EACS
European
AIDS
Clinical
Society

12

GUIDELINES

Version 12.0
October 2023

English

Table of Contents

Part V

Part VI

Part VII

References

Introduction to the EACS Guidelines 2023

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 pdf version continues 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. Unless mentioned otherwise, they always refer to the specific management of people with HIV.

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 2023 version of the Guidelines includes updates of all existing sections. The most essential changes are listed in the Summary of changes from v11.1 to v12.0

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do not provide formal grades of evidence, panels make decisions by consensus or by vote when necessary and we do not publish results of the votes or discrepancies if any occur.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. A short summary of the key findings of highlighted references is included.

Please reference the EACS Guidelines as follows: EACS Guidelines version 12.0, October 2023.
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 2023 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 panelists, 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!

Jürgen Rockstroh and Juan Ambrosioni

October 2023

Summary of Changes from v11.1 to v12.0

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 www.eacsociety.org/home/covid-19-and-hiv.html

ART section

- Change the order of priority of the third drug associated with 2 NRTIs when starting ART: preferably a second generation INSTI or alternatively a PI/b
- Recommendations for Initiation of ART in persons with Chronic Infection without Prior ART Exposure, page 12
  - Threshold of HIV VL lowered to < 200 cp/ml in a possible exception to immediate start of ART
- Primary HIV Infection, page 15
  - Specify that the treatment should be a 3DR and that a 2DR is not recommended
- Switch Strategies for Virologically Suppressed Persons, page 16
  - New paragraph on injectable CAB/RPV
- Virological Failure, page 17
  - Add lenacapavir to the therapeutic spectrum
- Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy, page 18
  - Change phrasing about breastfeeding which is now not recommended
  - ABC moved out from recommended regimens to alternative regimens
  - Deletion of the foot notes rising concerns about DTG and TAF during pregnancy
- ART in TB/HIV Co-infection, page 20
  - Add TAF in antiretroviral regimens in TB/HIV co-infection
- PEP, page 22
  - Lighten recommendation of PEP in case of receptive oral sex with ejaculation and not on PrEP or low PrEP adherence
- PrEP, page 23
  - Need of a fourth generation HIV test before starting PrEP
  - Recommendation of vaccination for all persons under PrEP
  - Suggestions to propose doxycycline PEP on a case by case basis
  - New paragraph on the different drugs available for PrEP
  - Precision about population with the highest risk of adverse renal outcomes under PrEP
  - New paragraph on PrEP to PEP transition with specification of what is defined as low adherence

DDI section

- The section on long-acting cabotegravir and rilpivirine has been expanded to indicate factors that can potentially impact the drug release from the depot and factors that can increase the risk of virologic failure. The section includes also dosing recommendations in case of missed injections, page 26
- The capsid inhibitor lenacapavir administered subcutaneously every 6 months in combination with other antiretrovirals has been added to all DDI tables
- A novel table has been added for DDI between antiretrovirals and anti-infective drugs for opportunistic infections and sexually transmitted infections, page 35
- All DDI tables have been updated to include changes implemented in the HIV drug interaction website (University of Liverpool) in the past year
- A novel resource has been added for drug classes to deprescribe in older person with HIV in presence of certain conditions, page 60

Co-morbidity section

- A new section on the use of Patient Reported Outcome Measures has been added, page 115
- A new section on alcohol use has been added, page 63
- Updated guidance on the management of cognitive and central nervous system symptoms in persons with HIV
- Updated guidance to the travel section
- Updated guidance on management of sexual and reproductive health
- Updated guidance on management of type 2 diabetes mellitus
- Updates to cancer screening including anal cancer are included
- Updates on deprescribing in persons with HIV are included
- Updated guidance on managing chronic lung disease

Viral Hepatitis Co-infections section

- Screening for complications
  - HCC screening recommendations have been updated with special regard to validation of PAGE-B-score in persons with HIV
  - For Hepatitis B vaccination the use of the more immunogenic vaccination Heplisav B should be considered where available with the aim to potentially reach better responses

- Treatment and Monitoring of Persons with HBV/HIV Co-infection
  - Caution is warranted when switching from a TDF/TAF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, and persons with HIV with isolated Anti-HBc concerning viral breakthrough or relapse of HBV. Transaminases and HBV-DNA should be checked regularly

- Management of Recently Acquired HCV Infection
  - The algorithm for the management of acute HCV-infection has been removed as current guidelines recommend immediate treatment of all persons with HIV with recently acquired HCV

Opportunistic Infections and COVID-19 section

- A section on clinical features and treatment of Mpox has been added, page 152
- COVID-19 section has been extensively modified according to the updated evidences from literature, page 151
- TMP-SMX has been moved from “alterative” to additional “preferred” treatment in toxoplasmic encephalitis. In addition, considerations on diagnostic value of toxoplasma PCR in CSF and corticosteroids use in the context of large lesions with mass effect have been added
- WHO-recommended single-dose liposomal amphotericin B+fluconazole regimen has been added as additional “preferred” regimen in resource limited settings for the treatment of cryptococcal meningitis. In addition, recommendations on primary prophylaxis have been reformulated
- Liposomal amphotericin B+miltefosine has been added as alterative regimen for the treatment of visceral leishmaniasis
- Recommendations on the ART initiation in the context of TB and cryptococcal meningitis have been reformulated, page 134
- Hyperlinks to the table describing drug-drug interactions between selected anti-infective agents and ART have been added
- A comment on desensitization in the context of non-severe TMP-SMX allergy has been added
- Minor stylistic changes and rephrasing were made throughout the text

Paediatric HIV Treatment section

- Updated table 1 “Preferred and Alternative First Line Options in Children and Adolescents” to include the most recent treatment options for children
- Removed table 2: Antiretroviral Formulations Useful for Paediatric and Adolescent Dosing and Administration due to redundancy
- Added section on “General principles of postnatal prophylaxis and infant feeding”, page 157
- Minor edits in the other sections

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

Imprint

Publisher	European AIDS Clinical Society (EACS)
Panel Chairs	Jean-Michel Molina, Giovanni Guaraldi, Alan Winston, Christoph Boesecke, Paola Cinque, Alasdair Bamford
Chair and Coordinator	Jürgen Rockstroh and Juan Ambrosioni
Graphic Design	Notice Kommunikation & Design, Zurich
Layout	SoPink, Brussels
Version, Date	12.0, October 2023
Copyright	EACS, 2023

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 six EACS panels.

Guidelines Chair: Jürgen Rockstroh	**Bonn, Germany**
Guidelines Coordinator: Juan Ambrosioni	**Barcelona, Spain**

HIV Treatment

Chair: Jean-Michel Molina	**Paris, France**
Vice-Chair: Alexandra Calmy	**Geneva, Switzerland**
Young Scientist: Laura Levi	**Paris, France**
Juan Ambrosioni	Barcelona, Spain
Andrea Antinori	Rome, Italy
Jose Ramón Arribas	Madrid, Spain
Margherita Bracchi	London, United Kingdom
Nikos Dedes	Athens, Greece
Rosa de Miguel Buckley	Madrid, Spain
Christian Hoffmann	Hamburg, Germany
Christine Katlama	Paris, France
Justyna Kowalska	Warsaw, Poland
Inga Latysheva	Saint Petersburg, Russia
Jens D. Lundgren	Copenhagen, Denmark
Sheena McCormack	London, United Kingdom
Cristina Mussini	Modena, Italy
Anton Pozniak	London, United Kingdom
Federico Pulido	Madrid, Spain
François Raffi	Nantes, France
Marc van der Valk	Amsterdam, The Netherlands
Marta Vasylyev	Lviv, Ukraine

Drug-drug Interactions

Chair: Giovanni Guaraldi	**Modena, Italy**
Vice-Chair: Catia Marzolini	**Basel/Lausanne, Switzerland**
Sara Gibbons	Liverpool, United Kingdom
Françoise Livio	Lausanne, Switzerland

Co-morbidities

Chair: Alan Winston	**London, United Kingdom**
Vice-Chair: Esteban Martínez	**Barcelona, Spain**
Young scientist: Jasmini Alagaratnam	**London, United Kingdom**
Georg Behrens	Hannover, Germany
Jordi Blanch	Barcelona, Spain
Franck Boccara	Paris, France
Mark Bower	London, United Kingdom
Fatima Brañas	Madrid, Spain
Paola Cinque	Milan, Italy
Juliet Compston	Cambridge, United Kingdom
Aoife Cotter	Dublin, Ireland
Alessia Dalla Pria	London, United Kingdom
Susanne Dam Nielsen	Copenhagen, Denmark
Leonardo M. Fabbri	Modena, Italy
Magnus Gisslen	Gothenburg, Sweden
Giovanni Guaraldi	Modena, Italy
Déborah Konopnicki	Brussels, Belgium
Justyna Kowalska	Warsaw, Poland
Patrick Mallon	Dublin, Ireland
Catia Marzolini	Basel/Lausanne, Switzerland
Luis Mendao	Lisbon, Portugal
José M. Miró	Barcelona, Spain
Eugenia Negredo	Barcelona, Spain
Lene Ryom	Copenhagen, Denmark
Giada Sebastiani	Montreal, Canada
Marc van der Valk	Amsterdam, The Netherlands

Viral Hepatitis Co-infections

Chair: Christoph Boesecke	**Bonn, Germany**
Vice-Chair: Juan Berenguer	**Madrid, Spain**
Young scientist: Kathrin van Bremen	**Bonn, Germany**
Charles Béguelin	Bern, Switzerland
Sanjay Bhagani	London, United Kingdom
Raffaele Bruno	Pavia, Italy
Svilen Konov	London, United Kingdom
Karine Lacombe	Paris, France
Stefan Mauss	Düsseldorf, Germany
Luís Mendão	Lisbon, Portugal
Lars Peters	Copenhagen, Denmark
Massimo Puoti	Milan, Italy
Andri Rauch	Bern, Switzerland
Jürgen K. Rockstroh	Bonn, Germany

Opportunistic Infections and COVID-19

Chair: Paola Cinque	**Milan, Italy**
Vice-Chair: Cristiana Oprea	**Bucharest, Romania**
Young Scientist: Andrea Mastrangelo	**Lausanne, Switzerland**
Juan Ambrosioni	Barcelona, Spain
Nathalie De Castro	Paris, France
Gerd Fätkenheuer	Cologne, Germany
Hansjakob Furrer	Bern, Switzerland
Ole Kirk	Copenhagen, Denmark
José M. Miró	Barcelona, Spain
Daria Podlekareva	Copenhagen, Denmark
Anton Pozniak	London, United Kingdom
Alain Volny-Anne	Paris, France

Paediatric HIV Treatment

Chair: Alasdair Bamford	**London, United Kingdom**
Co-Chair: Steven B Welch	**Birmingham, United Kingdom**
Young Scientist: Hylke Waalewijn	**Cape Town, South Africa**
Stefania Bernardi	Rome, Italy
David Burger	Nijmegen, The Netherlands
Guido Castelli Gattinara	Rome, Italy
Elena Chiappini	Florence, Italy
Angela Colbers	Nijmegen, The Netherlands
Alexandra Compagnucci	Villejuif, France
Catherine Dollfus	Paris, France
Caroline Foster	London, United Kingdom
Pierre Frange	Paris, France
Luisa Galli	Florence, Italy
Vania Giacomet	Milan, Italy
Tom Jacobs	Nijmegen, The Netherlands
Hermione Lyall	London, United Kingdom
Mariana Mardarescu	Bucharest, Romania
Laura Marques	Porto, Portugal
Lars Naver	Stockholm, Sweden
Tim Niehues	Krefeld, Germany
Antoni Noguera-Julian	Barcelona, Spain
Paolo Paioni	Zurich, Switzerland
Pablo Rojo	Madrid, Spain
Vana Spoulou	Goudi, Greece
Anna Turkova	London, United Kingdom
Alla Volokha	Kyiv, Ukraine
Wave Representative: Anna Koval	Kyiv, Ukraine

