
sDNA	stool DNA		
MRI	magnetic resonance imaging		
MX	methylxanthines		
N	norbuprenorphine		
NAFLD	non-alcoholic fatty liver disease		
NASH	non-alcoholic steatohepatitis		
NSAID	non-steroidal anti-inflammatory		
NP	neuropsychological		
OLIs	opportunistic infections		
OLT	orthotopic liver transplantation		
PAP	papanicolaou test		
PCI	percutaneous coronary intervention		
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		
PCSK9	proprotein convertase subtilisin/kexin type 9		
PTH	parathyroid hormone		

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)	62, 63-64
	• 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	61
	Employment	+	+	Every visit	Provide advice and support if needed	
	Social and welfare	+	+		Provide counselling if needed	
	Psychological morbidity	+	+			
	Partner and children	+				
Sexual and Reproductive Health	Sexual history	+		6-12 months	Address issues concerning sexual dysfunction	91-95
	Safe sex	+			Risk of sexual transmission should be addressed	
	Partner status and disclosure	+			Recommend starting ART in serodifferent couples	
	Conception issues	+	+			
	Hypogonadism	+	+	As indicated	Persons with complaints of sexual dysfunction	91, 94
	Menopause	+	+	Annual/ as indicated	Screen for perimenopause symptoms in women ≥ 40 years	91
HIV DISEASE						
Virology	Confirmation of HIV Ab pos	+		3-6 months	More frequent monitoring of HIV-VL at start of ART	12-14
	Plasma HIV-VL	+	+		Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection	
	Genotypic resistance test and sub-type	+	+/-	At virological failure		
	R5 tropism (if available)		+/-		Screen if considering R5 antagonist in regimen	
Immunology	CD4 absolute count and %, 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	12-14
	HLA-B*57:01 (if available)	+	+/-		Screen before starting ABC containing ART, if not previously tested, pages 12-13 , 24	
CO-INFECTIONS						
STIs	Syphilis serology	+		Annual/ as indicated	Consider more frequent screening if at risk	15, 91
	STI screen	+		Annual/ as indicated	Screen if at risk and during pregnancy	
Viral Hepatitis	HAV screen	+		As indicated	Screen if ongoing risk (e.g. MSM); vaccinate if non-immune	90, 115-117
	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	115, 122
	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 NAAT for HEV-RNA in blood and if possible in stool	122

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
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, 135
	PPD	+				
	IGRA in selected high-risk populations (if available)	+				
Others	Varicella zoster virus serology	+			Offer vaccination where indicated	90
	Measles/Rubella serology	+			Offer vaccination where indicated	
	Toxoplasmosis serology	+				
	CMV serology	+				
	Cryptococcus antigen	+/-			Consider screening for cryptococcus antigen in serum in persons with CD4 count < 100 cells/μL	
	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	90
	<i>Streptococcus pneumoniae</i>	+			No recommendations available regarding the need for a booster dose, see Vaccination	90
	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	90
	SARS-CoV-2				In a pandemic situation, vaccinate irrespective of CD4 count and HIV-VL according to national Guidelines	90
CO-MORBIDITIES						
Haematology	FBC	+	+	3-12 months		
	Haemoglobinopathies	+			Screen at risk persons	
	G6PD	+			Screen at risk persons	
Body Composition	Body-mass index	+	+	Annual		61
Cardiovascular Disease	Risk assessment (Framingham score ⁽ⁱⁱⁱ⁾)	+	+	Annual	Should be performed in all men > 40 years and women > 50 years without CVD	62
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
Hypertension	Blood pressure	+	+	Annual		63-64
Lipids	TC, HDL-c, LDL-c, TG ^(iv)	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	69
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)	67-68
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	105
	Spirometry			As indicated	Spirometry should be performed in all symptomatic persons ^(xii)	
Liver Disease	Risk assessment ^(v)	+	+	Annual		79-82
	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)	79-82
	Hepatic ultrasound			6 months	Persons with liver cirrhosis ^(xiii)	79-82
Renal Disease	Risk assessment ^(vi)	+	+	Annual	More frequent monitoring if eGFR < 90 mL/min, CKD risk factors present ^(vi) and/or prior to starting and on treatment with nephrotoxic drugs ^(ix)	74-75
	eGFR (CKD-EPI) ^(vi)	+	+	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		71-73
	Risk assessment ^(x) (FRAX ^(xi) in persons > 40 years)	+	+	2 years	Consider DXA in specific persons, see page 71 for details	
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons	72

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
Cognitive impairment	Screening questionnaire	+	+	As indicated	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 104 for further assessment.	104
Anxiety	Questionnaire	±	±	As indicated	Screen at risk persons	100-101
Depression	Questionnaire	+	+	As indicated	Screen at risk persons	96-97
Older PLWH	Polypharmacy review			Annual	Perform periodic medicines review	108-109
	Frailty			Annual	Screen with Frail Scale, Walking Speed or short physical performance battery	110-111
	Falls			Annual		112
Cancer	Mammography			1-3 years	Women 50-74 years	59
	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-fetoprotein			6 months	Controversial; persons with cirrhosis and persons with HBV co-infection at high risk of HCC ^(xiii)	
	Prostate cancer (PSA)			1-2 years	Men > 50 years with a life expectancy > 10 years	
	Others			As indicated	Lung cancer and colorectal cancer screening according to local screening programmes	

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 Analgesics and ARVs](#)
 - [Drug-drug Interactions between Anticoagulants/Antiplatelet Agents and ARVs](#)
 - [Drug-drug Interactions between Antidepressants and ARVs](#)
 - [Drug-drug Interactions between Antihypertensives and ARVs](#)
 - [Drug-drug Interactions between Anti-malarial Drugs and ARVs](#)
 - [Drug-drug Interactions between Anti-tuberculosis Drugs and ARVs](#)
 - [Drug-drug Interactions between Anxiolytics and ARVs](#)
 - [Drug-drug Interactions between Bronchodilators \(for COPD\) and ARVs](#)
 - [Drug-drug Interactions between Contraceptives and ARVs](#)
 - [Drug-drug Interactions between Corticosteroids and ARVs](#)
 - [Drug-drug Interactions between COVID-19 Therapies and ARVs](#)
 - [Drug-drug Interactions between Hormone Replacement Therapy \(HRT\) and ARVs](#)
 - [Drug-drug Interactions between Immunosuppressants \(for SOT\) and ARVs](#)
 - [Drug-drug Interactions between Pulmonary Antihypertensives and ARVs](#)
 - [Drug-drug Interactions between Viral Hepatitis Drugs and ARVs](#) and <http://www.hiv-druginteractions.org>
 - ii If stable on ART with undetectable HIV-VL and CD4 count > 350 cells/ μ L, 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 Cockcroft-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 74
 - 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
 - x Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m²), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (> 3 units/day), steroid exposure (minimum 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/publications/clinical-practice-guidelines/>). 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 59, 81 and 115
- * See table on cut-off values of non-invasive tests for the detection of significant fibrosis and cirrhosis, page 121. The combination of blood biomarkers, the combination of liver stiffness measurement and blood tests or repeated assessments may improve accuracy, see [EASL recommendations on treatment of Hepatitis C 2020 - EASL-The Home of Hepatology](#) (free registration needed to get access)

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 recommendation to start 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⁽ⁱ⁾

Goal: to help persons start and/or maintain ART	
<p>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). 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</p> <p>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</p>	<p>Identify the person's stage of readiness using WEMS⁽ⁱⁱ⁾ techniques, and start discussion with an open question/invitation: "I would like to talk about HIV medicines." <wait> "What do you think about them?"</p> <p>Based on the person's response, identify his/her stage of readiness and intervene accordingly⁽ⁱⁱⁱ⁾</p> <p>Immediate (i.e. same day) start of ART should be considered, and especially in the following situations:</p> <ul style="list-style-type: none"> - 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	
<p>Precontemplation: "I don't need it, I feel good" "I don't want to think about it"</p>	<p>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</p>
<p>Contemplation: "I am weighing things up and feel torn about what to do about it"</p>	<p>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</p>
<p>Preparation: "I want to start, I think the drugs will allow me to live a normal life"</p>	<p>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</p> <p>Ask: How confident are you that you can take your medicines as we discussed (specify) once you have started?</p> <p>Consider skills training:</p> <ul style="list-style-type: none"> • 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
<p>Action: "I will start now"</p>	<p>'Final check': With a treatment plan established, is the person capable of taking ART and is ART available?</p>
<p>Maintenance: "I will continue." or "I have difficulties continuing over the long run"</p> <p>Caveat: A person can relapse to an earlier stage, even from "maintenance" to "precontemplation"</p>	<p>Assess: Adherence every 3-6 months^(iv)</p> <p>Evaluate adherence: For persons with good adherence: show respect for their success</p> <p>Assess: The person's own perception of ability to adhere to and continue treatment</p> <p>Ask: In the next 3-6 months, how confident are you that you can take your medicines?</p> <p>For a person without sufficient adherence: use mirroring techniques^(v) on problems, ask open questions to identify dysfunctional beliefs</p> <p>Assess: Stage of readiness and provide stage-based support</p> <p>Assess: Barriers and facilitators^(vi)</p> <p>Schedule next appointment and repeat support</p>

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: <ul style="list-style-type: none"> • Depression^(vi), see pages 96-97 • Cognitive problems^(viii), see page 104 • Harmful alcohol^(ix) or recreational drug use, see page 58 	Consider talking about: <ul style="list-style-type: none"> • 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 Algorithm adapted from Fehr et al.
- ii WEMS: Waiting (> 3 sec), Echoing, Mirroring, Summarising
- iii 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/ μ L), 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
- iv Suggested adherence questions: "In the past 4 weeks, how often have you missed a dose of your HIV medicines: every day, more than once a week, once a week, once every 2 weeks, once a month, never?" /

- "Have you missed more than one dose in a row?"
- v Mirroring: reflecting back on what a person has said or non-verbally demonstrated (e.g. anger or disappointment) WITHOUT introducing new material by asking questions or giving information
 - vi Adherence to long-term therapies
 - vii See [Mental Health in PLWH, Depression: Screening and Diagnosis](#)
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.
 - viii See [Algorithm for Diagnosis and Management of Cognitive Impairment in PLWH without Obvious Confounding Conditions](#)
 - ix FAST-alcohol use, ask: How often have you had 6 or more units if female, or 8 or more units if male, on a single occasion in the last year? Never = 0, Less than monthly = 1, Monthly = 2, Weekly = 3, Daily or almost daily = 4. Stop if the answer is 0 (Never). Ask more questions if the answer is 1, 2, 3 or 4.

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 123, 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. Genotypic testing should not delay ART initiation (it may be re-adjusted after genotypic test results)
 - 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, including a PI/b or second generation INSTI
 - 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 or is pregnant**: [Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy](#)
- 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](#)
- If the person has **acquired HIV while receiving PrEP**: In this situation, change PrEP to a triple-drug ART regimen including a third drug with a high barrier to resistance (preferably DRV/b, DTG or BIC) plus two nucleoside analogues without interrupting antiretrovirals. The danger of acute seroconversion syndrome and higher infectiousness would be arguments for immediate switch to triple therapy. ART should be adjusted if more extensive resistance is demonstrated by genotypic resistance analysis
- Only drugs currently licensed for initiation of therapy by the EMA are included (in alphabetical order)
- Recommended regimens should be considered first and are preferable for most persons. Antiretroviral drugs in the Recommended category provide a combination of essential characteristics for an optimal treatment such as long-term efficacy, barrier to resistance, safety, tolerability and few drug-drug interactions. Alternative regimens should be considered if recommended regimens are not feasible
- 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 (see 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/BIC		II (Weight increase (BIC, TAF))
TAF/FTC or TDF/XTC + DTG		II (Weight increase (DTG, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing)
TAF/FTC or TDF/XTC + RAL qd or bid		II (Weight increase (RAL, TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IV (RAL: dosing)
1 NRTI + INSTI		
XTC + DTG or 3TC/DTG	HBsAg negative HIV-VL < 500,000 copies/mL Not recommended after PrEP failure	II (Weight increase (DTG)) V (3TC/DTG not after PrEP failure)
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + DOR or TDF/3TC/DOR		II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VI (DOR: caveats, HIV-2)
Alternative regimens		
2 NRTIs + NNRTI		
TAF/FTC or TDF/XTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VII (EFV: neuro-psychiatric adverse events. HIV-2 or HIV-1 group 0)
TAF/FTC or TDF/XTC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count > 200 cells/ μ L HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) VIII (RPV: HIV-2)
2 NRTIs + PI/r or PI/c		
TAF/FTC or TDF/XTC + DRV/c or DRV/r or TAF/FTC/DRV/c	With food	II (Weight increase (TAF)) III (TDF: prodrug types. Renal and bone toxicity. TAF dosing) IX (DRV/r: cardiovascular risk) X (Boosted regimens and drug-drug interactions)

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 62
- II Treatment with INSTIs or TAF may be associated with weight increase
- III 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
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 74;
 - coadministration of medicines with nephrotoxic drugs or prior TDF toxicity, see page 75;
 - osteoporosis / progressive osteopenia, high FRAX score or risk factors, see page 71;
 - history of fragility fracture, see pages 71 and 73
- IV 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
- V HIV infections occurring in the context of PrEP failure may be associated with resistance-associated mutations. 3TC/DTG may be used in this context only if there is no documented resistance in genotypic test
- VI DOR is not active against HIV-2. DOR has not demonstrated non-inferiority to INSTI. There is risk of resistance associated mutations in case of virological failure. Results of genotypic resistance test are necessary before starting DOR
- VII EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains
- VIII RPV is not active against HIV-2
- IX A single large study has shown increase in CVD risk with cumulative use of DRV/r, not confirmed in smaller studies
- X Boosted regimens with RTV or COBI are at higher risk of drug-drug interactions, see [Part III Drug-drug interactions](#)

*** There are limited data on use of TAF with eGFR < 10 mL/min

**** Expert opinion pending clinical data

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-v)

- 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
- 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)
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)

Starting treatment

Treatment of PHI is recommended for all PLWH

The recommendation is based on:

- Improvement of clinical symptoms of PHI, when present, especially severe general symptoms and/or neurological 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/ μ L
 - 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.
 - 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. More than three active drugs are not needed.
- 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 7-9. Antibody seroconversion can be delayed and tests to identify the viral RNA are required in order to identify a recent HCV infection, page 120
 - 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 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
 - iii Some centres may have access to sero-incidence markers (e.g., antibody avidity testing) that identify an infection acquired within the previous 3-6 months. Assay reliability varies and results should be interpreted with caution when they are the sole indicators of a recent infection
 - iv A small subset of PLWH can spontaneously control the infection without treatment (elite controllers)
 - v Post-treatment controllers. A few PLWH have been able to spontaneously control HIV-infection following ART discontinuation, when ART was initiated during PHI

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 Management of HIV and Co-infections

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, see [Adverse Effects of ARVs and Drug Classes](#)
2. **Prevention of long-term toxicity**, 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 Viral Hepatitis Drugs and ARVs](#)
4. **Planned pregnancy or women wishing to conceive**, see [Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy](#)
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 (i.e. TDF/FTC → TAF/FTC, EFV → DOR or 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. 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 Management of HIV and Co-infections

Dual therapies

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) HBV immunity or if non-immune concomitant HBV Vaccination

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

DTG + RPV
XTC + DTG
XTC + DRV/b
Long-acting CAB + RPV bi-monthly injections

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 and CAB + RPV

Dual therapy options supported only by small trials:

These regimens should be indicated only in persons not eligible for other treatment combinations due to intolerance or resistance to other drugs

DRV/b + RPV
DRV/b + DTG

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	<p>INCOMPLETE SUPPRESSION: HIV-VL > 50 copies/mL at 6 months after starting therapy in PLWH not previously on ART. In PLWH with very high baseline HIV-VL (> 100,000 copies/mL), achieving viral suppression may take longer than 6 months</p> <p>REBOUND: confirmed HIV-VL > 50 copies/mL in PLWH with previously undetectable HIV-VL</p>	In case of demonstrated resistance mutations	<p>General recommendations:</p> <p>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</p> <p>* If genotype shows only limited NRTI mutation(s) e.g. M184V and/or 1-2 TAMs⁽ⁱⁱⁱ⁾: new regimen can include 2 NRTIs (3TC or FTC plus another NRTI with at most low level resistance) and either 1 active PI/b (i.e. DRV/b) or BIC or DTG (RAL, EVG/c or NNRTI not recommended)</p> <p>* If genotype shows multiclass resistance (i.e. ≥ 2 classes): new regimen will usually use</p> <ul style="list-style-type: none"> - at least 1 fully active PI/b (i.e. DRV/b) or 1 fully active 2nd generation INSTI (BIC, DTG) - plus 1 or 2 drugs remaining fully active despite resistance to other drugs from the class (i.e. 1 or 2 NRTIs and/or DOR) - and/or from a class not used previously i.e. INSTI, NNRTI, PI/b, assessed by genotypic testing <p>* When a 2-3 drugs active regimen cannot be constructed with NRTI, NNRTI, PI/b and INSTI, a drug with a new mechanism of action such as fostemsavir or ibalizumab can be added to obtain such a 2-3 drugs active regimen</p> <p>* In any case monotherapy is not recommended. In such situations, consider access to experimental drug therapy through early access program or clinical trials (e.g. lenacapavir)</p> <p>If < 2 active drugs are available, discuss on case by case situation deferring change, 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 copies/mL reduction) by recycling drugs</p> <p>Other considerations:</p> <ul style="list-style-type: none"> - Treatment interruption is not recommended - Continuation of 3TC or FTC even if documented resistance mutation (M184V/I) might be beneficial <p>If many options are available, criteria of preferred choice include: simplicity of the regimen, toxicity risks evaluation, drug-drug interactions, and sparing of future salvage therapy</p>
General measures	<p>Review expected potency of the regimen, taking into account all available historical genotypes</p> <p>Evaluate adherence, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues</p> <p>Perform resistance testing preferably 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</p> <p>Tropism testing if considering MVC</p> <p>Consider TDM</p> <p>Review ART history</p> <p>Identify treatment options, active and potentially active drugs/combinations</p>		
Management of virological failure (VF)	<p>If HIV-VL > 50 and < 200 copies/mL:</p> <p>Check for adherence, reinforce adherence</p> <p>Check HIV-VL 1 to 2 months later⁽ⁱ⁾</p> <p>If genotype shows no resistance mutations⁽ⁱⁱ⁾: maintain current ART if it contains INSTI with high barrier to resistance (BIC, DTG) or PI/b, otherwise monitor carefully</p> <p>If HIV-VL confirmed > 200 copies/mL:</p> <p>Therapeutic decision will depend on the resistance testing (genotype) results:</p> <p>If no resistance mutations found: check for adherence, reinforce adherence, perform TDM, discuss change to a different regimen</p> <p>If resistance mutations found: switch to a suppressive regimen based on drug and genotype history; multidisciplinary expert discussion advised in case of multiclass resistance</p> <p>Goal of new regimen: HIV-VL < 50 copies/mL within 6 months</p>		

- i In the absence of resistance and in persons fully adherent to treatment, consider non-suppressible viremia due to cellular proliferation
- ii Take into consideration that certain mutations can revert and/or disappear if there is no drug pressure
- iii Thymidine Analog Mutations (TAMs) are non-polymorphic mutations selected by the thymidine analogs ZDV and/or d4T. For more detailed information NRTI Resistance Notes, see HIV Drug Resistance Database <https://hivdb.stanford.edu/> or French ANRS resistance web page www.hivfrenchresistance.org

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	<ul style="list-style-type: none"> - Maintain ART: The main goal of ART during pregnancy is maintaining treatment efficacy, both for the women's benefit and HIV transmission risk. - ART may be switched temporarily for the duration of pregnancy to the preferred combinations recommended for ART naïve pregnant women, see table 1 - The decision on switching ART should be individualized taking into account the person's history of treatment, adherence and tolerability, and weighed against potential risk coming from ART exposure or suboptimal pharmacokinetics in pregnancy - If the purpose for switching is insufficient data about safety and efficacy in pregnancy, it should be explained to the pregnant woman and her decision/ willingness to switch current regimen taken into account: <ul style="list-style-type: none"> • Lower serum concentration was observed in persons on therapies boosted with COBI, DRV/r qd and RPV • There is insufficient data in pregnancy for BIC, EVG, DOR, RAL qd, and dual regimens - Pregnant women 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
2. Women becoming pregnant while treatment-naïve	Starting ART as soon as possible is highly recommended, see table 1
3. Women whose follow-up starts late in the second or in the third trimester	Start ART immediately (see table 1) 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
6. Women diagnosed with HIV in labour	See labour and breastfeeding
7. Labour	<p>1) Women whose HIV-VL is > 50 copies/mL at week 34-36:</p> <ul style="list-style-type: none"> • Elective cesarean section to be planned at week 38 • iv ZDV: During labour and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery <ul style="list-style-type: none"> - Scheduled cesarean delivery: start iv ZDV 3 hours before surgery - Unscheduled cesarean delivery: consider administering loading dose then proceed to delivery <p>2) Women diagnosed with HIV during labour:</p> <ul style="list-style-type: none"> • If possible, perform caesarean section • iv ZDV: During labour 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 <p>PEP should be given to all newborns born to mothers living with HIV according to local guidelines. For antiretroviral therapy in children with HIV, See page 140</p>
8. Breastfeeding	<ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> - 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 <ul style="list-style-type: none"> - 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 cessation 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

Table 1. Antiretroviral regimen for ART-naïve pregnant women

ART-naïve pregnant women should initiate treatment as soon as possible. The decision of ART regimen should be discussed with the person and individualized taking into account tolerability, possible adherence issues, as well weighed against potential risk coming from ART exposure or suboptimal pharmacokinetics in pregnancy.

Pregnant women starting ART 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 (see footnotes)
Recommended regimens		
2 NRTIs + INSTI (PREFERRED)		
ABC/3TC + DTG or ABC/3TC/DTG	DTG to be discussed with women considering to become pregnant or if to be used in first 6 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/XTC or TAF/FTC + DTG	DTG to be discussed with women considering to become pregnant or if to be used in first 6 weeks of pregnancy. TAF/FTC not recommended in first 14 weeks of pregnancy	II (DTG: neural tube defects risk during periconception) III (Tenofovir salts) IV (TAF & pregnancy)
TDF/XTC or TAF/FTC + RAL 400 mg bid	TAF/FTC not recommended in first 14 weeks of pregnancy	III (Tenofovir salts) IV (TAF & pregnancy) V (RAL in pregnancy, bid dosing)
2 NRTIs + PI/r		
TDF/XTC or TAF/FTC + DRV/r 600 mg/100 mg bid	With food TAF/FTC not recommended in first 14 weeks of pregnancy	III (Tenofovir salts) IV (TAF & pregnancy) 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 bedtime or 2 hours before dinner	I (ABC: HLA-B*57:01, may delay starting ART) VIII (EFV HIV-2 & group O)
TDF/XTC or TAF/FTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner TAF/FTC not recommended in first 14 weeks of pregnancy	III (Tenofovir salts) IV (TAF & pregnancy) VIII (EFV HIV-2 & group O)
TDF/XTC or TAF/FTC + RPV or TDF/FTC/RPV or TAF/FTC/RPV	CD4 count > 200 cells/μL HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food TAF/FTC not recommended in first 14 weeks of pregnancy	II (Tenofovir salts) IV (TAF & pregnancy) IX (RPV exposure during 2 nd and 3 rd trimester, HIV-2) X (Interactions)
2 NRTIs + PI/r		
ABC/3TC + DRV/r 600 mg/100 mg bid	HLA-B*57:01 negative HBsAg negative With food	I (ABC: HLA-B*57:01, may delay starting ART) VI (DRV dosing) VII (COBI boosting)

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 there was a small non-statistically significant increase in neural tube defects among women receiving DTG from conception compared with all other antiretroviral exposure
- 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 not recommended in first 14 weeks of gestational age as IMPACT 2010/VESTED randomized study evaluating the safety and virologic efficacy of this combination recruited women only between 14-28 weeks of pregnancy
- 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

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

ART should be started as soon as possible (within two weeks of initiating TB treatment) regardless of CD4 count

However, if TB meningitis signs and symptoms are present ART initiation may be delayed. See [When to start ART in PLWH with Opportunistic Infections \(OIs\)](#)

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. 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. For a wider review of potential DDIs of ART and TB treatment, see page 35

Regimen	Main requirements	Additional guidance (footnotes)
Recommended regimens with rifampicin		
2 NRTIs + NNRTI		
TDF/XTC + EFV or TDF/FTC/EFV	At bedtime 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 bedtime 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/XTC + DTG bid		I (tenofovir salts) IV (DTG: dosing)
TDF/XTC + 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/XTC + 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. This dose adjustment should be maintained for 2 weeks after stopping rifampicin as the inducing effect persists after discontinuation of a strong inducer
- 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 compared to EFV. With 800 mg bid only limited data from a phase 2 study with potential increases in liver toxicity
- VI For guidance on ARV and rifabutin dosing, see [TB Drug Doses](#), [DDI table on Anti-tuberculosis drugs and ARVs](#)

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

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)
 - Follow-up HIV serology: mandatory at the end of PEP and repeat 6-8 weeks 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 virally suppressed on treatment. A recent STI, use of post-exposure prophylaxis or chem-sex may be markers of increased risk for HIV
- 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 may have untreated or inadequately suppressed HIV infection

2. PrEP is a medical intervention that provides a high level of protection against HIV acquisition but does not protect against other STIs or pregnancy 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 15. During PrEP, a fourth generation HIV test should be repeated at one month and then every 3 months. In stable long-term users who are on 6 monthly prescriptions an interim third generation test that can be performed without a visit to clinic is acceptable
- PrEP should be changed to triple-drug ART without interruption in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test which may necessitate referral for evaluation to an HIV unit, see ART initiation page 12
- PrEP may continue during pregnancy and breastfeeding if the risk of acquiring HIV persists
- 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 7-9
- Counsel that TDF-based PrEP may impact renal and bone health, see pages 71 and 73-75. Check renal function within the first 3 months of starting PrEP and check renal function and bone health during PrEP according to guidelines on TDF use
- Counsel that PrEP, like other prevention methods, only works when it is taken. An adherence check one month after starting is recommended, and counselling may be required in follow-up
- Counsel that PrEP can be prescribed long-term but that each consecutive PrEP prescription should cover the period to the next visit which will be every 3 months for the majority but could be a maximum of 6 months in stable long-term users (over one year of daily PrEP)

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
- For men 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; no data for TAF/FTC so far). 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
- Data on renal outcomes with use of TDF vs. TAF in those on PrEP with renal impairment is limited, recommendations to follow guidelines on TDF use in PLWH, see pages 74-76. Similarly, no data on use of "on demand" vs daily PrEP for renal outcomes

- * 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										
TDF ⁽ⁱⁱⁱ⁾			Hepatitis		↓ BMD, Osteoma-lacia	↓ eGFR, Fanconi syndrome				
TAF ⁽ⁱⁱⁱ⁾									Weight gain	
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							Sleep disturbance, Headache			
PIs										
ATV ^(v)		Nausea and Diarrhoea ^(vii)	Hyperbiliru-binaemia, Jaundice, Cholelithiasis			↓ eGFR, Nephrolithiasis			Dyslipi-daemia	
DRV ^(v)	Rash			IHD		Nephrolithiasis			Dyslipi-daemia	
LPV ^(vi)				IHD		↓ eGFR			Dyslipi-daemia	
Boosting										
RTV		Nausea and diarrhoea				↓ eGFR ^(iv)			Dyslipidae-mia	
COBI		Nausea and diarrhoea				↓ eGFR ^(iv)			Dyslipidae-mia	

INSTI									
RAL		Nausea			Myopathy, Rhabdomyolysis		Sleep disturbance, Headache	Weight gain	Systemic hypersensitivity syndrome ^(viii)
DTG	Rash	Nausea				↓ eGFR ^(iv)	Sleep disturbance, Headache	Weight gain	Systemic hypersensitivity syndrome (< 1%) ↑ Risk of neural tube defects (pre-conception) ^(ix)
EVG/c		Nausea, Diarrhoea				↓ eGFR ^(iv)	Sleep disturbance, Headache	Weight gain	
BIC						↓ eGFR ^(iv)	Sleep disturbance, Headache	Weight gain	
CAB	Injection site reactions ^(xi)						Sleep disturbance, Headache		Pyrexia ^(xi)
Entry inhibitors									
Ibalizumab	Rash	Nausea, Diarrhoea					Dizziness, Headache		
FTR	Rash	Nausea, Vomiting, Abdominal pain, Diarrhoea					Headache		
MVC			Hepatitis	Postural hypotension					
ENF	Injection site nodules								Hypersensitivity

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 non-bold black

- ii Still available, but generally not recommended due to toxicity
- iii TDF and TAF are prodrugs of tenofovir. TDF, but not TAF, may have kidney and bone toxicity particularly when co-administered with RTV or COBI boosting. TDF, but not TAF, decreases plasma lipids. TAF, but not TDF, may promote weight gain particularly when co-administered with DTG or BIC, see pages 71, 74, 75, 86
- 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 COBI-boosted DRV, although lipid effects lower)
- vi Still available but seldom used. Requires RTV-boosting
- vii Frequency and severity differs between individual PIs
- viii DRESS syndrome reported in a few cases, potentially associated to HLA-B*53
- ix See [Treatment of Pregnant Women or Women considering Pregnancy](#)
- x CAB is available in oral or injectable formulations; injection site reactions are an adverse effect of injectable CAB
- xi Pyrexia includes feeling hot or body temperature increased

* 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

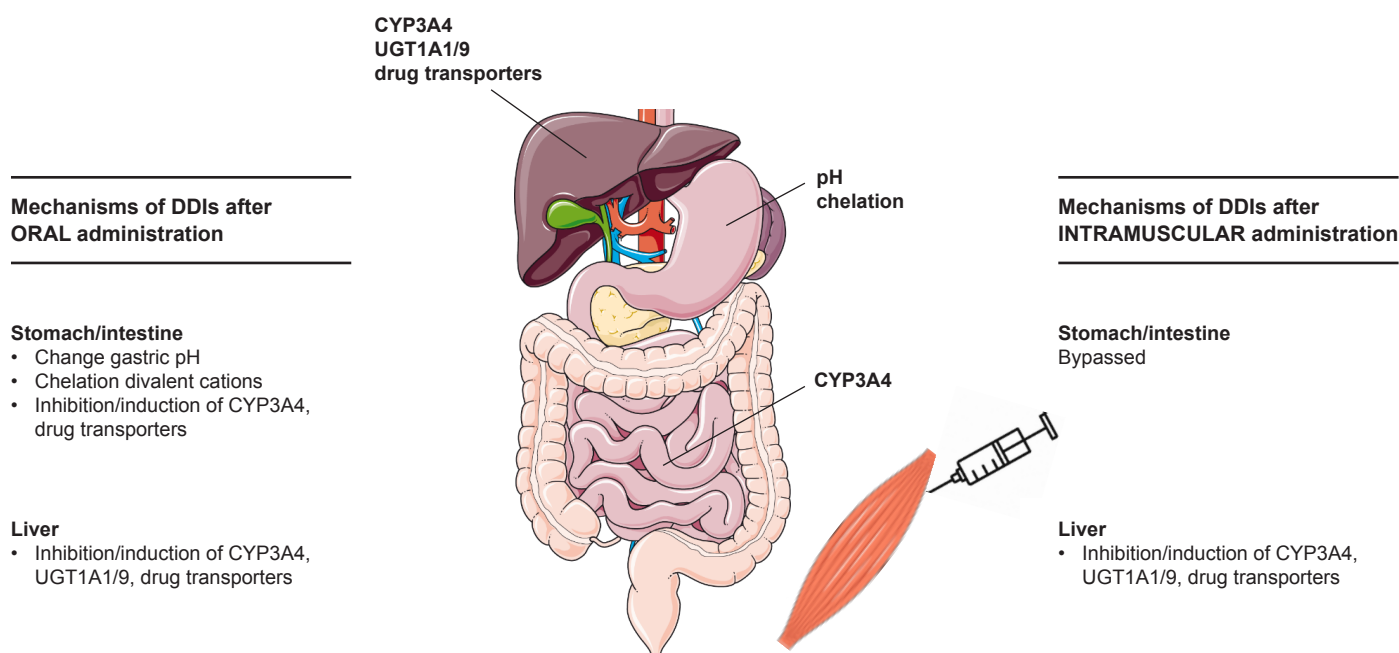
Part III Drug-drug Interactions and Other Prescribing Issues in PLWH

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 im administration of the ARVs CAB and RPV presents the advantage of eliminating DDIs occurring at the gastrointestinal level. However, DDIs can still occur at the hepatic level as illustrated below. Bypassing the gastrointestinal tract does not mitigate the magnitude of DDIs with drugs inducing metabolism.

Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

- Intramuscular administration: → DDIs at the gastrointestinal level are avoided
→ DDIs at the hepatic level can still occur (magnitude of DDIs with inducers is not mitigated)



Adapted from Hodge D et al. Clin Pharmacokinet 2021

Examples of medications interacting with the oral but not the intramuscular administration of RPV

Antacids; famotidine; lansoprazole; liraglutide; omeprazole; orlistat; pantoprazole; rabeprazole; ranitidine

Examples of medications interacting with the oral but not the intramuscular administration of CAB

Antacids; calcium; iron; magnesium; multivitamins containing divalent cations; orlistat; strontium ranelate

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 older PLWH to inappropriate drug use or dosing in addition to DDIs





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 older 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	FTR	MVC	BIC	CAB oral	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
Cardiovascular drugs	atorvastatin	↑822%	↑	↑290%	↑	↑490%	↓2%	↓43%	↓37%	↓	↑4% D10%	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔
	fluvastatin	↑	↑	↑	↑	↔	↔	↑	↑	↔	↔	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔
	pravastatin	↑	↑	↑	↑81%	↑33%	↔	↓44%	↓	↔	↔	↔	↔	↔	↔	↔	↔	↑	↓4%	↔	↔
	rosuvastatin	↑242%	↑213%	↑93%	↑48%	↑108%	↔	↔	↔	↔	↔	↑69%	↔	↔	↔	↔	↔	↑38%	↔	↔	↔
	simvastatin	↑	↑	↑	↑	↑	↔	↓68%	↓	↓	↔	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔
	amlodipine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	diltiazem	↑a	↑a	↑	↑	↑a	E	↓69%	↓E	↓	E	E	E	E	↔	E	↔	↑	↔	↔	↔
	metoprolol	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	verapamil	↑a	↑a	↑	↑	↑a	E	↓	↓E	↓	E	E	E	E	↔	E	↔	↑	↔	E	E
	warfarin	↑	↑ or ↓	↑	↓	↓	↔	↑ or ↓	↑	↑ or ↓	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔
CNS drugs	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↑?	↔	↔	↔
	carbamazepine	↑D	↑D	↑D	↑	↑D c	D	↓27% D36%	D	↓D	D	D	D	D	D	D	D49%	↑D	D c	D	↔
	citalopram	↑a,b	↑a,b	↑	↑	↑a,b	↔	↓	↓	↓	↔b	↔b	↔	↔	↔	↔b	↔	↑	↔	↔	↔
	diazepam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	lamotrigine	↔	↓32% d	↔	↓	↓50%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↓1%	↔	↔
	midazolam (oral)	↑	↑	↑	↑	↑	↓18%	↓	↓	↓	↔	↔	↑18%	↑15%	↑10%	↔	↔	↑	↓8%	↔	↔
	mirtazapine	↑b	↑b	↑	↑	↑b	↔	↓	↓	↓	↔b	↔b	↔	↔	↔	↔b	↔	↑	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔
	phenytoin	D	↓D	D	↓D	↓D c	D	↓D	D	D	D	D	D	D	D	D	D e	D	D c	D	↔
	pimozide	↑	↑	↑	↑	↑	↔	↑	↓	↓	↔b	↔b	↔	↔	↔	↔b	↔	↑	↔	↔	↔
	sertraline	↑	↓	↑	↓49%	↓b	↔	↓39%	↓	↓	↔	↔	↔	↔	↔	↔	↔	↓7%	↔	↔	↔
	triazolam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
Anti-infectives	clarithromycin	↑E a,b	↑E a,b	↑E	↑	↑ a,b	↑	↓39%	↓39% E42%	↓31% E26%	E b	E a,b	E	E	↔	E b	↔	↑E	↔	E	E
	fluconazole	↑? a,b	↔ a,b	↑?	↔	↔ a,b	↑	↔	E86%	E100%	E b	E a,b	↔	↔	↔	E b	↔	↑?	↔	E?	↔
	itraconazole	↑Eb	↑Eb	↑E	↑E	↑Eb	↑	↓39%	↓E	↓61%	E b	Eb	E	E	↔	E b	↔	↑E	↔	E	E
	rifabutin	↑D f	↑g	↑D f	↑g	↑g	D50% h	↓38% i	↓17% D37%	↑17%	D42% j	D30%	k	D38%	↔	D	↔	↑D f	E19%	D l	↔
	rifampicin	D	D72%	D	D57%	D75% m	D82%	D26%	D	D58%	D80%	D82%	D	D75%	D59%	D	D54% n	D	D40% o	D l	D12%
	voriconazole	↑↓ Eb	↑↓ Db	↑E	↓	↑↓ Eb	↑	↓E	↑14% E36%	↓E	E	E	E	E61%	↔	E	↔	↑E	↔	↔	↔
Miscellaneous	antacids	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	D	D	↔	D	D	D p	↔	↔
	PPIs	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	↔	↔	↔	E	↔	↔
	H2 blockers	D	D	↔	↔	↔	↔	↔	↔	↔	D	↔	↔	↔	↔	↔	↔	↔	E	↔	↔
	alfuzosin	↑b	↑b	↑	↑	↑b	↔	↓	↓	↓	↔ b	↔ b	↔	↔	↔	↔ b	↔	↑	↔	↔	↔
	beclo- metasone (inhaled)	↑ q	↑ q	↑? q	↓11% r	↑ q	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑q	↔	↔	↔
	budesonide (inhaled)	↑ s	↑ s	↑ s	↑ s	↑ s	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑ s	↔	↔	↔
	buprenor- phine	↑	↑67% t	↑	↓11% t	↑~2%	↔	↓50%	↓25%	↓9%	↔	↑30%	↔	↔	↔	↔	↔	↑35%	↔	↔	↑~5%
	ergot deriva- tives	↑	↑	↑	↑	↑	E	↑	↑	↓	E	↔	E	↔	↔	E	↔	↑	↔	↔	↔
	ethinylestra- diol	↑1% u	↓19% v	↓30%	↓44% u	↓42% u	↓2%	w	↑22%	↓20%	↑14%	↑40% x	↓<1%	↑4%	↑2%	↔	↑3%	↓25% y	↓2%	↑11%	↔
	fluticasone (inhaled)	↑s	↑ s	↑ s	↑ s	↑ s	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑ s	↔	↔	↔
	methadone	↑? ab	↔ ab	↑?	↓16%	↓53% ab	↓5%	↓52%	↑6%	↓~50%	↓16% ab	↑14% ab	↔	↔	↔	↔ ab	↓2%	↑7%	↔	↔	↑~5%
	salmeterol (inhaled)	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	sildenafil (erectile dys.)	↑	↑	↑	↑	↑	↔	↓	↓37%	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	St John's wort	D z	D z	D z	D z	D z	D z	D z	D z	D z	D z	D z	D z	D z	↔	D z	D e	D z	D	D z	↔
	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

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)
CAB/RPV	CAB and RPV in long acting injections (PK and/or QT interactions shown are with RPV)

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

* 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.

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)

Interactions with ABC, FTC, 3TC, ZDV

ABC:	decreased ABC exposure with phenytoin, rifampicin
ABC:	decreased methadone exposure
ABC:	increased carbamazepine exposure
FTC, 3TC:	no clinically relevant interactions expected.
ZDV:	decreased ZDV exposure with clarithromycin, rifampicin
ZDV:	increased ZDV exposure with fluconazole, methadone
ZDV:	increased carbamazepine exposure
ZDV:	decreased phenytoin exposure

Interactions with ibalizumab

None

Comments

- a ECG monitoring is recommended.
- b Caution as both drugs can induce QT interval prolongation.
- c 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.
- d No PK changes with unboosted ATV.
- e 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.
- f Reduce rifabutin to 150 mg 3 times per week.
- g Reduce rifabutin to 150 mg qd. Monitoring for rifabutin-related toxicities (i.e. uveitis or neutropenia) is advised with daily administration of rifabutin.
- h The product label for DOR recommends to increase DOR dosage to 100 mg bid when co-administered with rifabutin. DOR should be kept at 100 mg bid for at least another 2 weeks following cessation of rifabutin due to the persisting inducing effect upon discontinuation of a moderate/strong inducer.
- i Increase rifabutin to 450 mg daily.
- j The RPV dose should be increased to 50 mg qd during co-administration (and decreased to 25 mg qd when rifabutin is stopped). Note, it is recommended to maintain RPV 50 mg qd for at least another 2 weeks following cessation of rifabutin due to the persisting inducing effect upon discontinuation of a moderate/strong inducer.
- k Increase MVC to 600 mg bid in absence of PI. With PI (except TPV/r, FPV/r), give MVC 150 mg bid.
- l Rifamycins decrease the exposure of TAF when given 25 mg qd therefore the label recommends to use TAF 25 mg bid. However, the intracellular tenofovir diphosphate (active entity) concentrations are likely to be higher than those observed with TDF even without rifampicin suggesting that usage of TAF 25 mg qd with rifampicin, rifapentine or rifabutin may be acceptable.
- m If no other option use RTV 400 mg bid or double dose LPV/r.
- n Administer DTG 50 mg bid in treatment-naïve or INSTI-naïve PLWH. This dose adjustment should be maintained for 2 weeks after stopping rifampicin as the inducing effect persists after discontinuation of a strong inducer. Alternative to rifampicin should be used where possible for INSTI-experienced PLWH with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.
- o RAL 400 or 800 mg bid.
- p 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.
- q 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.
- r DRV/r decreased the exposure of active metabolite (beclomethasone-17-monopropionate), no significant effect on adrenal function was seen.
- s 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.
- t Concentrations of norbuprenorphine increased.
- u Alternative or additional contraceptive measures are recommended or, if used for hormone replacement therapy, monitor for signs of oestrogen deficiency.
- v Increase in ethinylestradiol with unboosted ATV.
- w 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 EFV is not recommended.
- x The daily dose of ethinylestradiol should not exceed 30 µg. Caution is advised, particularly in persons with additional risk factors for thromboembolic events.
- y European SmPC states a hormonal contraceptive should contain at least 30 µg ethinylestradiol.
- z A study suggests a low risk of a clinically relevant pharmacokinetic interaction with low-hyperforin formulations (< 1 mg/day) of St John's Wort (hyperforin is the constituent responsible for induction of CYPs and P-gp). Co-administration may be considered with St John's Wort formulations that clearly state the hyperforin content and which have a total daily hyperforin dose of 1 mg or less.

Drug-drug Interactions between Analgesics and ARVs

Analgesics		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
Non-opioid analgesics	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔b
	celecoxib	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔b
	diclofenac	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E b
	ibuprofen	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔b
	mefenamic acid	↔	↔	↔	↔	↔	↔	↑a	↑a	↔	↔	↔	↔	↔	↑11%	↔	↔	↔	↔	↔	↔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%	↔	↑30%	↔	↔	↔	↔	↔	↑35%	↔	↔	↑~5%
	codeine	↑ ^d	↑ ^d	↑ ^d	↑ ^d	↑ ^d	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑ ^d	↔	↔	↔
	diamorphine	↔ ^e	↓ ^{e,f}	↔ ^e	↓ ^{e,f}	↓ ^{e,f}	↔	↑	↔ ^e	↔	↔	↔	↔	↔	↔	↔	↔	↔ ^e	↔	↔	↔
	dihydrocodeine	↑	↑	↑	↓	↓	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	fentanyl	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	hydrocodone	↓ ^g	↓ ^g	↓ ^g	↓ ^g	↓ ^g	↔	↓ ^h	↓ ^h	↓ ^h	↔	↔	↔	↔	↔	↔	↔	↓ ^g	↔	↔	↔
	hydromorphone	↔	↓	↔	↓	↓	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	methadone	↑ ⁱ	↔ ⁱ	↑ ⁱ	↓16%	↓53% ⁱ	↓5%	↓52%	↑6%	↓~50%	↓16% ⁱ	↑14% ⁱ	↔	↔	↔	↔	↔	↓2%	↑7%	↔	↑~5%
	morphine	↔ ^e	↓ ^{e,f}	↔ ^e	↓ ^{e,f}	↓ ^{e,f}	↔	↑	↔ ^e	↔	↔	↔	↔	↔	↔	↔	↔	↔ ^e	↔	↔	↔
	oxycodone	↑	↑	↑	↑	↑160%	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	pethidine	↑	↓	↑	↓	↓	↔	↓ ^j	↓ ^j	↓ ^j	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	sufentanil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	tapentadol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tramadol	↑ ^d	↑ ^d	↑ ^d	↑ ^d	↑ ^d	↔	↓ ^k	↔	↓ ^k	↔	↔	↔	↔	↔	↔	↔	↑ ^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)
 CAB/RPV CAB and RPV im long acting injections

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

Interactions with ABC, FTC, 3TC, ZDV

ABC: decreased methadone exposure
 FTC, 3TC: no clinically relevant interactions expected.
 ZDV: potential additive haematological toxicity with ibuprofen, naproxen.
 ZDV: Moderately increased ZDV exposure with methadone; 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 Inhibition of P-gp by RTV, COBI or ETV could potentiate the effect of opiate in the CNS.
- f Concentrations of parent drug decreased but concentrations of active metabolite increased.
- g Concentrations of hydrocodone increased, but concentrations of active metabolites (norhydrocodone and hydromorphone) decreased. The clinical significance of this is unclear.
- h Concentrations of hydrocodone decreased, but concentrations norhydrocodone increased. The clinical significance of this is unclear.
- i Both drugs can potentially prolong the QT interval, ECG monitoring recommended.
- j Concentrations of parent drug decreased and concentrations of neurotoxic metabolite increased.
- k 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	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
Anticoagulants	acenocoumarol	↔	↓	↔	↓	↓	↔	↑or↓	↑	↓	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔
	apixaban	↑a	↑a	↑a	↑a	↑a	↔	↓	↓	↓	↔	↑?	↔	↔	↔	↔	↔	↑a	↔	↔	↔
	argatroban	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	betrixaban	↑b,c	↑b,c	↑c	↑c	↑b,c	↔	↔	↑	↔	↔b	↔b	↔	↔	↔	↔b	↔	↑c	↔	↔	↔
	dabigatran	↑d	↑e	↑d	↑e	↑?	↔	↔	↑	↔	↑?	↔	↔	↔	↔	↔	↔	↑d	↔	↔	↔
	dalteparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	edoxaban	↑f	↑f	↑f	↑f	↑f	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑f	↔	↔	↔
	enoxaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fondaparinux	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	heparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenprocoumon	↑	↑or↓g	↑	↑or↓	↑or↓	↔	↓	↑or↓	↓	↔	↔	↔	↔	↔	↔	↔	↑or↓	↔	↔	↔
	rivaroxaban	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↑?	↔	↔	↔	↔	↔	↑	↔	↔	↔
	warfarin	↑	↑or↓g	↑	↓	↓	↔	↑or↓	↑	↑or↓	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔
Antiplatelet agents	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	clopidogrel	↓h	↓h	↓h	↓h	↓h	↔	↓h E	↓h	↑i E	↔	↔	↔	↔	↔	↔	↔	↓h	↔	↔	↔
	dipyridamole	↑	↓j	↔	↓	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	prasugrel	↓k	↓k	↓k	↓k	↓k	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↓k	↔	↔	↔
	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)
- CAB/RPV CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

Interactions with ABC, FTC, 3TC, ZDV

ABC: may potentially reduce the pharmacodynamic effect of clopidogrel.
FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- a US label suggests to use apixaban at a reduced dose (2.5 mg bid) if needed.
- b Both drugs can potentially prolong the QT interval, ECG monitoring recommended.
- c US label recommends to use a reduced initial betrixaban dose of 80 mg followed by 40 mg qd.
- d Dabigatran should be reduced to 100 mg bid in persons with normal renal function and to 75 mg bid in case of moderate renal impairment. Coadministration should be avoided in case of severe renal impairment.
- e No significant increase in DRV/r exposure when administered simultaneously with dabigatran in persons with no renal impairment.
- f European label advises to consider a dose reduction of edoxaban from 60 mg to 30 mg, however, US label recommends no dose modification.
- g Unboosted ATV predicted to increase the anticoagulant, monitor INR and adjust the anticoagulant dosage accordingly.
- h Decreased conversion to active metabolite leading to non-responsiveness to clopidogrel. An alternative to clopidogrel should be considered.
- i Increase in amount of active metabolite via induction of CYP3A4 and CYP2B6.
- j Unboosted ATV predicted to increase dipyridamole exposure due to UGT1A1 inhibition.
- k 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 Antidepressants and ARVs

Antidepressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
NaSSA	mirtazapine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
SSRI	citalopram	↑a,b	↑a,b	↑	↑	↑a,b	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	escitalopram	↑a,b	↑a,b	↑	↑	↑a,b	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	fluoxetine	↑	↑	↑	↑	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	fluvoxamine	↑	↑	↑	↑	↑a	↔	↔	↔	E	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔
	sertraline	↑	↓	↑	↓49%	↓a	↔	↓39%	↓	↓	↔	↔	↔	↔	↔	↔	↔	↓7%	↔	↑9%	↔
	vortioxetine	↑c	↑c	↑c	↑c	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑c	↔	↔	↔
SNRI	desvenlafaxine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	duloxetine	↑	↑↓	↑	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	milnacipran	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	venlafaxine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔a	↔a	D	↔	↔	↔a	↔	↑	↔	↔	↔
TCA	amitriptyline	↑	↑	↑	↑	↑a,b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	clomipramine	↑a,b	↑a,b	↑b	↑b	↑a,b	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑b	↔	↔	↔
	desipramine	↑a	↑a	↑	↑	↑5%a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	doxepin	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	imipramine	↑a,b	↑a,b	↑b	↑b	↑a,b	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑b	↔	↔	↔
	nortriptyline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	trimipramine	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
TeCA	maprotiline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	mianserin	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
Others	agomelatine	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↑?	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↑	E	↓E	↓E	↓E	E	E	E	E	↔	E	↔	↑	↔	↔	↔
	phenelzine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	reboxetine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	St John's wort	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	↔	Dd	De	Dd	D	Dd	↔
	tranylcypromine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	trazodone	↑a,b	↑a,b	↑	↑	↑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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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

NaSSA noradrenergic specific serotonergic antidepressant
SSRI selective serotonin reuptake inhibitors
SNRI serotonin and norepinephrine reuptake inhibitors
TCA tricyclic antidepressants
TeCA tetracyclic antidepressants

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- a Caution as both drugs can induce QT interval prolongation.
- b ECG monitoring is recommended.
- c Based on the patient clinical response, a lower dose of vortioxetine may be needed in poor CYP2D6 metabolizers in the presence of a strong CYP3A4 inhibitor.
- d A study suggests a low risk of a clinically relevant pharmacokinetic interaction with low-hyperforin formulations (< 1 mg/day) of St John's Wort (hyperforin is the constituent responsible for induction of CYPs and P-gp). Coadministration may be considered with St John's Wort formulations that clearly state the hyperforin content and which have a total daily hyperforin dose of 1 mg or less.
- e 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	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
ACE inhibitors	captopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fosinopril	↔	↑	↔	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eprosartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔
	losartan	↔	↓a	↔	↓a	↓a	↔	↑b	↑b	↔	↔	↔	↔	↔	↔	↔	↔	↓a	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	atenolol	↑c	↔c	↑	↔	↔c	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↑	↑	↔	↔	↔
β blockers	bisoprolol	↑c	↑c	↑	↑	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	carvedilol	↑c	↑↓c	↑	↑↓	↑↓c	↔	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	labetolol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nebivolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	oxprenolol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pindolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	propranolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	amlodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
Calcium channel blockers	diltiazem	↑d	↑d	↑	↑	↑e	E	↓69%	↓E	↓	E	E	E	E	↔	E	↔	↑	↔	↔	↔
	felodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	lacidipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔f	↔f	↔	↔	↔	↔f	↔	↑	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nicardipine	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	Ef	Ef	E	↔	↔	Ef	↔	↑	↔	↔	↔
	nifedipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nisoldipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	verapamil	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	E	E	E	E	↔	E	↔	↑	↔	E	E
	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔
	bendroflu-methiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Diuretics	chlorthalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eplerenone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E
	hydrochloro-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indapamide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	torasemide	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔
	xipamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	clonidine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	doxazosin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
Others	hydralazine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔g	↔	↔	↔	↔	↔	↔	↔	↔h	↔
	methylidopa	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔g	↔	↔	↔	↔	↔	↔	↔	↔	↔
	moxonidine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑?
	prazosin	↑?	↑?	↑?	↑?	↑?	↔	↓?	↓?	↓?	↔	↑	↔	↔	↔	↔	↔	↑?	↔	↔	↔
	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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

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

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

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, ZDV: no clinically relevant interactions expected.
3TC: increased 3TC exposure with atenolol and amiloride.
3TC: increased exposure of atenolol and amiloride.

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.
- f Caution as both drugs can induce QT interval prolongation.
- g Use with caution in persons with a history of postural hypotension or on concomitant medicinal products known to lower blood pressure, and those at increased risk of cardiovascular events.
- h Hydralazine has some nephrotoxic potential. If co-administration is unavoidable, monitor renal function closely.

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 Anti-malarial Drugs and ARVs

Antimalarial drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
First line and second line drugs	amodiaquine	↑	↑	↔	↑	↑	↔	↑ ^a	↓?	↓29% ^a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	artemisinin	↑	↑	↑	↑	↑	D	↓	↓D	↓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	↔ ^{c,g}	↔ ^{c,g}	↔	↔	↔	↔ ^{c,g}	↔	↔ ^d	↔	↔	↔
	clindamycin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	doxycycline	↔	↔	↔	↔	↔	↔	↓?	↓?	↓?	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	halofantrine	↑ ^g	↑ ^g	↑	↑	↑ ^g	↔	↓	↓	↓	↔ ^g	↔ ^{c,g}	↔	↔	↔	↔ ^g	↔	↑	↔	↔	↔
	hydroxy-chloroquine	↑ ^{c,g}	↑ ^{c,g}	↑	↑	↑ ^{c,g}	↔	↔ ^e	↓	↓	↔ ^g	↔ ^{c,g}	↔	↔	↔	↔ ^g	↔	↑	↔	↔	↔
	lumefantrine	↑ ^{c,g}	↑ ^{c,g}	↑	↑175%	↑382% ^{c,g}	↔	↓~40%	↓	↓D46%	↔ ^g	↔ ^g	↔	↔	↔	↔ ^g	↑10%	↑	↔	↔	↔
	mefloquine	↑ ^{c,g}	↑ ^{c,g}	↑	↑	↓28% ^{c,g}	↔	↓	↓	↓	↔ ^g	↔ ^g	↔	↔	↔	↔ ^g	↔	↑	↔	↔	↔
	piperaquine	↑ ^{c,g}	↑ ^{c,g}	↑ ^c	↑ ^c	↑ ^{c,g}	E	↓	↓	↓	E ^g	↔ ^g	E	E	↔	↔ ^g	↔	↑ ^c	↔	↔	↔
	primaquine	↔ ^g	↔ ^g	↔	↔	↔ ^g	↔	↔ ^h	↔ ^h	↔ ^h	↔ ^g	↔ ^g	↔	↔	↔	↔ ^g	↔	↔	↔	↔	↔
	proguanil	↔	↓41% ^b	↔	↓ ^b	↓38% ^b	↔	↓44% ^b	↓E55% ^b	↓ ^b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pyrimethamine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinine	↑ ^{c,g}	↑ ^{c,g}	↑	↑	↓56% ^{c,g}	↔	↓	↓	↓	↔ ^g	↔ ^{c,g}	E	↔	↔	↔ ^g	↔	↑	↔	↔	↔
	sulfadoxine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

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 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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

Interactions with ABC, FTC, 3TC, ZDV

ABC: no clinically relevant interactions expected.
 FTC: increased FTC exposure with pyrimethamine, sulfadoxine.
 3TC: increased 3TC exposure with pyrimethamine, sulfadoxine.
 ZDV: potential additive haematological toxicity with amodiaquine, atovaquone, primaquine, pyrimethamine, sulfadoxine.

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/hydroxychloroquine 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 Caution as both drugs can induce QT interval prolongation.
- ^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 Anti-tuberculosis Drugs and ARVs

Anti-tuberculosis drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
First line and second line drugs	amikacin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a
	bedaquiline	↑ b	↑ b	↑	↑	↑62% b	↔	↓18%	↓	↑3%	↔ b	↔ b	↔	↔	↔	↔ b	↔	↑	↔	↔	↔
	capreomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑ c	↔	↔	↔	↑ E a
	clofazimine	↔ b	↔ b	↔	↔	↔ b	E	↔	↔	↔	E b	E b	E	E	↔	↔ b	↔	↔	↔	↔	↔
	cycloserine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	delamanid	d	d	d	d	d	↔	↔ e	↔	↔	↔ f	↔ f	↔	↔	↔	↔ f	↔	d	↔	↔	↔
	ethambutol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ethionamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	isoniazid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	kanamycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a
	moxifloxacin	↑ b	↓ b	↔	↓	↓ b	↔	↓	↓	↔	↔ b	↔ b	↔	↔	↔	↔ b	↔	↔	↔	↔	↔
	para-aminosalicylic acid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↑ E
	pyrazinamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	rifabutin	↑ D g	↑ h	↑ D g	↑ h	↑ h	D50% ⁱ	↓38% ^j	D37%	↑17%	D42% ^k	D30%	I	D38%	↔	D	↔	↑ D g	E19%	Dm	↔
	rifampicin	D	D72%	D	D57%	D75% ⁿ	D82%	D26%	D	D58%	D80%	D82%	D o	D75%	D59%	D	D54% ^p	D	D40% ^q	Dm	D12%
	rifapentine	D	D	D	D	D	D	D	D	D	D	D	D o	D	D	D	D r	D	D	Dm	↔
	streptomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a

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 anti-tuberculosis drug
- ↓ Potential decreased exposure of the anti-tuberculosis 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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

Interactions with ABC, FTC, 3TC, ZDV

- ABC: potentially moderately increased ABC exposure with rifampicin but no a priori dose adjustment required.
- FTC: Exposure of FTC and/or capreomycin may increase when co-administered. Monitor renal function as appropriate.
- FTC: Exposure of FTC and/or para-aminosalicylic acid may increase when co-administered.
- 3TC: Exposure of 3TC and/or capreomycin may increase when co-administered. Monitor renal function as appropriate.
- 3TC: Exposure of 3TC and/or para-aminosalicylic acid may increase when co-administered.
- ZDV: Rifampicin decreased ZDV AUC by 47%. Co-administration is not recommended in ZDV's European label, but the US label says routine dose modification is not warranted.

Interactions with ibalizumab

None

Comments

- a Co-administration should be avoided due to the risk of additive tubular toxicity, but if such use is unavoidable, closely monitor renal function.
- b Both drugs can potentially prolong the QT interval, ECG monitoring recommended.
- c Aminoglycosides are nephrotoxic (risk is dose and treatment duration related). Renal function should be monitored as clinically appropriate and the dosage of the ARV adjusted accordingly.

- d Co-administration is expected to increase concentrations of DM-6705, a delamanid metabolite which is associated with QT prolongation. Frequent ECG monitoring is recommended.
- e A higher rate of neuropsychiatric adverse effects (e.g., euphoric mood and abnormal dreams) was observed with delamanid plus EFV compared to either drug alone.
- f RPV, FTR and DM-6705 (a delamanid metabolite) can potentially prolong the QT interval, ECG monitoring recommended.
- g Reduce rifabutin to 150 mg 3 times per week.
- h Reduce rifabutin to 150 mg qd. Monitoring for rifabutin-related toxicities (i.e. uveitis or neutropenia) is advised with daily administration of rifabutin.
- i The product label for DOR recommends to increase DOR dosage to 100 mg bid when co-administered with rifabutin. DOR should be kept at 100 mg bid for at least another 2 weeks following cessation of rifabutin due to the persisting inducing effect upon discontinuation of a moderate/strong inducer.
- j Increase rifabutin to 450 mg daily.
- k The RPV dose should be increased to 50 mg qd during co-administration (and decreased to 25 mg qd when rifabutin is stopped). Note, it is recommended to maintain RPV 50 mg qd for at least another 2 weeks following cessation of rifabutin due to the persisting inducing effect upon discontinuation of a moderate/strong inducer.
- l Increase MVC to 600 mg bid in absence of PI. With PI (except TPV/r, FPV/r), give MVC 150 mg bid.
- m Rifamycins decrease TAF exposure when given 25 mg qd therefore the label recommends to use TAF 25 mg bid. However, the intracellular tenofovir diphosphate (active entity) concentrations are likely to be higher than those observed with TDF even without rifampicin [1] suggesting that usage of TAF 25 mg qd may be acceptable.
- n If no other option use RTV 400 mg bid or double dose LPV/r
- o Give MVC 600 mg bid.
- p A dose adjustment of DTG to 50 mg bid is recommended in treatment-naïve or INSTI-naïve persons. This dose adjustment should be maintained for 2 weeks after stopping rifampicin as the inducing effect persists after discontinuation of a strong inducer. Alternatives to rifampicin should be used where possible for INSTI-experienced persons with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.
- q RAL 400 or 800 mg bid.
- r Based on DTG interactions studies with rifabutin and rifampicin, consider administering DTG at 50 mg bid in the presence of rifapentine. This dose adjustment should be maintained for 2 weeks after stopping rifapentine as the inducing effect persists after discontinuation of a strong inducer.

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 Anxiolytics and ARVs

Anxiolytics		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
BZD	alprazolam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	chlor-diazepoxide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	clonazepam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
SSRI	escitalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔b	↔	↔	↔	↔b	↔	↑	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔
SNRI	duloxetine	↑	↑↓	↑	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	venlafaxine	↑b	↑b	↑	↑	↑b	↔	↓	↓	↓	↔b	↔b	D	↔	↔	↔b	↔	↑	↔	↔	↔
Others	buspirone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	hydroxyzine	↑a,b	↑a,b	↑a,b	↑a,b	↑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 anxiolytic therapy
↓	Potential decreased exposure of the anxiolytic therapy
↔	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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

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

BZD	benzodiazepines
SSRI	selective serotonin reuptake inhibitors
SNRI	serotonin and norepinephrine reuptake inhibitors

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- a ECG monitoring is recommended.
- b Caution as both drugs can induce QT interval prolongation.

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	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
LAMA	acridinium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	glycopyrronium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tiotropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	umeclidinium bromide	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
SAMA	ipratropium	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
LABA	formoterol	↔a	↔a	↔	↔	↔a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↔	↔	↔	↔
	indacaterol	↑b	↑b	↑b	↑b	↑b	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑b	↔	↔	↔
	olodaterol	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	salmeterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	vilanterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
SABA	salbutamol (albuterol)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	terbutaline	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
MX	aminophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	theophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
PDE4	roflumilast	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
ICS	beclometasone	↑c	↑c	↑?c	↓11% ^d	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑c	↔	↔	↔
	budesonide	↑e	↑e	↑e	↑e	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑e	↔	↔	↔
	ciclesonide	↑f	↑f	↑f	↑f	↑f	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑f	↔	↔	↔
	fluticasone	↑e	↑e	↑e	↑e	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑e	↔	↔	↔
	mometasone	↑e	↑e	↑e	↑e	↑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 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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 ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

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** 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.
- d** DRV/r decreased the exposure of active metabolite (beclometasone-17-monopropionate), no significant effect on adrenal function was seen.
- e** 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.
- f** No dose adjustment required but monitor closely, especially for signs of Cushing's syndrome when using a high dose or prolonged administration.