Governing Board Members

President: Esteban Martínez	**Barcelona, Spain**
Vice President: Miłosz Parczewski	**Szczecin, Poland**
Treasurer: Christoph Boesecke	**Bonn, Germany**
Secretary: Ann Sullivan	**London, United Kingdom**
Immediate Past President: Sanjay Bhagani	**London, United Kingdom**
Karoline Aebi-Popp	Bern, Switzerland
Juan Berenguer	Madrid, Spain
Antonella Castagna	Milan, Italy
Justyna Kowalska	Warsaw, Poland
Jens D. Lundgren	Copenhagen, Denmark
Paddy Mallon	Dublin, Ireland
Jean-Michel Molina	Paris, France
Cristina Mussini	Modena, Italy
Cristiana Oprea	Bucharest, Romania
Jürgen Rockstroh	Bonn, Germany
Marta Vasylyev	Lviv, Ukraine

Abbreviations

Antiretroviral drug (ARV) abbreviations

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

Other abbreviations

ACEi	angiotensin converting enzyme inhibitor
AFP	alpha-foetoprotein
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aMDRD	abbreviated modification of diet in renal disease formula
ARB	angiotensin receptor blocker
ART	antiretroviral therapy
AST	aspartate aminotransferase
ASCVD	atherosclerotic cardiovascular disease
B	buprenorphine
bid	twice daily
BMD	bone mineral density
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CAPD	continuous ambulatory peritoneal dialysis
CAD	coronary artery disease
cART	combination antiretroviral treatment
CBT	cognitive behavioural therapy
CCB	calcium channel blocker
CGA	comprehensive geriatric assessment
CKD	chronic kidney disease
CKD-EPI	CKD epidemiology collaboration formula
CMV	Cytomegalovirus
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
CSF	cerebrospinal fluid
CTC	computed tomography colonoscopy
CVD	cardiovascular disease
CXR	chest X-ray
DAA	direct acting antiviral drug
DDI	drug-drug interaction
DPP-4i	dipeptidyl peptidase 4 inhibitor
DRESS	drug rash with eosinophilia and systemic symptoms
DXA	dual energy X-ray absorptiometry
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESLD	end stage liver disease
FBC	full blood count
FH	familial hypercholesterolaemia
FIT	faecal immunochemistry test
FRAX®	fracture risk assessment tool
FRAT	falls risk assessment tool
FS	frailty scale
GAD-2	generalized anxiety disorder 2-item screening tool
GDR	genotypic drug resistance test
GLP1RA	glucagon like peptide 1 receptor agonist
GT	genotype
HAV	Hepatitis A virus
HAD	HIV-associated dementia
HBV	Hepatitis B virus
HCC	hepatocellular carcinoma
HCV	Hepatitis C virus
HDL-c	HDL-cholesterol
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HF	heart failure
HIVAN	HIV-associated nephropathy
HIV-VL	HIV viral load (HIV-RNA)
HMOD	hypertension-mediated organ disease
HPV	Human papillomavirus
HRS	hepatorenal syndrome
HSR	hypersensitivity reaction
HSV	Herpes simplex virus
ICS	Inhaled corticosteroid
IFG	Impaired Fasting Glucose
IFN	interferon
IGRA	interferon-gamma release assay
IGT	impaired glucose tolerance
IHD	ischaemic heart disease
im	intramuscular
IRIS	immune reconstitution inflammatory syndrome
iv	intravenous
IVDU	intravenous drug use
LA	long-acting
LABA	long-acting β2-agonist
LAMA	long-acting muscarinic antagonist
LDL-c	LDL-cholesterol
LGV	lymphogranuloma venereum
LOQ	limit of quantification
MDR-TB	multidrug resistant TB
Mg	magnesium
MND	mild neurocognitive disorder
MRI	magnetic resonance imaging
MSM	men who have sex with men
MTCT	mother to child transmission
MT	multitarget
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
OIs	opportunistic infections
OLTX	orthotopic liver transplantation
PAP	papanicolaou test
PCI	percutaneous coronary intervention
PD4	phosphodiesterase 4 inhibitors
PEP	post-exposure prophylaxis
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
qd	once daily
qid	four times daily
RAS	resistance-associated substitutions
RBV	ribavirin
RCT	randomized controlled trial
RIG	Rabies Immunoglobulin
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus-2
SABA	short-acting β2-agonist
SAMA	short-acting muscarinic antagonist
sc	subcutaneous
SCORE	systemic coronary risk estimation
SGLT-2i	sodium/glucose co-transporter 2 inhibitor
SOT	solid organ transplant
SPPB	short physical performance battery
SSRI	selective serotonin-reuptake inhibitor
STI	sexually transmitted infection
SU	sulfonylurea
SVR	sustained virological response
TBS	trabecular bone score
TC	total cholesterol
TDM	therapeutic drug monitoring
TG	triglycerides
TIA	transient ischaemic attack
tid	three times daily
TMP-SMX	trimethoprim-sulfamethoxazole
TZD	thiazolidinediones
UA/C	urine albumin/creatinine ratio
UP/C	urine protein/creatinine ratio
US	ultrasound
VL	viral load (HIV-RNA)
VZV	varicella-zoster virus
WB	western blot
XDR-TB	extensively drug-resistant TB
Zn	zinc

Part I Assessment of 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)	68, 69-70
	• 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 See Substance use: Alcohol Provide advice, support and counselling if needed	63
	Employment	+	+	Every visit		
	Social and welfare	+	+			
	Psychological morbidity	+	+			
	Partner and children	+			Test partner and children if at risk	
Sexual and Reproductive Health	Sexual history	+		6-12 months	Risk of sexual transmission should be addressed	101-105
	Safe sex	+				
	Partner status and disclosure	+			Recommend starting ART in serodifferent couples See Sexual and Reproductive Health	
	Conception issues	+	+		See Sexual and Reproductive Health	
	Hypogonadism	+	+	As indicated	Persons with complaints of sexual dysfunction	101-105
	Menopause	+	+	Annual/ as indicated	Screen for perimenopause symptoms in women ≥ 40 years	101-103
HIV DISEASE						
Virology	Confirmation of HIV Ab pos	+		3-6 months	More frequent monitoring of HIV-VL at start of ART Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection	12-14
	Plasma HIV-VL	+	+			
	Genotypic resistance test and sub-type	+	+/-	At virological failure		
	R5 tropism (if available)		+/-		Screen if considering R5 antagonist in regimen	
Immunology	CD4 absolute count and %, CD4/CD8 ratio (optional: CD8 and %)	+	+	3-6 months	Annual CD4 count if stable on ART and CD4 count > 350 cells/μL[(ii)] CD4/CD8 ratio is a stronger predictor of serious outcomes	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	101-103
	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	99, 127-129
	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	127, 133
	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	133

	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	20, 147
	PPD	+				
	IGRA in selected high-risk populations (if available)	+				
Others	Varicella zoster virus serology	+			Offer vaccination where indicated	99
	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 persons with HIV, see Vaccination	99
	Streptococcus pneumoniae	+			No recommendations available regarding the need for a booster dose, see Vaccination	99
	Human papilloma virus	+		As indicated	Vaccinate all persons with HIV with 3 doses between ages 9 and 40. If HPV infection is established, efficacy of vaccine is questionable, see Vaccination	99
	SARS-CoV-2				In a pandemic situation, vaccinate irrespective of CD4 count and HIV-VL according to national guidelines	99
CO-MORBIDITIES						
Haematology	FBC	+	+	3-12 months		
	Haemoglobinopathies	+			Screen at risk persons	
	G6PD	+			Screen at risk persons	
Body Composition	Body mass index	+	+	Annual		67
Cardiovascular Disease	Risk assessment [iii]	+	+	Annual	Should be performed in all men > 40 years and women > 50 years without CVD	68
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
Hypertension	Blood pressure	+	+	Annual		69-70
Lipids	TC, HDL-c, LDL-c, TG [iv]	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8 h without caloric intake)	76
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)	73-74
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	116
	Spirometry			As indicated	Spirometry should be performed in all symptomatic persons [xii]	
Liver Disease	Risk assessment [v]	+	+	Annual		86-91
	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 and/or persons with HIV at risk for NAFLD (as per algorithm on page 82) —> every 2-3 years (e.g. FibroScan, serum fibrosis markers)	86-91
	Hepatic ultrasound			6 months	Persons with liver cirrhosis [xiii]	86-91
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]	81-82
	eGFR (CKD-EPI) [vii]	+	+	3-12 months		
	Urine dipstick analysis [viii]	+	+	Annual	Every 6 months if eGFR < 60 mL/min or rapid decline in eGFR, if proteinuria ≥ 1+ and/or eGFR < 60 mL/min perform UA/C or UP/C [viii]	
Bone Disease	Bone profile: calcium, PO_4, ALP	+	+	6-12 months		78-80
	Risk assessment [x] (FRAX® [xi] in persons > 40 years)	+	+	2 years	Consider DXA in specific persons, see page 78 for details	

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
Vitamin D	25(OH) vitamin D	+		As indicated	Screen at risk persons	79
Cognitive impairment	Screening questionnaire	+	+	As indicated	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 114 for further assessment.	114
Anxiety	Questionnaire	±	±	As indicated	Consider screening at each routine HIV clinic visit	110-111
Depression	Questionnaire	+	+	As indicated	Consider screening at each routine HIV clinic visit	106-107
Older persons	Polypharmacy review			Annual	Perform periodic medicines review	120-121
	Frailty			Annual	Screen with Gait walking speed, Short Physical Performance Battery (SPPB), FRAIL Scale (FS) or Clinical Frailty Scale (CFS)	122-123
	Falls			Annual		124
Cancer	Mammography			1-3 years	Women 50-74 years	65
	Cervical PAP or liquid based cytology			1-3 years	Women with HIV > 21 years, as per national guidelines	
	Rectal exam, anal cytology and anoscopy			1-3 years	MSM and persons with HPV-associated dysplasia	
	Ultrasound and alpha-foetoprotein			6 months	Controversial; persons with cirrhosis and persons with HBV co-infection at high risk of HCC[xiii]	
	Prostate cancer (PSA)			1-2 years	Controversial; men > 50 years with a life expectancy >10 years	
	Others			As indicated	Lung cancer and colorectal cancer screening according to local screening programmes	

If a person has 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 www.emergeproject.eu

i Review all concomitant medicines which may potentially interact with ARVs or increase co-morbidities, see
Drug-drug Interactions between ARVs and Non-ARVs
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-infective Drugs for OIs and STIs 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 Intercations between Immunosuppressants (for SOT) and ARVs
Drug-drug Interactions between Pulmonary Antihypertensives and ARVs
Drug-drug Interactions between Viral Hepatitis Drugs and ARVs
and www.hiv-druginteractions.org

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

iii SCORE2 (40-69y) or SCORE2-OP (>70y) is the principal tool for cardiovascular disease risk estimation in primary prevention in "apparently heathy people". The cardiovascular disease risk estimation calculator can be found here: www.heartscore.org/en_GB/
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 www.mdcalc.com/ldl-calculated

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

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

vii eGFR: use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated > 60 mL/min.
The abbreviated modification of diet in renal disease (aMDRD) or the Cockroft-Gault (CG) equation may be used as an alternative, see 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 75

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/m^2), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (> 3 units/day), steroid exposure (minimum 5 mg for > 3 months)

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

xii 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 (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, 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