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

Fixed dose combinations are available for LAMA + LABA + ICS, e.g., mometasone + indacaterol + glycopyrronium
 fluticasone + umeclidinium + vilanterol
 formoterol + glycopyrronium + beclometasone
 budesonide + formoterol + glycopyrronium

Drug-drug Interactions between Contraceptives and ARVs

Contraceptives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
Es	ethinylestradiol (COC, TS, VR)	↑1% ^a	↓19% ^b	↓30%	↓44% ^a	↓42% ^a	↓2%	c	↑22%	↓20%	↑14%	↑40% ^d	↓<1%	↑4%	↑2%	↔	↑3%	↓25% ^e	↓2%	↑11%	↔
Progestins	desogestrel (COC)	↑	↑ ^{f,b}	↑	↑ ^g	↑ ^g	↔	↓ ^h	↓	↓	↔	↔ ^d	↔	↔	↔	↔	↔	↑ ^{e,f}	↔	↔	↔
	desogestrel (POP)	↑	↑	↑	↑	↑	↔	↓ ^h	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	drosiprone (COC)	↑130%	↑ ^{f,b}	↑58% ^g	↑ ^g	↑ ^g	↔	↓ ^h	↓	↓	↔	↔ ^d	↔	↔	↔	↔	↔	↑ ^{e,f}	↔	↔	↔
	etonogestrel (IP)	↑	↑	↑	↑	↑52%	↔	↓63% ^h	↓	↓	↑18%	↔	↔	↔	↔	↔	↑19-54%	↑	↔	↔	↔
	etonogestrel (VR)	↑	↑~79% ⁱ	↑ ⁱ	↑ ⁱ	↑ ⁱ	↔	↓~79% ^h	↓	↓	↔	↔ ^d	↔	↔	↔	↔	↔	↑ ⁱ	↔	↔	↔
	gestodene (COC)	↑	↑ ^{f,b}	↑	↑ ^g	↑ ^g	↔	↓ ^h	↓	↓	↔	↔ ^d	↔	↔	↔	↔	↔	↑ ^{e,f}	↔	↔	↔
	levonorgestrel (COC)	↓8%	↑ ^{f,b}	↑	↑ ^g	↑ ^g	↑21%	↓ ^h	↓	↑	↔	↔ ^d	↓2%	↔	↑12%	↔	↔	↑	↔	↔	↔
	levonorgestrel (IP)	↑	↑	↑	↑	↑	↔	↓57% ^h	↓	↑14%	↑28%	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	levonorgestrel (IUD)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel (POP)	↑	↑	↑	↑	↑	↔	↓ ^h	↓	↑	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	medroxy-progesterone (POI)	↔	↔	↔	↔	↑~70%	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	norelgestromin (TS)	↑	↑ ^{f,b}	↑	↑ ^g	↑83% ^g	↔	↓ ^h	↓	↓	↔	↔ ^d	↔	↔	↔	↔	↔	↑ ^{e,f}	↔	↔	↔
	norethisterone (COC)	↑	↑ ^{f,j}	↑	↓14% ^g	↓17% ^g	↔	↓ ^h	↓5%	↓19%	↓11%	↑8% ^d	↔	↔	↔	↔	↔	↑ ^{e,f}	↔	↔	↔
	norethisterone (POI)	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	norethisterone (POP)	↑	↑50%	↑	↑50%	↑50%	↔	↓ ^h	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	norgestimate (COC)	↑	↑85% ^{f,b}	↑	↑ ^g	↑ ^g	↔	↓64% ^h	↓	↓	↔	↔ ^d	↔	↑8%	↔	↔	↓2%	↑126% ^{e,f}	↑14%	↔	↔
	norgestrel (COC)	↑	↑ ^{f,b}	↑	↑ ^g	↑ ^g	↔	↓ ^h	↓	↑	↔	↔ ^d	↔	↔	↔	↔	↔	↑ ^{e,f}	↔	↔	↔
Other	levonorgestrel (EC)	↑ ^k	↑ ^k	↑ ^k	↑ ^k	↑ ^k	↔	↓58% ^l	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑ ^k	↔	↔	↔
	mifepristone	↑ ^k	↑ ^k	↑ ^k	↑ ^k	↑ ^k	Fk	↓	↓	↓	Fk	↔	Fk	Fk	↔	↔	↔	↑ ^k	↔	↔	↔
	ulipristal	↑ ^k	↑ ^k	↑ ^k	↑ ^k	↑ ^k	↔	↓ ^m	↓ ^m	↓ ^m	↔	↔	↔	↔	↔	↔	↔	↑ ^k	↔	↔	↔

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 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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

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	intrauterine device
POI	progestin only injectable
POP	progestin only pill
TS	transdermal patch
VR	vaginal ring

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

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 Daily dose of ethinylestradiol should not exceed 30 µg. Caution is advised, particularly in patients with additional risk factors for thrombo-embolic events.
- e European SmPC states a hormonal contraceptive should contain at least 30 µg ethinylestradiol.
- f When used in a combination pill, the estrogen component is reduced to a small extent.
- g When used in a combination pill, the estrogen component is significantly reduced, caution is recommended and additional contraceptive measures should be used.
- h 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.
- i 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.
- j 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.
- k Unlikely to have clinical consequences as hormone is administered as single dose.
- l Use 3 mg as a single dose for emergency contraception. Note, doubling the standard dose may be outside the product license in some regions, but a pharmacokinetic study showing that a 3 mg single dose of levonorgestrel compensated for the reduction in levonorgestrel supports this recommendation.
- m 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	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
Inhaled, oral, topical and/or injected corticosteroids	beclometasone (inhalation)	↑a	↑a	↑?a	↑11%b	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑a	↔	↔	↔
	betamethasone	↑c	↑c	↑c	↑c	↑c	D	↓	↓	↓	D	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 f	D	↔	D	↔	↑c D	↔	↔	↔
	flunisolide (inhalation)	↑g	↑g	↑g	↑g	↑g	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑g	↔	↔	↔
	flucinolone (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)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	methyl-prednisolone	↑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 elevated 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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

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

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- 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.
- DRV/r decreased the exposure of active metabolite (beclometasone-17-monopropionate), no significant effect on adrenal function was seen.
- 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.
- No dose adjustment required but monitor closely, especially for signs of Cushing's syndrome when using a high dose or prolonged administration.
- 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.
- Consider using MVC a dose of 600 mg bid with dexamethasone in the absence of a PI or other potent CYP3A4 inhibitors, particularly if dexamethasone is used at a high dose and in case of long-term treatment. Consider decreasing MVC to 150 mg bid with dexamethasone in presence of a protease inhibitor or strong CYP3A4 inhibitor.
- 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 COVID-19 Therapies and ARVs

COVID-19 Therapy		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
Antiviral Drugs and mAbs	bamlanivimab/etesevimab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	casirivimab/imdevimab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	remdesivir	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Immune Therapies	anakinra	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	baricitinib	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	canakinumab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	convalescent plasma	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	COVID-19 vaccines	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	dexamethasone (low dose*)	↑ a	↑ a	↑ a	↑ a	↑ a	D b	↓ c	↓ c	↓ c	D d	D	D e	↔	↔	D	↔	↑ a	↔	D	↔
	hydrocortisone	↑ a	↑ a	↑ a	↑ a	↑ a	↔	↓ c	↓ c	↓ c	↔	↔	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	methyl-prednisolone	↑ a	↑ a	↑ a	↑ a	↑ a	↔	↓ c	↓ c	↓ c	↔	↔	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	ruxolitinib	↑ f	↑ f	↑ f	↑ f	↑ f	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑ f	↔	E	E
	sarilumab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tocilizumab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

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 COVID therapy
- ↓ Potential decreased exposure of the COVID therapy
- ↔ 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

* Evaluation of the DDI risk refers to a dexamethasone dose of 6 mg qd and does not apply to higher doses of dexamethasone.

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

mAbs monoclonal antibodies

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC: no clinically relevant interactions expected.
 ZDV: potential additive haematological toxicity with anakinra, baricitinib, canakinumab, ruxolitinib, sarilumab, tocilizumab.

Interactions with ibalizumab

None

Comments

- Product labels for dexamethasone, hydrocortisone and methylprednisolone do not recommend co-administration of strong CYP3A4 inhibitors but this is unlikely to be clinically significant given the low dose of corticosteroids used in COVID-19 treatment.
- Consider increasing DOR to 100 mg bid during treatment for COVID-19 and for approximately 2 weeks after the end of treatment.
- Doubling the dose of dexamethasone, hydrocortisone or methylprednisolone is recommended.
- Dexamethasone is a dose dependent CYP3A4 inducer and may decrease RPV concentrations. Although the level of induction at the dose recommended for COVID (6 mg/day) is likely to be relatively modest, it is advised either using hydrocortisone (IV, 200 mg/day) or, alternatively, giving dexamethasone but doubling the dose of RPV to 50 mg qd. This dose should be maintained for 2 weeks after the end of treatment as any reduction in RPV concentrations may persist for up to 14 days after stopping dexamethasone.
- Consider using MVC at a dose of 600 mg bid with dexamethasone in the absence of a PI or other potent CYP3A4 inhibitors. Consider decreasing MVC to 150 mg bid with dexamethasone in presence of a PI or strong CYP3A4 inhibitor. These dose adjustments should be considered during treatment for COVID-19 and for approximately 2 weeks after the end of treatment.
- The ruxolitinib European product label advises reducing ruxolitinib dose by half and administering bid. Monitor closely for cytopenia and titrate ruxolitinib based on safety and efficacy.

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
<http://www.covid19-druginteractions.org> (University of Liverpool)

Refer to the DDI table between anticoagulants/antiplatelet agents and ARVs for COVID patients receiving anticoagulants.

Drug-drug Interactions between Hormone Replacement Therapy (HRT) and ARVs

Hormone replacement therapy		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
Estrogen & Progestogen	estradiol	↑ a	↓ b	↑ a	↓ b	↓ b	↔	↓ b	↓ b	↓ b	↔	↑ a	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	drospirenone	↑ a,c	↑ a	↑ a	↑ a	↑ a	↔	↓ b	↓ b	↓ b	↔	↔ a,d	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	dydrogesterone	↑ a	↑ a	↑ a	↑ a	↑ a	↔	↓ b	↓ b	↓ b	↔	↔ a,d	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	levonorgestrel	↑ a	↑ a	↑ a	↑ a	↑ a	↔	↓ b	↓ b	↓ b	↔	↔ a,d	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	medroxyprogesterone (oral)	↑ a	↑ a	↑ a	↑ a	↑ a	↔	↓ b	↓ b	↓ b	↔	↔ a,d	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	norethisterone	↑ a	↑ a	↑ a	↑ a	↑ a	↔	↓ b	↓ b	↓ b	↔	↔ a,d	↔	↔	↔	↔	↔	↑ a	↔	↔	↔
	norgestrel	↑ a	↑ a	↑ a	↑ a	↑ a	↔	↓ b	↓ b	↓ b	↔	↔ a,d	↔	↔	↔	↔	↔	↑ a	↔	↔	↔

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 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)
- CAB/RPV CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

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

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- a** The clinical significance of increased estradiol exposure in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke and myocardial infarction in postmenopausal women receiving substitution hormones is unknown. The use of estrogen alone or in combination with a progestogen should be used at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for individual women. Postmenopausal women should be re-evaluated.
- b** Monitor for signs of estrogen deficiency.
- c** Coadministration is contraindicated in the US product label due to the potential for hyperkalaemia. The European product label recommends clinical monitoring for hyperkalaemia.
- d** No effect on progestogen but potential increase in estrogen exposure.

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

Immu-no-suppressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/ RPV	DTG	EVG/c	RAL	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	↔	E	↔	↑a	↔	E	Eb
	tacrolimus*	↑a,c	↑a,c	↑a	↑a	↑a,c	↓a	↓a	↓a	↓a	↔c	↔c	↔	↔	↔	↔c	↔	↑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 elevated 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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

* 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 ABC, FTC, 3TC, ZDV

ABC: potential decrease in mycophenolate exposure.
ZDV: potential risk of additive haematotoxicity with azathioprine.
ZDV: potential alteration in mycophenolate exposure, monitor plasma concentrations.

Interactions with ibalizumab

None

Comments

- a TDM of immunosuppressant is recommended.
- b Monitor renal function.
- c Both drugs can potentially prolong the QT interval, ECG monitoring 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)

Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

Pulmonary antihypertensives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
ERA	ambrisentan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bosentan	↑a	↑a	↑a	↑a	↑a	D	↓	↓	↓b	D	↑	D	D	↔	D	D	↑a	↔	↔	↔
	macitentan	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
PDE5	sildenafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↓3%	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	tadalafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
SGC	riociguat	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔
PA	epoprostenol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	iloprost	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	treprostinil	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
IP [†]	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 elevated 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: No clinically relevant interactions expected.

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 persons already on PI/b 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/b 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 Viral Hepatitis Drugs and ARVs

Viral hepatitis drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
HCV DAAs	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%
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↓6%	↔	↔	↑9%	↑	↔	↔	↔	↔	↔	↔	↓5% D27%	↔	↓6%
	sofosbuvir/ ledipasvir	↑ a	↑8% ↑113%a	↑ a	↑34% ↑39%a	↔ a	↑4% ↓8%	↓6% ↓34%a	↔	↔	↑10% ↑8%a	↑	E	↑7% ↓13%	↔	↔	↔	↑36% ↑78%a	↓5% ↓9% D~20%	E32%	E a
	sofosbuvir/ velpatasvir	↔ a	↑22% ↑142%a	↔ a	↓28% ↓16%a	↓29% ↑2%a	↔	↓3% ↓53%	↓	↓	↑16% ↓1%	↑	E	↔	↔	↔	↓8% ↓9%	↑ a	↑24% ↓2%	↔	E a
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40% ↑93% ↑331%	↑ a	↓28% ↓5% ↑143%b	↑	↔	↓	↓	↓	↔	↑	E	↑9% ↓4% ↓9%	↔	↔	↔	↑22% ↑16% ↑171%a	↔	E	E a
HDV	Bulevirtide	↑	↑	↑	↑	↑	E	↑	↑	↔	E	↔	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 elevated exposure of the hepatitis therapy
↓	Potential decreased exposure of the hepatitis therapy
↔	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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

Numbers refer to decreased or increased AUC as observed in drug-drug interaction 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 ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- a** Monitoring of renal function recommended due to increase of tenofovir concentration if the regimen contains TDF.
- b** Study details are with DRV/r qd. DRV bid has not been studied and should be used with caution as voxilaprevir concentrations may increase more than with DRV qd (this would be of further significance in cirrhotic patients). Monitoring of renal 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 $\mu\text{mol/mL}$ 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) granules (33 mg/g)	yes		Better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste) Mix granules in a container with soft food not requiring chewing (e.g. yoghurt or applesauce). Granules must not be mixed with liquids
ZDV	capsule (100, 250 mg) oral solution (10 mg/mL), iv infusion (10 mg/mL)	no	no	Sticky, bitter taste Better: use oral solution or iv 6 mg/kg per day in glucose 5%
TAF/FTC	tablet (25/200 mg and 10/200 mg) ^(vi)	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		Tablets may be divided for ease of swallowing. Capsules can be opened and the content administered with a small amount of food using the capsule sprinkle method of administration
	capsule (50, 100, 200 mg)	no	yes	
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 (100, 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		Tablets must be swallowed whole
TAF/FTC/RPV	tablet (25/200/25 mg) ^(vi)	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 (100, 150, 200, 300 mg) oral powder (50 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. Not recommended for use with polyurethane feeding tubes due to potential incompatibility. Feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used.
RTV	tablet (100 mg) oral suspension (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. Not recommended for use with polyurethane feeding tubes due to potential incompatibility. Feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used.
TAF/FTC/DRV/c	tablet (10/200/800/150 mg) ^(vi)	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 bioavailability is not changed when splitting the pill) ^(viii)

Drug	Formulation	Crush tablets	Open capsules	Comment
Others				
CAB	tablet (30 mg)	no		Tablets must be swallowed whole
CAB/RPV LA	injectable	NA	NA	
DTG	tablet (10, 25, 50 mg) dispersable tablet (5 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
FTR	tablet (600 mg)	no		The prolonged released tablet should be swallowed whole
Ibalizumab	injectable	NA	NA	
MVC	tablet (25, 75, 150, 300 mg) oral solution (20 mg/mL)	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, 600 mg) chewable tablets (25, 100 mg) granule oral suspension (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
TAF/FTC/BIC	tablet (25/200/50 mg) ^(vi)	no		Tablets should be swallowed whole and should not be chewed, crushed or split
TAF/FTC/EVG/c	tablet (10/200/150/150 mg) ^(vi)	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). The 245 mg dose is equivalent to 7.5 scoops of granules
- 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. 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

- 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
- 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)
- 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)
- 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

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
AI	
FTR	No dosage adjustment
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
CAB	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 ^(a) (mL/min)					Haemodialysis ^(b)
	≥ 50	30-49	10-29	< 10	
NRTIs					
Individual agents					
ABC ⁽ⁱⁱⁱ⁾		300 mg q12h or 600 mg q24h	No dose adjustment required		
FTC ^(iv)		200 mg q24h	200 mg q72h	200 mg q96h	200 mg q24h ^(iv)
3TC ^(iv)		300 mg q24h	150 mg q24h	100 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)
TAF ^(ix, x)		25 ^(xi) mg q24h		No data	25 mg q24h ^(iv)
ZDV		300 mg q12h	No dose adjustment required		100 mg q8h
Combinations					
ABC ⁽ⁱⁱⁱ⁾ /3TC ^(iv)		600/300 mg q24h	Use individual drugs		
ZDV/3TC		300/150 mg q12h			
ABC/3TC/ZDV		300/150/300 mg q12h			
TAF ^(ix) /FTC ^(iv)		25 ^(xi) /200 mg q24h	Use individual drugs ^(xv)		25/200 mg q24 ^(iv)
TDF ^(viii) /FTC ^(iv)		300 ^(viii) /200 mg q24h	300 ^(viii) /200 mg q48h	Use individual drugs	
NNRTIs					
EFV		600 mg q24h	No dose adjustment required		
ETV		200 mg q12h	No dose adjustment required		
NVP		200 mg q12h	No dose adjustment required		Additional 200 mg ^(iv)
RPV		25 mg q24h	No dose adjustment required		
TAF ^(ix) /FTC ^(iv) /RPV		25 ^(xi) /200/25 mg q24h	Use individual drugs ^(xv)		25/200/25 mg q24h ^(iv)
TDF ^(viii) /FTC ^(iv) /RPV		300 ^(viii) /200/25 mg q24h	Use individual drugs		
DOR		100 mg q24h	No dose adjustment required; < 10: no PK data		
TDF ^(viii) /3TC ^(iv) /DOR		300 ^(viii) /300/100 mg q24h	Use individual drugs		
PIs ^(vii)					
ATV/c		300/150 mg q24h Do not initiate if eGFR < 70 mL/min if used with TDF *	No dose adjustment required ^(xiii)		Not recommended
ATV/r		300/100 mg q24h	No dose adjustment required ^(xiii)		Not recommended
DRV/r		800/100 mg q24h 600/100 mg q12h	No dose adjustment required ^(xiii)		
DRV/c		800/150 mg q24h Do not initiate if eGFR < 70 mL/min if used with TDF *	No dose adjustment required ^(xiii)		Not evaluated
TAF ^(ix) /FTC ^(iv) /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 ^(iv) /DTG		300/50 mg q24h	Use individual drugs		
ABC ⁽ⁱⁱⁱ⁾ /3TC ^(iv) /DTG		600/300/50 mg q24h	Use individual drugs ^(xvi)		
RPV/DTG		25/50 mg q24h	No dose adjustment required ^(xiii)		
TAF ^(ix) /FTC ^(iv) /BIC		25/200/50 mg q24h	No dose adjustment required ^(xviii)	Not recommended if eGFR > 15 - < 30 mL/min or if eGFR < 15 mL/min without chronic HD as safety not established ^(xviii)	No adjustment if on HD, however, use should generally be avoided and only used if potential benefits outweigh potential risks ^(xviii)
TAF ^(ix) /FTC ^(iv) /EVG/c		10/200/150/150 mg q24h	Not recommended ^(xii)		10/200/150/150 mg q24h ^(iv)
TDF ^(viii) /FTC ^(iv) /EVG/c		300 ^(viii) /200/150/150 mg q24h Do not initiate if eGFR < 70 mL/min	Not recommended		

CAB	30 mg q24h	No dose adjustment required ^(xvii)
CAB LA RPV LA	400/600 mg 1x/4 w 600/900 mg 1x/8 w	No dose adjustment required ^(xvii)
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	
FTR	600 mg q12h	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](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 HBV
- 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 clinical study has demonstrated safety of TAF/FTC/EVG/c for PLWH on chronic dialysis
- 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/min. 10 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, however these findings need to be confirmed in a larger trial
- xvii In PLWH with eGFR < 30 mL/min, co-administration with a strong CYP3A4 inhibitor (e.g. ketoconazole, posaconazole) should be used only if the benefit outweighs the risk
- xviii According to the product label
- * Due to lack of COBI data in PLWH with renal impairment

For recommendations on ART use in PLWH undergoing renal transplantation, see [Solid Organ Transplantation in PLWH](#)

Selected Non-ARV Drugs Requiring Dosage Adjustment in Renal Insufficiency

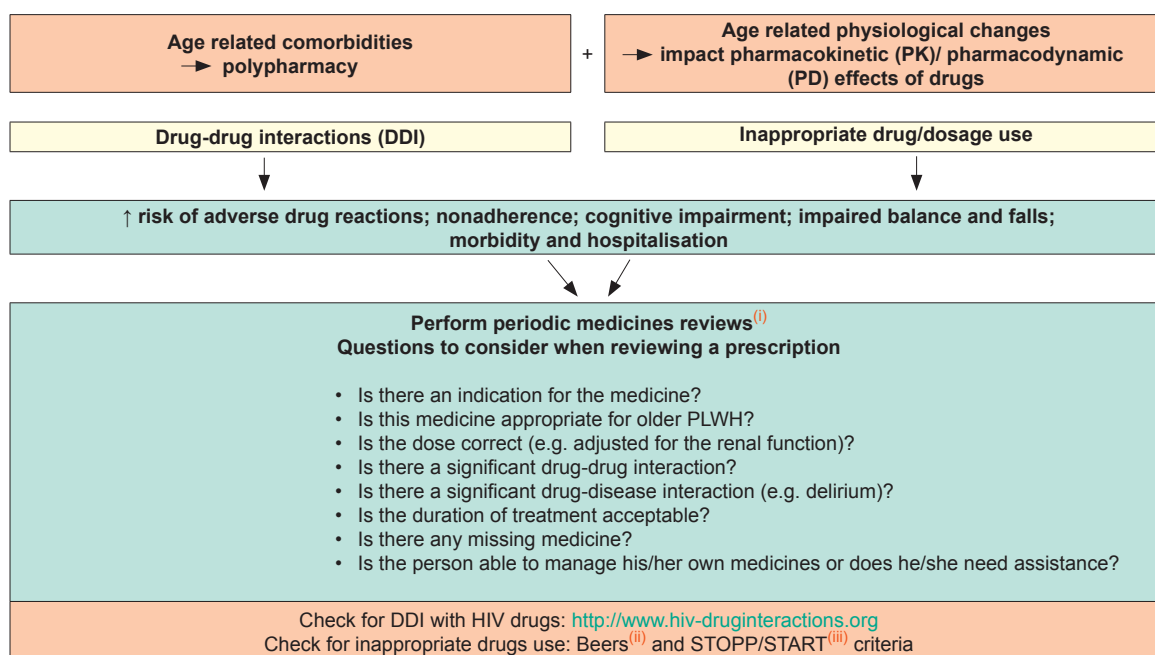
Therapeutic class and drugs	CL _{CRT} threshold for adjustment ^{a,b}	Additional information ^c
ANTIBACTERIALS ^d		
Fluoroquinolones		
Ciprofloxacin	≤ 60 mL/min	
Delafloxacin	< 30 mL/min	iv dosage: 200 mg every 12 hours; oral dosage: 450 mg every 12 hours
Levofloxacin	≤ 50 mL/min	
Ofloxacin	≤ 50 mL/min	
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		
Eslicarbazepine	30-60 mL/min	Start with a dose of 200 mg qd or 400 mg every other day for 2 weeks followed by 400 mg qd Not recommended in case of severe renal impairment
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

Prescribing in Older PLWH



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 older persons (note: these tools were established for persons > 65 years old given that PK and PD effects may be more apparent after this age cut-off). Inappropriate medicines include, for instance, those which in older persons with certain diseases can lead to drug-disease interactions, are associated with a higher risk of adverse drug reactions in older persons, medicines that predictably increase the risk of falls in the older persons or those to be avoided in case of organ dysfunction. The START criteria consist of evidence-based indicators of potential prescribing omission in older persons with specific medical conditions

Selected Top 10 Drug Classes To Avoid in Older 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., amitriptyline, 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.

Legend

NSAID nonsteroidal anti-inflammatory drug

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
		Inhibits metabolism b,f	1 mg/day	2 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	1.5 mg tid
		Inhibits metabolism b,f	0.5 mg bid	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
		Inhibits metabolism b,f	25 µg/day*	37.5-75 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
		Inhibits metabolism b,f	0.625-1.25 mg/day	2.5 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,f	Not recommended	
		Induces metabolism c	Not recommended	
Androgen Blockers ‡	Spironolactone	No predicted effect a	50 mg/day	150 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
		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
		No predicted effect a	25 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
		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
		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
		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
		Inhibits metabolism d	12.5-25 mg in the morning	25-50 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
		Inhibits metabolism d	Not applicable	25-50 mg/week
		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
		Inhibits metabolism d	Not applicable	375-500 mg IM, repeat after 4 weeks and then every 10 weeks
		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
		Inhibits metabolism d	Not applicable	125 mg/2-3 weeks
		Induces metabolism e	Increase testosterone dosage as needed based on clinical effects and monitored hormone levels.	

Comments

- a** ARVs with no predicted effect: CAB, 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
- f** FTR inhibits only estrogens
- * 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, FTR, 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

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 mental health issues (particularly depression and anxiety disorders), cardiovascular, pulmonary, hepatic, metabolic, neoplastic, renal, bone, central nervous system disorders as well as sexual dysfunction (including age-related changes such as menopause). Collectively, these conditions can significantly impact the physical and mental health of PLWH 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 greater focus on prevalent conditions such as weight gain and obesity and age-related conditions such as frailty.

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.

The COVID-19 pandemic has brought many challenges to the care of PLWH, including interruption or significant changes to routine healthcare provision. In this setting, it is of particular importance that healthcare 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, or even interrupted, 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.

Many HIV doctors are not specialists in managing co-morbidities and, although general guidance on management of common co-morbidities is included in these Guidelines, HIV doctors should seek expert advice where appropriate in the prevention and management of such conditions. Situations where consultation is generally recommended are indicated within this document.

In particular, as individuals with treated HIV age, some may experience multiple co-morbidities occurring together, 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 older PLWH. A suggested approach for the management of older PLWH are included in this version of the Guidelines.

Depending on future clinical research findings, and the constantly evolving challenges presented by the COVID-19 pandemic these recommendations will be regularly updated as required, <http://www.eacsociety.org> and in the EACS Guidelines App.

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.

Opioid 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	<p>Methadone plasma concentrations are reduced if used together with:</p> <ul style="list-style-type: none"> • NVP & EFV: ↓ 50% • LPV/r: ↓ 50% <p>• No clinically significant alterations of methadone PK with other commonly used ART agents</p>	<p>Buprenorphine (B) and active metabolite norbuprenorphine (N) plasma concentrations are reduced if combined with NNRTIs and increased if combined with some PIs or INSTIs</p> <ul style="list-style-type: none"> • EFV: ↓ up to 50% (B) and 70% (N) • ETV: ↓ 25% (B) • ATV/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, CAB, DOR, DTG, FTR, RAL, RPV & LPV/r do not affect B & N metabolism)
	<p>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</p>	
Risk of overdose	Yes	No, if used as a co-formulation with naloxone
Causing QT prolongation on ECG	Yes (dose-response relationship) ⁽ⁱⁱ⁾	No
Risk of obstipation	High	High
Type of administration	Tablet or liquid	Tablet applied sublingual
Risk of further impairment in persons with existing liver impairment	Yes	Yes

ⁱ See [Drug-drug Interactions between Analgesics and ARVs](#)

ⁱⁱ ECG recommended for daily methadone doses exceeding 50 mg; special caution with concomitant use of other drugs known to cause QT prolongation (e.g. certain ARVs (such as LPV/r, RPV, FTR), amiodarone, astemizole, azithromycin, clarithromycin, chloroquine, citalopram, domperidone, escitalopram, fluconazole 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 50-74 years ⁽ⁱⁱⁱ⁾	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 50-75 years or with a life expectancy > 10 years	According to local screening programme practice. Colonoscopy every 10 years if willing/able. If unable, annual faecal immunochemistry test (FIT) for occult blood, or multitarget stool DNA (MT-sDNA) testing every 3 years, or computed tomography colonography (CTC) every 5 years	↓ Colorectal cancer mortality	Depending on screening method used	
HepatoCellular Carcinoma (HCC)	HCC screening should follow current EASL guidelines* see pages 8, 81 and 115 ^(iv)	Ultrasound (and alpha-fetoprotein)	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 ^(v)	Use of PSA is controversial	1-2 years	Pros: ↑ early diagnosis and modest ↓ prostate cancer specific mortality. Cons: overtreatment, adverse effects of treatment on quality of life
Lung Cancer	Age 50-80 years old who are at high risk of lung cancer (at least a 20 pack-year smoking history, and are either current smokers or former smokers having quit within the past 15 years)	Low-dose helical CT (where local screening programs are available)	↓ Lung cancer related mortality	Every year	Evidence confirmed in large RCT, but PLWH not included and there may be a higher false positive rate among PLWH

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 US and Australian national Guidelines recommend an upper age limit of 74 years, whilst some other national Guidelines suggest 70 years.

iv 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 81 and 115

v 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.

Cancer: Treatment Monitoring

- Chemotherapy and radiotherapy are associated with an unpredictable decline in CD4 counts even in PLWH stable on ART, OI prophylaxis should therefore be considered at any CD4 count threshold in PLWH undergoing cancer treatment with chemotherapy and radiotherapy
- Persons affected by KS treated with either liposomal doxorubicin or paclitaxel are not at increased risk of CD4 count decline and standard OI prophylaxis Guidelines should be followed, see pages [123-139](#)
- One month after the end of the chemo- or radiotherapy treatment we recommend repeating CD4 counts and following standard OI recommendations, see pages [123-139](#)
- PLWH undergoing autologous or allogenic stem cell transplantation should follow standard national/local guidance for anti-infective prophylaxis

Specific OI prophylaxis recommended in PLWH undergoing cancer treatment

- PCP prophylaxis, see page [126](#)
- Fungal prophylaxis, fluconazole 50 mg qd
Although the evidence for azole antifungal prophylaxis originates from haematological malignancy in HIV seronegative populations, we recommend use of antifungal prophylaxis in PLWH on chemotherapy or radiotherapy especially those affected by haematological malignancies. Fluconazole is the agent of choice because of the favorable interaction profile despite lack of activity against invasive Aspergillosis, see [Drug-drug interactions between ARVs and Non-ARVs](#), page [27](#)
- HSV/VZV prophylaxis, see pages [93](#) and [130](#)
- NTM prophylaxis only in those with a detectable plasma HIV-VL, see page [125](#)

Lifestyle Interventions

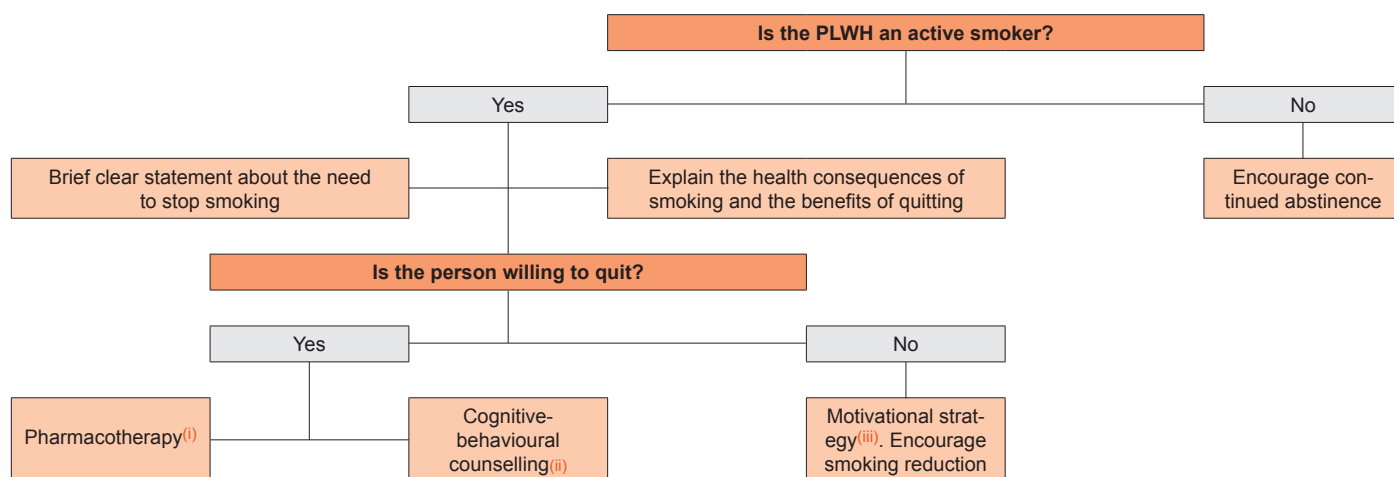
Adults who adhere to Guidelines which promote a healthy diet and physical activity have lower rates of cardiovascular morbidity and mortality than those who do not. In adults without overt cardiovascular risk factors counselling interventions result in improvements in health-promoting behaviors and a positive but small benefit in preventing CVD. In adults with cardiovascular risk factors, counselling interventions have a moderate benefit in preventing CVD. Most important among lifestyle interventions is the recommendation of smoking cessation. All adults should be advised to stop smoking; the benefit of smoking cessation is substantial.

This table may be used as an example, but referring to individual national Guidelines would be just as appropriate.