This section provides an overview of the important aspects of ART management. 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 Readiness to Start and Maintain ART[i]

Goal: to help persons start and/or maintain ART	
Starting ART is recommended for all persons with HIV 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 for newly-diagnosed individuals. Nevertheless, assessment of the readiness to start ART is essential to allow to express the person's preference and not feel pressured to start ART immediately, unless clinically indicated Given the need for lifelong treatment, successful ART requires a person's readiness to start and adhere to the regimen in a sustained manner. The trajectory from problem awareness to maintenance on ART can be divided into five stages. Knowing a person's stage, health care providers use appropriate techniques to assist them to start and maintain ART	Identify the person's stage of readiness using WEMS[i] techniques, and start discussion with an open question/invitation: "I would like to talk about HIV medicines." <wait> "What do you think about them?" Based on the person's response, identify his/her stage of readiness and intervene accordingly[ii] Immediate (i.e. same day) start of ART should be considered, and especially in the following situations: - In the setting of primary HIV infection, especially in case of clinical signs and symptoms of meningoencephalitis (within hours). In this situation, the clinician may start ART immediately after a positive screening HIV test and before obtaining confirmatory HIV test results such as a HIV-VL - The wish to start ART immediately - In a setting where loss-to-follow-up is more likely if ART is not started the same day

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

Several barriers are known to influence ART decision making and adherence to ART	
Screen for and talk about problems and facilitators	
Consider systematic assessment of: • Depression[vi], see pages 106-107 • Cognitive problems[vii], see page 114 • Harmful alcohol[viii] or recreational drug use, see page 64	Consider talking about: • Social support and disclosure • Health insurance and continuity of drug supply • Therapy-related factors
Recognise, discuss and reduce problems wherever possible in a multi-disciplinary team approach	

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

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

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

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

v Adherence to long-term therapies

vi See Mental Health section, 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.

vii See Algorithm for Diagnosis and Management of Cognitive and Central Nervous System Neurological Symptoms

viii See Substance use: alcohol

Recommendations for Initiation of ART in Persons 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 persons with HIV, 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 134, 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 < 200 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, preferably a second generation INSTI or alternatively a PI/b
- 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-naive Adults

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 persons with swallowing difficulties
- If the person has **acquired HIV while on regular PrEP intake**: In this situation, change PrEP to a triple-drug ART regimen including a third drug with a high barrier to resistance (preferably, DTG, BIC or alternatively DRV/b) plus TDF/XTC 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-naive persons 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, dosing)
TAF/FTC or TDF/XTC + RPV or TAF/FTC/RPV or TDF/FTC/RPV	CD4 count > 200 cells/µL 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, not to be used for same day start. 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 68

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 81;
- coadministration of medicines with nephrotoxic drugs or prior TDF toxicity, see page 82;
- osteoporosis / progressive osteopenia, high FRAX score or risk factors, see page 78;
- history of fragility fracture, see pages 78 and 80

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

VI DOR is not active against HIV-2. DOR has not been compared to an INSTI and was shown to be non inferior to EFV and DRV. 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; 400 or 600mg daily should be used; if rifampicine based regimen for tuberculosis is used, 600 mg dosing must be used; 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 other studies. DRV/r should be used with caution in persons with a high risk of cardiovascular risk

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 cases.
    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 cases

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/µL
- Potential benefits of treatment for the community: reduced risk of transmission. Most infections are transmitted by persons who are unaware of their HIV status
- Reduced anxiety and facilitated disclosure to contacts
  The person 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 person 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 three drug regimen including preferably a second generation INSTI with high barrier to resistance (DTG or BIC) or a PI/b, 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.
  It is recommended to select a first-line regimen with a high barrier to resistance, preferably a second generation INSTI or alternatively a PI/b plus TDF or TAF and XTC, 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. A two drug regimen is not recommended.

Other considerations

- All newly infected persons 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
- All women living with HIV of reproductive age should have a pregnancy test
- All persons should be counselled about the high risk of transmission, preventive measures, and importance of notifying partners

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

ii 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 persons can spontaneously control the infection without treatment (elite controllers)

v Post-treatment controllers. A small proportion of recently-infected persons have been able to spontaneously control HIV-infection following ART discontinuation, when ART was initiated during PHI

See online lectures for ART from the EACS online course
https://iversity.org/en/courses/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 person 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 an NNRTI, INSTIs RAL 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. Persons 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 someone 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 with anti-HBs antibodies (if non-immune provide HBV Vaccination, if isolated HBc antibodies see the section on Treatment and Monitoring of Persons with HBV/HIV Co-infection for details)

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

DTG + RPV
XTC + DTG
XTC + DRV/b

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

Long-acting intramuscular dual therapy CAB + RPV

- The use of oral lead-in (1 month) is optional
- Injections are administered every 2 months. In case of bridging, see the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV

Initiation phase (start on day of last oral pills)	Continuation phase
Day 0: CAB 600 mg/ RPV 900 mg Month 1: CAB 600 mg/ RPV 900 mg	From month 2 onwards: CAB 600 mg/ RPV 900 mg every 2 months

The following baseline factors, when combined, are associated with risk of virologic failure and resistance:

- Archived RPV-associated mutations
- HIV subtype A6/A1
- BMI ≥ 30 kg/m^2

See the section on Drug-Drug Interactions after Oral and Intramuscular Administration of CAB and RPV for details, page 27

Strategies not recommended

a. Monotherapy
b. Dual or triple NRTIs combinations
c. 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
d. Intermittent therapy, sequential or prolonged treatment interruptions. In one open-label randomized study, 4 consecutive days a week of triple therapy was non inferior to 7 days a week, at 48 weeks in the context of close monitoring and counseling with visits every 3 months

Virological Failure

Definition	**INCOMPLETE SUPPRESSION:** HIV-VL > 50 copies/mL at 6 months after starting therapy in a person not previously on ART. In persons with very high baseline HIV-VL (> 100,000 copies/mL), achieving viral suppression may take longer than 6 months **REBOUND:** confirmed HIV-VL > 50 copies/mL in someone with previously undetectable HIV-VL
General measures	Review expected potency of the regimen, taking into account all available historical genotypes
	Evaluate adherence, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues
	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
	Tropism testing if considering MVC
	Consider TDM
	Review ART history
	Identify treatment options, active and potentially active drugs/combinations
Management of virological failure (VF)	**If HIV-VL > 50 and < 200 copies/mL:**
	Check for adherence, reinforce adherence
	Check HIV-VL 1 to 2 months later[i]
	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
	If HIV-VL confirmed > 200 copies/mL:
	Therapeutic decision will depend on the resistance testing (genotype) results:
	If no resistance mutations found: check for adherence, reinforce adherence, perform TDM, discuss change to a different regimen
	If resistance mutations found: switch to a suppressive regimen based on drug and genotype history; multidisciplinary expert discussion advised in case of multiclass resistance
	Goal of new regimen: HIV-VL < 50 copies/mL within 6 months, sooner if possible

In case of demonstrated resistance mutations	**General recommendations:**
	Use at least 2 and preferably 3 fully active drugs in the new regimen (including active drugs from previously used classes) based on resistance mutations present in current and earlier genotypic analyses
	* 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 TDF or TAF) and either 1 active PI/b (i.e. DRV/b) or BIC or DTG (RAL or NNRTI not recommended) * If genotype shows multiclass resistance (i.e. ≥ 2 classes): new regimen will usually use - 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 * 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, lenacapavir or ibalizumab (where it is available on compational use) can be selected to obtain such a 2-3 drugs active regimen * In any case monotherapy is not recommended
	If < 2 active drugs are available, discuss on case by case situation deferring change, except in persons with low CD4 count (< 100 cells/μL) or with high risk of clinical deterioration for whom the goal is the preservation of immune function through partial reduction of HIV-VL (> 1 $\log_{10}$ copies/mL reduction) by recycling drugs
	Other considerations: - Treatment interruption is not recommended - Continuation of 3TC or FTC even if documented resistance mutation (M184V/I) might be beneficial
	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

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 may have reverted and/or no longer be detectable in the absence of drug pressure. Always refer to cumulative genotype

iii Thymidine Analog Mutations (TAMs) are non-polymorphic mutations selected by the thymidine analogs ZDV and/or d4T. For more detailed information on NRTI Resistance, see HIV Drug Resistance Database 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	- 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: • 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, 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	**1) Women whose HIV-VL is > 50 copies/mL at week 34-36:** • Elective cesarean section to be planned at week 38 • iv ZDV: During labour and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery - Scheduled cesarean delivery: start iv ZDV 3 hours before surgery - Unscheduled cesarean delivery: consider administering loading dose then proceed to delivery **2) Women diagnosed with HIV during labour:** • If possible, perform caesarean section • iv ZDV: During 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 Postnatal prophylaxis (PNP) 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 153
8. Breastfeeding	• **Breastfeeding is not recommended routinely** • **In situations where there is persistently undetectable maternal HIV viral load and very low risk of transmission, breastfeeding may be facilitated by joint decision making and with appropriate close monitoring of mother and infant. Please see the section on General Principles of Postnatal Prophylaxis and Infant Feeding for details, on page 157**

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)		
TDF/XTC or TAF/FTC + DTG		I (Tenofovir salts)
TDF/XTC or TAF/FTC + RAL 400 mg bid		I (Tenofovir salts) II (RAL in pregnancy, bid dosing)
2 NRTIs + PI/r		
TDF/XTC or TAF/FTC + DRV/r 600 mg/100 mg bid	With food	I (Tenofovir salts) III (DRV dosing) IV (COBI boosting)
Alternative regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG or ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	V (ABC: HLA-B*57:01, may delay starting ART)
ABC/3TC + RAL 400 mg bid	HLA-B*57:01 negative HBsAg negative	II (RAL in pregnancy, bid dosing) V (ABC: HLA-B*57:01, may delay starting ART)
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	V (ABC: HLA-B*57:01, may delay starting ART) VI (EFV HIV-2 & group O)
TDF/XTC or TAF/FTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	I (Tenofovir salts) VI (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	I (Tenofovir salts) VII (RPV exposure during 2nd and 3rd trimester, HIV-2) VIII (Interactions)
2 NRTIs + PI/r		
ABC/3TC + DRV/r 600 mg/100 mg bid	HLA-B*57:01 negative HBsAg negative With food	III (DRV dosing) IV (COBI boosting) V (ABC: HLA-B*57:01, may delay starting ART)

Additional guidance

I 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 disoprox- il fumarate)

II 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

III DRV/r 800/100 mg qd not recommended as initial ART during pregnancy due to decreased levels, but could be continued if the woman has already undetectable VL. DRV/c is not recommended during pregnancy due to significant lower exposures of DRV and COBI in the second and third trimester of pregnancy

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

V 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

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

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

VIII 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

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

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

In case of TB meningitis, see When to start ART in persons with Opportunistic Infections (OIs)

Table 1. Antiretroviral regimens in TB/HIV co-infection

These recommendations are for persons 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		
TXF/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		
TXF/XTC + DTG bid		I (tenofovir salts) IV (DTG: dosing)
TXF/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		
TXF/XTC + DRV/r	With food	VI (rifabutin dosing)
ABC/3TC + DRV/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 persons 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
	Consider PEP in case of receptive oral sex with ejaculation and not on PrEP or low PrEP adherence[1]	Viraemic HIV-positive
Intravenous drug use	Exchange of syringe, needle, preparation material or any other material	HIV-positive

1 As defined in PrEP section

- 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.or + DTG qd or TAF/FTC/BIC
- 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 partners with HIV 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 fourth generation test that can be performed without a visit to clinic
- 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
- 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
  All persons under PrEP should be offered vaccinations against HAV, HBV, HPV and monkeypox virus.
  Doxycycline post exposure prophylaxis, 200 mg within 24 to 72h after sexual intercourse, proved to be effective in preventing bacterial STIs in MSM with the caveat of the unknown long terms effects on microbiota and STIs resistance. It can be proposed to persons with repeated STIs on a case by case basis
- Counsel that TDF-based PrEP may rarely impact renal and bone health, see pages 78 and 80-82. 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

- The most common drug available is a generic version with 300mg of tenofovir (formulated as disoproxil fumarate/maleate/phosphate) combined with 200mg of emtricitabine (TDF/FTC). 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 effectiveness of daily and on-demand regimens of TDF/FTC has been extensively evaluated in clinical studies in men, but on demand has only been evaluated in pharmacokinetic/pharmacodynamic (PK/PD) studies for the female genital tract (FGT) and not at all for neovaginal/neopenile tissues
- TAF/FTC could be considered, if available, when creatinine clearance or bone mineral density preclude TDF/FTC. TAF/FTC has been evaluated as a daily regimen in comparison to TDF/FTC in men and transgender women. It was non-inferior, with a statistically significant benefit for renal and bone biomarkers
- Long-acting cabotegravir is available on application to compassionate release program, pending EMA approval, for individuals for whom TDF/FTC is contraindicated

- 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
- 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
- PK/PD studies comparing TAF/FTC to TDF/FTC suggest that the recommandations for starting and stopping TAF/FTC can be extrapolated from TDF/FTC
- 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
- Rates of adverse eGFR declines are generally low for those using TDF for PrEP, but PrEP users with the highest risk of adverse renal outcomes on TDF and most in need for systematic monitoring of renal function are older individuals and those with pre-existing renal impairment. 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 persons with HIV, see pages 81-83. Similarly, no data on use of “on demand” vs daily PrEP for renal outcomes
- Any person presenting with low PrEP adherence and a condomless at risk sexual intercourse should benefit from post exposure prophylaxis. Low adherence is defined :
  - For men and women on daily regimen: less than 4 pills a week, regardless of the distribution
  - For men on on demand regimen: less than 1 pill before and 1 pill after sexual intercourse

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 pigmentation	Nausea	Steatosis		Myopathy, Rhabdomyolysis			**Lipoatrophy**	Dyslipidaemia, Hyperlactataemia	Anaemia
3TC										
FTC										
TDF[iii]			Hepatitis		↓ BMD, Osteomalacia	↓ **eGFR**, Fanconi syndrome				
TAF[iii]									**Weight gain**	
NNRTIs										
EFV	Rash		Hepatitis				**Neuropsychiatric events including: depression, sleep disturbance, headache**		**Dyslipidaemia,** Gynaecomastia	↓ **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]	**Hyperbilirubinaemia,** Jaundice, Cholelithiasis			↓ eGFR, Nephrolithiasis			Dyslipidaemia	
DRV[v]	Rash			IHD		Nephrolithiasis			Dyslipidaemia	
LPV[vi]				IHD		↓ eGFR			**Dyslipidaemia**	
Boosting										
RTV		**Nausea and diarrhoea**				↓ **eGFR**[iv]			**Dyslipidaemia**	
COBI		Nausea and diarrhoea				↓ **eGFR**[iv]			Dyslipidaemia	

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%)
EVG/c		**Nausea,** Diarrhoea				↓ **eGFR**[iv]	Sleep disturbance, Headache		**Weight gain**	
BIC						↓ eGFR[iv]	Sleep disturbance, Headache		**Weight gain**	
CAB	Injection site reactions[ix]						Sleep disturbance, Headache			Pyrexia[x]
Entry inhibitors										
LEN	**Injection site reactions**									
Ibalizumab	Rash	Nausea Diarrhoea					Dizziness Headache			
FTR	Rash	**Nausea, Vomiting, Abdominal pain, Diarrhoea**					**Headache**			
MVC			Hepatitis	Postural hypotension						
ENF	**Injection site reactions**									Hypersensitivity

i **"Frequent effects" (events expected in at least 10% of treated individuals), 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 78, 81, 82, 95

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 CAB is available in oral or injectable formulations; injection site reactions are an adverse effect of injectable CAB

x Pyrexia includes feeling hot or body temperature increased

* Refers to effects seen in relation to hypersensitivity reactions

\# For "Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management" see page 96

Notes:

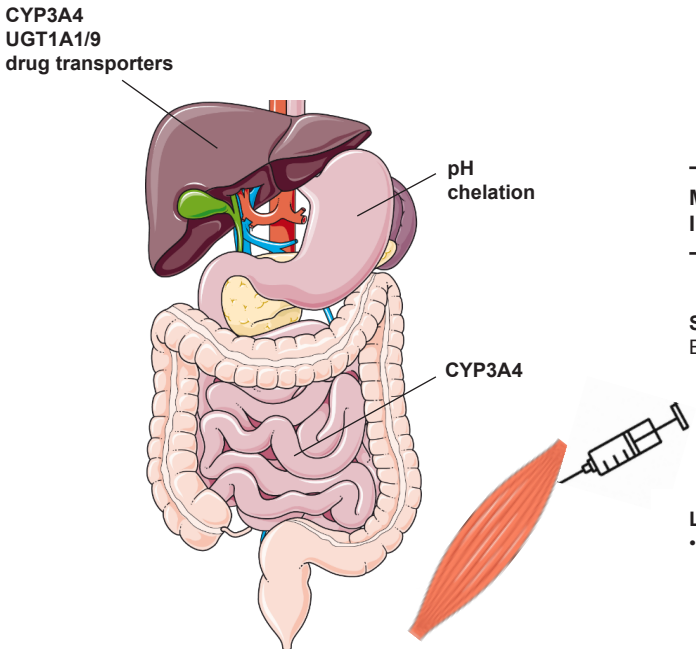
1. The adverse effects listed in the table above are not exhaustive, but represent the most important effects with a likely causal relation. Nausea, diarrhoea and rash are frequently observed in persons on ART, and these symptoms are indicated in the table for drugs where clinical experience suggests a possible causal link
2. D4T, ddI, FPV, IDV, SQV and TPR removed. Please refer to EACS v9.1 for details, www.eacsociety.org/files/2018_guidelines-9.1-english.pdf

Part III Drug-drug Interactions and Other Prescribing Issues

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 persons with HIV and 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 due to changes in gastric pH (rilpivirine requires a low pH for optimal absorption); chelation (cabotegravir forms a complex with divalent cations thereby impairing its absorption) or inhibition/induction of intestinal drug metabolizing enzymes. However, escaping the first-pass metabolism does not necessarily mitigate the DDI magnitude if the drug is minimally metabolized in the gut such as cabotegravir. Conversely, the magnitude of DDIs is mitigated for rilpivirine due to its high first-pass metabolism [Bettonte S et al. Clin Infect Dis 2023]. Regardless, strong and moderate inducers are predicted to cause a significant decrease in cabotegravir and rilpivirine exposure after intramuscular administration and therefore coadministration is not recommended with inducers.

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



Mechanisms of DDIs after ORAL administration

Stomach/intestine
- Change gastric pH
- Chelation divalent cations
- Inhibition/induction of CYP3A4, drug transporters

Liver
- Inhibition/induction of CYP3A4, UGT1A1/9, drug transporters

Mechanisms of DDIs after INTRAMUSCULAR administration

Stomach/intestine
Bypassed

Liver
- Inhibition/induction of CYP3A4, UGT1A1/9, drug transporters

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

Comments

- The rich vascular supply of the muscle favors the drug release from the depot therefore the injection technique is critical to ensure that cabotegravir and rilpivirine are not deposited in the subcutaneous adipose tissue (where blood flow and release from the depot are reduced leading potentially to lower initial drug concentrations). Thus, a longer needle is recommended when administering cabotegravir/rilpivirine to individuals with a BMI ≥ 30 kg/m^2. Another factor that could potentially enhance the drugrelease from the depot includes high physical activity as it increases the blood flow in the muscle.
- Multivariate models using data from phase 3 trials have shown that a combination of ≥ 2 baseline factors (including pre-existing rilpivirine RAMs, HIV subtype A6/A1 and/or BMI ≥ 30 kg/m^2) increased the risk of virologic failure. Orkin C et al. Clin Infect Dis 2023.
- Dosing recommendations in case of missed injections: doses can be administered between 7 days before and 7 days after the dose is due.
  If an 8-weekly injection is missed by < 2 months, treatment can be resumed as normal; however, if it is missed by > 2 months, cabotegravir/rilpivirine 600/900 mg dose must be administered as soon as possible, followed by a second dose after 4 weeks, before treatment may continue as normal.
  If an individual plan to miss a scheduled injection visit by more than 7 days, oral cabotegravir/rilpivirine 30/25 mg once daily may be used for up to 2 months to replace one missed injection visit (every 2-month dosing schedule).

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: www.hiv-druginteractions.org and www.hep-druginteractions.org

Real-life experiences on the clinical management of drug-drug interactions can be found in: clinicalcasesddis.com

Age-related physiological changes and co-morbidities predispose older persons with HIV 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 persons with HIV including drug classes to avoid or to deprescribe in presence of certain conditions.

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	LEN	BIC	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%	↔	↑31%	↔	↔	↔	↑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%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↑?	↔	↔	↔
	carbamaze-pine	↑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%	↔	↓	↓50%	↔	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↓1%	↔	↔
	midazolam (oral)	↑	↑	↑	↑	↑	↓18%	↓	↓	↓	↔	↔	↑18%	↑308%^	↑15%	↔	↔	↑	↓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 d	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	E b	↔	↑E	↔	E	E
	fluconazole	↑? a,b	↔ a,b	↑?	↔	↔ a,b	↑	↔	E86%	E100%	E b	E a,b	↔	↔	↔	E b	↔	↑?	↔	E?	E
	itraconazole	↑E b	↑E b	↑E	↑E	↑E b	↑	↓39%	↓E	↓61%	E b	E b	E	E	E	E b	↔	↑E	↔	E	E
	rifabutin	↑D e	↑ f	↑D e	↑ f	↑ f	D50% g	↓38% h	↓17% D37%	↑17%	D42% i	D30%	j	D #	D38%	D	↔	↑D e	E19%	D k	↔
	rifampicin	D	D72%	D	D57%	D75% l	D82%	D26%m	D	D58%	D80%	D82%	D	D84% #	D75%	D	D54%n	D	D40%o	D k	D12%
	voriconazole	↑↓ Eb	↑↓ Db	↑E	↓	↑↓ Eb	E	↓E	↑14% E36%	↓E	E	E	E	E41%	E61%	E	↔	↑E	↔	↔	E
Miscellaneous	antacids	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	↔	↔	↔	↑ s	↔	↔	↔
	buprenor-phine	↑	↑67%t	↑	↓11%t	↑~2%	↔	↓50%	↓25%	↓9%	↔	↑30%	↔	↑	↔	↔	↔	↑35%	↔	↔	↑~5%
	ergot derivatives	↑	↑	↑	↑	↑	E	↑	↑	↓	E	↔	E	↑ ^	↔	E	↔	↑	↔	↔	↔
	ethinylestra-diol	↑1%u	↓19%v	↓30%	↓44%u	↓42%u	↓2%	w	↑22%	↓20%	↑14%	↑40%x	↓<1%	↑	↑4%	↔	↑3%	↓25%y	↓2%	↑11%	↔
	fluticasone (inhaled)	↑ s	↑ 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 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 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

* 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:
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 cabotegravir (oral)

Decreased CAB exposure with carbamazepine, phenytoin, rifampicin (59%); these drugs should not be coadministered.
Decreased CAB exposure with antacids; potentially clinically significant interaction.