Dietary counselling	<ul style="list-style-type: none"> 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 salt in adults have been estimated mostly around 3 g/day Emphasise consumption of fish, poultry (without skin) and lean meat Consider referral to dietician, one-week food and drink diary to discover 'hidden' calories Avoid binge eating ('yo-yo dieting') In persons with HIV-related wasting and dyslipidaemia, address wasting first and consider referral to dietician Persons who are obviously overweight should be motivated to lose weight. Starvation diets are not recommended (immune defence mechanisms potentially decreased). Malnutrition has to be addressed where observed. Normal BMI range: 18.5-24.9; Overweight: 25.0-29.9, Obesity: > 30.0 kg/m² 	<ul style="list-style-type: none"> The following questions are helpful to determine average alcohol intake <ol style="list-style-type: none"> How often do you drink alcohol: never, ≤ 1/month, 2-4x/month, 2-3x/week, > 4x/week If you drink alcohol, how much typically at a time: 1-2, 3-4, 5-6, 7-9, > 10 drinks 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		<ul style="list-style-type: none"> Promote active lifestyle to prevent and treat obesity, hypertension and diabetes Encourage self-directed moderate level physical activity (take the stairs, 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

Smoking cessation

PLWH who smoke tobacco 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 the European Smoking Cessation Guidelines and Calvo-Sanchez M., et al, 2015

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 intervention: Use specific available resources

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. Explain 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 person is not willing/ready enough to quit smoking

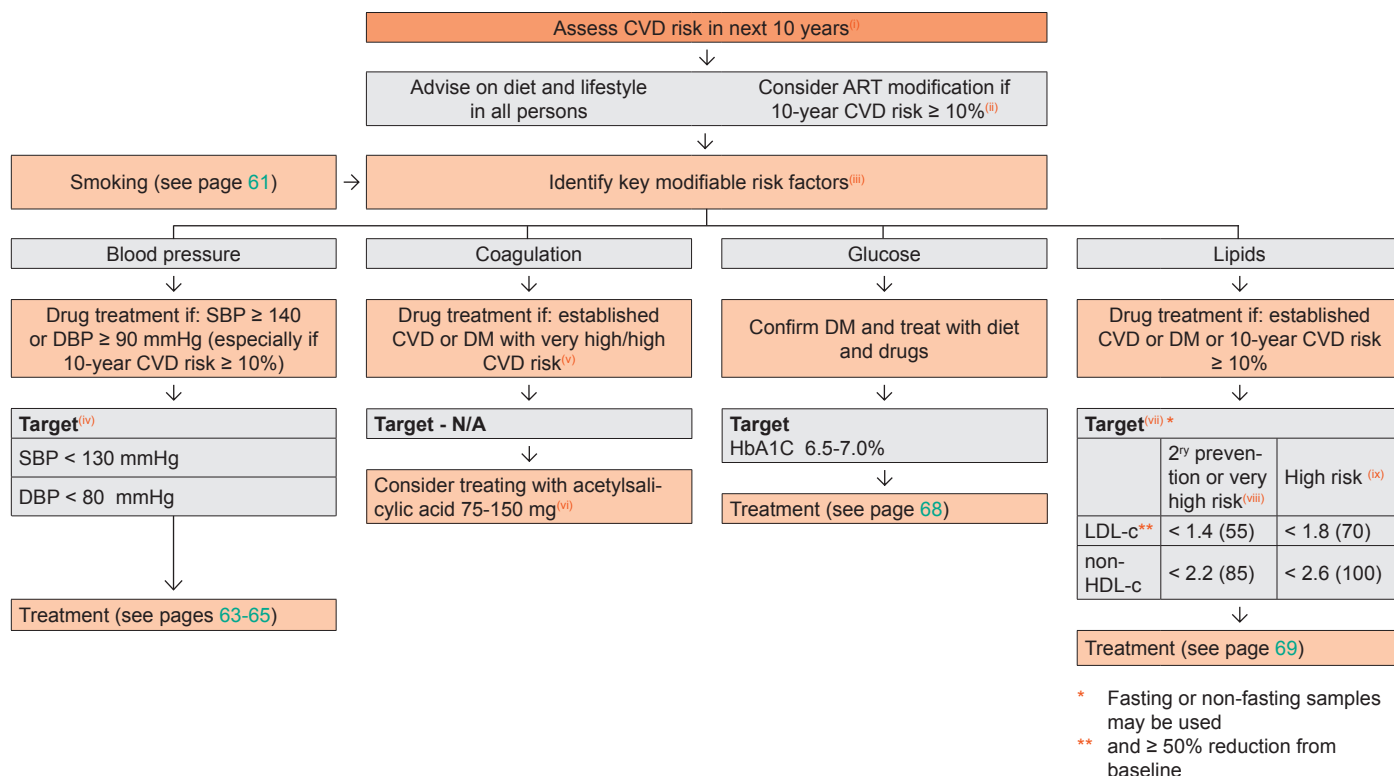
At this moment, neither EMA nor FDA approve e-cigarettes as a smoking cessation agent. In PLWH there is no data on long-term outcomes and it is not possible to add any more specific recommendations. EACS follows the statement issued by the CDC in 2018

There is inadequate evidence to determine the effect of e-cigarettes on achievement of smoking cessation as well as the harms of e-cigarettes when used as a smoking cessation tool

Prevention of Cardiovascular Disease (CVD)

Principles:

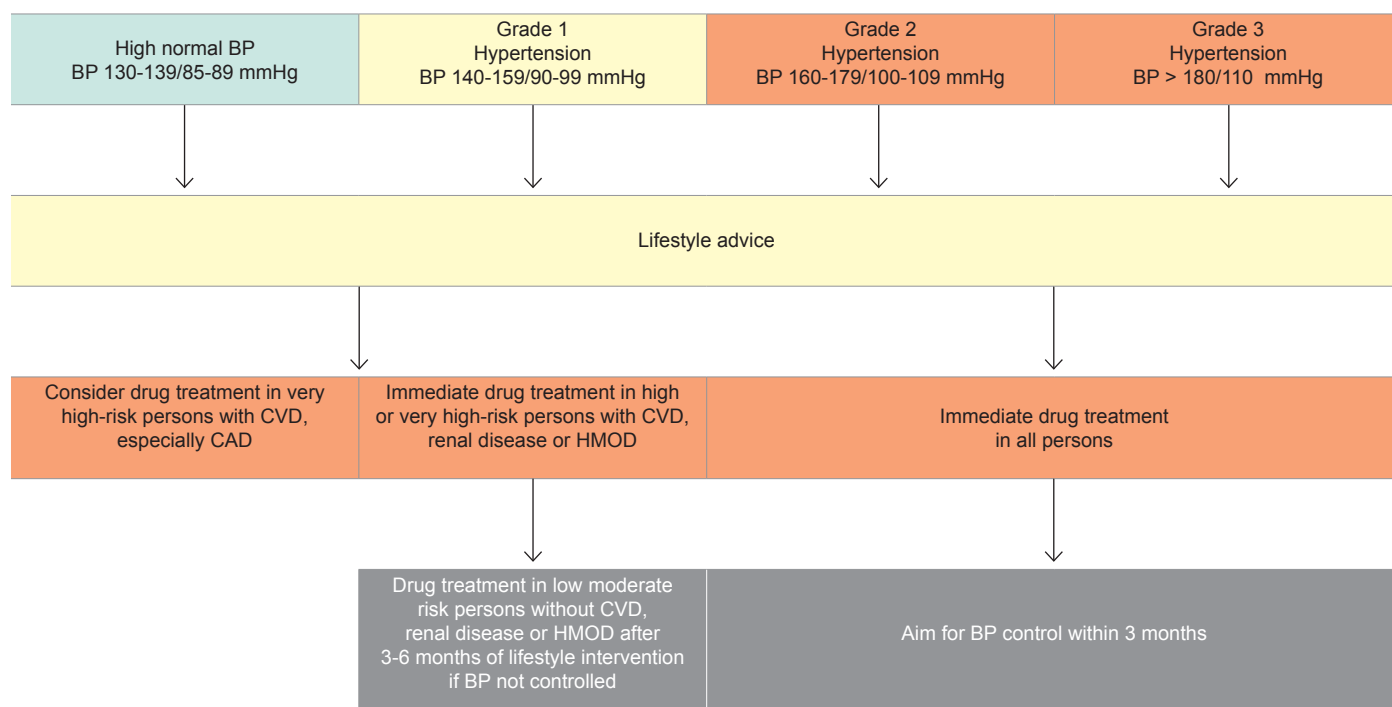
The intensity of efforts to prevent CVD depends on the underlying risk of CVD, which can be estimated⁽ⁱ⁾. The preventive efforts are diverse in nature and require involvement of a relevant specialist, in particular if the risk of CVD is high and always in persons with a history of CVD.



- i Use the Framingham equation or whatever system local National Guidance recommends; a risk equation developed from HIV populations without history of CVD 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 8, 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 16
 - (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 Age 65+: Target 130-139 SBP 70-79 DBP
Age 18-65: 120-129 SBP 70-79 DBP
Ambulatory blood pressure monitoring is recommended using home BP
- v Persons with DM in the absence of clear contraindications and established CVD or other target organ damage (any proteinuria, UA/C > 3, eGFR < 30 mL/min, left ventricular hypertrophy, or retinopathy) or ≥ 3 major risk factors (age, hypertension, dyslipidemia, smoking, obesity) or early T1DM (> 20 years) or DM ≥ 10 years plus any other risk factor

- vi In acute settings (Post-MI, ischemic, stroke or stent insertion) dual antiplatelet therapy is recommended for up to 1 year
- vii Target levels are to be used as guidance and are not definitive – expressed as mmol/L with mg/dL in parenthesis. In case LDL-c 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 mmol/L (150 mg/dL) but the independent contribution from TG to CVD risk is uncertain
- viii Very high-risk persons: Documented atherosclerotic CVD (ASCVD), either clinical [ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease] or unequivocal on imaging [significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having > 50% stenosis), or on carotid ultrasound]. DM with target organ damage, or at least three major risk factors, or early onset of T1DM of long duration (> 20 years). Severe CKD (eGFR < 30 mL/min). A calculated SCORE ≥ 10% for 10-year risk of fatal CVD. Familial hypercholesterolemia with ASCVD or with another major risk factor
- ix High-risk persons: Markedly elevated single risk factors, in particular TC > 8 mmol/L (> 310 mg/dL), LDL-c > 4.9 mmol/L (> 190 mg/dL), or BP ≥ 180/110 mmHg. Familial hypercholesterolemia without other major risk factors. Persons with DM without target organ damage, a with DM duration ≥ 10 years or another additional risk factor. Moderate CKD (eGFR > 30 - < 60 mL/min). A calculated SCORE ≥ 5% and < 10% for 10-year risk of fatal CVD

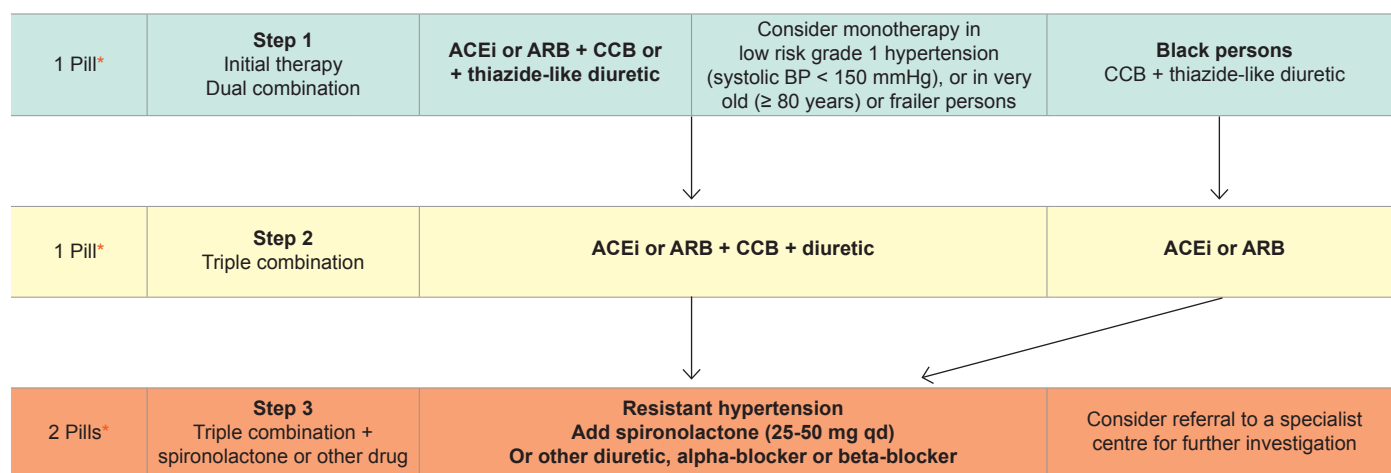
Hypertension: Diagnosis, Grading and Management



Adapted from: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) European Heart Journal (2018) 39, 3021–3104.

Initiation of blood pressure-lowering treatment (lifestyle changes and medication) at different initial office blood pressure levels.
BP = blood pressure; CAD = coronary artery disease; CVD = cardiovascular disease; HMOD = hypertension-mediated organ damage.

Hypertension: Drug Sequencing Management



Beta-blockers
Consider beta-blockers at any treatment step, when there is a specific indication for their use, e.g. heart failure, angina, post-MI, atrial fibrillation, or younger women with, or planning, pregnancy

Adapted from: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) European Heart Journal (2018) 39, 3021–3104





ACEi: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, CCB: calcium channel blocker

* Where combination pill is not available single tablets should be used

Drug-drug Interactions between Antihypertensives and ARVs

Antihypertensives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
ACE inhibitors	captopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	cilazapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	enalapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fosinopril	↔	↑	↔	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	lisinopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	perindopril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ramipril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	trandolapril	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Angiotensin antagonists	candesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eprosartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	irbesartan	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔
	losartan	↔	↓a	↔	↓a	↓a	↔	↑b	↑b	↔	↔	↔	↔	↔	↔	↔	↔	↓a	↔	↔	↔
	olmesartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	telmisartan	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	valsartan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	atenolol	↑c	↔c	↑	↔	↔c	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↑	↑	↔	↔	↔
β blockers	bisoprolol	↑c	↑c	↑	↑	↑c	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	carvedilol	↑c	↑↓c	↑	↑↓	↑↓c	↔	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	labetolol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nebivolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	oxprenolol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pindolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	propranolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	amlodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
Calcium channel blockers	diltiazem	↑d	↑d	↑	↑	↑e	E	↓69%	↓E	↓	E	E	E	E	↔	E	↔	↑	↔	↔	↔
	felodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	lacidipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔f	↔f	↔	↔	↔	↔f	↔	↑	↔	↔	↔
	lercanidipine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nicardipine	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	Ef	Ef	E	↔	↔	Ef	↔	↑	↔	↔	↔
	nifedipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nisoldipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	verapamil	↑d	↑d	↑	↑	↑e	E	↓	↓E	↓	E	E	E	E	↔	E	↔	↑	↔	E	E
	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔
	bendroflu-methiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Diuretics	chlorthalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eplerenone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E
	hydrochloro-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indapamide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	torasemide	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔
	xipamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	clonidine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	doxazosin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
Others	hydralazine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔g	↔	↔	↔	↔	↔	↔	↔	↔h	↔
	methylidopa	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔g	↔	↔	↔	↔	↔	↔	↔	↔	↔
	moxonidine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑?
	prazosin	↑?	↑?	↑?	↑?	↑?	↔	↓?	↓?	↓?	↔	↑	↔	↔	↔	↔	↔	↑?	↔	↔	↔
	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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

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

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

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, ZDV: no clinically relevant interactions expected.
3TC: increased 3TC exposure with atenolol and amiloride.
3TC: increased exposure of atenolol and amiloride.

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.
- f** Caution as both drugs can induce QT interval prolongation.
- g** Use with caution in persons with a history of postural hypotension or on concomitant medicinal products known to lower blood pressure, and those at increased risk of cardiovascular events.
- h** Hydralazine has some nephrotoxic potential. If co-administration is unavoidable, monitor renal function closely.

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)

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)	

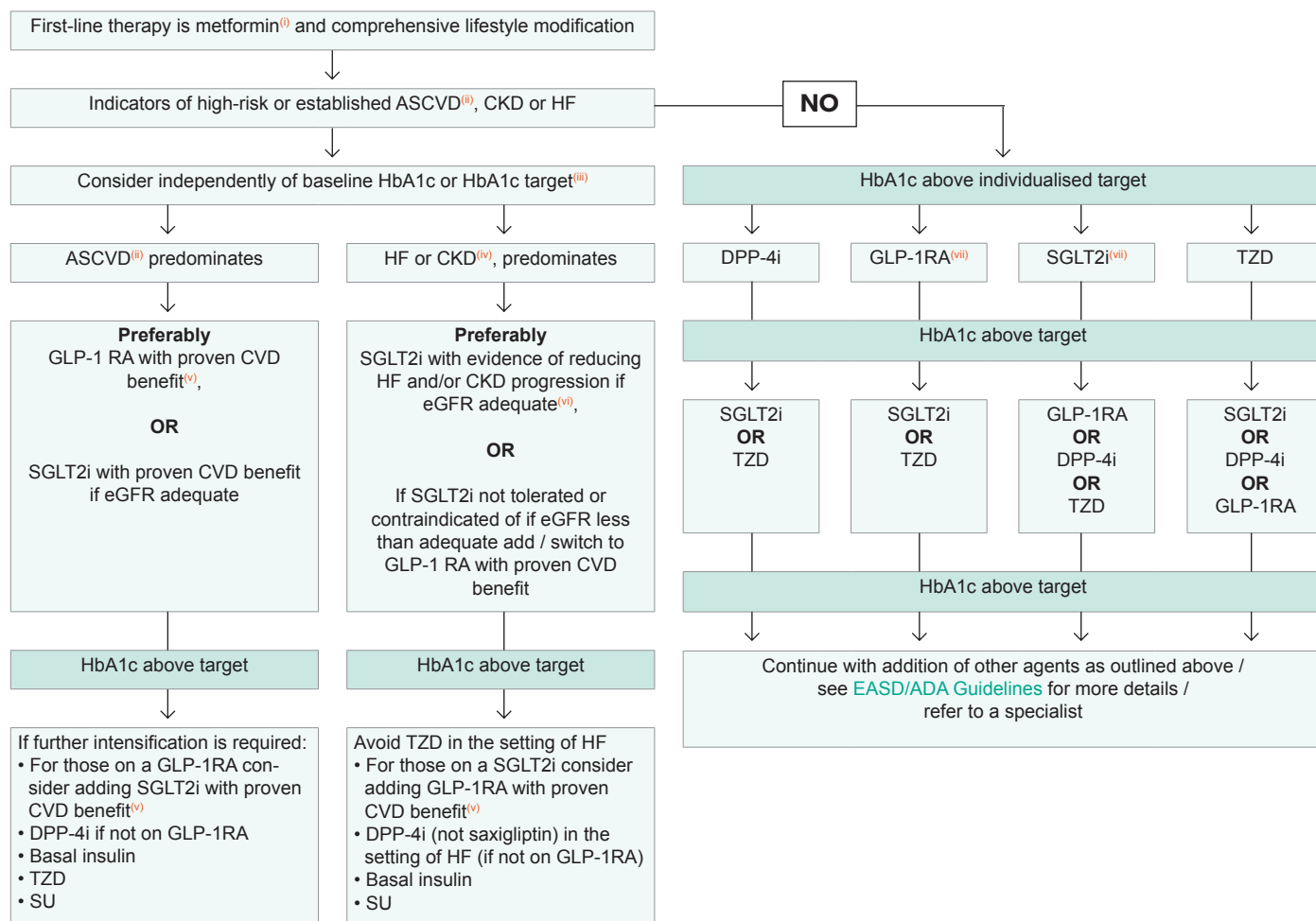
ⁱ As defined by WHO

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: Management



- ⁱ Metformin may worsen lipodystrophy. Consider lower dose in PLWH with mild to moderate CKD or in individuals receiving DTG
- ⁱⁱ Established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD (age ≥ 55 years + left ventricular hypertrophy or coronary, carotid, lower extremity artery stenosis > 50%)
- ⁱⁱⁱ No data for any oral anti-diabetic agents in terms of CVD prevention in PLWH. 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. Always consider individualised HbA1c targets, which depend on e.g. disease duration, life expectancy, risk for hypoglycemia, individual preference
- ^{iv} Heart failure (HF) defined as reduced ejection fraction < 45%, chronic kidney disease (CKD): eGFR > 30 - < 60 mL/min or UA/C > 30 mg/mmol, particularly UA/C > 300 mg/mmol
- ^v Proven CVD benefit means it has label indication of reducing CVD events
- ^{vi} Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression
- ^{vii} Compelling need to minimise weight gain or promote weight loss use GLP-1RA or SGLT2i. GLP-1RA with good efficacy for weight loss: semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

Dyslipidaemia

Principles: Higher LDL-c levels increase risk of CVD and reduction diminishes this risk (see table below for drugs used on this indication). For triglycerides (TG), there is no goal, but < 1.7 mmol/L (< 150 mg/dL) indicates lower risk and higher levels indicate a need to look for other risk factors. Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridemia [TG > 2.3 mmol/L (> 200 mg/dL)]. Confirmation of hypertriglyceridemia needs to be verified with fasting lipid testing. Very high TG (> 10 mmol/L or > 900 mg/dL) increase risk of pancreatitis, fibrates should be used.

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 62.

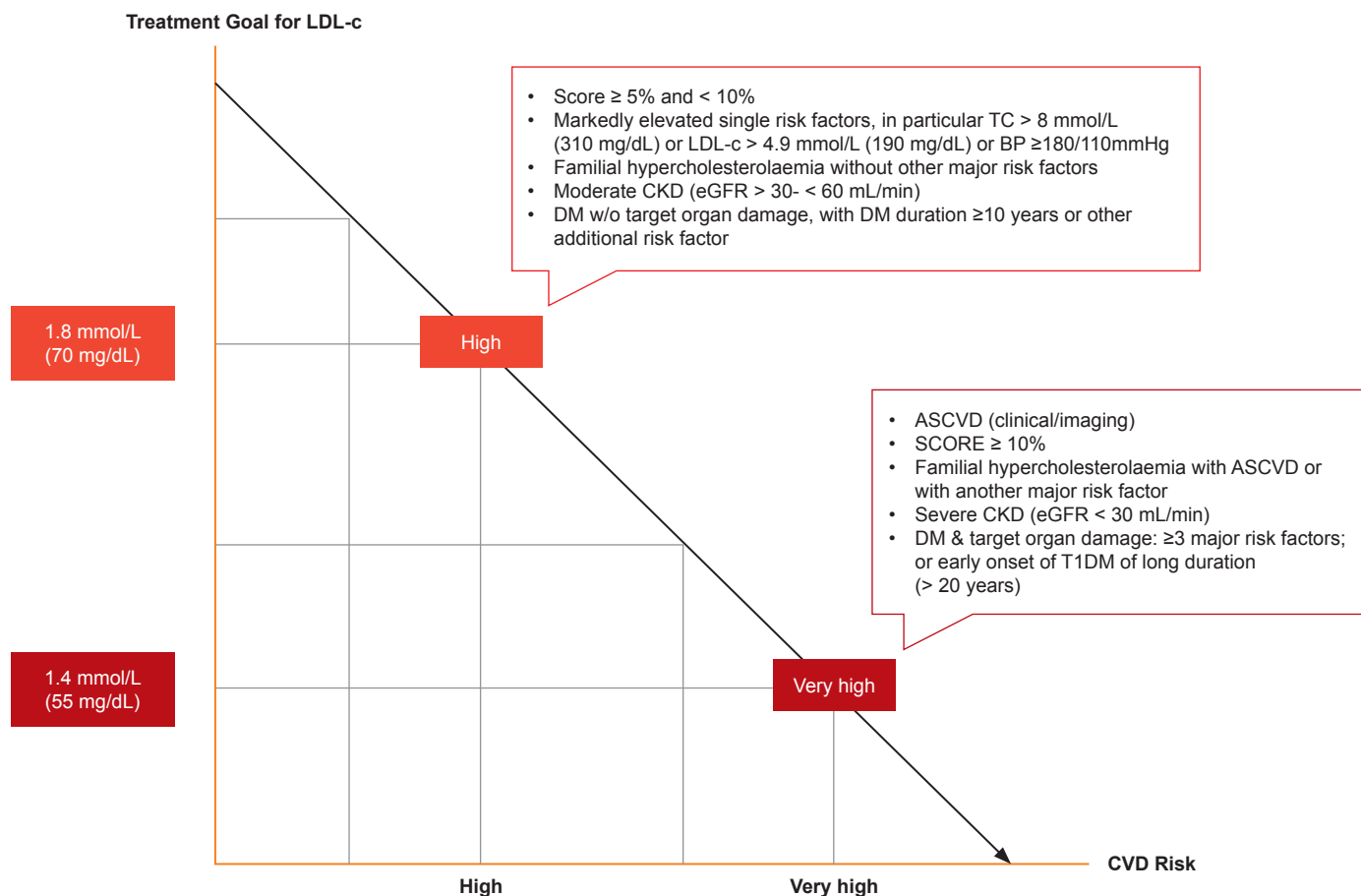
Statins should be used by all those with established vascular disease and in persons who are not at LDL-c goals considering their level of CVD risk, irrespective of lipid levels, see [Treatment goal for LDL-c for very high and high CVD risk persons](#). In high risk PLWH with statin intolerance, drug-drug interactions between high intensity statins and ART, or those 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	Adverse effects	Advice on use of lipid lowering therapy together with ART	
				use with PI/r	use with NNRTIs
Statin ^(i,viii)	Atorvastatin ⁽ⁱⁱ⁾	10-80 mg qd	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Start with low dose ^(v) (max daily dose: 10 mg (ATV/r); 20 mg (LPV/r); 40 mg (DRV/r))	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 daily dose: 10 mg (ATV/r, LPV/r) 20 mg (DRV/r))	Start with low dose ^(v)
	Simvastatin ⁽ⁱⁱ⁾	10-40 mg qd		Contraindicated	
	Pitavastatin ^(viii)	1-4 mg qd		No interaction expected	
Intestinal cholesterol absorption inhibitor ^(i,ix)	Ezetimibe ^(iv)	10 mg qd	Gastrointestinal symptoms	No interaction expected	
PCSK9-inhibitors ^(x)	Evolocumab	140 mg 2 weekly or 420 mg monthly	Nil	No interaction expected	
	Alirocumab	75 mg or 150 mg 2 weekly			

- 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 70. 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** 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
- ix** This agent can be used for PLWH intolerant of statins or added to a statin when LDL-c reduction is inadequate despite maximally tolerated statin
- x** Data in PLWH available for evolocumab

Treatment Goals for LDL-c for Very High and High CVD Risk Persons



Adapted from: 2019 ESC/EAS Guidelines for the management of dyslipidaemia: lipid modification to reduce cardiovascular risk. Eur Heart J 2020 Jan 1;41(1):111-188.

Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering.
Treatment goals for low-density lipoprotein cholesterol, very-high and high CVD risk.

ASCVD = atherosclerotic cardiovascular disease; BP = blood pressure; CKD = chronic kidney disease; CVD = cardiovascular disease; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9; SCORE = Systematic Coronary Risk Estimation; T1DM = type 1 DM; T2DM = type 2 DM; TC = total cholesterol

Moderate CVD risk:

Young persons (T1DM < 35 years; T2DM < 50 years) with DM duration < 10 years, without other risk factors. Calculated SCORE $> 1\%$ and $< 5\%$ for 10-year risk of fatal CVD/. LDL-c goal 2.6 mmol/L (100 mg/dL)

Low CVD risk:

Calculated SCORE $< 1\%$ for 10-year risk of fatal CVD. LDL-c goal 3.0 mmol/L (116 mg/dL)

Bone Disease: Screening and Diagnosis

Condition	Characteristics	Risk factors	Diagnostic tests									
Osteoporosis <ul style="list-style-type: none">Postmenopausal women and men age ≥ 50 years with BMD T-score ≤ -2.5 at hip or lumbar spinePremenopausal women and men age < 50 years with BMD Z-score ≤ -2 at hip or lumbar spine and fragility fracture	<ul style="list-style-type: none">Reduced bone mass and altered bone qualityIncreased risk of fractures in PLWHAsymptomatic until fractures occurAetiology multifactorialLoss of BMD observed with ART initiation (mainly during 1st year)Greater loss of BMD with initiation of certain ARVs⁽ⁱ⁾	<p>Consider classic risk factors⁽ⁱⁱ⁾ and estimate fracture risk using FRAX in people ≥ 40 years</p> <p>Consider DXA in any person with ≥ 1 risk of:⁽ⁱⁱⁱ⁾</p> <ol style="list-style-type: none">Postmenopausal womenMen ≥ 50 yearsHigh risk for falls^(iv)Those with high fracture risk (> 20% 10-year major osteoporotic fracture risk based on FRAX assessment without DXA)History of low impact fractureClinical hypogonadism (symptomatic, see Sexual Dysfunction)Oral glucocorticoid use (minimum 5 mg/d prednisone equivalent for > 3 months)	<p>DXA scan</p> <p>In those with classic risk factors who require DXA, where feasible consider DXA scan prior to ART initiation or soon after initiation.</p> <p>Add DXA result to FRAX® to refine fracture risk prediction (http://www.shef.ac.uk/FRAX)</p> <ul style="list-style-type: none">May underestimate risk in PLWHConsider using HIV as a cause of secondary osteoporosis^(v)Trabecular Bone Score (TBS: derived from DXA scan result) may also be added to FRAX® risk prediction. <p>Rule out causes of secondary osteoporosis if BMD low^(vi)</p> <p>Lateral spine X-rays (lumbar and thoracic) if osteoporosis on DXA, or significant height loss (≥ 4 cm) or kyphosis develops. (DXA-based vertebral fracture assessment can be used as an alternative to lateral spine X-ray)</p>									
Osteomalacia	<ul style="list-style-type: none">Defective bone mineralisationAssociated with vitamin D deficiencyIncreased risk of fractures and bone painVitamin D deficiency may cause proximal muscle weaknessHigh prevalence (> 80%) of vitamin D insufficiency in some HIV cohorts and in the general population	<ul style="list-style-type: none">Dark skinDietary deficiencyAvoidance of sun exposureMalabsorptionObesityRenal phosphate wasting^(vii)	<p>Measure serum 25(OH) vitamin D, see page 72. If deficient or insufficient, check PTH levels and consider vitamin D replacement if clinically indicated, see page 72</p> <table><tr><td></td><td>ng/mL</td><td>nmol/L</td></tr><tr><td>Deficiency</td><td>< 10</td><td>< 25</td></tr><tr><td>Insufficiency</td><td>< 20</td><td>< 50</td></tr></table> <p>X-rays and bone biopsy can also help in the diagnosis</p>		ng/mL	nmol/L	Deficiency	< 10	< 25	Insufficiency	< 20	< 50
	ng/mL	nmol/L										
Deficiency	< 10	< 25										
Insufficiency	< 20	< 50										
Osteonecrosis	<ul style="list-style-type: none">Infarct of epiphyseal plate of long bones resulting in acute bone painRare but increased prevalence in PLWH	<p>Risk factors:</p> <ul style="list-style-type: none">Low CD4 countGlucocorticoid exposureIVDUAlcoholBlood coagulation disorders	<p>MRI</p>									

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 if:

- Osteoporosis / progressive bone loss
- History of fragility fracture

* There are limited data on use of PIs and changes after their replacement.

ii Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m²), 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 BMD T-score normal (≥ -1), repeat after 3-5 years in risk groups 1, 2 and 3; no need for re-screening with DXA in risk groups 4, 5 and 6 unless risk factors change and only rescreen group 7 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.

vi However, if the contribution of HIV infection to fracture risk is partially independent of BMD, fracture probability may be underestimated by FRAX

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) Supplementation with vitamin D may reduce bone loss with initiation of ART, see page 71 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 Vitamin D insufficiency 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 76. 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 in that situation are not completely understood

Approach to Fracture Reduction in PLWH

Reducing risk of fractures Persons at high risk of fractures: <ul style="list-style-type: none"> • Frail or sarcopenic persons • Previous fracture, particularly if recent • Low BMD 	<ul style="list-style-type: none"> • Aim to decrease falls by addressing frailty and fall risks⁽ⁱ⁾ • Consider bisphosphonate⁽ⁱⁱ⁾ <ul style="list-style-type: none"> – Treatment based on fracture history and FRAX score (see section on Bone Disease Screening and Diagnosis). – Ensure adequate calcium and vitamin D intake⁽ⁱⁱⁱ⁾ • Consider choice of ARV in those at high risk of fractures^(iv) <ul style="list-style-type: none"> – No significant interactions between bisphosphonates and ARVs • Optimal management of frailty includes optimising nutrition, exercise (aerobic and resistance training), see section on frailty, page 110 • 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. Persons without response to treatment refer to osteoporosis specialist for second line treatment. Re-assess need for continued treatment after 3-5 years
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- i Falls Risk Assessment Tool (FRAT), See page 72 for diagnosis and management of vitamin D deficiency
<https://www2.health.vic.gov.au/about/publications/policiesandguidelines/falls-risk-assessment-tool>
- ii 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; zoledronate 5 mg by iv infusion once yearly
- iii See page 72 for diagnosis and management of vitamin D deficiency
- iv See page 71; some ARVs can affect BMD but relationship to increased fractures are not well defined. Consider relative risk/benefit of using these agents in persons with high fracture risk

Kidney Disease: Definition, Diagnosis and Management

Diagnosis of kidney disease

		eGFR ⁽ⁱ⁾			
		> 60 mL/min	> 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	<ul style="list-style-type: none"> Check risk factors for CKD, use of nephrotoxic medicines including ART and potential artificial decline in eGFR^(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⁾ 3-30				
	UA/C ⁽ⁱⁱⁱ⁾ > 30		<ul style="list-style-type: none"> 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 In PLWH with ESRD consider transplantation evaluation, see page 113 		

* 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	<p>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</p> <p>Consider discontinuing or replacing TDF** by non-tenofovir drug or by TAF*** if:</p> <ul style="list-style-type: none"> 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/b as a third agent <p>Discontinue or Replace TDF** by non-tenofovir drug or by TAF*** if:</p> <ul style="list-style-type: none"> eGFR ≤ 60 mL/min UP/C > 50 mg/mmol nephrotoxic comedication previous TDF toxicity (proximal renal tubulopathy) <p>** Expert opinion pending clinical data</p> <p>***There are limited data on use of TAF with low eGFR, particularly eGFR ≤ 10 mL/min</p>
2. Start ACE inhibitors or angiotensin-II receptor antagonists if:	<p>Monitor eGFR and K⁺ level closely on starting treatment or increasing dose</p> <p>a. Hypertension and/or proteinuria</p> <p>a. Blood pressure target: < 130/80 mmHg</p>
3. General measures:	<p>CKD and proteinuria are independent risk factors for CVD</p> <p>a. Avoid nephrotoxic drugs including NSAID</p> <p>b. Lifestyle measures (smoking, weight, diet)</p> <p>c. Treat dyslipidaemia^(viii) and diabetes^(ix)</p> <p>d. Adjust drug dosages where necessary^(v)</p>

- 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. Several medications and/or dietary elements or supplements may artificially increase serum creatinine and thus reduce eGFR without affecting UP/C, including the use of creatinine and protein supplements. Renal function should be reassessed after ceasing dietary supplements and/or, where available, using cystatin C-based eGFR measurements (in stable PLWH on ART). Use of DTG, BIC, RPV, RAL, COBI and RTV boosted PIs is also independently associated with increases in serum creatinine and reduction of eGFR (10-15 mL/min or up to 25%) due to inhibition of proximal tubular creatinine transporters and/or intestinal transporters without impairing actual glomerular filtration. Consider a new set point after 1-2 months. Use of NSAID and recreational drugs may also affect renal perfusion and thereby cause transient creatinine increase.
- 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 those with DM 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. 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 69-70
- ix See page 68
- 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

ARV-associated Nephrotoxicity

Renal abnormality*	ARV	Management
Proximal tubulopathy with any combination of: <ol style="list-style-type: none"> 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: <ul style="list-style-type: none"> • Tests for proximal renal tubulopathy/renal Fanconi syndrome⁽ⁱⁱⁱ⁾ (less frequent in Black PLWH) • 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: <ul style="list-style-type: none"> • 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: <ol style="list-style-type: none"> 1. Crystalluria 2. Haematuria^(iv) 3. Leukocyturia 4. Loin pain 5. Acute renal insufficiency 	IDV ATV (DRV)	Assessment: <ul style="list-style-type: none"> • Urinalysis for crystalluria/stone analysis • Exclude other cause for nephrolithiasis • Renal tract imaging including CT scan Consider stopping IDV/ATV if: <ul style="list-style-type: none"> • Confirmed renal stones • Recurrent loin pain +/- haematuria
Interstitial nephritis: <ol style="list-style-type: none"> 1. Progressive decline in eGFR⁽ⁱⁱ⁾ 2. Tubular proteinuria⁽ⁱⁱⁱ⁾/ haematuria 3. Eosinophiluria (if acute) 4. Leukocyte casts 	IDV ATV	Assessment: <ul style="list-style-type: none"> • Renal ultrasound • Refer to nephrologist Consider stopping IDV/ATV if: <ul style="list-style-type: none"> • Progressive decline in eGFR and no other cause
Progressive decline in eGFR, but none of the above⁽ⁱⁱ⁾	TDF** PI/r ^(vi)	Complete assessment: <ul style="list-style-type: none"> • Risk factors for CKD^(v) (see Kidney Disease: Definition, Diagnosis and Management) • PRT, UA/C, UP/C (see Kidney Disease: Definition, Diagnosis and Management and Indications and Tests for Proximal Renal Tubulopathy (PRT)) • Renal tract ultrasound, see page 74 Consider stopping ARVs with potential nephrotoxicity if: <ul style="list-style-type: none"> • Progressive decline in eGFR and no other cause^(v)

- * Use of DTG, BIC, RPV, COBI and PI/b is associated with an increase in serum creatinine/reduction of eGFR (10-15 mL/min or up to 25%) 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
- *** There are limited data on use of TAF with low eGFR, particularly eGFR ≤ 10 mL/min
- 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 5-year CKD risk score while using different nephrotoxic ARVs integrating HIV-independent and HIV-related risk factors
- vi RTV used as a boosting agent may induce nephrosclerosis

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:
<ul style="list-style-type: none"> 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) 	<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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, $\alpha 1$ - or $\beta 2$ -microglobulinuria, urine cystatin C, aminoaciduria
- vi** Quantified as fractional excretion of phosphate (FEPHos): $(\text{PO}_4(\text{urine}) / \text{PO}_4(\text{serum})) / (\text{Creatinine}(\text{urine}) / \text{Creatinine}(\text{serum}))$ 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): $(\text{UricAcid}(\text{urine}) / \text{UricAcid}(\text{serum})) / (\text{Creatinine}(\text{urine}) / \text{Creatinine}(\text{serum}))$ in a spot urine sample collected in the morning in fasting state; abnormal > 0.1
- *** There are limited data on use of TAF with eGFR ≤ 10 mL/min

Dose Adjustment of ARVs for Impaired Renal Function

eGFR ^(a) (mL/min)					Haemodialysis ^(b)
	≥ 50	30-49	10-29	< 10	
NRTIs					
Individual agents					
ABC ⁽ⁱⁱⁱ⁾		300 mg q12h or 600 mg q24h	No dose adjustment required		
FTC ^(iv)		200 mg q24h	200 mg q72h	200 mg q96h	200 mg q24h ^(iv)
3TC ^(iv)		300 mg q24h	150 mg q24h	100 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)
TAF ^(ix, x)		25 ^(xi) mg q24h		No data	25 mg q24h ^(iv)
ZDV		300 mg q12h	No dose adjustment required		100 mg q8h
Combinations					
ABC ⁽ⁱⁱⁱ⁾ /3TC ^(iv)		600/300 mg q24h	Use individual drugs		
ZDV/3TC		300/150 mg q12h			
ABC/3TC/ZDV		300/150/300 mg q12h			
TAF ^(ix) /FTC ^(iv)		25 ^(xi) /200 mg q24h	Use individual drugs ^(xv)		25/200 mg q24 ^(iv)
TDF ^(viii) /FTC ^(iv)		300 ^(viii) /200 mg q24h	300 ^(viii) /200 mg q48h	Use individual drugs	
NNRTIs					
EFV		600 mg q24h	No dose adjustment required		
ETV		200 mg q12h	No dose adjustment required		
NVP		200 mg q12h	No dose adjustment required		Additional 200 mg ^(iv)
RPV		25 mg q24h	No dose adjustment required		
TAF ^(ix) /FTC ^(iv) /RPV		25 ^(xi) /200/25 mg q24h	Use individual drugs ^(xv)		25/200/25 mg q24h ^(iv)
TDF ^(viii) /FTC ^(iv) /RPV		300 ^(viii) /200/25 mg q24h	Use individual drugs		
DOR		100 mg q24h	No dose adjustment required; < 10: no PK data		
TDF ^(viii) /3TC ^(iv) /DOR		300 ^(viii) /300/100 mg q24h	Use individual drugs		
PIs ^(vii)					
ATV/c		300/150 mg q24h Do not initiate if eGFR < 70 mL/min if used with TDF *	No dose adjustment required ^(xiii)		Not recommended
ATV/r		300/100 mg q24h	No dose adjustment required ^(xiii)		Not recommended
DRV/r		800/100 mg q24h 600/100 mg q12h	No dose adjustment required ^(xiii)		
DRV/c		800/150 mg q24h Do not initiate if eGFR < 70 mL/min if used with TDF *	No dose adjustment required ^(xiii)		Not evaluated
TAF ^(ix) /FTC ^(iv) /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 ^(iv) /DTG		300/50 mg q24h	Use individual drugs		
ABC ⁽ⁱⁱⁱ⁾ /3TC ^(iv) /DTG		600/300/50 mg q24h	Use individual drugs ^(xvi)		
RPV/DTG		25/50 mg q24h	No dose adjustment required ^(xiii)		
TAF ^(ix) /FTC ^(iv) /BIC		25/200/50 mg q24h	No dose adjustment required ^(xviii)	Not recommended if eGFR > 15 - < 30 mL/min or if eGFR < 15 mL/min without chronic HD as safety not established ^(xviii)	No adjustment if on HD, however, use should generally be avoided and only used if potential benefits outweigh potential risks ^(xviii)
TAF ^(ix) /FTC ^(iv) /EVG/c		10/200/150/150 mg q24h	Not recommended ^(xii)		10/200/150/150 mg q24h ^(iv)
TDF ^(viii) /FTC ^(iv) /EVG/c		300 ^(viii) /200/150/150 mg q24h Do not initiate if eGFR < 70 mL/min	Not recommended		

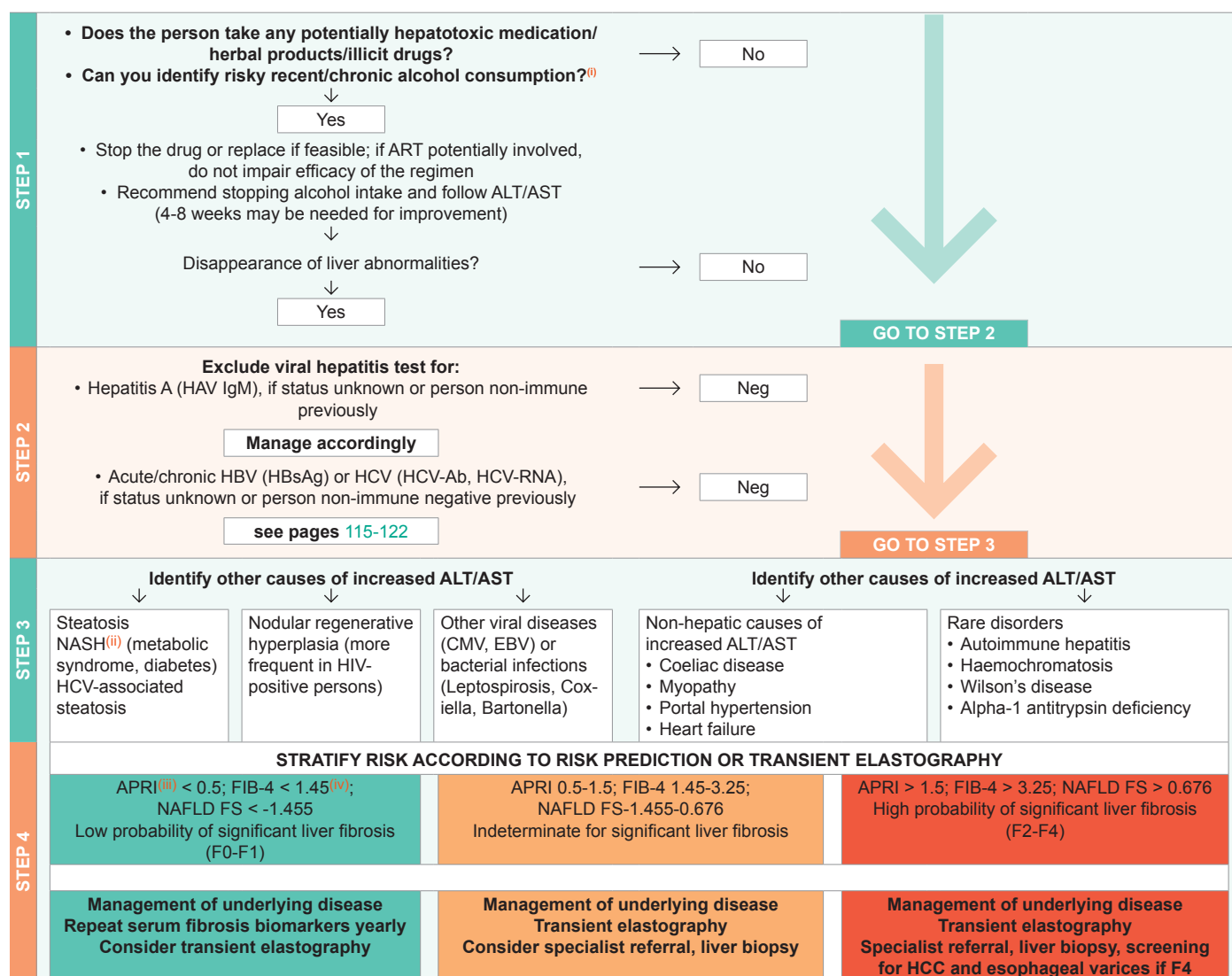
CAB	30 mg q24h	No dose adjustment required ^(xvii)
CAB LA RPV LA	400/600 mg 1x/4 w 600/900 mg 1x/8 w	No dose adjustment required ^(xvii)
MVC: co-administered without CYP3A4 inhibitors^(xiv)	300 mg q12h	No dose adjustment required ^(xiii)
MVC: co-administered with CYP3A4 inhibitors^(xiv)	If eGFR < 80 mL/min 150 mg q24h ^(xiv)	
Ibalizumab	2000 mg loading dose followed by 800 mg every 2 weeks. No dose adjustment required	
FTR	600 mg q12h	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](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 HBV
- 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 clinical study has demonstrated safety of TAF/FTC/EVG/c for PLWH on chronic dialysis
- 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/min. 10 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, however these findings need to be confirmed in a larger trial
- xvii In PLWH with eGFR < 30 mL/min, co-administration with a strong CYP3A4 inhibitor (e.g. ketoconazole, posaconazole) should be used only if the benefit outweighs the risk
- xviii According to the product label
- * Due to lack of COBI data in PLWH with renal impairment

For recommendations on ART use in PLWH undergoing renal transplantation, see [Solid Organ Transplantation in PLWH](#), page 113

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

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



See pages 80-81 and 83-84

i > 20 g in women, > 30 g in men

ii Non-Alcoholic Steatohepatitis, see NAFLD

iii APRI, AST to Platelet Ratio Index = (AST in IU/L) / (AST Upper Limit of Normal in IU/L) / (Platelets in 10⁹/L)

iv FIB-4 = Age ([years] x AST [U/L]) / ([platelet [10⁹/L] x ALT [U/L]). For NAFLD aetiology FIB-4 cut offs are as follows: < 1.30 (low risk), > 2.67 high risk. FIB-4 cut off < 2.0 (instead of < 1.30) should be considered in persons aged > 65 years

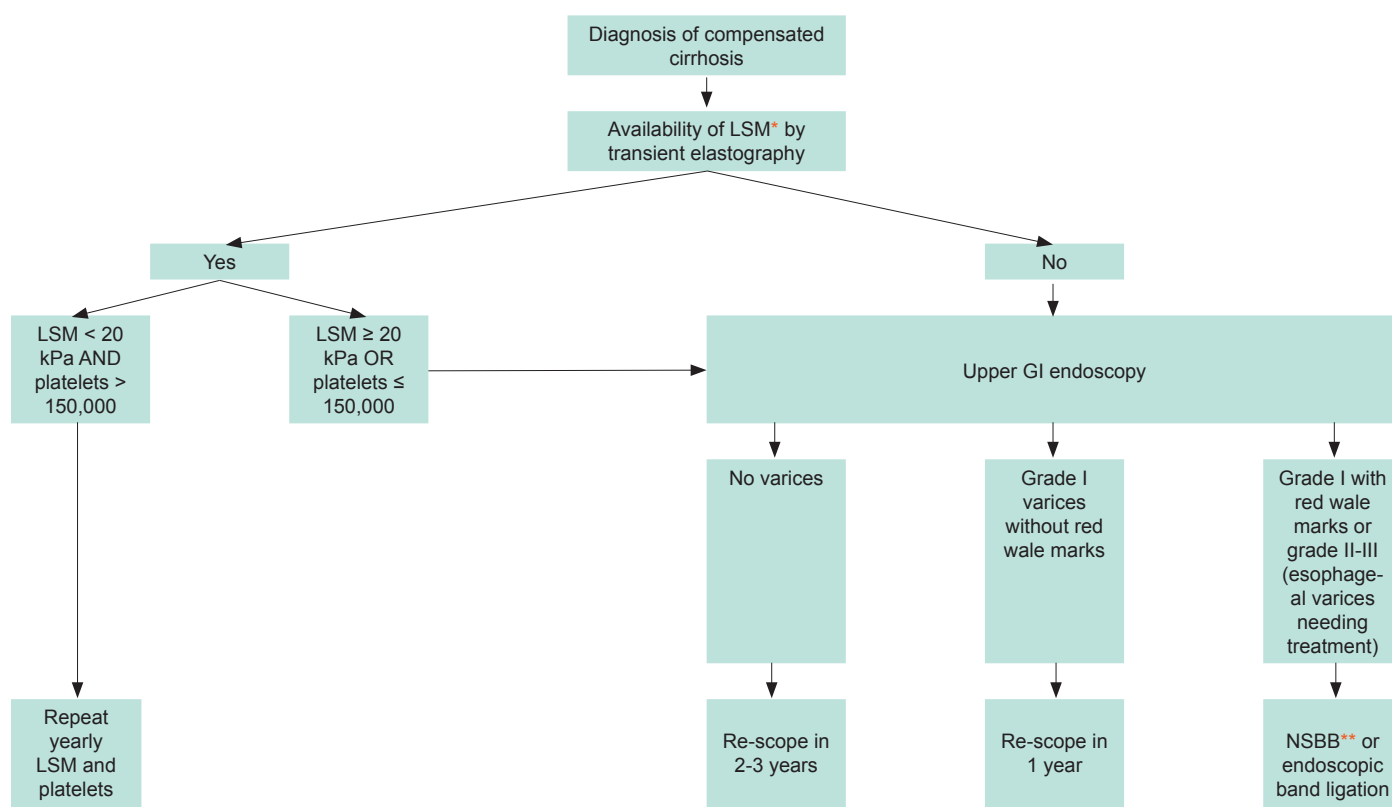
Liver Cirrhosis: Classification and Surveillance

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)

* 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, obesity or alcohol use or every 3 years if liver injury is quiescent, e.g., after viral clearance, 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)
<ol style="list-style-type: none"> Fluid restriction: 1000-1500 mL/day (consumption of bouillon as required / directed by physician) If fluid restriction is ineffective, consider use of oral tolvaptan <ol style="list-style-type: none"> 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)) S-Na should be monitored closely, particularly after initiation, dose modification or if clinical status changes Rapid increases in s-Na concentration (> 8 mmol/L/day) should be avoided to prevent osmotic demyelination syndrome Persons may be discharged after s-Na levels are stable and without need to further adjust dose 	<p>General management</p> <ol style="list-style-type: none"> Identify and treat precipitating factor (GI haemorrhage, infection, pre-renal azotaemia, constipation, sedatives) Short-term (< 72 hours) protein restriction may be considered if HE is severe <p>Specific therapy</p> <p>Lactulose 30 cm³ po every 1-2 hours until bowel evacuation, then adjust to a dosage resulting in 2-3 formed bowel movements per day (usually 15-30 cm³ po bid)</p> <p>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</p> <p>Rifaximin 550 mg po bid is an effective add-on therapy to lactulose for prevention of overt hepatic encephalopathy recurrence</p>

Management strategy in uncomplicated ascites	
General management	<ul style="list-style-type: none"> Treat ascites once other complications have been treated Avoid NSAIDs Prophylaxis (Norfloxacin 400 mg po qd) should be given to persons at high risk of spontaneous bacterial peritonitis (SBP) <ol style="list-style-type: none"> Persons with cirrhosis and gastrointestinal bleeding Persons who have had one or more episodes of SBP. (Recurrence rates of SBP within one year have been reported to be close to 70%) Persons in which ascitic fluid protein is < 1.5 g/dL along with <ul style="list-style-type: none"> Impaired renal function: creatinine ≥ 1.2 mg/dL (106 µmol/L), blood urea nitrogen ≥ 25 mg/dL (8.9 mmol/L), or serum sodium ≤ 130 mEq/L (130 mmol/L) Liver failure: Child-Pugh score ≥ 9 with bilirubin ≥ 3 mg/dL
Specific management	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Adjust diuretic dosage every 4-7 days Weigh the person at least weekly and BUN, uric acid (UA) as surrogate for volume status 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, UA, 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, UA, creatinine or electrolytes Maximum diuretic dosage: spironolactone (400 mg qd) and furosemide (160 mg qd)

Nutrition of cirrhotic persons	
<p>Caloric requirements</p> <ul style="list-style-type: none"> 25-30 Kcal/kg/day of normal body weight <p>Protein requirements</p> <ul style="list-style-type: none"> Protein restriction is not recommended (see above for exception if HE) 	<ul style="list-style-type: none"> 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 NH₃ <p>Micronutrients</p> <ul style="list-style-type: none"> Mg and Zn

Analgesia in PLWH with hepatic failure	
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Opiate analgesics are not contraindicated but must be used with caution in persons with pre-existing hepatic encephalopathy

Screening for HepatoCellular Carcinoma (HCC)	
<ul style="list-style-type: none"> 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 individual risk assessment https://easl.eu/publications/clinical-practice-guidelines/ 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, 59 and 115. Table on fibrosis cut-offs, page 121 Ultrasound (US), with or without alpha-fetoprotein (AFP), every 6 months. AFP should not be used alone. AFP is a suboptimal surveillance tool because of low sensitivity and specificity 	

When to refer for liver transplantation	
<p>Best to refer early as disease progresses rapidly</p> <p>= MELD⁽ⁱ⁾ score 12 (listing at 15)</p> <p>Decompensated cirrhosis (at least one of the following complications)</p> <ul style="list-style-type: none"> Ascites Hepatic encephalopathy Variceal bleeding Spontaneous bacterial peritonitis Hepatorenal syndrome Hepatopulmonary syndrome NASH cirrhosis⁽ⁱⁱ⁾ HCC <p>See Solid Organ Transplantation (SOT) in PLWH</p>	

- 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)

Non-alcoholic fatty liver disease (NAFLD) is characterized by fatty infiltration of the liver (hepatic steatosis involving > 5% of hepatocytes) either on liver histology or imaging.

To be diagnosed with NAFLD, a person must not have a history of heavy alcohol use or another condition that may be causing the liver condition (such as HCV).

It is often associated with components of the metabolic syndrome: obesity, type 2 diabetes, dyslipidemia and hypertension.

There are two types of NAFLD:

1. Non-alcoholic fatty liver (NAFL), fatty infiltration but no inflammation
2. Non-alcoholic steatohepatitis (NASH), with fatty infiltration along with liver inflammation (hepatocyte injury with or without fibrosis)

The prevalence of NAFLD is higher in PLWH (30 - 40%) than in the general population. Nearly half of the PLWH who undergo evaluation for unexplained liver test abnormalities are found to have NAFLD.

Non-Alcoholic SteatoHepatitis (NASH)

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

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. Few studies have validated CAP cut-off in HIV-associated NAFLD using different values (248 dB/m or 285 dB/m)

- A quantitative estimation of liver fat can only be obtained by MR spectroscopy 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

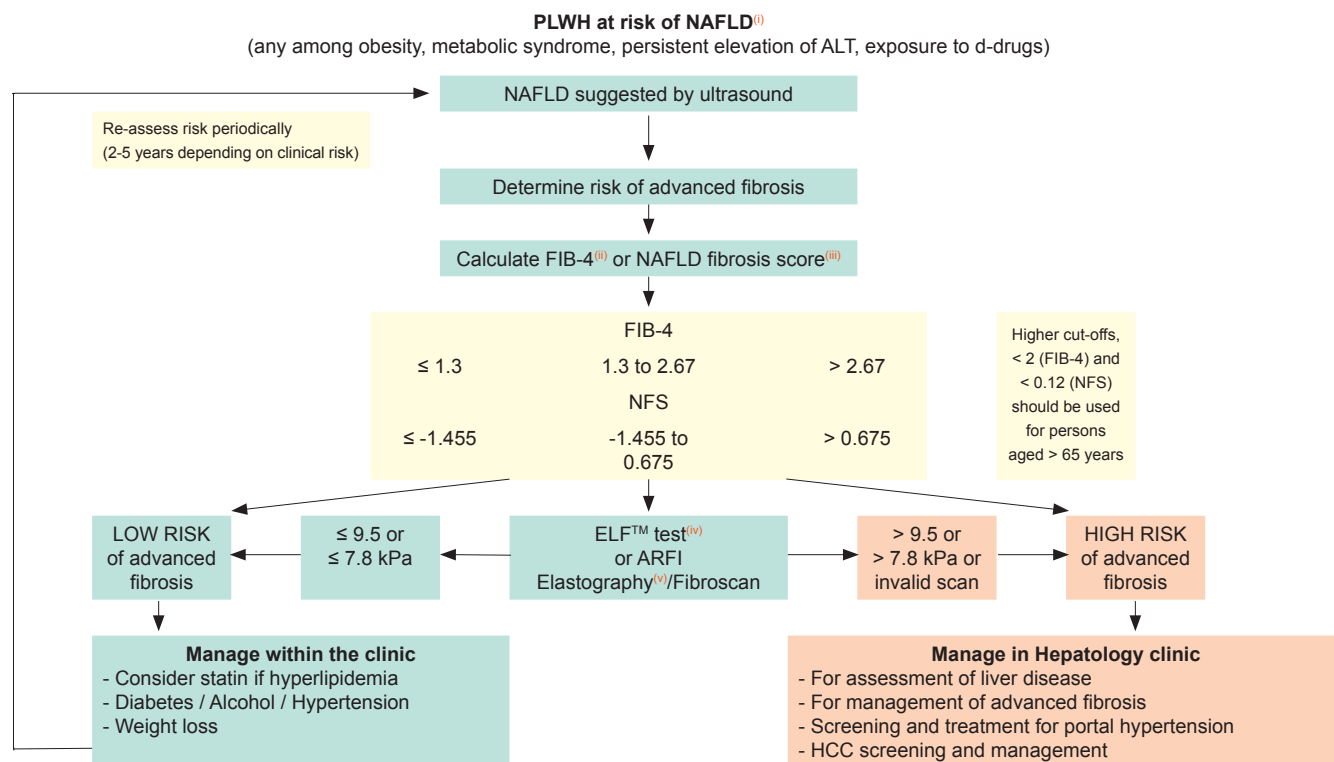
Consideration of ARV drugs

- Consider use of metabolic neutral ART regimens in individuals at risk of or with NAFLD (e.g. risk of weight gain induced by INSTI or TAF)

Treatment of NAFLD

- Lifestyle modification and weight reduction is the cornerstone of treatment
- Dietary restriction **PLUS** progressive increase in aerobic exercise/resistance training: Caloric restriction (500-1,000 /day) targeting 7-10% weight loss 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 \geq 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 of NASH should be discussed with hepatologists. Options with proven efficacy include pioglitazone, vitamin E and bariatric surgery. In the specific setting of HIV-associated NAFLD, tesamorelin and vitamin E have demonstrated efficacy, however larger studies are needed. Researchers advocate for inclusion of PLWH in ongoing global trials of new antifibrotic molecules for NASH
- Statins may be safely used but have demonstrated no impact on NAFLD thus far. 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

ⁱ NAFLD, Non-alcoholic fatty liver disease

ⁱⁱ FIB-4 = Age (years) x AST [U/L] / ([platelet [109/L]] x ALT [U/L])

ⁱⁱⁱ NFS, Non-alcoholic fatty liver disease Fibrosis Score = $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{impaired fasting glucose/diabetes mellitus}^{(iv)}$ (yes = 1/ no = 0) + $0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (x10}^9\text{)} - 0.66 \times \text{albumin (g/dL)}$

^{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 / Acute Kidney Injury (HRS-AKI)

Diagnosis	<ul style="list-style-type: none"> • Cirrhosis; acute liver failure; acute-on-chronic liver failure • Increase in serum creatinine ≥ 0.3 mg/dl (≥ 26.5 $\mu\text{mol/L}$) within 48 h or $\geq 50\%$ from baseline value according to ICA consensus document and/or Urinary output ≤ 0.5 mL/kg bodyweight ≥ 6h • No full or partial response, after at least 2 days of diuretic withdrawal and volume expansion with albumin (recommended dose of albumin is 1g/kg of body weight per day to a maximum of 100 g/day) • Absence of shock • No current or recent treatment with nephrotoxic drugs • Absence of parenchymal disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field, urinary injury biomarkers (if available) and/or abnormal renal ultrasonography Suggestion of renal vasoconstriction with FENa of $< 0.2\%$ (with levels $< 0.1\%$ being highly predictive) 		
Recommended therapy	Liver transplant (priority dependent on MELD score, see page 81). 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
AI	
FTR	No dosage adjustment
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
CAB	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

Lipodystrophy and Obesity: Prevention and Management

Lipodystrophy	Lipohypertrophy ⁽ⁱ⁾
Prevention <ul style="list-style-type: none"> • 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 	Prevention <ul style="list-style-type: none"> • No proven strategy • No contemporary ART has been specifically associated with increased visceral adiposity • An excess of visceral fat has been reported in HIV vs. non-HIV non-obese persons for the same BMI • Weight reduction or avoidance of weight gain may decrease visceral fat • Avoid corticosteroids with RTV or COBI-boosted drugs as it may cause Cushing syndrome or adrenal insufficiency, see Drug-Drug Interactions between Corticosteroids and ARVs
Management <ul style="list-style-type: none"> • Modification of ART: Switch away from d4T or ZDV <ul style="list-style-type: none"> – 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 <ul style="list-style-type: none"> – Offered for cosmetic relief of (facial) lipoatrophy 	Management <ul style="list-style-type: none"> • Diet and exercise may reduce visceral adiposity; <ul style="list-style-type: none"> – Limited data, but not consistently associated with improvement in insulin sensitivity and blood lipids – No prospective trials in PLWH to indicate degree of diet and/or exercise needed to maintain reduction in visceral fat • Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects and may introduce new complications; • Growth hormone (not approved for this indication in Europe) <ul style="list-style-type: none"> – Decreases visceral adipose tissue – May worsen insulin resistance • Tesamorelin (not approved in Europe; approved for this indication by FDA⁽ⁱⁱ⁾) • Metformin (not approved for this indication in Europe) <ul style="list-style-type: none"> – Decreases visceral adipose tissue in insulin resistant persons – May worsen subcutaneous lipoatrophy • Surgical therapy can be considered for localised lipomas/buffalo humps <ul style="list-style-type: none"> – Duration of effect variable

i Lipohypertrophy may occur as localised lipomas in the subcutaneous region or as increased visceral adiposity, both intra-abdominally and/or in the epicardium. Lipohypertrophy may occur without obesity.

Increased visceral adiposity is defined by waist circumference:

- for men: ≥ 94 cm (≥ 90 cm for Asian men) is high, and > 102 cm is very high

- for women: ≥ 80 cm is high and > 88 cm is very high

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

Weight gain and Obesity

	Weight Gain	Obesity	Comments
Definition	It is a physiological phenomenon associated with aging. Body weight of an average European adult is estimated to increase by 0.3 - 0.5 kg per year Definition is lacking. An increase > 5% of weight is often used, as opposed to the magnitude of weight loss recommended in lifestyle interventions as initial treatment of cardiometabolic conditions	BMI-based definitions (WHO): Overweight: BMI 25 to < 30 kg/m ² Class I obesity: BMI 30 to < 35 kg/m ² Class II obesity: BMI 35 to < 40 kg/m ² Class III obesity: BMI ≥ 40 kg/m ² For Asian populations, overweight is defined as BMI 23 to 27.5 kg/m ² and obesity ≥ 27.5 kg/m ²	Weight gain and obesity represent a continuum associated with negative health outcomes
Consequences	Increased risk of DM, hypertension, dyslipidaemia, and CVD	Body image disturbance Increased risk of DM, hypertension, CVD, some cancers, obstructive sleep apnea, cholecystitis, erectile dysfunction, non-alcoholic fatty liver disease, osteoarthritis, depression, and neurocognitive impairment	
Contributing factors	Older age Sedentary lifestyle Altered sleep pattern 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)		
Impact of ART	Initiation of ART in PWH increases weight as part of a return-to-health phenomenon INSTI and TAF may induce greater weight gain than other ARVs		See Adverse effects of ARVs and drug classes
Aim of intervention	Emphasise the importance of behaviour goals rather than weight loss goals An objective of 5 - 10% weight loss may have benefits on: <ul style="list-style-type: none"> • ↑ 5% HDL cholesterol • ↓ 5 mmHg systolic and diastolic BP in hypertension • ↓ 0.5% (decrease 2.55 mmol/mol) HbA1c in DM • Improving sleep apnoea 		
Management	Motivation to change: Discuss support systems (e.g. family, friends), motivating factors, and barriers to change Discuss benefits of making changes Set realistic and achievable lifestyle changes		
Lifestyle recommendations	Consider behavioral intervention (motivational interviewing, stimulus control or cognitive restructuring) along with self-monitoring; intensify behavioral intervention if several unsuccessful weight loss attempts		See Lifestyle Interventions
General principles	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 (DM, hypertension) (e.g. orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, liraglutide). These drugs should be prescribed by an endocrinologist or obesity expert. All of them may have adverse effects and drug-drug interactions with ART		Consider TDM (therapeutic drug monitoring) in obese PLWH. ↑ risk of virological failure with long acting CAB/RPV in obese PLWH
Bariatric surgery		Medical devices or endoscopic procedures (e.g intragastric balloon, aspiration therapy, endoscopic sleeve gastropasty) or bariatric surgery should be considered in persons with a BMI ≥ 40 kg/m ² or ≥ 35 kg/m ² with obesity-related co-morbidities 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

Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management

Risk factors	Prevention/Diagnosis	Symptoms
<ul style="list-style-type: none"> • HCV/HBV co-infection • Use of ribavirin • Liver disease • Low CD4 count • Pregnancy • Female sex • Obesity 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, elevated ALT and/or AST, weight loss • Acidaemia: asthenia, dyspnoea, arrhythmias • Guillain-Barré-like syndrome

Management

Serum lactate (mmol/L)	Symptoms	Action
> 5 ⁽ⁱ⁾	Yes / No	<ul style="list-style-type: none"> • Repeat test under standardised conditions to confirm & obtain arterial pH and bicarbonate⁽ⁱ⁾ • If confirmed, exclude other causes <ul style="list-style-type: none"> – 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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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	<p>1. Observe food hygiene</p> <ul style="list-style-type: none"> • Particularly important for travellers visiting friends and relatives (VFR) • Bacterial enterocolitis e.g. diarrhoeagenic <i>E. coli</i>, <i>Salmonella</i>, <i>Shigella</i>, <i>Campylobacter</i> • Opportunistic intestinal parasitosis <i>Cryptosporidium</i>, <i>Cyclospora</i>, <i>Cystoisospora</i>, <i>Microsporidia</i> <p>2. Prevent insect bites</p> <ul style="list-style-type: none"> • Repellents (DEET ≥ 30%), spray clothing with insecticide (permethrin) • Sleep under insecticide-treated bednet • Malaria chemoprophylaxis/emergency standby treatment⁽ⁱⁱ⁾ (to be taken with meals) • Yellow fever, see page 90 • 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 Anti-malarial Drugs and ARVs](#)

Drug-drug Interactions between Anti-malarial Drugs and ARVs

Antimalarial drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
First line and second line drugs	amodiaquine	↑	↑	↔	↑	↑	↔	↑ a	↓?	↓29% a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	artemisinin	↑	↑	↑	↑	↑	D	↓	↓D	↓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	↔ c,g	c,g	↔	↔	↔	↔ c,g	↔	↔ d	↔	↔	↔
	clindamycin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	doxycycline	↔	↔	↔	↔	↔	↔	↓?	↓?	↓?	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	halofantrine	↑ g	↑ g	↑	↑	↑ g	↔	↓	↓	↓	↔ g	↔ c,g	↔	↔	↔	↔ g	↔	↑	↔	↔	↔
	hydroxy-chloroquine	↑ c,g	↑ c,g	↑	↑	↑ c,g	↔	↔ e	↓	↓	↔ g	↔ c,g	↔	↔	↔	↔ g	↔	↑	↔	↔	↔
	lumefantrine	↑ c,g	↑ c,g	↑	↑175%	↑382% c,g	↔	↓~40%	↓	↓D46%	↔ g	↔ g	↔	↔	↔	↔ g	↑10%	↑	↔	↔	↔
	mefloquine	↑ c,g	↑ c,g	↑	↑	↓28% c,g	↔	↓	↓	↓	↔ g	↔ g	↔	↔	↔	↔ g	↔	↑	↔	↔	↔
	piperavaquine	↑ c,g	↑ c,g	↑ c	↑ c	↑ c,g	E	↓	↓	↓	E g	↔ g	E	E	↔	↔ g	↔	↑ c	↔	↔	↔
	primaquine	↔ g	↔ g	↔	↔	↔ g	↔	↔ h	↔ h	↔ h	↔ g	↔ g	↔	↔	↔	↔ g	↔	↔	↔	↔	↔
	proguanil	↔	↓41% b	↔	↓ b	↓38% b	↔	↓44% b	↓E55% b	↓ b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pyrimethamine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	quinine	↑ c,g	↑ c,g	↑	↑	↓56% c,g	↔	↓	↓	↓	↔ g	↔ c,g	E	↔	↔	↔ g	↔	↑	↔	↔	↔
	sulfadoxine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

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 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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

Interactions with ABC, FTC, 3TC, ZDV

ABC: no clinically relevant interactions expected.
 FTC: increased FTC exposure with pyrimethamine, sulfadoxine.
 3TC: increased 3TC exposure with pyrimethamine, sulfadoxine.
 ZDV: potential additive haematological toxicity with amodiaquine, atovaquone, primaquine, pyrimethamine, sulfadoxine.