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 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.
e Reduce rifabutin to 150 mg 3 times per week.
f Reduce rifabutin to 150 mg qd. Monitoring for rifabutin-related toxicities (i.e. uveitis or neutropenia) is advised with daily administration of rifabutin.
g 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.
h Increase rifabutin to 450 mg daily.
i 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.
j Increase MVC to 600 mg bid in absence of PI. With PI (except TPV/r, FPV/r), give MVC 150 mg bid.
k 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.
l If no other option, use RTV 400 mg bid or double dose LPV/r.
m EFV should be used at 600 mg qd in presence of rifampicin (in absence of rifampicin, EFV can be used at 400 mg qd or 600 mg qd).
n Administer DTG 50 mg bid 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. Alternative to rifampicin should be used where possible for INSTI-experienced persons 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 (beclometasone-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). 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.
^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.
# At least a 2-week (moderate inducers) or 4-week (strong inducers) cessation period is recommended prior to initiation of LEN due to the persisting inducing effect after discontinuation of an inducer.

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	LEN	BIC	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	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔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	↑?	↓16%	↓53%i	↓5%	↓52%	↑6%	↓~50%	↓16%i	↑14%i	↔	↑	↔	↔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 cabotegravir (oral)
None

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.
- ^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	CAB/RPV	DTG	EVG/c	RAL	TAF	TDF
Anticoagulants	acenocoumarol	↔	↓	↔	↓	↓	↔	↑or↓	↑	↓	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔
	apixaban	↑a	↑a	↑a	↑a	↑a	↔	↓	↓	↓	↔	↑?	↔	↑	↔	↔	↔	↑a	↔	↔	↔
	argatroban	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	betrixaban	↑b,d	↑b,d	↑d	↑d	↑b,d	↔	↔	↑	↔	↔b	↔b	↔	↔ c	↔	↔b	↔	↑d	↔	↔	↔
	dabigatran	↑e	↑f	↑e	↑f	↑?	↔	↔	↑	↔	↑?	↔	↔	↔ c	↔	↔	↔	↑e	↔	↔	↔
	dalteparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	edoxaban	↑g	↑g	↑g	↑g	↑g	↔	↔	↔	↔	↔	↔	↔	↔ c	↔	↔	↔	↑g	↔	↔	↔
	enoxaparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fondaparinux	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	heparin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	phenprocoumon	↑	↑or↓h	↑	↑or↓	↑or↓	↔	↓	↑or↓	↓	↔	↔	↔	↑	↔	↔	↔	↑or↓	↔	↔	↔
	rivaroxaban	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↑?	↔	↑	↔	↔	↔	↑	↔	↔	↔
	warfarin	↑	↑or↓h	↑	↓	↓	↔	↑or↓	↑	↑or↓	↔	↔	↔	↑ ^	↔	↔	↔	↓	↔	↔	↔
Antiplatelet agents	aspirin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	clopidogrel	↓i	↓i	↓i	↓i	↓i	↔	↓i E	↓i	↑j E	↔	↔	↔	↓i	↔	↔	↔	↓i	↔	↔	↔
	dipyridamole	↑	↓k	↔	↓	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	prasugrel	↓l	↓l	↓l	↓l	↓l	↔	↔	↔	↔	↔	↔	↔	↓l	↔	↔	↔	↓l	↔	↔	↔
	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 cabotegravir (oral)

None

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 LEN is not considered to be a meaningful inhibitor of P-gp. No a priori dose adjustment of betrixaban, dabigatran or edoxaban is needed. However, monitoring for increased side effects is recommended.
d US label recommends to use a reduced initial betrixaban dose of 80 mg followed by 40 mg qd.
e 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.
f No significant increase in DRV/r exposure when administered simultaneously with dabigatran in persons with no renal impairment.
g European label advises to consider a dose reduction of edoxaban from 60 mg to 30 mg, however, US label recommends no dose modification.
h Unboosted ATV predicted to increase the anticoagulant, monitor INR and adjust the anticoagulant dosage accordingly.
i Decreased conversion to active metabolite leading to non-responsiveness to clopidogrel. An alternative to clopidogrel should be considered.
j Increase in amount of active metabolite via induction of CYP3A4 and CYP2B6.
k Unboosted ATV predicted to increase dipyridamole exposure due to UGT1A1 inhibition.
l Reduced active metabolite, but without a significant reduction in prasugrel activity.
^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	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	E	↔	↑	↔	↔	↔
	phenelzine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	reboxetine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	St John's wort	Dd	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 cabotegravir (oral)
None

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.
- # At least a 2-week (moderate inducers) or 4-week (strong inducers) cessation period is recommended prior to initiation of LEN due to the persisting inducing effect after discontinuation of an inducer.

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	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	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↑c	↔c	↑	↔	↔c	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↑	↑	↔	↔	↔
	bisoprolol	↑c	↑c	↑	↑	↑c	↔	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	carvedilol	↑c	↑↓c	↑	↑↓	↑↓c	↔	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	labetalol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nebivolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	oxprenolol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pindolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	propranolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
Calcium channel blockers	amlodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	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
Diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔
	bendroflu-methiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chlortalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eplerenone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E
	hydrochloro-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indapamide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	torasemide	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔
	xipamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Others	clonidine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	doxazosin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	hydralazine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔g	↔	↔	↔	↔	↔	↔	↔	↔h
	methyldopa	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔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 cabotegravir (oral)

None

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.
^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information

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

Drug-drug Interactions between Anti-infective Drugs for OIs and STIs and ARVs

Anti-infectives		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
Antiviral	aciclovir	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑ E
	brincidofovir	↑	↑	↑	↑	↑	↔	E	↔	↔	↔	↑	↔	↔	E	↔	↔	↑	↔	E	E
	cidofovir	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑E a
	famciclovir	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑ E
	foscarnet	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a
	ganciclovir	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑E a
	tecovirimat	↑	↓	↔	↓	↓	↔	↓	↓	↔	D	↔	D	D	E	D	↔	E	↔	E	E
	valaciclovir	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑E a
Antibacterial	azithromycin	↑ b,c	↑ b,c	↔	↔	↑ b,c	↔	↔	↔	↔	↔ c	↔b,c	↔	↔	↔	↔ c	↔	↔	↔	↔	↔
	ceftriaxone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ciprofloxacin	↔ b,c	↔ b,c	↔	↔	↔ b,c	↔	↔	↔	↔	E c	↔b,c	E	↔	↔	E c	↔	↔	↔	↔	↔
	clarithromycin	↑E b,c	↑E b,c	↑E	↑	↑ b,c	↑	↓39%	↓39% E42%	↓31% E26%	E c	E b,c	E	E	E	E c	↔	↑ E	↔	E	E
	erythromycin	↑ b,c	↑ b,c	↑ b	↑ b	↑ b,c	E	E	E	E	E c	E b,c	E	↑ E	E	E c	↔	↑	↔	↔	↔
	levofloxacin	↔ b,c	↔ b,c	↔	↔	↔ b,c	↔	↔	↔	↔	↔ c	↔b,c	↔	↔	↔	↔ c	↔	↔	↔	↔	↔
	sulfadiazine	↔	↓	↔	↓	↓	↔	↑	↑ E	↔	↔	↔	↔	↔	↔	↔	↔	↓	↔	↔	↔ a
	trimethoprim/ sulfamethoxazole	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Antifungal	amphotericin B	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a
	caspofungin	↑	↑	↔	↔	↔	↔	↓	↓	↓	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fluconazole	↑? b,c	↔ b,c	↑?	↔	↔ b,c	↑	↔	E86%	E100%	E c	E b,c	↔	↔	↔	E c	↔	↑?	↔	E?	E
	flucytosine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ d
	itraconazole	↑E c	↑E c	↑E	↑E	↑E c	↑	↓39%	↓E	↓61%	E c	E c	E	E	E	E c	↔	↑E	↔	E	E
	nystatin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	posaconazole	E c	E246%c	E	E	E c	E	↓50%	E	E	E c	E c	E	E	E	E c	↔	E	↔	↔	E
	voriconazole	↑↓ E c	↑↓ D c	↑E	↓	↑↓ E c	E	↓E	↑14% E36%	↓E	E	E	E	E41%	E61%	E	↔	↑E	↔	↔	E
Antiparasitic	dapsone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	meglumine antimoniate	↔ b,c	↔ b,c	↔	↔	↔ b,c	↔	↔	↔	↔	↔ c	↔b,c	↔	↔	↔	↔ c	↔	↔	↔	↔	↔ e
	miltefosine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	paromomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pentamidine	↔ b,c	↔ b,c	↔	↔	↔ b,c	↔	↔	↔	↔	↔ c	↔b,c	↔	↔	↔	↔ c	↔	↔	↔	↔	↔ 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 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

Antibacterial	Refer to the Anti-tuberculosis table for interactions with amikacin, moxifloxacin and rifabutin. Refer to the Anti-malarial table for interactions with clindamycin and doxycycline.
Antiparasitic	Refer to the Anti-malarial table for interactions with atovaquone, primaquine and pyrimethamine.

Interactions with ABC, FTC, 3TC, ZDV

ABC: no clinically relevant interactions expected.
FTC: potential additive renal toxicity with sulfadiazine and flucytosine.
FTC: potential increased FTC exposure with trimethoprim, but no dose adjustment required in patients with normal renal function.
3TC: potential additive renal toxicity with sulfadiazine and flucytosine.
3TC: increased 3TC exposure (43%) with trimethoprim, but no dose adjustment required in patients with normal renal function. Some trimethoprim/sulfamethoxazole liquid preparations may contain sorbitol which decreases the bioavailability of lamivudine solutions.
ZDV: potential risk of additive haematoxicity with brincidofovir and flucytosine.
ZDV: increased ZDV exposure (20%) with ganciclovir.
ZDV: decreased ZDV exposure (12%) with clarithromycin.
ZDV: potential increased risk of ZDV adverse reactions with trimethoprim, sulfamethoxazole, amphotericin B and flucytosine.
ZDV: increased ZDV exposure (74%) with fluconazole. Routine ZDV dose modification not required, but monitor for potential ZDV toxicity.
ZDV: no PK interaction observed with dapsone but potential increased risk of ZDV adverse reactions.
ZDV: potential increased risk of ZDV adverse reactions with pentamidine (but not with aerosolised pentamidine at doses used in prophylaxis).

Interactions with cabotegravir (oral)

None

Interactions with ibalizumab

None

Comments

a TDF should be avoided with concurrent or recent use of a nephrotoxic agent. If co-administration is unavoidable, monitor renal function closely.
b ECG monitoring is recommended.
c Caution as both drugs can induce QT interval prolongation.
d Co-administration could potentially increase haematological toxicity. Monitor haematological parameters and consider dose reduction if required.
e Renal impairment and sometimes fatal renal failure have been described with meglumine antimoniate treatment. Close monitoring of renal function is warranted.