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/hydroxychloroquine 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 Caution as both drugs can induce QT interval prolongation.
- 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

<ul style="list-style-type: none"> • 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 (e.g. rabies, tick-borne encephalitis, HAV/HBV) and consider antibody titres to assess their effectiveness if vaccinated at CD4 count < 200 cells/μL or unsuppressed viraemia (e.g. rabies, tick-borne encephalitis, HAV, meningococci). Be attentive to observe boosters and all post-exposure measures (particularly after potential rabies exposure) • Avoid polysaccharide vaccination • For background data, see http://www.bhiva.org/vaccination-guidelines.aspx 	<ul style="list-style-type: none"> • For attenuated live vaccines⁽ⁱ⁾ (in addition to restrictions for general population): <ul style="list-style-type: none"> • *Varicella, measles, mumps, rubella, yellow fever Contraindicated if CD4 count < 200 cells/μL (14%) and/or AIDS. Impaired protection after vaccination with unsuppressed viraemia. Administer immunoglobulins if exposed and not yet vaccinated • Oral live typhoid Preferred if CD4 count > 200 cells/μL (> 14%). Contraindicated if CD4 count < 200 cells/μL (14%): then give inactivated parenteral polysaccharide vaccine
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Infection	Vaccination rationale in PLWH	Comment
Influenza Virus	Higher rate of pneumonia. Explicitly recommended in all PLWH	Yearly, use 4-valent vaccine if available
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 45 (health insurance coverage differs by country according to age, sex, sexual orientation). Use 9-valent vaccine if available. Persons treated for high grade dysplasia could benefit from a full course vaccination for secondary prevention
Hepatitis B Virus (HBV)	Shared risk with HIV of contracting infection. Untreated HIV accelerates progression of liver disease	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. No benefit for intradermal application. See page 115
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 115
<i>Neisseria meningitidis</i>	According to risk profile (travel, close contact with children, MSM)	Use conjugated ⁽ⁱⁱⁱ⁾ 4-valent vaccine (for serotypes A, C, W-135, Y; 2 doses 1-2 months apart) if available. Booster every five years if exposure continues. Polysaccharide vaccine no longer recommended. Vaccination against <i>Meningococcus</i> serotype B according to national Guidelines
<i>Streptococcus pneumoniae</i>	Higher rate and severity of invasive disease. Vaccine explicitly recommended for all PLWH	One dose of conjugated ⁽ⁱⁱⁱ⁾ 13-valent vaccine (PCV-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 PCV-13 for all PLWH
Varicella Zoster Virus (VZV)	Higher rate and severity of both chicken-pox and zoster	Perform serology if exposure history negative. Vaccinate if seronegative. For contraindications, see*. To prevent shingles, preferably use adjuvant recombinant sub-unit vaccine over 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 viraemia consider pre-exposure vaccination with 3 doses (0, 7, 28 days) and titre control 14 days later. In case of exposure: full post-exposure prophylaxis including rabies immunoglobulins (RIG). If pre-exposure rabies vaccination administered when CD4 > 200 cells/μL: Post-exposure prophylaxis as for immunocompetent (one dose day 0 and day 3, without RIG)
Severe Acute Respiratory Syndrome 2 (SARS-CoV-2)	A higher prevalence of poor socio-economic circumstances and specific co-morbidities in PLWH (e.g. obesity, hypertension, CVD, DM) may increase the risk of acquiring SARS-CoV-2 infection and/or progressing to severe COVID-19 compared to the general population	In a pandemic situation, vaccinate irrespective of CD4 count and HIV-VL according to national Guidelines

- 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 PLWH

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
ART for HIV-positive partner	<ul style="list-style-type: none"> Undetectable equals untransmissible (U=U) from 6 months of fully suppressive ART if no active STIs Consider in e.g. sero-different couples⁽ⁱ⁾
Pre-exposure prophylaxis (PrEP)	<ul style="list-style-type: none"> Effective in HIV-negative persons with high risk sexual situations, see Pre-exposure prophylaxis (PrEP)
Post-exposure prophylaxis (PEP)	<ul style="list-style-type: none"> 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)
Male condom or female condom use	<ul style="list-style-type: none"> Effective in treated and untreated PLWH

U=U should be discussed with all PLWH, at diagnosis and when starting/switching ART. The evidence is now clear that PLWH 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 12

Reproductive health

All PLWH should be asked about their reproductive goals at HIV diagnosis and in follow-up and receive appropriate and ongoing reproductive counselling. Providing contraception and reproductive counselling to women living with HIV is essential if pregnancy is not currently desired.

Conception:

Reproductive health issues should be preferentially discussed with all partners, particularly in sero-different couples. See [Drug-drug Interactions between Contraceptives and ARVs](#)

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

Ensuring the partner living with HIV is on fully suppressive ART should be a primary goal for people who wish to conceive. Screening for STIs (and treatment, if required) of both partners is strongly recommended if conception is planned.

For ART in women living with HIV wishing to conceive, see pages 18-19

The following list represents selected measures with increasing safety for sero-different couples without active STIs:

- Intercourse without condoms 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 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 recommended 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

Menopause

Education

Healthcare providers should present accessible information on menopause to women and encourage the use of self-assessment tools (eg. Menopause Rating Scale (MRS), Greene Climacteric Scale (GCS), see also [Mental Health in PLWH, Depression: Screening and Diagnosis, Anxiety Disorders: Screening and Diagnosis](#)

Screening

We recommend yearly, pro-active assessment of menopausal symptoms in women living with HIV aged > 40 years using a validated menopause symptom questionnaire, such as the MRS or GCS

General health risk assessment for women age > 40 years

- Cancer, see [Cancer screening methods](#)
- Assessment of bone mineral density (BMD), see [Bone Disease: Screening and Diagnosis](#)
 - Assess risk factors for low BMD. If BMD is normal at initial assessment, consider fracture risk using FRAX® every 3-5 years
 - Consider DXA in women with 10-year major osteoporotic fracture risk > 20% based on FRAX® regardless of menopausal status
 - Consider DXA in women with prior history of low impact fracture regardless of menopausal status
 - Reassess DXA in those with osteoporosis after 2 years if on treatment to ensure response and reassess need for continued treatment after 3-5 years
- CVD risk assessment yearly, especially in women with vasomotor symptoms, see [Prevention of Cardiovascular Disease](#)
- Mental health - screen for anxiety and depression, consider screening tools such as GAD-2, see also [Mental Health in PLWH, Depression: Screening and Diagnosis](#)

Treatment for menopausal women

- Topical (vaginal) hormone replacement therapy (HRT) should be considered in all women given the positive effects on sexual health and urogenital symptoms
- Systemic HRT should be considered in women experiencing vasomotor, mood or urogenital symptoms.
- Transdermal estrogen (with progesterone if a woman has a uterus) is the preferred HRT option due to the lower thromboembolic risk. See [Drug-drug interactions between HRT and ARVs](#)
- Women with premature ovarian insufficiency should be offered HRT until at least the expected age of menopause (eg. aged 50-52 years) to reduce longer term morbidity and mortality risk

Special considerations regarding transgender people

HIV and general medical care, including sexual health services, are often not designed to cover the specific needs of transgender people. Transgender people are often not included in gender-specific health care surveillance programmes.

Using a two-stage question helps both individual care and the development of appropriate services.

- (i) What is your current sex?
- (ii) Is this the same sex you were given at birth?

Sex, gender and sexuality

Although sex is sometimes wrongly decided at birth, it is also independent of sexuality. Specific care for people who are transgender includes medical issues linked to biology (for example cervical screen for some trans men) and social factors (linked to the design of services in a clinic setting, appropriate naming, gender-neutral facilities).

Sexuality cannot be assumed by either sex or gender

In general:

- ART is equally effective for trans and cis gender people
- Access to and management of gender affirming hormones
- See dosage recommendation for hormone therapy when used at high doses for gender transitioning
- Support for good sexual health and access to reproductive services are equally important for trans people
- There are minimal data about STIs

Sexual dysfunction

Guidelines for treatment of sexual dysfunction in the general population are available. Refer to specialist where appropriate, see [Sexual Dysfunction](#) and [Treatment of Sexual Dysfunction in PLWH](#)

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, 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 <i>Lymphogranuloma venereum</i> (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)	<ul style="list-style-type: none"> 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 <i>Neisseria gonorrhoeae</i> 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	<ul style="list-style-type: none"> 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/HSV co-infections, pages 116-117	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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 doxycycline (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 ⁱⁱ	<ul style="list-style-type: none"> 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 Rosen RC, Riley A, Wagner G et al Women Female Sexual Function Index (FSFI), see http://www.fsquestionnaire.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: luteinizing 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, recreational drugs, alcohol, smoking and other 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 PLWH

Men	Women
Treatment of erectile dysfunction	Sexual pain
<p>Primarily oral PDE5-inhibitors (sildenafil, tadalafil, vardenafil).</p> <ul style="list-style-type: none"> • All at least 30 minutes before initiation of sexual activity • Use lower dose if on PI/b <ul style="list-style-type: none"> - 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 <p>Cave: Poppers have a synergistic effect with PD5-blockers which can lead to profound hypotension thus concurrent use is not recommended</p> <ul style="list-style-type: none"> • Tadalafil also licensed for use as an everyday ongoing therapy 	<p>Counselling Local hormone therapy Pelvic physiotherapy Vaginal/rectal suppositories Topical lidocaine Capsaicin Vestibulectomy</p>
Treatment of premature ejaculation	Low desire
<ul style="list-style-type: none"> • Consider behavioural interventions and/or psychosexual counselling, SSRIs, tricyclic antidepressants, clomipramine and topical anaesthetics • Use lower dose of clomipramine and other tricyclic antidepressants if on PI/r, see Drug-drug interactions between antidepressants and ARV • Dapoxetine, a short-acting SSRI, is the only drug approved for on-demand treatment of premature ejaculation in Europe. Dapoxetine is contraindicated with boosted ARVs • Treatment must be maintained as recurrence is highly likely following withdrawal of medicine 	<p>Counselling Hormonal therapy Bupropion Flibanserin (contraindicated with boosted ARVs due to risk of hypotension)</p>
	Low arousal
	<p>Counselling Hormonal therapy PDE5 inhibitors (e.g., sildenafil)</p>
	Orgasmic dysfunction
	<p>Mindfulness, sex therapy Hormonal therapy Bupropion PDE inhibitors (e.g., sildenafil) Yohimbine hydrochloride (concomitant use of boosted ARVs may increase BP)</p>

Mental Health in PLWH: Depression and Anxiety Disorders

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 <ul style="list-style-type: none"> • 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 neuro-cognitive impairment, see page 104 • Socially isolated (particular relevance during COVID-19 pandemic) 	<ul style="list-style-type: none"> • Screen every 1-2 years • Two questions: <ol style="list-style-type: none"> 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? • Rule out other medical conditions (such as hypothyroidism, hypogonadism, Cushing's syndrome, vitamin B12 deficiency) • Rule out depressive symptoms secondary to ART and non-ART medication (such as EFV) • Assessment of the risk of suicide should be done with the following questions : <ul style="list-style-type: none"> • Are these just ideas? • Are they intrusive and how many? • How much control do you have over these ideas? • Have you made a plan? • Are you about to take action? 	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: <ol style="list-style-type: none"> 1. Weight change of $\geq 5\%$ 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 96: A, B or C + 4/7)	Treatment	Consultation with expert
No	< 4	No	
Mild	4	<ul style="list-style-type: none"> • Problem-focused consultation • Consider antidepressant treatment⁽ⁱ⁾ • Recommend physical activity 	<ul style="list-style-type: none"> • 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 • Clinical improvement with antidepressants may take up to 4 weeks; there is no need to change antidepressants before this time. Dose increment of antidepressant may be considered
Intermediate	5-6	Start antidepressant treatment ^(i,ii,iii)	
Severe	> 6	Refer to expert (essential) ^(iv)	

ⁱ See [Drug-drug Interactions between Antidepressants and ARVs](#)

ⁱⁱ There is an increased risk of suicide and serious traffic accident in the first 15 days of antidepressant treatment; frequent monitoring in groups 5 and 6 is required during this period

ⁱⁱⁱ In groups 4, 5 and 6, psychotherapeutic follow-up (e.g. cognitive behavioral therapy CBT) may be indicated (consult with expert advice)

^{iv} Mental health professionals should always be consulted if there is a risk of suicide

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 ⁽ⁱ⁾	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	+	- / +	+	+	+(iii)
citalopram	10-20	20-40	Low	+	- / +	+	+	+(iii)
escitalopram	5-10	10-20	Low	+	- / +	+	+	+(iii)
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
- iii Weight gain may be significant but gradual and insidious

Drug-drug Interactions between Antidepressants and ARVs

Antidepressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
NaSSA	mirtazapine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
SSRI	citalopram	↑a,b	↑a,b	↑	↑	↑a,b	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	escitalopram	↑a,b	↑a,b	↑	↑	↑a,b	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	fluoxetine	↑	↑	↑	↑	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	fluvoxamine	↑	↑	↑	↑	↑a	↔	↔	↔	E	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔
	sertraline	↑	↓	↑	↓49%	↓a	↔	↓39%	↓	↓	↔	↔	↔	↔	↔	↔	↔	↓7%	↔	↑9%	↔
	vortioxetine	↑c	↑c	↑c	↑c	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑c	↔	↔	↔
SNRI	desvenlafaxine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	duloxetine	↑	↑↓	↑	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	milnacipran	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	venlafaxine	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔a	↔a	D	↔	↔	↔a	↔	↑	↔	↔	↔
TCA	amitriptyline	↑	↑	↑	↑	↑a,b	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	clomipramine	↑a,b	↑a,b	↑b	↑b	↑a,b	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑b	↔	↔	↔
	desipramine	↑a	↑a	↑	↑	↑5%a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	doxepin	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	imipramine	↑a,b	↑a,b	↑b	↑b	↑a,b	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑b	↔	↔	↔
	nortriptyline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	trimipramine	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
TeCA	maprotiline	↑a	↑a	↑	↑	↑a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
	mianserin	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔a	↔a	↔	↔	↔	↔a	↔	↑	↔	↔	↔
Others	agomelatine	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bupropion	↔	↓	↔	↓	↓57%	↔	↓55%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↑?	↔	↔	↔
	nefazodone	↑	↑	↑	↑	↑	E	↓E	↓E	↓E	E	E	E	E	↔	E	↔	↑	↔	↔	↔
	phenelzine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	reboxetine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	St John's wort	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	Dd	↔	Dd	De	Dd	D	Dd	↔
	tranylcypromine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	trazodone	↑a,b	↑a,b	↑	↑	↑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)
CAB/RPV	CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

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

NaSSA	noradrenergic specific serotonergic antidepressant
SSRI	selective serotonin reuptake inhibitors
SNRI	serotonin and norepinephrine reuptake inhibitors
TCA	tricyclic antidepressants
TeCA	tetracyclic antidepressants

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- a Caution as both drugs can induce QT interval prolongation.
- b ECG monitoring is recommended.
- c Based on the patient clinical response, a lower dose of vortioxetine may be needed in poor CYP2D6 metabolizers in the presence of a strong CYP3A4 inhibitor.
- d A study suggests a low risk of a clinically relevant pharmacokinetic interaction with low-hyperforin formulations (< 1 mg/day) of St John's Wort (hyperforin is the constituent responsible for induction of CYPs and P-gp). Coadministration may be considered with St John's Wort formulations that clearly state the hyperforin content and which have a total daily hyperforin dose of 1 mg or less.
- e 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)

Anxiety Disorders: Screening and Diagnosis

Significance

- Studies which included a diagnostic interview report a high prevalence of anxiety disorders in PLWH⁽ⁱ⁾
- Specific anxiety disorders include the following:
 - panic disorder (10% in PLWH)
 - generalized anxiety disorder (5.6% PLWH)
 - social anxiety disorder (9% PLWH)
 - post-traumatic stress disorder (PTSD)
- Significant disability and poorer HIV treatment outcomes are associated with anxiety
- Anxiety disorders are often associated with substance use behavior in PLWH

Screening and diagnosis of anxiety

Who?	How to screen?	How to diagnose?
<p>Consider screening all PLWH recommended at each clinic visit (in view of the high prevalence of anxiety)</p> <p>Populations at particularly high risk</p> <ul style="list-style-type: none"> • Positive history of anxiety disorders in family • Anxious personality • Alcohol excess • As part of investigation of cognitive impairment, see page 104 • Multiple stressful life events (particular relevance during COVID-19 pandemic) 	<p>Generalised Anxiety Disorder-2 (GAD-2) Screening tool⁽ⁱ⁾:</p> <p>‘Over the last 2 weeks, how often have you been bothered by the following problems?’</p> <ul style="list-style-type: none"> • Feeling nervous, anxious or on edge • Not being able to stop or control worrying <p>Score each question and calculate sum:</p> <ol style="list-style-type: none"> 0. Not at all 1. Several days 2. More than half the days 3. Nearly every day 	<p>If GAD-2 cut-off score of ≥ 3, ask the following questions to diagnose General Anxiety Disorder:</p> <ul style="list-style-type: none"> • excessive anxiety for more days than not over 6 months • difficulty controlling worry • associated with at least three of these symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, sleep disturbances) • significant life impairment • not attributable to another substance or medical condition • not being better explained by another medical disorder <p>Seek expert advice to diagnose panic disorders, social phobia and PTSD</p> <p>Rule out hyperthyroidism, hypoglycemia and hyperadrenocorticism. Exclude caffeine excess and use of stimulants (such as cocaine, crystal meth, amphetamines)</p>

ⁱ GAD-2 score is a validated screening tool in PLWH, <https://www.hiv.uw.edu/page/mental-health-screening/gad-2>

Anxiety Disorders: Management

Degree of anxiety disorders	GAD-2 Score	Treatment	Consultation with expert
Minimal	< 3	Relaxation techniques	
Significant	≥ 3	<ul style="list-style-type: none"> • Recommend relaxation techniques • Consider benzodiazepines, mainly clonazepam or lorazepam for a short period of time (less than 4 weeks) • Consider antidepressant treatment with SSRI⁽ⁱ⁾ • Consider psychotherapeutic intervention: <ul style="list-style-type: none"> • Cognitive Behavioral Therapy • Cognitive Behavioral Stress Management • Mindfulness-based Cognitive Therapy • Peer Support Counseling 	<ul style="list-style-type: none"> • 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 • Clinical improvement with antidepressants may take up to 4 weeks; there is no need to change antidepressants before this time Dose increment of antidepressant may be considered
Generalized anxiety disorder		Start antidepressant treatment with SSRI and benzodiazepine if needed (to reduce anxiety faster) ^(i, ii) Refer to mental health expert to start psychotherapeutic intervention	

ⁱ See [Drug-drug Interactions between Anxiolytics and ARVs](#)

ⁱⁱ Mental health professionals should always be consulted if there is a risk of suicide

Classification, Doses and Adverse Effects of Anxiolytics

Mechanisms & classification	Starting dose	Usual therapeutic daily dose	Lethality in overdose	Insomnia and/or agitation	Sedation	Nausea or GI effects	Sexual dysfunction	Weight gain
Benzodiazepines								
alprazolam	0.25-0.5 mg tid	1-4 mg	no (unless if combined with other CNS drugs)	++	+++	++	++	++
chlordiazepoxide	5 mg qd	10-100 mg	no (unless if combined with other CNS drugs)	frequency unknown	++	rare	rare	frequency unknown
clonazepam	0.25 mg bid	1-2 mg	no (unless if combined with other CNS drugs)	+	++	rare	+	+
oxazepam	10 mg tid	30-60 mg	no (unless if combined with other CNS drugs)	frequency unknown	++	rare	rare	no
Selective serotonin reuptake inhibitors								
escitalopram	10 mg qd	10-20 mg	no (unless if combined with other CNS drugs)	++	++	+++	++	+
paroxetine	20 mg qd	20-60 mg	no (unless if combined with other CNS drugs)	++	++	+++	+++	++
Serotonin and norepinephrine reuptake inhibitors								
duloxetine	30 mg qd	30-60 mg	yes (at > 1000 mg)	++	+++	+++	++	+
venlafaxine	75 mg qd	75-225 mg	yes	+++	+++	+++	++	++
Others								
buspirone	5 mg bid or tid	15-60 mg (60 mg)	no	++	+++	++	no	frequency unknown
hydroxyzine	12.5 - 12.5 - 25 mg	25-100 mg (100 mg)	no	frequency unknown	+++	frequency unknown	no	no

Frequencies of adverse effects as reported in clinical studies, frequencies are not placebo-corrected.

Rare (> 1/10,000 to < 1/1000): rare

Uncommon (> 1/1000 to < 1/100): +

Common (> 1/100 to < 1/10): ++

Very common (> 1/10): +++

The information on the starting dose and side effects is mostly issued from the European product label of the individual drug

Drug-drug Interactions between Anxiolytics and ARVs

Anxiolytics		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
BZD	alprazolam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	chlor-diazepoxide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	clonazepam	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	oxazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
SSRI	escitalopram	↑a	↑a	↑	↑	↑a	↔	↓	↓	↓	↔b	↔b	↔	↔	↔	↔b	↔	↑	↔	↔	↔
	paroxetine	↑↓?	↑↓?	↑↓?	↓39%	↑↓?	↔	↔	↑3%	↔	↔	↔	↔	↔	↔	↔	↔	↑↓?	↔	↔	↔
SNRI	duloxetine	↑	↑↓	↑	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	venlafaxine	↑b	↑b	↑	↑	↑b	↔	↓	↓	↓	↔b	↔b	D	↔	↔	↔b	↔	↑	↔	↔	↔
Others	buspirone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	hydroxyzine	↑a,b	↑a,b	↑a,b	↑a,b	↑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 anxiolytic therapy
- ↓ Potential decreased exposure of the anxiolytic therapy
- ↔ 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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

BZD benzodiazepines
SSRI selective serotonin reuptake inhibitors
SNRI serotonin and norepinephrine reuptake inhibitors

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

- a ECG monitoring is recommended.
- b Caution as both drugs can induce QT interval prolongation.

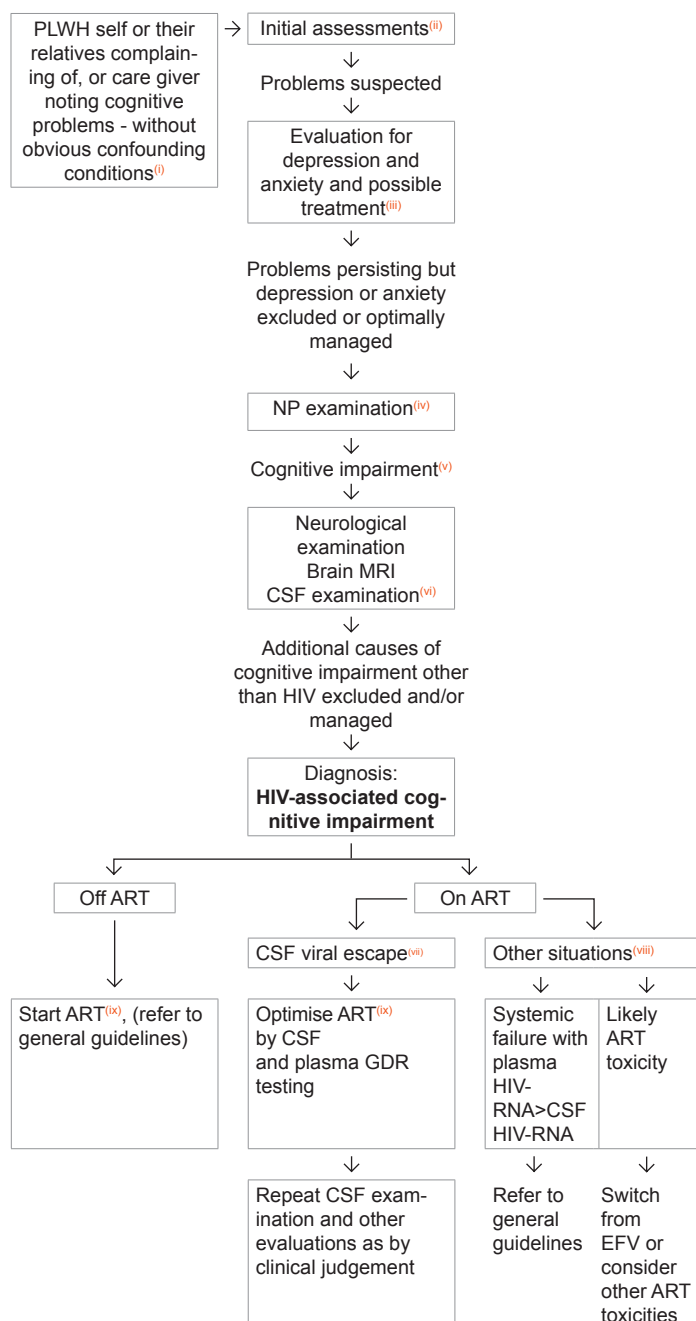
Further Information

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	randomised controlled trial



i Obvious confounding conditions:

1. Severe psychiatric conditions
2. Use of anticholinergic drugs with high burden score for cognitive impairment (e.g. amitriptyline, chlorpromazine)
3. Abuse of psychotropic drugs
4. Alcohol abuse
5. Sequelae from previous CNS-OIs, pre-treatment cognitive disease or other neurological diseases
6. Current CNS-OIs or other neurological diseases

ii The following questions may be used to guide initial assessments (other screening assessments are acceptable)

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](#) and [Anxiety Disorders: 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 cognitive 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
- Include dual nucleoside backbones in ART regimens where possible
- Avoid ATV (boosted or unboosted) due to association with CSF escape in retrospective cohorts
- Avoid RAL 1200 mg qd due to lack of evidence in CSF escape
- Consider DTG 50 mg bid in cases with documented or suspected INSTI resistance

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

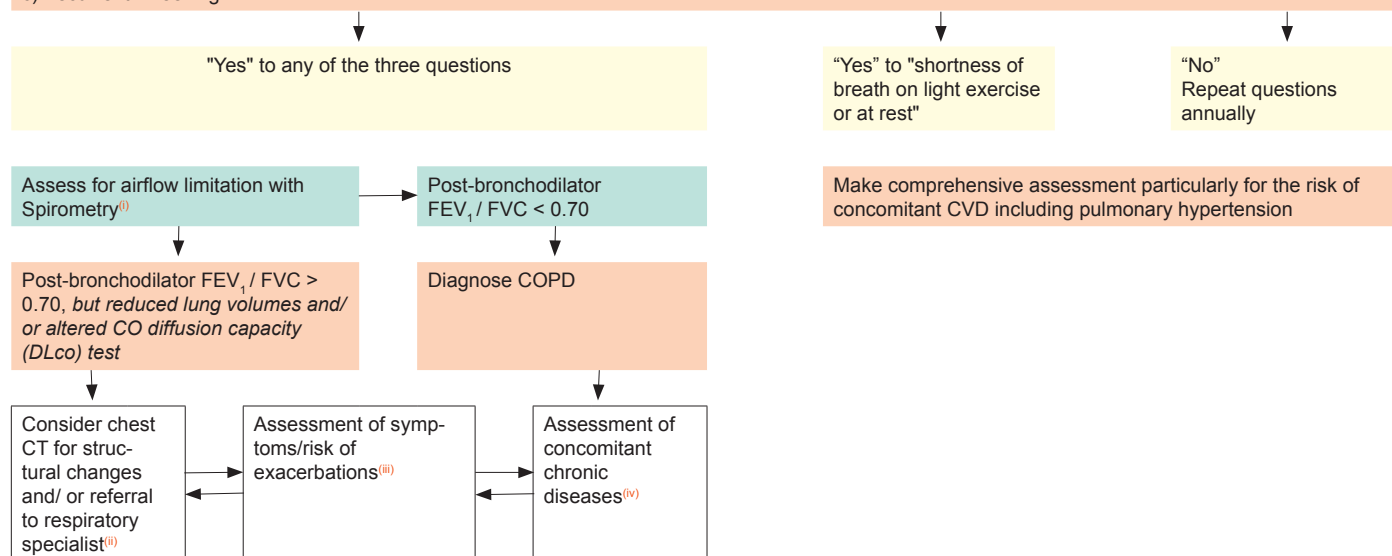
ix Avoid EFV because of its possible effects on cognitive function and potentially confounding CNS effects due to neuropsychiatric effects

Chronic Lung Disease in PLWH

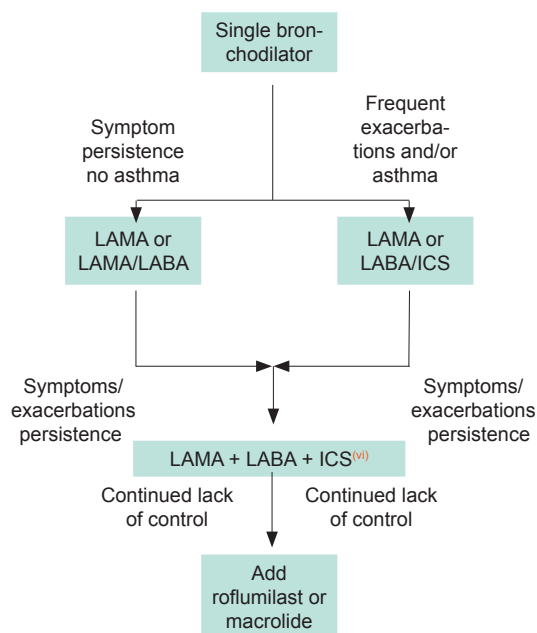
Screen for chronic lung disease:

Do you have ANY of the following on a regular basis:

- shortness of breath when walking up a slight hill or hurrying on flat ground;
- cough and/or sputum;
- recurrent wheezing



Treatment of COPD(v)



LABA: long-acting β_2 -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 lifesaving interventions in COPD:

- Smoking cessation
- Chronic oxygen when stable (non-exacerbated) resting $\text{SpO}_2 \leq 88\%$ (or $\text{PaO}_2 \leq 55 \text{ mmHg}$)
- Non-invasive ventilation (NIV) in individuals with persistent hypercapnic respiratory failure after an acute exacerbation

- Risk assessment for spirometry should be undertaken in the setting of COVID-19
- Based on expert opinion, also consider interstitial lung disease, CT scan may help to identify people with interstitial lung disease and lung cancer
- Assessment of either dyspnoea using mMRC, see <https://www.verywell-health.com/guidelines-for-the-mmrc-dyspnea-scale-914740> or symptoms using CAT™, see <http://www.catestonline.org/> and history of exacerbations (including prior hospitalisations)
- COPD itself has significant extra-pulmonary (systemic) effects including weight loss, nutritional abnormalities and skeletal muscle dysfunction
- 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 high dose ICS and/or use of oral glucocorticoids has no evidence of benefits in COPD and increase the risk of pneumonia. The addition of medium dose ICS to LABA or 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 ($< 1\%$)
- Antibiotics should be used to treat acute exacerbation or in case of high CRP and purulent sputum (PCT is a more questionable biomarker). Azithromycin may also be considered in non-smokers, not well controlled with maximal inhaled drug dosage.
- LABA/LABA/ICS are now available in a fixed dose combination. This drug combination improves clinical control of COPD and increases life expectancy.

With the exception of low dose beclometasone, do not use inhaled glucocorticoids with boosted ART regimens, see [Drug-drug Interactions between Corticosteroids and ARVs](#).

Influenza, SARS-CoV-2 and pneumococcal vaccination decrease rates of lower respiratory tract infections, see [Vaccination](#). Pertussis vaccination is also suggested in people with COPD

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	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
LAMA	acridinium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	glycopyrronium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tiotropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	umeclidinium bromide	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
SAMA	ipratropium	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
LABA	formoterol	↔a	↔a	↔	↔	↔a	↔	↔	↔	↔	↔a	↔a	↔	↔	↔	↔a	↔	↔	↔	↔	↔
	indacaterol	↑b	↑b	↑b	↑b	↑b	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑b	↔	↔	↔
	olodaterol	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	salmeterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	vilanterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
SABA	salbutamol (albuterol)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	terbutaline	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
MX	aminophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	theophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
PDE4	roflumilast	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
ICS	beclometasone	↑c	↑c	↑?c	↓11% ^d	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑c	↔	↔	↔
	budesonide	↑e	↑e	↑e	↑e	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑e	↔	↔	↔
	ciclesonide	↑f	↑f	↑f	↑f	↑f	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑f	↔	↔	↔
	fluticasone	↑e	↑e	↑e	↑e	↑e	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑e	↔	↔	↔
	mometasone	↑e	↑e	↑e	↑e	↑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 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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 ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

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 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.
- d DRV/r decreased the exposure of active metabolite (beclometasone-17-monopropionate), no significant effect on adrenal function was seen.
- e 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.
- f No dose adjustment required but monitor closely, especially for signs of Cushing's syndrome when using a high dose or prolonged administration.

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

Fixed dose combinations are available for LAMA + LABA + ICS, e.g., mometasone + indacaterol + glycopyrronium
 fluticasone + umeclidinium + vilanterol
 formoterol + glycopyrronium + beclometasone
 budesonide + formoterol + glycopyrronium

Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

Pulmonary antihypertensives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
ERA	ambrisentan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bosentan	↑a	↑a	↑a	↑a	↑a	D	↓	↓	↓b	D	↑	D	D	↔	D	D	↑a	↔	↔	↔
	macitentan	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
PDE5	sildenafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↓3%	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	tadalafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
sGC	riociguat	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔
PA	epoprostenol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	iloprost	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	treprostinil	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
IP [†]	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 elevated 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

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

Interactions with ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: No clinically relevant interactions expected.

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 persons already on PI/b 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/b 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)

Managing Older PLWH

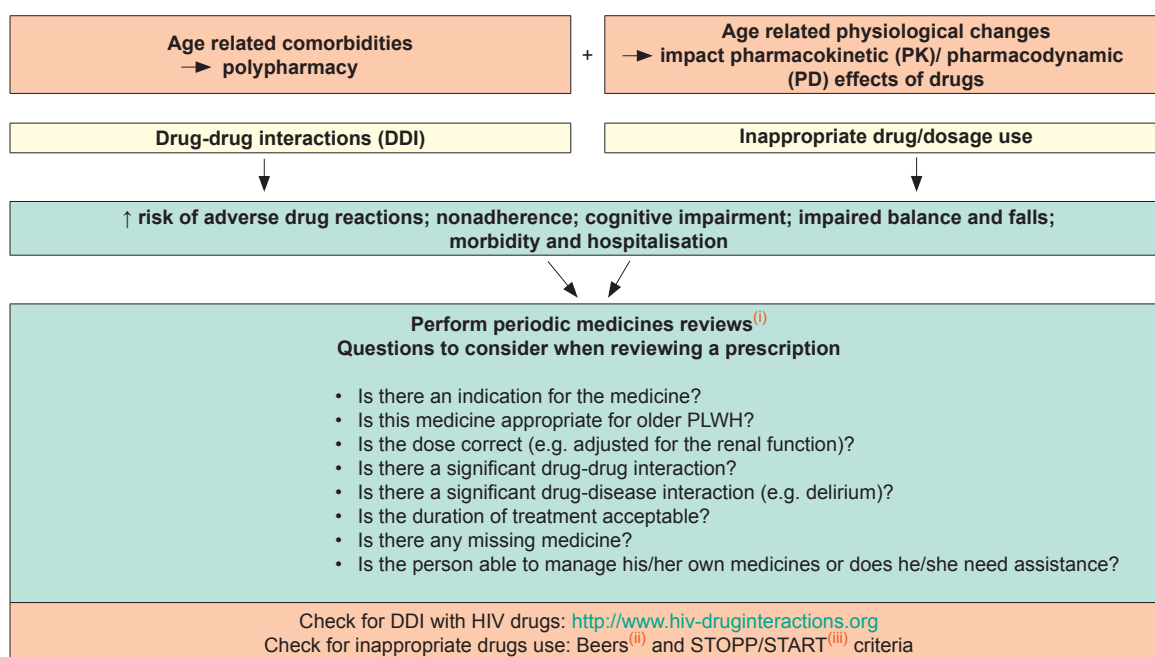
Physical function, frailty and geriatric syndromes have shown to better predict survival and quality of life among older people in the general population than co-morbidity alone. Managing older people with HIV has to move from the management of each condition separately to a multidimensional assessment focused on preserving physical function, aimed at promoting health aging and quality of life. This section will focus on important geriatric issues: polypharmacy, frailty and falls.

Polypharmacy

Polypharmacy is defined as the concurrent use of > 5 drugs, a cut-off that has been associated with an increased risk of adverse health outcomes. In HIV medicine, the term polypharmacy most often refers to non-HIV medications given in addition to ARVs.

The complexity of medication burden should be considered owing to its clinical consequences: the higher risk of drug-drug interactions and adverse events, the risk of non-adherence to HIV and non-HIV medications, and the risk of hospitalisation, falls, other geriatric syndromes and death. Polypharmacy is often unavoidable when treating a patient with multiple co-morbid conditions making the use of polypharmacy appropriate in this context whereas “unnecessary or inappropriate polypharmacy” is deleterious and should be avoided. Interventions to prevent unnecessary/inappropriate polypharmacy include medication reconciliation and medication review. The concept of ‘deprescribing’ or the planned and supervised process of dose reduction or stopping of medication that may cause harm, or no longer provide benefit has gained increasing attention as a means to reduce unnecessary/inappropriate polypharmacy in older PLWH. A freely-accessible resource to help deprescribe can be found at medstopper.com.

Prescribing in Older PLWH



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 older persons (note: these tools were established for persons > 65 years old given that PK and PD effects may be more apparent after this age cut-off). Inappropriate medicines include, for instance, those which in older persons with certain diseases can lead to drug-disease interactions, are associated with a higher risk of adverse drug reactions in older persons, medicines that predictably increase the risk of falls in the older persons or those to be avoided in case of organ dysfunction. The START criteria consist of evidence-based indicators of potential prescribing omission in older persons with specific medical conditions

Selected Top 10 Drug Classes To Avoid in Older 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., amitriptyline, 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.

Legend

NSAID nonsteroidal anti-inflammatory drug

Frailty

Frailty is defined as a clinical syndrome associated with decreased reserve, high vulnerability to stressors and associated with risk of negative health-related outcomes including mortality. Frailty should be regarded as a distinct entity to the disease or condition that may be contributing to it. This geriatric syndrome is more prevalent than expected in PLWH compared to HIV-negative matched controls and may occur at an earlier age. Early identification and management of frailty is a priority since it is potentially reversible. Older PLWH aged 50 years and over should be offered screening for frailty using a validated rapid frailty instrument. An algorithm to identify those PLWH who may benefit from a frailty assessment is detailed below.

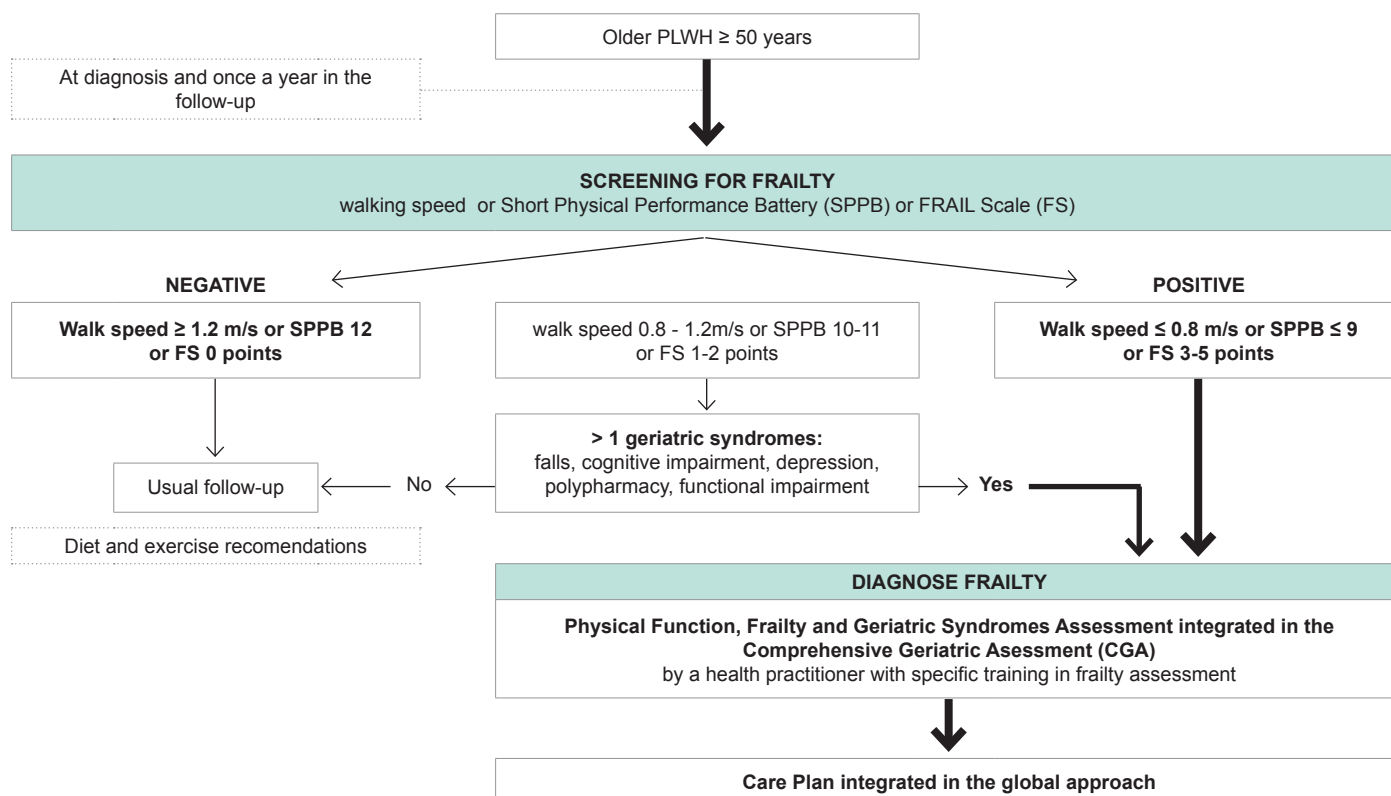
Screening for Frailty

Screening for frailty in PLWH above 50 years of age should be considered. The age cut-off was chosen as the incidence of frailty in PLWH has been shown to increase in PLWH above this age. Evidence of benefit is still unknown. It is advocated by some experts.

Screening has to be performed using validated tools for this purpose and can be provided by any trained health staff (nurses, general practitioners, etc.). In the absence of a gold standard, the instrument to screen frailty we suggest is the FRAIL Scale (FS) because it is easy, cheap and quick to develop but other validated tools, such as walking speed measurement or Short Physical Performance Battery (SPPB) can also be used.

FRAIL SCALE	
How much time during the previous 4 weeks did you feel tired?	All the time, most of the time = 1 point
Do you have any difficulty walking up 10 steps alone without resting and without aids?	Yes = 1 point
Do you have any difficulty walking several hundred meters alone with/without aids?	Yes = 1 point
How many illnesses do you have from this list?: hypertension, DM, cancer, chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke and kidney disease.	> 5 = 1 point
Have you had weight loss of 5% or more?	Yes = 1 point

Algorithm Recommended for Frailty Screening



Adapted from Brañas F, et al. European Geriatric Medicine. 2019;10(2):259-265

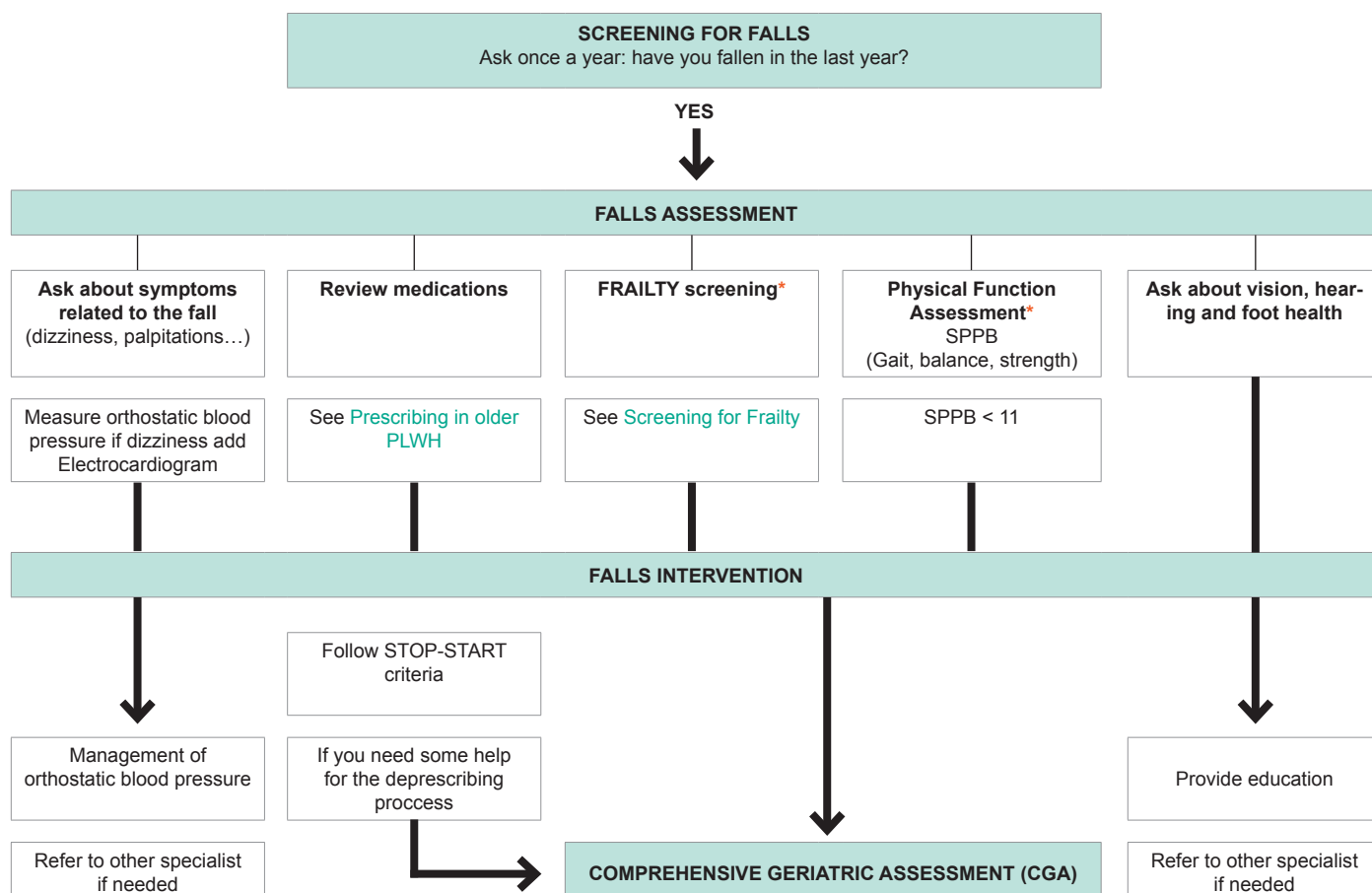
Formal Frailty Assessment and Management

How to diagnose frailty		
	Frailty Phenotype	Frailty Index
Clinical definition	Clinical syndrome based on presence of specific signs and symptoms	Based on accumulation of deficits
How to assess	Assessed by five specific features: 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 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		
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		
<p>In PLWH who are frail:</p> <ol style="list-style-type: none"> 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 older 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 72 		

- (a) **Self-reported unintentional weight loss** was considered present if exceeding 4.5 kg or ≥5% of body weight in the last year
- (b) **Exhaustion** is present if the participant answers “occasionally” or “most of the time” to both of the following statements (questions from the Center for Epidemiologic Studies Depression Scale): During the last week, how often have you felt that 1. everything you did was an effort, or 2. you could not ‘get going’
- (c) **Low physical activity** as considered present if the participant’s physical activity is lower than 383 kcal/week in men and 270 kcal/week in women which is equivalent to < 2.5 hours/week in men and < 2 hours/week in women using the Minnesota Leisure Time Activity Questionnaire
- (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):
- 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

Falls

A fall is defined as an event which results in a person coming to rest inadvertently on the ground or floor or other lower level. Falls are a common geriatric syndrome in PLWH, as the prevalence is estimated to be between 25% and 30%, affect independent movement and mobility in older people and therefore their quality of life



* If FRAIL Scale is > 1 point, as the PLWH has 1 geriatric syndrome (falls), then is not necessary to perform the SPPB in the HIV clinic as the CGA is already recommended

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
- Unboosted INSTIs plus 2 NRTIs are the preferred regimens
- 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 115-120. 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 137, 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 prevention

- Transplant recipients living with HIV should receive the same surveillance, immunisation prophylaxis and pre-emptive regimens as HIV-negative SOT recipients
- Screening and treatment for latent TB is a priority, see page 137

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

Screening for co-morbidities and frailty

PLWH undergoing SOT have higher risk for some comorbidities including, CVD, DM, bone disease (osteoporosis and aseptic necrosis of the femur) and frailty, see [Prevention of Cardiovascular Disease \(CVD\)](#), [Type 2 Diabetes Mellitus: Diagnosis](#), [Type 2 Diabetes Mellitus: Management](#), [Bone Disease: Screening and Diagnosis](#) and [Managing Frailty in Older People Living with HIV](#)

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	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	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	↔	E	↔	↑a	↔	E	Eb
	tacrolimus*	↑a,c	↑a,c	↑a	↑a	↑a,c	↓a	↓a	↓a	↓a	↔c	↔c	↔	↔	↔	↔c	↔	↑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 elevated 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)
 CAB/RPV CAB and RPV im long acting injections
 (PK and/or QT interactions shown are with RPV)

* 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 ABC, FTC, 3TC, ZDV

ABC: potential decrease in mycophenolate exposure.
 ZDV: potential risk of additive haematotoxicity with azathioprine.
 ZDV: potential alteration in mycophenolate exposure, monitor plasma concentrations.

Interactions with ibalizumab

None

Comments

- a TDM of immunosuppressant is recommended.
- b Monitor renal function.
- c Both drugs can potentially prolong the QT interval, ECG monitoring 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)

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 which is not mandatory if pangenotypic drugs are to be used. 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 advanced 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 59. 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 9, 59 and 81
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 80

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 80-81 and [Diagnosis and Management of Hepatorenal Syndrome / Acute Kidney Injury \(HRS-AKI\)](#)
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 > 12^(vi), CD4 count > 100 cells/μL and options for efficacious and durable ART should be evaluated for liver transplantation (OLT), see [Solid Organ Transplantation \(SOT\) in PLWH](#)
11. Renal complications are frequent, see page 74 and [Diagnosis and Management of Hepatorenal Syndrome / Acute Kidney Injury \(HRS-AKI\)](#)

Vaccination, see page 90

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 HBsAg 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, 2 and 6) 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 [Opioid 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)^(vi), 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. HBV therapy should be continued throughout pregnancy.
 - i Screening intervals to detect recently acquired HCV infection should be adapted to individual risk assessments and local epidemiology as described in the [Recommendations on recently acquired and early chronic hepatitis C in MSM from the European treatment network for HIV, hepatitis and global infectious diseases consensus panel](#)
 - 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 [EASL recommendations on treatment of Hepatitis C 2020 - EASL-The Home of Hepatology](#) (free registration needed to get access) and page 121
 - vi MELD calculation, see page 81

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 80-84). 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 71-76

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 after confirmed HBsAg-seroconversion. 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
HBsAg should be checked at 12 months intervals at least until loss of HBsAg⁽⁹⁾

HBV reactivation

11. 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 ETV, 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

i Quantitative HBsAg < 1000 IU/mL predicts HBsAg loss

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 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. DAA combinations are now standard of care for chronic HCV infection, see Tables HCV Treatment Options in HCV/ HIV Co-infected Persons. IFN-based therapies and first generation PIs (boceprevir and telaprevir) are not recommended because of insufficient efficacy and increased toxicities.
4. Selection of DAA combinations is based upon stage of liver fibrosis, HCV GT¹⁰, pre-treatment history and resistance-associated substitutions (RAS) if tested
5. 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 Viral Hepatitis Drugs and ARVs](#) or <http://www.hep-druginteractions.org>
6. 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

7. The primary aim of HCV treatment is SVR₁₂ 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. SVR₁₂ corresponds to a definitive cure of HCV infection in the vast majority of cases
- i If pangenotypic regimens are foreseen, HCV GT determination is not mandatory before starting treatment. HCV GT determination should be considered in persons at risk of reinfection in order to differentiate between relapse and re-infection in case of reemergence of HCV RNA after therapy

See online video lectures [HCV/HIV Co-infection-Part 1](#) from the EACS online course Management of HIV and Co-infections

Treatment monitoring

8. In PLWH 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
9. In PLWH with impaired renal function undergoing SOF based treatment creatinine should also be monitored
10. 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
11. HIV-VL every 12 weeks

Post-Treatment monitoring

12. Surveillance for HCC and for oesophageal varices should be continued if the respective indications were present pre-treatment, despite achieving SVR, see pages 9, 59, 80 and 81
13. All PLWH with concurrent causes of liver disease should undergo periodical clinical assessments
14. 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 85

Treatment of recently acquired HCV infection

15. IFN-containing HCV regimens are no longer recommended
16. 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 page 118
17. If treatment is not indicated immediately, HCV-RNA should be re-measured 4 weeks later. Treatment is recommended in PLWH without a decrease of 2*log₁₀ 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 [Management of Recently acquired HCV in Persons with HIV Co-infection](#)
18. For more detailed information on the management of recently acquired HCV infection we refer to the [Recommendations on Recently acquired and early chronic hepatitis C in MSM from the European treatment network for HIV, hepatitis and global infectious diseases consensus panel](#)

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	8-12 weeks ⁽ⁱⁱ⁾	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV ^(ix)
	SOF/LDV +/- RBV	8-12 weeks without RBV ⁽ⁱⁱⁱ⁾	12 weeks with RBV ^(iv)	12 weeks with RBV ^(ix)
2	GLE/PIB	8 weeks	8-12 weeks ⁽ⁱⁱ⁾	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV ^(ix)
3	GLE/PIB	8 weeks ^(v)	8-12 weeks ^(ii,v)	Not recommended
	SOF/VEL +/- RBV	12 weeks ^(vi)	12 weeks with RBV ^(vii)	12 weeks with RBV ^(ix)
	SOF/VEL/VOX	-	12 weeks	Not recommended
5 & 6	GLE/PIB	8 weeks	8-12 weeks ⁽ⁱⁱ⁾	Not recommended
	SOF/LDV +/- RBV	12 weeks +/- RBV ^(viii)	12 weeks with RBV ^(iv)	12 weeks with RBV ^(ix)
	SOF/VEL	12 weeks		12 weeks with RBV ^(ix)

For HCV treatment options to be used if preferred options are not available, please see version 10.1 of the EACS Guidelines

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 can be considered in treatment naïve PLWH
- iii** 8 weeks treatment without RBV only in treatment-naïve PLWH with F < 3 and baseline HCV-RNA < 6 million IU/mL
- iv** 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
- v** Treatment duration in HCV GT3 who failed previous treatment with IFN and RBV +/- SOF or SOF and RBV should be 16 weeks
- vi** 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
- vii** If RAS testing is available and demonstrates absence of NS5A RAS Y93H, RBV can be omitted in treatment naïve PLWH with compensated cirrhosis
- viii** In treatment experienced (exposure to IFN/RBV/SOF) PLWH add RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV
- ix** In persons intolerant to RBV, treatment may be prolonged to 24 weeks

Drug-drug Interactions between Viral Hepatitis Drugs and ARVs

Viral hepatitis drugs		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	BIC	CAB oral	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF	
HCV DAAs	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%	
	sofosbuvir	↔	↔	↑	↑34%	↔	↔	↓6%	↔	↔	↑9%	↑	↔	↔	↔	↔	↔	↔	↓5% D27%	↔	↓6%	
	sofosbuvir/ ledipasvir	↑ a	↑8% ↑113%a	↑ a	↑34% ↑39%a	↔ a	↑4% ↓8%	↓6% ↓34%a	↔	↔	↑10% ↑8%a	↑	E	↑7% ↓13%	↔	↔	↔	↑36% ↑78%a	↓5% ↓9% D~20%	E32%	E a	
	sofosbuvir/ velpatasvir	↔ a	↑22% ↑142%a	↔ a	↓28% ↓16%a	↓29% ↑2%a	↔	↓3% ↓53%	↓	↓	↑16% ↓1%	↑	E	↔	↔	↔	↓8% ↓9%	↑ a	↑24% ↓2%	↔	E a	
	sofosbuvir/ velpatasvir/ voxilaprevir	↑	↑40% ↑93% ↑331%	↑ a	↓28% ↓5% ↑143%b	↑	↔	↓	↓	↓	↔	↑	E	↑9% ↓4% ↓9%	↔	↔	↔	↑22% ↑16% ↑171%a	↔	E	E a	
HDV	Bulevirtide	↑	↑	↑	↑	↑	E	↑	↑	↔	E	↔	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 elevated exposure of the hepatitis therapy
- ↓ Potential decreased exposure of the hepatitis therapy
- ↔ 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)
- CAB/RPV CAB and RPV im long acting injections (PK and/or QT interactions shown are with RPV)

Numbers refer to decreased or increased AUC as observed in drug-drug interaction 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 ABC, FTC, 3TC, ZDV

ABC, FTC, 3TC, ZDV: no clinically relevant interactions expected.

Interactions with ibalizumab

None

Comments

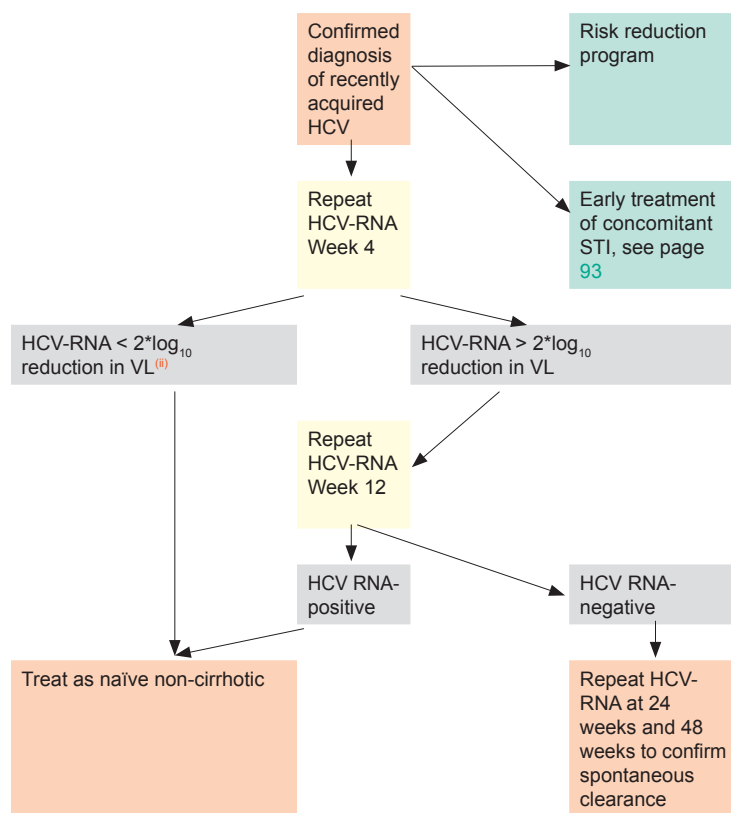
- a Monitoring of renal function recommended due to increase of tenofovir concentration if the regimen contains TDF.
- b Study details are with DRV/r qd. DRV bid has not been studied and should be used with caution as voxilaprevir concentrations may increase more than with DRV qd (this would be of further significance in cirrhotic patients). Monitoring of renal 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)

Management of Recently Acquired HCV Infection in PLWH

1. DAA based HCV treatment immediately after diagnosis is recommended in PLWH with ongoing risk behavior
2. If immediate treatment is not indicated, the algorithm below should be used



- i HCV-RNA < 2*log₁₀ reduction at week 4 is considered as early chronic HCV infection (eg: 2*log₁₀ reduction = reduction from 100,000 to 1000 IU/mL)
- ii See also [Recommendations on Recently acquired and early chronic hepatitis C in MSM from the European treatment network for HIV, hepatitis and global infectious diseases consensus panel](#)

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 2020)

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

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 (\geq 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, as part of ART, to PEG-IFN in order to reduce HBV-DNA load
6. Bulevirtide is a new treatment option for HDV which should also be considered if available.
7. PLWH should be referred to university centers for treatment and if possible enrolled in trials on new drugs active against HDV
8. Treatment efficacy should be monitored with HBV-DNA and HDV-RNA measurements, when available, and with follow-up of biochemical and liver fibrosis estimates
9. 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
10. 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)

11. 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-Barré, encephalitis or proteinuria
12. Screening should include anti-HEV IgG and IgM and HEV-RNA in blood and if possible in stool
13. 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 and COVID-19

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
- Overview of management of COVID-19 in PLWH

See online videos [Tuberculosis and HIV Co-infection-Part 1](#) and [Tuberculosis and HIV Co-infection-Part 2](#) from the EACS online course Management of HIV and Co-infections

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

	Initiation of ART	Comments
General recommendation	As soon as possible within 2 weeks after starting treatment for the opportunistic infection	
Tuberculosis	As soon as possible within two weeks of starting TB treatment, regardless of CD4 count	For details, see ART in TB/HIV Co-infection section, page 20
- TB meningitis	ART should be delayed for 4 weeks, but can be initiated within the first 2 weeks in PLWH with TB meningitis and CD4 < 50 (100) cells/μL	Corticosteroids are recommended as adjuvant treatment for TB meningitis
Cryptococcal meningitis	Defer initiation of ART for at least 4 weeks (WHO recommends a delay of 4-6 weeks and some specialists recommend a delay of 6-10 weeks in severe cryptococcal meningitis)	Corticosteroids are not recommended as adjuvant treatment

Immune Reconstitution Inflammatory Syndrome (IRIS)

Definition	
Paradoxical IRIS	Paradoxical worsening 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
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
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/ μ L. 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/ μ L, 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
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)
Life-threatening CNS-IRIS:	
TB-meningitis	Prednisone (1.5 mg/kg/day po for 2 weeks, then tapering)
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 <i>Pneumocystis jirovecii</i> Pneumonia (PcP) & <i>Toxoplasma gondii</i> 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)	400/80 mg qd po or 800/160 mg qd po or 800/160 mg x 3/week 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 <i>P. jirovecii</i>
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	
Positive cryptococcal serum antigen and CD4 count < 100 cells/μL	fluconazole	800 mg qd po for 2 weeks followed by 400 mg qd po for 8 weeks	Asymptomatic individual and cryptococcal meningitis, pulmonary or other site infection ruled out
CD4 count < 50 cells/μL			
Prophylaxis against Non-Tuberculous Mycobacteria (NTM) (<i>M. avium</i> complex, <i>M. genavense</i>, <i>M. kansasii</i>)			
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/ μ L, CD4 percentage < 14%, oral thrush or relevant concomitant immunosuppression, see Primary Prophylaxis of OIs Stop: if CD4 count > 100 cells/ μ L and HIV-VL undetectable over 3 months			
	Drug	Dose	Comments
Negative or positive serology for toxoplasmosis	TMP-SMX	400/80 mg qd po or 800/160 mg qd po or 800/160 mg x 3/week 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 <i>P. jirovecii</i>
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 > 100 cells/ μ L 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/ μ L AND dyspnoea / desaturation on exertion and cough AND radiology compatible with PcP AND no evidence for bacterial pneumonia AND response to PcP treatment. SARS-CoV-2 pneumonia can resemble PcP and should therefore be included in the differential diagnoses			
	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 <i>moderate to severe</i> 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	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 Some studies support the addition of caspofungin or other echinocandins to standard treatment in persons with moderate-severe PcP (can be considered, but not mandatory)
Alternative therapy for <i>mild to moderate</i> 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
	+ trimethoprim	5 mg/kg tid po	In case of rash: reduce dose of TMP (50%), use antihistamines