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	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	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	↔	↑ E	↔	↔ 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	↔	↑ E	↔	↔ 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 cabotegravir (oral)

None

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.
^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	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	↔	↑ c	↔	↔ b	↔	↑	↔	↔	↔
	capreomycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑ d	↔	↔	↔	↑ E a
	clofazimine	↔	↔	↔	↔	↔	E	↔	↔	↔	E	E	E	↔	E	E	↔	↔	↔	↔	↔
	cycloserine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	delamanid	e	e	e	e	e	↔	↔ f	↔	↔	↔ g	↔ g	↔	h	↔	↔ g	↔	e	↔	↔	↔
	ethambutol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	ethionamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	isoniazid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	kanamycin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔ a
	linezolid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	moxifloxacin	↑ b	↓ b	↔	↓	↓ b	↔	↓	↓	↔	↔ b	↔ b	↔	↔	↔	↔ b	↔	↔	↔	↔	↔
	para-aminosali-cylic acid	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↑E
	pretomanid	↓ b	↓ b	↓	↓	↓17% b	↔	↓35%	↓	↓	↔ b	↔ b	↔	↔	↔	↔ b	↔	↓	↔	↔	↔
	pyrazinamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	rifabutin	↑ D i	↑ j	↑ D i	↑ j	↑ j	D50% k	↓38% l	D37%	↑17%	D42% m	D30%	n	D #	D38%	D	↔	↑ D i	E19%	D o	↔
	rifampicin	D	D72%	D	D57%	D75% p	D82%	D26% q	D	D58%	D80%	D82%	D r	D82% #	D75%	D	D54% s	D	D40% t	D o	D12%
	rifapentine	D	D	D	D	D	D	D	D	D	D	D	D r	D #	D	D	D u	D	D	D o	↔
	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 cabotegravir (oral)

Decreased CAB exposure with rifampicin (59%) and rifapentine; these drugs should not be co-administered

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 Systemic use for >14 consecutive days should be avoided. If coadministration is necessary, clinical monitoring including frequent ECG assessment and monitoring of transaminases is recommended.
d 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.
e Co-administration is expected to increase concentrations of DM-6705, a delamanid metabolite which is associated with QT prolongation. Frequent ECG monitoring is recommended.
f 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.
g RPV, FTR and DM-6705 (a delamanid metabolite) can potentially prolong the QT interval, ECG monitoring recommended.
h Co-administration is expected to increase concentrations of DM-6705, a delamanid metabolite which is associated with QT prolongation, although to a limited extent that is not expected to increase the risk of QT prolongation.
i Reduce rifabutin to 150 mg 3 times per week.
j Reduce rifabutin to 150 mg qd. Monitoring for rifabutin-related toxicities (i.e. uveitis or neutropenia) is advised with daily administration of rifabutin.
k The product label for DOR recommends to increase DOR to 100 mg bid if 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.
l Increase rifabutin to 450 mg qd.
m 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.
n Increase MVC to 600 mg bid in absence of PI. With PI (except TPV/r, FPV/r), give MVC 150 mg bid.
o Rifamycins decrease TAF exposure when given 25 mg. 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 may be acceptable.
p If no other option, use RTV 400 mg bid or double dose LPV/r.
q Efavirenz should be used at 600 mg qd in presence of rifampicin (in absence of rifampicin, efavirenz can be used at 400 mg qd or 600 mg qd).
r Give MVC 600 mg bid.
s 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.
t RAL 400 or 800 mg bid.
u 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.
At least a 2-week (moderate inducers) or 4-week (strong inducers) cessation period is recommended prior to initiation of LEN due to the persisting inducing effect after discontinuation of an inducer.

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	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 cabotegravir (oral)
None

Interactions with ibalizumab
None

Comments

- a ECG monitoring is recommended.
- b Caution as both drugs can induce QT interval prolongation.
- ^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
LAMA	aclidinium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	glycopyrronium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tiotropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	umeclidinium bromide	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
SAMA	Ipratropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
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	↔	↔	↔	↑ e	↔	↔	↔
	ciclesonide	↑ f	↑ f	↑ f	↑ f	↑ f	↔	↔	↔	↔	↔	↔	↔	↑ f	↔	↔	↔	↑ f	↔	↔	↔
	fluticasone	↑ e	↑ e	↑ e	↑ e	↑ e	↔	↓	↓	↓	↔	↔	↔	↑ e	↔	↔	↔	↑ e	↔	↔	↔
	mometasone	↑ e	↑ 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 cabotegravir (oral)
None

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:
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	LEN	BIC	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%	↔	↑3%	↓25%e	↓2%	↑11%	↔
Progestins	desogestrel (COC)	↑	↑f,b	↑	↑g	↑g	↔	↓h	↓	↓	↔	↔d	↔	↑	↔	↔	↔	↑e,f	↔	↔	↔
	desogestrel (POP)	↑	↑	↑	↑	↑	↔	↓h	↓	↓	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	drospirenone (COC)	↑130%	↑f,b,i	↑58%g,i	↑g,i	↑g,i	↔	↓h	↓	↓	↔	↔d	↔	↑	↔	↔	↔	↑e,f,i	↔	↔	↔
	etonogestrel (IP)	↑	↑	↑	↑	↑52%	↔	↓63% h	↓	↓	↑18%	↔	↔	↑	↔	↔	↑ 19-54%	↑	↔	↔	↔
	etonogestrel (VR)	↑	↑~71% j	↑j	↑j	↑j	↔	↓~79% h	↓	↓	↔	↔d	↔	↑	↔	↔	↔	↑j	↔	↔	↔
	gestodene (COC)	↑	↑f,b	↑	↑g	↑g	↔	↓h	↓	↓	↔	↔d	↔	↑	↔	↔	↔	↑e,f	↔	↔	↔
	levonorgestrel (COC)	↓8%	↑f,b	↑	↑g	↑g	↑21%	↓h	↓	↑	↔	↔d	↓2%	↑	↔	↔	↔	↑	↔	↔	↔
	levonorgestrel (IP)	↑	↑	↑	↑	↑	↔	↓57%h	↓	↑14%	↑28%	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	levonorgestrel (IUD)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	levonorgestrel (POP)	↑	↑	↑	↑	↑	↔	↓h	↓	↑	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	medroxy-proges-terone (POI)	↔	↔	↔	↔	↑~70%	↔	↔ k	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔ l
	norelgestromin (TS)	↑	↑f,b	↑	↑g	↑83%g	↔	↓h	↓	↓	↔	↔d	↔	↑	↔	↔	↔	↑e,f	↔	↔	↔
	norethisterone (COC)	↑	↑f,m	↑	↓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)	↑n	↑n	↑n	↑n	↑n	↔	↓58%o	↔	↔	↔	↔	↔	↑n	↔	↔	↔	↑n	↔	↔	↔
	mifepristone	↑n	↑n	↑n	↑n	↑n	En	↓	↓	↓	En	↔	En	↑n	En	↔	↔	↑n	↔	↔	↔
	ulipristal	↑n	↑n	↑n	↑n	↑n	↔	↓p	↓p	↓p	↔	↔	↔	↑n	↔	↔	↔	↑n	↔	↔	↔

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 cabotegravir (oral)

None

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 persons with additional risk factors for thromboembolic 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 Clinical monitoring is recommended due to the potential for hyperkalaemia.

j 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.

k A modeling study predicted a higher risk of having subtherapeutic medroxyprogesterone concentrations (i.e. <0.1 ng/mL) at week 12 in women with higher BMI on EFV treatment and even higher risk when EFV was given together with rifampicin. The risk of subtherapeutic concentrations is prevented by dosing medroxyprogesterone every 8-10 weeks in women with a higher body weight on EFV and particularly on efavirenz plus rifampicin.

l Concurrent use of TDF and medroxyprogesterone has been shown to increase bone mineral density loss compared to TDF alone.

m 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.

n Unlikely to have clinical consequences as hormone is administered as single dose.

o 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.

p 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:
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	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
Inhaled, oral, topic and/or injected corticosteroids	beclometasone (inhalation)	↑a	↑a	↑?a	↑11%b	↑a	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑a	↔	↔	↔
	betamethasone	↑c	↑c	↑c	↑c	↑c	D	↓	↓	↓	D	D	D	↑c^ D#	D	D	↔	↑c	↔	↔	↔
	budesonide (inhalation)	↑c	↑c	↑c	↑c	↑c	↔	↓	↓	↓	↔	↔	↔	↑c	↔	↔	↔	↑c	↔	↔	↔
	ciclesonide (inhalation)	↑d	↑d	↑d	↑d	↑d	↔	↔	↔	↔	↔	↔	↔	↑d	↔	↔	↔	↑d	↔	↔	↔
	clobetasol (topical)	↑c,e	↑c,e	↑c,e	↑c,e	↑c,e	↔	↔	↔	↔	↔	↔	↔	↑c,e	↔	↔	↔	↑c,e	↔	↔	↔
	dexamethasone (>16 mg)	↑c D	↑c D	↑c D	↑c D	↑c D	D	↓	↓ D	↓	D	D	D f	↑c D#	D	D	↔	↑c D	↔	↔	↔
	flunisolide (inhalation)	↑g	↑g	↑g	↑g	↑g	↔	↓	↓	↓	↔	↔	↔	↑g	↔	↔	↔	↑g	↔	↔	↔
	fluocinolone (topical)	↑c,e	↑c,e	↑c,e	↑c,e	↑c,e	↔	↔	↔	↔	↔	↔	↔	↑c,e	↔	↔	↔	↑c,e	↔	↔	↔
	fluticasone (inhalation)	↑c	↑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	↔	↔	↔	↑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	↔	↔	↔	↑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 cabotegravir (oral)
None

Interactions with ibalizumab
None

Comments

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

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

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

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

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

f 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.

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

^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

\# At least a 2-week (moderate inducers) or 4-week (strong inducers) cessation period is recommended prior to initiation of LEN due to the persisting inducing effect after discontinuation of an inducer.

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
Antiviral Drugs and mAbs	molnupiravir	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	nirmatrelvir/r	↔ a	↔ a	↔ a	↔ a	↔ a	E	↔ b	↔	↔ b	E	↔	E c	E	E	E	↔	↔ a	↔	↔	↔
	remdesivir	↔ d	↔ d	↔	↔	↔ d	↔	↔	↔	↔	↔ d	↔ d	↔	↔	↔	↔ d	↔	↔	↔	↔	↔
	tixagevimab/ cilgavimab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Immune Therapies	anakinra	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	baricitinib	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	canakinumab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	convalescent plasma	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	COVID-19 vaccines	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	dexamethasone (low dose*)	↑ e	↑ e	↑ e	↑ e	↑ e	D f	↓	↓	↓	D h	D	D i	↑ e	↔	D	↔	↑ e	↔	D	↔
	hydrocortisone	↑ e	↑ e	↑ e	↑ e	↑ e	↔	↓	↓	↓	↔	↔	↔	↑ e	↔	↔	↔	↑ e	↔	↔	↔
	infliximab	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	methyl-prednisolone	↑ e	↑ e	↑ e	↑ e	↑ e	↔	↓	↓	↓	↔	↔	↔	↑ e	↔	↔	↔	↑ e	↔	↔	↔
	ruxolitinib	↑ j	↑ j	↑ j	↑ j	↑ j	↔	↓	↓	↓	↔	↔	↔	↑ k	↔	↔	↔	↑ j	↔	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 cabotegravir (oral)

None

Interactions with ibalizumab

None

Comments

a RTV or COBI containing regimens are continued with no dosage modification. Inform about potential occurrence of adverse effects.

b Ritonavir bid is expected to counteract the inducing effect of EFV, NVP.

c Consider using MVC at a dose of 150 mg bid.

d Remdesivir has a possible risk of QT prolongation and/or TdP on the CredibleMeds.org website.

e 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.

f Consider increasing DOR to 100 mg bid during treatment for COVID-19 and for approximately 2 weeks after the end of treatment.

g Doubling the dose of dexamethasone, hydrocortisone or methylprednisolone is recommended.

h 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.

i 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.

j 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.

k Monitor closely for cytopenia.

Further Information

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

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	LEN	BIC	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 cabotegravir (oral)
None

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 in 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:
www.hiv-druginteractions.org (University of Liverpool)

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

Immuno-suppressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	LEN	BIC	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	↑a ^	E	E	↔	↑a	↔	E	Eb
	tacrolimus*	↑a,c	↑a,c	↑a	↑a	↑a,c	↓a	↓a	↓a	↓a	↔c	↔c	↔	↑a ^	↔	↔c	↔	↑a	↔	↔	↔b
mTOR	everolimus	↑	↑	↑	↑	↑	↔	↓a	↓a	↓a	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	sirolimus	↑	↑	↑	↑	↑	↓a	↓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 haematoxicity with azathioprine.
ZDV: potential alteration in mycophenolate exposure, monitor plasma concentrations.

Interactions with cabotegravir (oral)

None

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.
- ^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
ERA	ambrisentan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bosentan	↑a	↑a	↑a	↑a	↑a	D	↓	↓	↓b	D	↑	D	D #	D	D	D	↑a	↔	↔	↔
	macitentan	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
PDE5	sildenafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↓3%	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	tadalafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
sGC	riociguat	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↑	↔	↑	↔	↔	↔	↑	↔	↔	↔
PA	epoprostenol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	iloprost	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	treprostinil	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
IPr	selexipag	↔c	↔c	↔c	↔c	↑120%d	↔	↔	↔	↔	↔	↔	↔	↔c	↔	↔	↔	↔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
Ipr	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 cabotegravir (oral)

None

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.

^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

At least a 2-week (moderate inducers) or 4-week (strong inducers) cessation period is recommended prior to initiation of LEN due to the persisting inducing effect after discontinuation of an inducer.

Further Information

For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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	LEN	BIC	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 cabotegravir (oral)
None

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:
www.hiv-druginteractions.org (University of Liverpool)

Administration of ARVs in Persons with Swallowing Difficulties

Drug	Formulation	Crush tablets	Open capsules	Comment
NRTIs				
ABC	tablet (300 mg) solution (20 mg/mL)	yes		Bitter taste. Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately
FTC	capsule (200 mg) solution (10 mg/mL)	no	yes	Dissolve in ≥ 30 mL of water, contains Na 460 µmol/mL Bioequivalence: 240 mg solution = 200 mg capsule; adjust dosage accordingly
3TC	tablet (150, 300 mg) solution (10 mg/mL)[vii]	yes		Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately
TDF	tablet (300[i] mg) 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)	no	no	Sticky, bitter taste
	oral solution (10 mg/mL), iv infusion (10 mg/mL)			Better: use oral solution or iv 6 mg/kg per day in glucose 5%
TAF/FTC	tablet (25/200 mg and 10/200 mg)[v]	yes		Crushing of tablets is not recommended in the product information. However based on data with the fixed-dose combination tablet (TAF/FTC/DRV/c), crushing of tablets does not impact significantly TAF/FTC pharmacokinetics (of note: TAF bioavailability is reduced by 20% (crushing) but this decrease is unlikely to be clinically significant)[viii]
TDF/FTC	tablet (300[i]/200 mg)	yes		Better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste)
ABC/3TC	tablet (600/300 mg)	no		Use solution of individual compounds
ZDV/3TC	tablet (300/150 mg)	yes		Disperse in ≥ 15 mL water, alternative: use solution of individual compounds
ABC/3TC/ZDV	tablet (300/150/300 mg)	no		Use solution of individual compounds
NNRTIs				
DOR	tablet (100 mg)	no		Tablet must be swallowed whole
TDF/3TC/DOR	tablet (300/300/100 mg)	no		Tablet must be swallowed whole
EFV	tablet (600 mg)	yes		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)[v]	no		Tablets should be swallowed whole and should not be chewed, crushed or split
TDF/FTC/RPV	tablet (300[i]/200/25 mg)	no		Crushing of tablets and dispersion into a liquid is not recommended. RPV is insoluble in water over a wide pH range
PIs				
ATV	capsule (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)[v]	yes		Crushing of tablets has no significant effect on the pharmacokinetics of the components of the tablet (of note: TAF bioavailability is reduced by 20% (crushing) but this decrease is unlikely to be clinically significant. TAF 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	
LEN	Tablet (300 mg) injectable	no NA	NA	Tablets should not be chewed, crushed, or split, because the effects on LEN absorption have not been studied.
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)[v]	no		Tablets should be swallowed whole and should not be chewed, crushed or split
TAF/FTC/EVG/c	tablet (10/200/150/150 mg)[v]	yes		Crushing of tablets is not recommended in the product information. However, a clinical study showed that dissolving a tablet in water resulted in a modest increase in bictegravir bioavailability. Crushing the tablet and administering with apple sauce resulted in reduced emtricitabine (by 16%) and TAF (by 14%) bioavailability. If a tablet cannot be swallowed whole, it is recommended to dissolve it in water and take it immediately.
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 persons 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: use with caution
	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
Capsid Inhibitor	
LEN	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
INSTI	
RAL	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
EVG	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
DTG	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
DTG/3TC	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
DTG/RPV	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
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, not recommended
TDF/FTC/EVG/c	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
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, not recommended
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[ii] (mL/min)				Haemodialysis[iii]
	≥ 50	30-49	10-29	< 10	
NRTIs					
Individual agents					
ABC[iii]	300 mg q12h or 600 mg q24h	No dose adjustment required			
FTC[v]	200 mg q24h		200 mg q72h	200 mg q96h	200 mg q24h[iv]
3TC[v]	300 mg q24h	150 mg q24h	100 mg q24h[vi]	50 mg q24h[vi]	25 mg q24h[iv, vi]
TDF[vii]	300[viii] mg q24h	300[viii] mg q48h	Not recommended (300[viii] mg q72-96h, if no alternative	Not recommended (300[viii] mg q7d, if no alternative)	300[viii] mg q7d[iv]
TAF[ix,x]	25[xi] mg q24h			No data	25 mg q24h[iv]
ZDV	300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h[iv]
Combinations					
ABC[iii]**/3TC**[v]	600/300 mg q24h	Use individual drugs			
ZDV/3TC	300/150 mg q12h				
ABC/3TC/ZDV	300/150/300 mg q12h				
TAF[ix]**/FTC**[v]	25[xi]/200 mg q24h		Use individual drugs[xv]		25/200 mg q24[iv]
TDF[vii]**/FTC**[v]	300[viii]/200 mg q24h	300[viii]/200 mg q48h	Use individual drugs		
NNRTIs					
EFV	600 mg q24h	No dose adjustment required			
ETV	200 mg q12h	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**[v]**/RPV**	25[xi]/200/25 mg q24h		Use individual drugs[xv]		25/200/25 mg q24h[iv]
TDF[vii]**/FTC**[v]**/RPV**	300[viii]/200/25 mg q24h	Use individual drugs			
DOR	100 mg q24h	No dose adjustment required; < 10: no PK data[xix]			
TDF[vii]**/3TC**[v]**/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**[v]**/DRV/c**	10/200/800/150 mg q24h		Use individual drugs		
LPV/r	400/100 mg q12h	No dose adjustment required[xiii]			
Other ART					
RAL	1 x 400 mg tablet q12h or 2 x 600 mg tablets q24h	No dose adjustment required[xiii]			
DTG	50 mg q24h	No dose adjustment required[xiii]			
3TC[v]**/DTG**	300/50 mg q24h	Use individual drugs			
ABC[iii]**/3TC**[v]**/DTG**	600/300/50 mg q24h	Use individual drugs[xvi]			
RPV/DTG	25/50 mg q24h	No dose adjustment required[xiii]			
TAF[ix]**/FTC**[v]**/BIC**	25/200/50 mg q24h	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**[v]**/EVG/c**	10/200/150/150 mg q24h		Not recommended[xii]		10/200/150/150 mg q24h[iv]
TDF[vii]**/FTC**[v]**/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
LEN	600 mg q24h on days 1 & 2, 300 mg q24h on day 8, 927 mg sc on day 15 followed by maintenance dose: 927 mg sc every 6 months (26 weeks +/- 2 weeks)	No dose adjustment required[XX]

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 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; 50 mg loading dose for haemodialysis

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 persons with end-stage renal disease on chronic dialysis. However, TAF/FTC/EVG/c may be used with caution if the potential benefits are considered to outweigh potential risks. One clinlical study has demonstrated safety of TAF/FTC/EVG/c for persons 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 persons 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 persons 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 persons on chronic dialysis, however these findings need to be confirmed in a larger trial

xvii In persons 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

xix Doravirine is modestly removed by heamodialysis so that no dosage adjustment is needed

xx LEN has not been studied in individuals with end stage renal disease (CrCL <15 mL/min or on renal replacement therapy and therefore should be used with caution in these individuals)

* Due to lack of COBI data in persons with HIV with renal impairment

For recommendations on ART use in persons with HIV undergoing renal transplantation, see Solid Organ Transplantation, page 125

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
Solriamfetol	<60 mL/min	≥30-60 mL/min: initial dose 37.5 mg daily, may increase to max 75 mg daily after at least 7 days based upon efficacy and tolerability <30 mL/min: max 37.5 mg daily <15 mL/min: not recommended
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		
Nirmatrelvir/r	<60 mL/min	≥30-60 mL/min: nirmatrelvir/r 150 /100 mg BID <30 mL/min incl. Hemodialysis*[e] D1: nirmatrelvir/r 300/100 mg then D2-D5: nirmatrelvir/r 150/100 mg daily * after hemodialysis
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

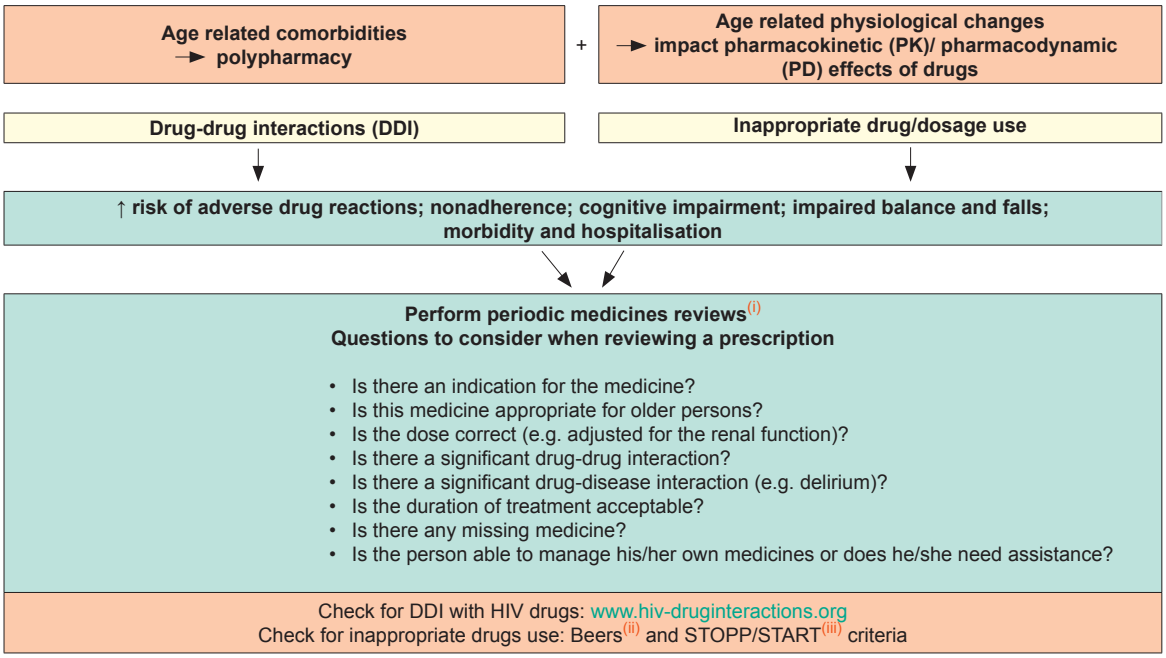
c The drug package insert should be consulted for specific dose adjustments

d No dose adjustment on antibacterial loading dose

e The product label does not recommend nirmatrelvir/ritonavir for patients with eGFR <30 mL/min. However, on the basis of clinical, modelling and patient data, an adjusted dose given at a lower frequency has been proposed for use in people with eGFR <30 mL/min and those on dialysis. The adjusted dose of nirmatrelvir/ritonavir was found to be safe and well tolerated in a small sample of 134 maintenance dialysis patients (Hiremath S et al. Clin J Am Soc Nephrol 2023.