Secondary prophylaxis / Maintenance treatment			
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	400/80 mg qd po or 800/160 mg x 3/week 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 <i>P. jirovecii</i>
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	400/80 mg qd po or 800/160 mg qd po or 800/160 mg x 3/week 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. This is the standard in most clinical settings			
	Drug	Dose	Comments
Preferred therapy	pyrimethamine	Day 1: 200 mg qd po, then • If ≥ 60 kg: 75 mg qd po • If < 60 kg: 50 mg qd po	Monitor for myelotoxicity of pyrimethamine , mostly neutropenia
	+ sulfadiazine	• If ≥ 60 kg: 3000 mg bid po/iv • If < 60 kg: 2000 mg bid po/iv	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
	+ folinic acid	10-15 mg qd po	
Alternative therapy	pyrimethamine	Day 1: 200 mg qd po, then • If ≥ 60 kg: 75 mg qd po • If < 60 kg: 50 mg qd po	Monitor for myelotoxicity of pyrimethamine , mostly neutropenia Additional PcP prophylaxis is necessary
	+ clindamycin + folinic acid	600-900 mg qid po/iv 10-15 mg qd po	
	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 showed that an enhanced infection prophylaxis in severely immunosuppressed persons (CD4 < 50 cells/μL) including **TMP-SMX** 160/800 mg for 12 weeks, **isoniazid** 300 mg/day for 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 ₂ O: - 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 i) one week of amphotericin B + flucytosine followed by one week of fluconazole 1200 mg qd or ii) two weeks of fluconazole 1200 mg qd plus flucytosine may be acceptable induction regimens
	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 1 st 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 po 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			
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. <i>Aspergillus</i> 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. 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 trough 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	3 mg/kg qd iv	For 2 weeks or until clinical improvement
	Consolidation therapy: itraconazole	200 mg tid po for 3 days, then 200 mg bid po	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	5 mg/kg qd iv	For 4-6 weeks
	Consolidation therapy: itraconazole	200 mg bid - tid po	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			
Consider diagnosis in PLWH who live/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. <i>Aspergillus</i> galactomannan assays may be helpful to diagnose disseminated infections as cross reactivity occurs			
	Drug	Dose	Comments
Severe disseminated talaromycosis	Induction therapy: liposomal amphotericin B	3 mg/kg qd iv	For 2 weeks or until clinical improvement
	Consolidation therapy: itraconazole	200 mg tid po for 3 days, then 200 mg bid po	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/ μ L 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 PLWH section, page 91
Severe mucocutaneous lesions	aciclovir	5 mg/kg tid iv	After lesions begin to regress, switch to oral treatment for 21-28 days or longer, 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 If foscarnet is not available, cidofovir 5 mg/kg once weekly can be used. Topical cidofovir and foscarnet can be used for external lesions

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	500 mg tid po	
	or aciclovir	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 (switch to oral valganciclovir once tolerated)
	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	5 mg/kg bid iv	Treat until symptoms resolved and CMV replication in CSF has cleared (negative PCR DNA-CMV in CSF)
	foscarnet	90 mg/kg bid iv	Treatment is individualised according to clinical symptoms and response to treatment. Some guidelines recommend ganciclovir combined with foscarnet especially in relapse
Secondary Prophylaxis / Maintenance therapy: Cytomegalovirus (CMV) Retinitis			
Stop: Treated lesions inactive and 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 within 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	
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 (pembrolizumab , nivolumab), but no conclusive data, e.g., from clinical trials or broader clinical experience, are currently supporting their recommendation for clinical use. If used, participation in treatment protocols is strongly encouraged

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)			
<i>Mycobacterium avium</i> -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
<i>Mycobacterium kansasii</i>			
	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			
<i>Mycobacterium avium</i> (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 x 3/week po or 800/160 mg qd po or 1600/320 mg x 3/week 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 <i>Mycobacterium tuberculosis</i>			
Initial phase	rifampicin + isoniazid (+ pyridoxine) + pyrazinamide + ethambutol	Weight based	Initial phase for 2 months. Possibility to omit ethambutol , if <i>M. tuberculosis</i> is known to be fully drug sensitive. Preventive steroid therapy may be considered to avoid IRIS, see IRIS section
Alternative Initial phase	rifabutin + isoniazid (+ pyridoxine) + pyrazinamide + ethambutol	Weight based	Initial phase for 2 months. Possibility to omit ethambutol , if <i>M. tuberculosis</i> is known to be fully drug sensitive
Continuation phase	rifampicin/rifabutin + isoniazid (+ pyridoxine)	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

An alternative shorter regimen of **rifapentine**, **isoniazid**, **pyrazinamide** and **moxifloxacin** for 2 months, followed by **rifapentine**, **isoniazid** and **moxifloxacin** for 2 months can be used, if **rifapentine** is available

* Intermittent regimens (2 or 3 times per week) are contraindicated in PLWH. Missed doses can lead to treatment failure, relapse or acquired drug resistance
i For dose details, please see separate table [TB drug doses](#), page 138

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

XDR-TB 2021 update: Resistance to **isoniazid** AND **rifampicin** AND **fluoroquinolones** AND at least one additional **Group A** drug, see below

Rapid detection

Gene Xpert or similar technology has the advantage of rapid detection of rifampicin resistance. Drug susceptibility testing is important for optimising treatment

Treatment of resistant TB

Isoniazid-resistant TB

- **rifampicin/rifabutin + pyrazinamide + ethambutol + fluoroquinolone** for 6 months, [WHO 2020 recommendations](#)

Rifampicin-resistant (RR) and MDR/XDR-TB

- Treatment of MDR/XDR-TB is a specialist area. WHO has recently published new [Guidelines](#)

Shorter 9-12 months all oral regimen

Can be used in PLWH with confirmed RR/MDR-TB who have not been exposed to treatment with second-line TB drugs, used in this regimen, for more than 1 month, and in whom resistance to fluoroquinolones has been excluded.

Intensive phase: 4 months (can be extended to 6 months if positive sputum smear at the end of 4 months):

bedaquiline (used for 6 months) + **levo-/moxifloxacin + ethionamide + ethambutol + isoniazid** (high-dose) + **pyrazinamide + clofazimine**

Continuation phase: 5 months:

levo-/moxifloxacin + clofazimine + ethambutol + pyrazinamide

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

Longer TB treatment regimens

All three Group A drugs and at least one Group B drug should be included to ensure that treatment starts with at least four TB drugs likely to be effective, and that at least three agents are included for the rest of treatment if **bedaquiline** is stopped.

If only one or two Group A drugs are used, both Group B drugs are to be included.

If the regimen cannot be composed with drugs from Groups A and B alone, Group C drugs are added to complete it

Drug choices

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

Group A: Include all three drugs	<ul style="list-style-type: none"> • levofloxacin or moxifloxacin • bedaquiline • linezolid
Group B: Add one or both drugs	<ul style="list-style-type: none"> • clofazimine • cycloserine or terizidone
Group C: Add to complete the regimen and when drugs from Groups A and B cannot be used	<ul style="list-style-type: none"> • 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

For longer treatment regimens, a duration of 18-20 months is suggested, but should be individualized. For details, see [WHO Guidelines](#)

For XDR-TB, a 3-drug combination of **pretomanid**, **bedaquiline**, and **linezolid** during 6 months (3 additional months if culture positive at 4th month) showed promising results, 88% favourable outcomes at 2 years post treatment

Drug interactions with ART and MDR/XDR regimens

When treating RR/MDR/XDR-TB careful review of DDIs and potential toxicities is mandatory before initiating ART, see [Drug-drug Interactions between Anti-tuberculosis Drugs and ARVs](#)

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) 20 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) 20 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) 20 mg qd po	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

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, DOR, ETR, NVP, RPV, FTR, BIC, CAB, CAB/RPV LA, EVG/c. see Drug-drug Interactions between Anti-tuberculosis Drugs and ARVs and 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 30-45 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 30-45 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-aminosalicylic acid	4000 mg bid	In weight > 70 kg can be increased to 4000-6000 mg bid Caution: gastrointestinal toxicity
Pretomanid	200 mg qd	Use with Bedaquiline and Linezolid for 26 weeks Monitor ECG in respect of QT prolongation Peripheral neuropathy is common adverse effect

Management of COVID-19 in PLWH

Introduction

Epidemiology of COVID-19 among PLWH

- SARS-CoV-2 infection incidence in PLWH seems to be similar to that reported in the general population

Risk factors for severe COVID-19 and outcomes among PLWH

- No clear evidence for more severe disease course in PLWH, compared to the general population. Among hospitalized COVID-19 patients, most studies reported a younger age of PLWH vs. HIV-negative patients, but higher rates of co-morbidities among PLWH. Severe COVID-19 has also been described in patients with concomitant TB and/or PCP. PLWH with CD4 count < 200 cells/μL and co-morbidities might have poorer outcomes, however the evidence is scarce

HIV care during COVID-19 epidemic

- It is important to ensure continuum of HIV-care during lock-down and isolation due to COVID-19
- Switching ARVs is not recommended, and may occur only in critical situations, e.g. virological failure
- It is recommended to develop local country-specific strategies to prevent disruption in HIV care, including teleconsultation and tele-pharmacy, and ensure continuous ART supply
- Position of EACS on SARS-CoV-2 risk and prevention in PLWH can be consulted [here](#)

Management of COVID-19 in PLWH

Diagnostic approach:

- The same approach, as for general population should be applied, according to the national or international recommendations (RT-PCR, SARS-CoV-2 antibodies and antigen detection). For details, see [WHO recommendations](#)

Differential diagnosis:

- For PLWH, particularly for those with poor immune status, other respiratory diseases (e.g. PCP, and TB) should be considered as differential diagnosis. Consider BAL to obtain sufficient material for microbiological investigation

Treatment approach:

- Treatment of COVID-19 in PLWH should be the same as for general population. As treatment guidelines for COVID-19 might vary between countries, please use your national guidelines. In absence of those, please follow international recommendations: [NIH](#); [WHO](#)
- Check for drug-drug interactions between COVID-19 treatments and ARV drugs, see [Drug-drug Interactions and Other Prescribing Issues in PLWH](#), [Drug-drug Interactions between COVID-19 Therapies and ARVs](#), [Drug-drug Interactions between Corticosteroids and ARVs](#)
- Isolation precautions should be the same as for general population, although longer periods of viral shedding have been described for immunocompromised patients. Follow local recommendations

Management of HIV infection while on treatment for COVID-19

- ART should neither be stopped, nor modified, unless strictly necessary (no proven activity of any ARV drugs against SARS-CoV-2, studies are ongoing)
- For persons who are unable to swallow their usual ART (such as those on mechanical ventilation or ECMO therapy), the ART regimen may be adapted. see [Administration of ARVs in PLWH with Swallowing Difficulties](#)
- CD4 count may decrease during COVID-19; in these cases, consider appropriate OI prophylaxis, see [Primary Prophylaxis of OIs According to stage of Immunodeficiency](#)
- HIV-RNA blips have been described during COVID-19, their clinical relevance is currently unknown
- In case of lockdowns, ARVs provision should be assured and tele-pharmacy can be considered; provide ART supply for at least 3 months at a time
- New development or worsening of mental health problems (anxiety, depression, increased loneliness and stigma) have been very common during pandemic waves and following social distancing and lockdowns; psychological and social support should be actively offered to PLWH
- Telemedicine and phone visits can be used for chronically stable persons, not requiring ART or co-medications changes. Retain in-person visits for persons complaining of acute problems, adverse effects due to ART, STIs or other complaints/ co-morbidities requiring clinical evaluation
- Co-morbidities and co-infections should be managed as indicated in specific sections of the Guidelines, see [Prevention and Management of Co-morbidities in PLWH](#), [Viral hepatitis co-infections](#), [Opportunistic infections](#)
- Accessibility to specialist consultations should be evaluated and well-being (diet/ exercise) recommendations should be intensified

Management of long-term symptoms and sequelae of COVID-19

- A substantial proportion of COVID-19 patients may evolve with persistent symptoms or develop sequelae (respiratory or in any other involved organ)
- These conditions should be specifically addressed and evaluated; refer to the appropriate specialist consultations following local/national guidelines for persistent COVID-19 sequelae
- Consider drug-drug interactions if steroids or anticoagulants or other drugs are indicated for COVID-19 complications (organizing pneumonia, pulmonary embolism), see [Drug-drug Interactions and Other Prescribing Issues in PLWH](#), [Drug-drug Interactions between COVID-19 Therapies and ARVs](#), [Drug-drug Interactions between Corticosteroids and ARVs](#)

Prophylaxis of COVID-19

SARS-CoV-2 vaccines:

- Numerous COVID-19 vaccine candidates are in development and several have been approved in Europe and other countries worldwide
- There are multiple vaccine platforms including mRNA vaccines, adenovirus-vectored (Ad)-DNA vaccines and protein (subunit) vaccines
- Overall efficacy of different vaccines varies, although their direct comparison is lacking, and data for PLWH is limited
- It is recommended for all PLWH to be vaccinated against SARS-CoV-2. Priority should be given to those with immunosuppression (CD4 count < 350 cells/μL), if access to vaccines is limited. There is no data to recommend a specific vaccine and the choice depends on the availability in individual countries. As with other vaccines, response in PLWH could be poorer compared to the general population (particularly in those with low CD4 count and high HIV-VL); however, there have so far been no safety concerns with SARS-CoV-2 vaccines in PLWH and vaccination schedule is the same as for the general population. Serological testing before vaccination is not required
- Other vaccines (particularly *S. pneumoniae* and influenza) should be given as scheduled, but at least 1 week before or after SARS-CoV-2 vaccines

Monoclonal antibodies:

- Passive immunization with antibodies against the SARS-CoV-2 spike protein is currently being considered as SARS-CoV-2 infection pre-exposure prophylaxis and to prevent progression of an initial SARS-CoV-2 infection. The approach may be useful and appropriate for immunocompromised PLWH but currently there are no available recommendations
- Links to an overview of available vaccines and information regarding SARS-CoV-2 vaccination in PLWH: [WHO](#) [BHIVA](#) [EACS](#)

Part VII Paediatric HIV Treatment

Initiation of ART in Children and Adolescents Living with HIV

- We recommend the initiation of ART in all children and adolescents diagnosed with HIV irrespective of age, clinical stage, CD4 count and VL
- We emphasise the need for urgent diagnosis for infants born to women living with HIV and prompt treatment of infants diagnosed with HIV infection
- We endorse the “U=U” campaign (undetectable (defined as VL < 200 copies/mL for > 6 months) = untransmissible) for sexual transmission of HIV, which is particularly relevant to sexually active adolescents and is potentially a motivational message to enhance adherence and prevent onward HIV transmission

Initial Combination Regimen for ART-naïve Children and Adolescents Living with HIV, **Table 1**

- Where available, baseline resistance testing should be performed
- All first line regimens currently include 2 NRTIs together with a drug from a different class (third agent)
- DTG plus 2NRTI combination is the preferred option in all children over 4 weeks of age and 3 Kg
- Evidence for superiority of DTG compared to NNRTI or PI/b has been demonstrated by the ODYSSEY trial
- Whilst “preferred options” are recommended, “alternative options” are acceptable and remain important choices in settings where ART availability is limited or in individuals at particular risk of specific toxicity or DDIs
- Whenever possible first line 3rd agents with high barrier to resistance have been selected in view of potential difficulties with adherence in children and adolescents
- Potential transmitted resistance and resistance resulting from maternal or infant ART exposure during failed prevention of vertical transmission should also be considered when choosing a regimen
- When NVP has been used in pregnancy non-NNRTI-based ART, including RAL from birth, LPV/r from 2 weeks and DTG from 4 weeks are preferred

Additional Specific Paediatric Considerations

- **It should be noted that these Guidelines occasionally include recommendations for use of ARVs outside their European licence**
- Local policy for the use of unlicensed medication in children and adolescents should be followed
- Apart from decisions on standard first line in high prevalence setting, options should ideally be discussed within a multidisciplinary team (MDT)/paediatric virtual clinic (PVC)
- If local MDT or PVC are unavailable, an international PVC is accessible by contacting the [Guideline Team](#).
- Adherence is key to achieving and maintaining viral suppression and adherence support and assessment should be provided at/prior to initiation of ART and at all subsequent visits
- The use of peer mentors, where available, is strongly recommended
- Although age cut offs are used in [Table 1](#) it should be noted that weight as well as age restrictions are also included in the licensing of ARVs in children
- Detailed guidance on paediatric dosing is available from the Penta website, <https://penta-id.org/hiv/treatment-guidelines/>
- Drug formulations that are useful for paediatric dosing and administration are summarised in [Table 2](#)

Table 1. Preferred and Alternative First Line Options in Children and Adolescents Living with HIV

Age	Backbone		3 rd Agent (in alphabetical order)	
	Preferred	Alternative	Preferred	Alternative
0 - 4 weeks	ZDV ⁽ⁱ⁾ + 3TC	-	LPV/r ^(ii, iii) NVP ⁽ⁱⁱⁱ⁾ RAL ⁽ⁱⁱⁱ⁾	-
4 weeks - 3 years	ABC ^(iv) + 3TC ^(v)	ZDV ⁽ⁱ⁾ + 3TC ^(vi) TDF ^(vii) + 3TC	DTG ^(viii)	LPV/r NVP RAL
3 - 6 years	ABC ^(iv) + 3TC ^(v)	TDF + XTC ^(ix) ZDV + XTC ^(ix)	DTG	DRV/r EFV LPV/r NVP RAL
6 - 12 years	ABC ^(iv) + 3TC ^(v) TAF ^(x) + XTC ^(ix)	TDF + XTC ^(ix)	DTG	DRV/r EFV EVG/c RAL
> 12 years	ABC ^(iv) + 3TC ^(v) TAF ^(x) + XTC ^(ix)	TDF + XTC ^(ix)	BIC ^(xi) DTG	DRV/b EFV ^(xii) RAL ^(xii) RPV ^(xii)

Notes:

- i In view of potential long-term toxicity, any child on ZDV should be switched to ABC or TAF (preferred) or TDF (alternative) once increase in age and/or weight makes licensed formulations available
- ii LPV/r should not be administered to neonates before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days although it may be considered if there is a risk of transmitted NVP resistance and INSTI in appropriate formulations are unavailable. In these circumstances the neonate should be monitored closely for LPV/r related toxicity
- iii If starting a non-DTG 3rd agent in the neonatal period it is acceptable to continue this option. However, when over 4 weeks and 3 kg, a switch to DTG is recommended if and when an appropriate formulation is available
- iv ABC should NOT be prescribed to HLA-B*57:01 positive individuals (where screening is available). ABC is not licensed under 3 months of age but dosing data for younger children are available from the [WHO](#) and [DHHS](#)
- v At HIV-VL > 100,000 copies/mL ABC + 3TC should not be combined with EFV as 3rd agent
- vi If using NVP as a 3rd agent in children aged 2 weeks to 3 years, consider using 3 NRTI backbone (ABC + ZDV + 3TC) until VL consistently < 50 copies/mL
- vii TDF is only licensed from 2 years of age
- viii DTG is licensed from 4 weeks and 3 kg
- ix XTC indicates circumstances when FTC or 3TC may be used interchangeably
- x TAF is only licensed in Europe for treatment of HIV in combination with FTC from 12 years of age and 35 kg in TAF/FTC and from 6 years of age and 25 kg in TAF/FTC/EVG/c
- xi BIC is a preferred first line option in adult PLWH. At time of writing it is not licensed under 18 years of age but may be considered in those aged 12-18 years following discussion at MDT/PVC
- xii Due to predicted poor adherence in adolescence, PI/b are favoured as alternative first line 3rd agent options due their high barrier to resistance

Table 2. Antiretroviral Formulations Useful for Paediatric and Adolescent Dosing and Administration

NRTI	
ABC	tablet (300 mg) solution (20 mg/mL)
FTC	capsule (200 mg) solution (10 mg/mL)
3TC	tablet (300, 150 mg) solution (10 mg/mL)
TDF	tablet (245, 204, 163, 123 mg) granules (33 mg/g)
ZDV	capsule (250 mg, 100 mg) solution (10 mg/mL) iv infusion: 10 mg/mL (20 mL/vial)
TAF/FTC	tablet (25/200 mg and 10/200 mg)
TDF/FTC	tablet (300/200 mg)
ABC/3TC	tablet (600/300 mg)
ZDV/3TC	tablet (300/150 mg)
NNRTI	
EFV	tablet (600 mg) capsule (200, 100, 50 mg)
NVP	tablet (200 mg) prolonged release tablet (400, 100 mg) suspension (10 mg/mL)
RPV	tablet (25 mg)
TDF/FTC/EFV	tablet (300/200/600 mg)
TAF/FTC/RPV	tablet (25/200/25 mg)
TDF/FTC/RPV	tablet (300/200/25 mg)
PI	
DRV	tablet (800, 600, 400, 150, 75 mg) solution (100 mg/mL)
DRV/c	tablet (800/150 mg)
LPV/r	tablet (200/50 mg and 100/25 mg) solution (80/20 mg/mL)
RTV	tablet (100 mg) powder for oral suspension (100 mg sachet)
TAF/FTC/DRV/c	tablet (10/200/800/150 mg)
INSTI	
DTG	tablet (50, 25, 10 mg) dispersible tablets (5 mg)
RAL	tablet (600 mg, 400 mg) chewable tablets (100, 25 mg) granules for oral suspension (100 mg)
ABC/3TC/DTG	tablet (600/300/50 mg)
TAF/FTC/BIC	tablet (25/200/50 mg)
TAF/FTC/EVG/c	tablet (10/200/150/150 mg)
TDF/FTC/EVG/c	tablet (300/200/150/150 mg)

Switch Strategies for virologically suppressed children and adolescents

- The general indications for switching when virologically suppressed are as for adult PLWH, see page 16 but with some additional considerations for children and adolescents relating to increasing age and weight, licensing, formulation availability, vulnerability to toxicity and predicted adherence issues in adolescence
- As children age and grow on suppressive ART, consideration should be given to simplification to robust once daily low pill burden regimens with optimal toxicity profiles and efficacy data. For example, in children aged less than 3 years commenced on liquid LPV/r, consider switching to once daily regimens when pill swallowing achieved or dispersible DTG is available
- If “preferred” options become available for a child as they get older then a switch to this option can be considered. However, if they are fully virologically suppressed on their current regimen with no toxicity or problems with convenience or adherence it is reasonable to remain on an alternative regimen
- Children and their carers should be involved in discussing the relative risk/benefit of switching when well and stable on an effective regimen
- Dual therapy is not recommended in first line or for simplification but can be considered on a case by case basis in adherent children and adolescents living with HIV
- Simplification to monotherapy and treatment interruptions are not recommended and are discouraged

Special Populations

- Seek specialist expert advice e.g. through an MDT/PVC. If local MDT or PVC are unavailable, an international PVC is accessible by contacting the [Guideline Team](#)
- **Adolescent girls of child bearing potential:** First line options for adolescents of child bearing potential share the same considerations as discussed elsewhere in the EACS Guideline, see page 18, and should bear in mind contraceptive choices and DDIs with ARVs, see page 38, or whether the young person is trying to conceive
- **HBV co-infection:** requires an ART regimen that includes TAF or TDF in the NRTI backbone typically with 3TC or FTC, for recommendation in adults with HBV/HIV co-infection see pages 115-116
- **HCV co-infection:** DAAs are licensed and available in paediatric formulations down to 3 years of age. Seek specialist advice for consideration of curative HCV therapy for children and adolescents with HCV co-infection, for recommendation in adults with HCV/HIV co-infection see pages 115 and 117-120
- **TB co-infection:** From 3 years of age, EFV, DTG bid or double dose RAL can all be considered as 3rd agents for children when co-administered with rifampicin. Under 3 years of age, EFV is not recommended, access to paediatric INSTI formulations and data on INSTI dosing are limited, super boosted LPV/r can be also be considered. Specialist advice should be sought with therapeutic drug monitoring recommended where available. For treatment recommendation in adults with TB/HIV co-infection see page 20

Adherence, Virological Failure and Second Line ART

- Virological failure (defined as 2 consecutive VL >200 copies/mL at least 3 months apart with adherence support) is almost always due to suboptimal ART adherence, and always requires adherence assessment and support
- Resistance testing is recommended where possible. Choice of second line therapy is dependent both on ALL previous ART exposure and documented HIV resistance mutations at all times tested
- Second line options should ideally be discussed at a PVC/MDT including a virologist, especially if resistance has been found

Choosing a 3rd agent

Failed on first line NNRTI

- Switch to INSTI with a high barrier to resistance (i.e. DTG or BIC) or PI/b with optimised 2 NRTI
- If high VL and extensive resistance impacting on NRTIs consider using regimen with at least 2 fully active drugs (e.g. INSTI with PI/b and 2 NRTI)

Failed on first line PI/b

- If no significant resistance to PIs, consider continuation of PI/b (consider switch to DRV/b) with optimised 2 NRTI or PI/b based STR to reduce pill burden
- Consider switch to INSTI with high barrier to resistance (i.e. DTG or BIC)
- Consider INSTI or PI based single tablet FDC with 2 NRTI to reduce pill burden (e.g. DRV/c (only in the absence of significant PI resistance), DTG or BIC where/when licensing allows)

Failed on first line INSTI

- If resistance testing demonstrates no INSTI resistance, consider switch to/continue INSTI with high barrier to resistance with optimised 2 NRTI
- Switch to PI/b with optimised 2 NRTI is also an option especially if INSTI resistance is demonstrated
- If INSTI resistance and substantial NRTI resistance, consider initial therapy with DTG (bid) + PI/b + optimised 2 NRTI ideally discussed at MDT/PVC

Optimising NRTI backbone

- If resistance testing available use results to guide choice of 2 NRTI
- If NRTI resistance is demonstrated, XTC with either TAF or TDF are the preferred options, used according to license. If TAF or TDF are not available or contraindicated then ZDV can be considered but alternatives to ZDV should be regularly assessed in order to remove from the regimen as soon as possible
- If resistance testing not available, switch to (or continue) TDF or TAF (or ZDV as per above) with 3TC or FTC (see below rationale)
- TDF or TAF are preferred in second line in combination with 3TC or FTC (even if failing on TDF or TAF)
- It is well established that M184V causes high level resistance to both FTC and 3TC. However ongoing use of either FTC or 3TC is still recommended in the presence of this mutation (especially if it minimises pill burden) as it is associated with an increased susceptibility to tenofovir and ZDV

Virological Failure on Second Line Combination

- Subsequent virological failure on second line therapy requires further assessment of adherence and resistance testing, if available
- TDM may be useful if concerned about subtherapeutic drug levels
- Choice of subsequent regimens should be made through an MDT/PVC
- ART should continue despite virological failure (ideally with a robust INSTI or PI/b based regimen including 3TC or FTC) to maintain CD4 count whilst additional adherence support is provided

References

Video links

EACS Guidelines	Video lectures	Link to video lecture
Primary HIV Infection	When to Start ART Part 1	https://region-hovedstaden-ekstern.23video.com/secret/69954554/c401f8cf-3bea2c6bb851a0886f523745
	When to Start ART Part 2	https://region-hovedstaden-ekstern.23video.com/secret/69954596/4dbab429a86e-ebc401f4c7cb6b66313f
	What ART to Start Part 1	https://region-hovedstaden-ekstern.23video.com/secret/68809298/066ed5598aa3f94768fc5fba5b33ad2c
	What ART to Start Part 2	https://region-hovedstaden-ekstern.23video.com/secret/68809642/82861519cd6bdcbec65c49924b013b92
Diagnostic Procedures for HCV in Persons with HCV/HIV Co-infection	Hepatitis C and HIV Co-infection Part 1	https://region-hovedstaden-ekstern.23video.com/secret/57391741/33aeca1d4a9baa8b-9f7f408890f19f1f
Diagnosis and Treatment of TB in PLWH	Tuberculosis and HIV Co-infection Part 1	https://region-hovedstaden-ekstern.23video.com/secret/69954460/7427cd7a76ac33897ed905a5899278ba
	Tuberculosis and HIV Co-infection Part 2	https://region-hovedstaden-ekstern.23video.com/secret/69954502/e94125a138e-7644680c22a589074a371

References to All Sections

Part I Assessment of PLWH at Initial & Subsequent Visits

Please see references for Part IV

Part II ARV Treatment of PLWH

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New WHO guidance including updated recommendation to initiate ART as soon as possible after initiating TB treatment when there is TB-HIV co-infection, irrespective of CD4 count (except if signs/symptoms of TB meningitis are present)

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

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Part VI Opportunistic Infections and COVID-19

Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions *J Antimicrob Chemother*. 2006; 57:167-70

The article introduces criteria for IRIS diagnosis and definitions for paradoxical and unmasking IRIS

Meintjes G, Stek C, Blumenthal L, et al.; PredART Trial Team. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. *N Engl J Med*. 2018; 379:1915-1925

Randomized, double-blind, placebo-controlled trial documenting advantage of Prednisone use to prevent TB-associated IRIS after ART initiation in PLWH

Atkinson A, Miro JM, Mocroft A, et al. No need for secondary *Pneumocystis jirovecii* pneumonia prophylaxis in adult people living with HIV from Europe on ART with suppressed viraemia and a CD4 cell count greater than 100 cells/ μ L. *J Int AIDS Soc*. 2021 Jun;24(6):e25726. doi: 10.1002/jia2.25726

The study provides rationale for discontinuation of secondary PCP prophylaxis at lower, than previously recommended CD4 count (i.e. > 100 cells/ μ L)

Hakim J, Musiime V, Szubert AJ et al for the REALITY Trial Team. Enhanced Prophylaxis plus Antiretroviral Therapy for Advanced HIV Infection in Africa. *N Engl J Med*. 2017 Jul 20;377(3):233-245

The study provides rationale for use of enhanced antimicrobial prophylaxis (TMP-SMX, isoniazid, fluconazole, azithromycin and albendazole) combined with ART in PLWH and advanced immunosuppression in order to reduce mortality without compromising viral suppression or increasing toxic effects

Molloy SF, Kanyama C, Heyderman RS, et al. Antifungal Combinations for Treatment of Cryptococcal Meningitis in Africa. *N Engl J Med*. 2018 Mar 15;378(11):1004-1017

Randomized trial documenting noninferiority of alternative induction phase regimen for treatment of Cryptococcal meningitis, i.e. high dose fluconazole plus flucytosine for 2 weeks or 1 week of amphotericin B with either fluconazole or flucytosine vs. standard regimen of 2 weeks amphotericin B with either fluconazole or flucytosine. The study results are beneficial for resource-limited settings, where amphotericin B availability is limited

Ferretti F, Bestetti A, Yiannoutsos CT, et al. Diagnostic and prognostic value of JC virus DNA in plasma in Progressive Multifocal Leukoencephalopathy. *Clin Infect Dis*. 2018 Jan 15. doi: 10.1093/cid/ciy030

A retrospective study analyzing JCV-DNA in plasma prior to PML onset. Study results provide evidence for using JCV-DNA in plasma as a marker for PML diagnosis and disease progression, especially if CSF is not available

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Dorman SE, Nahid P, Kurbatova EV, et al. Four-Month Rifapentine Regimens with or without Moxifloxacin for Tuberculosis. *N Engl J Med*. 2021 May 6; 384(18):1705-1718. doi: 10.1056/NEJMoa2033400

Open-label, phase 3, randomized, controlled trial involving persons with newly diagnosed pulmonary TB and documenting non-inferior efficacy of a 4-month rifapentine-based regimen containing moxifloxacin to the standard 6-month regimen in the treatment of TB

Gopalan N, Santhanakrishnan RK, Palaniappan AN, et al. Daily vs Intermittent Antituberculosis Therapy for Pulmonary Tuberculosis in Patients With HIV: A Randomized Clinical Trial. *JAMA Intern Med*. 2018. Apr 1;178(4):485-493

Open-label randomized clinical trial comparing daily, part-daily and intermittent antituberculosis therapy in PLWH. In this study, daily anti-TB regimen proved superior to a thrice-weekly regimen in terms of efficacy and emergence of rifampicin resistance in PLWH

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. <https://www.who.int/publications/item/9789240007048>

Extended guidelines, providing up-to-date recommendations for treatment of drug-resistant TB, explains rationale and evidence behind current treatment principles

F Conradie, AH Diacon, N Ngubane, et al. Nix-TB Trial Team. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *N Engl J Med*. 2020 Mar 5;382(10):893-902. doi: 10.1056/NEJMoa1901814

An open-label, single-group study evaluated the safety, adverse effect, efficacy, and pharmacokinetics of a regimen with bedaquiline, linezolid and pretomanid in persons with XDR- and MDR-TB. The study documents a favorable outcome after 6 months of treatment in app. 90% of patients

Sterling TR, Njie G, Zenner D, et al. Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020. *MMWR Recomm Rep* 2020;69(No. RR-1):1–11. DOI: <http://dx.doi.org/10.15585/mmwr.rr6901a1>

Swindells S, Ramchandani R, Gupta A, et al. BRIEF TB/A5279 Study Team. One Month of Rifapentine plus Isoniazid to Prevent HIV-Related Tuberculosis *N Engl J Med*. 2019 Mar 14;380(11):1001-1011. doi: 10.1056/NEJMoa1806808

A randomized, open-label, phase 3 study documenting that 1-month regimen of rifapentine plus isoniazid was noninferior to 9 months of isoniazid alone for preventing TB in PLWH

BHIVA guidelines for the management of tuberculosis in adults living with HIV 2018 (2021 interim update). <https://www.bhiva.org/TB-guidelines>

Ambrosioni J, Blanco JL, Reyes-Urueña JM, et al. Overview of SARS-CoV-2 infection in adults living with HIV. *Lancet HIV*. 2021 May;8(5):e294-e305. doi: 10.1016/S2352-3018(21)00070-9

The article provides an extensive overview of up-to-date evidence regarding SARS-CoV-2 infection in PLWH, including risk factors, pathogenesis, clinical manifestation, management, prognostic factors and outcomes

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Part VII Paediatric HIV Treatment

PENTA Guidelines <https://penta-id.org/hiv/treatment-guidelines>

WHO Guidelines https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf?ua=1

Paediatric use of ABC <https://clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/abacavir>