* Hiremath S et al. Prescribing nirmatrelvir/ritonavir for COVID-19 in advanced CKD. Clin J Am Soc Nephrol 2022

Prescribing in Older Persons with HIV



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

Drug Classes To Avoid in Older Persons with HIV

Drug class	Problems/alternatives
First generation antihistamines e.g., clemastine, diphenhydramine, doxylamine, hydroxyzine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: cetirizine, desloratadine, loratadine
Tricyclic antidepressants e.g., amitryptiline, clomipramine, doxepin, imipramine, trimipramine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: citalopram, escitalopram, mirtazapine, venlafaxine
Benzodiazepines Long and short acting benzodiazepines e.g., clonazepam, diazepam, midazolam Non-benzodiazepines hypnotics, Z-drugs e.g., zapleton, 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 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

Drug Classes to Deprescribe in Older Persons with HIV in Presence of Certain Conditions

Deprescribing should aim to reduce pill burden, drug toxicities, falls, hospital admission, mortality and improve Health related Quality of Life.

Drug class	Conditions for which deprescribing should be considered	Problems caused by drug class	Alternatives or information on how to stop drug
Acetylcholinesterase inhibitors e.g, donepezil, rivastigmine	History of persistent bradycardia (< 60 beats/min), heart block, or recurrent syncope or coadministration of beta-blocker, digoxin, diltiazem, verapamil	Increase the risk of cardiac conduction failure, syncope and injury	Taper gradually, consider halving the dose every 4 weeks
Antipsychotics e.g., haloperidol, lurasidone, paliperidone, perphenazine	Parkinson	Severe extra-pyramidal symptom	quetiapine, clozapine
Aspirin	Low cardiovascular risk and/or advanced age and/or high risk of gastrointestinal bleeding (e.g., concurrent use of NSAIDs, SSRIs, corticosteroids) and/or prior gastrointestinal disease and/or coadministration of a second antiplatelet or anticoagulant (continued beyond the recommended duration)	Risk of bleeding	No need to taper
Biphosphonates e.g., alendronate, ibandronate, risedronate, zoledronate	Low risk of fracture or history of 5 years of continuous treatment with a bisphosphonate	Biphosphonates keep showing a benefit in non-vertebral fractures in the 5 years after an initial treatment particularly if the T score is above -2.5. Prolonged use increases the risk of osteonecrosis of the jaw, hypocalcemia and/or severe vitamin D deficiency.	No need to taper
Opioids e.g, codeine, fentanyl, morphine, oxycodone, tramadol	Chronic non-cancer pain	Tolerance to analgesic effect of opioids with long-term use. Associated with adverse psychological effects, higher risk of death from drug overdose with opioids.	Multidisciplinary pain management program. Written and verbal instructions should be provided to patients and families to educate about the tapering protocol that will minimize the withdrawal symptoms
Proton pump inhibitors (PPIs) e.g, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	Uncomplicated peptic ulcer disease	Long-term use is linked with increased risk of fracture, enteric infections, mineral deficiencies	Use low dose of PPI -> if symptoms well controlled -> use PPI on demand -> if symptoms well controlled -> stop PPI
Selective serotonin re-uptake inhibitors (SSRIs) e.g., citalopram, fluoxetine, paroxetine, sertraline	Current or recent significant hyponatremia (i.e. serum Na+ <130 mmol/L)	Syndrome of inappropriate antidiuretic hormone secretion (SIADH) and aggravation hyponatremia	agomelatine, bupropion, mianserin, trazodone. Note: tricyclic antidepressants should be avoided as associated with a higher risk of adverse effects (e.g., life-threatening arrhythmias and heart block)

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

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

Comments

a ARVs with **no predicted effect**: 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
- Note: hormone therapy doses in the table are indicative, dose titration upwards may occur in practice based on single individual goals, clinical response and hormone levels.

Part IV Prevention and Management of Co-morbidities

Successful management of persons with HIV goes beyond provision of effective ART, with increasing focus attributed to the appropriate management of other medical conditions in order to ensure the best outcomes for persons with HIV. This section provides recommendations for the best management of recognized comorbidities which may occur more frequently in persons with HIV including mental health issues (particularly depression and anxiety disorders), cardiovascular, pulmonary, hepatic, metabolic, neoplastic, renal, bone, central nervous system disorders as well as sexual function.

Many HIV clinicians are not specialists in managing co-morbidities and, although general guidance on management of common co-morbidities is included in these Guidelines, HIV clinicians 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.

Depending on future clinical research findings, and the constantly evolving changes in healthcare models posed by challenges such as the COVID-19 pandemic these recommendations will be regularly updated as required, www.eacsociety.org and in the EACS Guidelines App.

Substance Use: Alcohol

Substance use
Definition: Use of different legal and illegal substances such as alcohol, cannabis, cocaine, 3,4-methylenedioxymethamphetamine (MDMA), methamphetamine, lysergic acid diethylamide (LSD), heroin and others. The use of these substances is considered problematic if the consequences of use have a harmful and negative impact to the person, their family, close relatives or social environment.
In people with HIV, substance use may interfere with adherence to ART, is associated with poorer outcomes and can trigger mental health disorders.

Alcohol use in people with HIV
Untreated alcohol use disorder (AUD) is associated with worse outcomes along the HIV care continuum and increased risk of morbidity. Further, people with HIV may experience mortality and physiologic injury at lower levels of alcohol consumption compared with people without HIV.

Screening for alcohol use

Who?	How to screen?	How to diagnose alcohol use dependence?
Recommend screening people with HIV at least once a year (in view of the high prevalence of problematic alcohol use) **Populations at particularly high risk** • Positive family and personal history of substance use • Persons with mental health problems, particularly depression • Adolescence • Use of neurotropic and recreational drugs • When assessing readiness to start and maintain ART, see page 10 • As part of investigation of cognitive impairment, see page 114	• **Ask: Do you ever consume alcoholic drinks?** - **If yes:** explore with the Alcohol Use Disorders Identification Test-Concise (AUDIT-C), which is a brief alcohol screening instrument that identifies persons who are hazardous drinkers or have active alcohol use disorders (including alcohol abuse or dependence): 1. Within the past year, how often did you have a drink of alcohol? 0. Never 1. Monthly (e.g., on special or rare occasions) 2. 2-4 times a month 3. 2-3 times a week 4. 4 or more times a week 2. Within the past year, how many standard drinks containing alcohol did you have on a typical day? 0. 1 or 2 1. 3 or 4 2. 5 or 6 3. 7 to 9 4. 10 or more 3. Within the past year, how often did you have six or more drinks on one occasion? 0. Never 1. Less than monthly 2. Monthly 3. Weekly 4. Daily or almost daily **> Alcohol use at risk if score is ≥ 5 (men) or ≥ 4 (women)**	**Explore whether three or more of the following characteristics appear simultaneously, or have been present in the last 12 months (ICD-10 criteria)** 1. Intense desire or compulsion to consume 2. Decreased ability to control: • difficulties in controlling the onset of consumption • difficulties in ending intake and controlling the amount 3. Withdrawal symptomatology 4. Tolerance or neuroadaptation 5. Progressive abandonment of activities 6. Persistence in consumption despite the harmful consequences Does the person meet ICD-10 criteria? • NO: risky / harmful consumption • YES: alcohol dependence - refer the patient to the addiction unit For risky consumption or where alcohol services are not available, initiate brief intervention or motivational interviewing

The Alcohol Use Disorders Identification Test (AUDIT) is a validated screening test to screen for unhealthy drinking.
The shorter 3-question version AUDIT-C (www.integration.samhsa.gov/images/res/tool_auditc.pdf) has a sensitivity of 86% and a specificity of 72%.

Opioid Addiction, Pharmacological Treatment

Opioid substitution therapy (OST), also called opioid agonist therapy (OAT) is used to prevent withdrawal symptoms in persons who discontinue long term use of analgesics that act on opioid receptors or as a treatment for people with opioid use disorder. OST includes conventional treatments such as methadone maintenance therapy and buprenorphine maintenance therapy.

Comorbid mental health disorders can interfere with the adherence to OST, and result in poorer outcomes of addiction treatment.

Characteristics of drugs used as OST[i]

Feature	Methadone	Buprenorphine
Dose required to prevent withdrawal symptoms according to degree of opioid dependency	Linear relationship (from 10-300 mg per day)	Linear relationship for persons with less opioid dependency only – ceiling effect (max daily dose 24 mg)
Interaction with ARVs	Methadone plasma concentrations are reduced if used together with: • NVP & EFV: ↓ 50% • LPV/r: ↓ 50% • No clinically significant alterations of methadone PK with other commonly used ART agents	Buprenorphine (B) and active metabolite norbuprenorphine (N) plasma concentrations are reduced if combined with NNRTIs and increased if combined with some PIs or INSTIs • EFV: ↓ up to 50% (B) and 70% (N) • ETV: ↓ 25% (B) • ATV/r: ↑ 50-100% (B&N) • DRV/r: ↑ 50% (N) • **Caution:** 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) • LEN may increase B however to an extent that does not warrant dose adjustment
	Caution: withdrawal symptoms if combined with ARV that decreases plasma concentration and risk of drug toxicity if such ARVs are interrupted – reverse if ARVs increase plasma concentration	
Risk of overdose	Yes	See[iii]
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)

iii Buprenorphine is commonly used as a fixed-dose combination with naloxone. Risk of overdose of buprenorphine may be reduced with the use of fixed dose combination with naloxone

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, high resolution anoscopy & anal cytology	Reduces incidence of anal cancer	1-3 years	Ongoing research may identify at risk groups for screening
Breast cancer	Women 50-74 years[iii]	Mammography	↓ Breast cancer mortality	1-3 years	
Cervical cancer	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, 89 and 127[iv]	Ultrasound (and alpha-foetoprotein)	Earlier diagnosis allowing for improved ability for surgical eradication. The clinical management of nodules should be in line with EASL treatment strategy guidelines	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
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 persons with HIV not included and there may be a higher false positive rate among people with HIV

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. Most US guidelines encourage shared decision-making for women in their 40s because of trade-offs between benefits and harms, whilst some European screening guidelines recommend starting screening at age 45.

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, see pages 89 and 127

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

- Careful attention must be paid to potential drug-drug interactions between systemic anti-cancer therapy and ART.
  Advice is available at www.hiv-druginteractions.org
- Chemotherapy and radiotherapy are associated with an unpredictable decline in CD4 counts even in persons stable on ART, OI prophylaxis should therefore be considered at any CD4 count threshold in persons 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 134-152
- One month after the end of the chemo- or radiotherapy treatment we recommend repeating CD4 counts and following standard OI recommendations, see pages 134-152
- Persons undergoing autologous or allogenic stem cell transplantation should follow standard national/local guidance for anti-infective prophylaxis

Specific OI prophylaxis recommended in persons undergoing cancer treatment

- PCP prophylaxis, see page 137
- 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 persons with HIV 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 28
- HSV/VZV prophylaxis, see pages 103 and 142
- NTM prophylaxis only in those with a detectable plasma HIV-VL, see page 136

Lifestyle Interventions

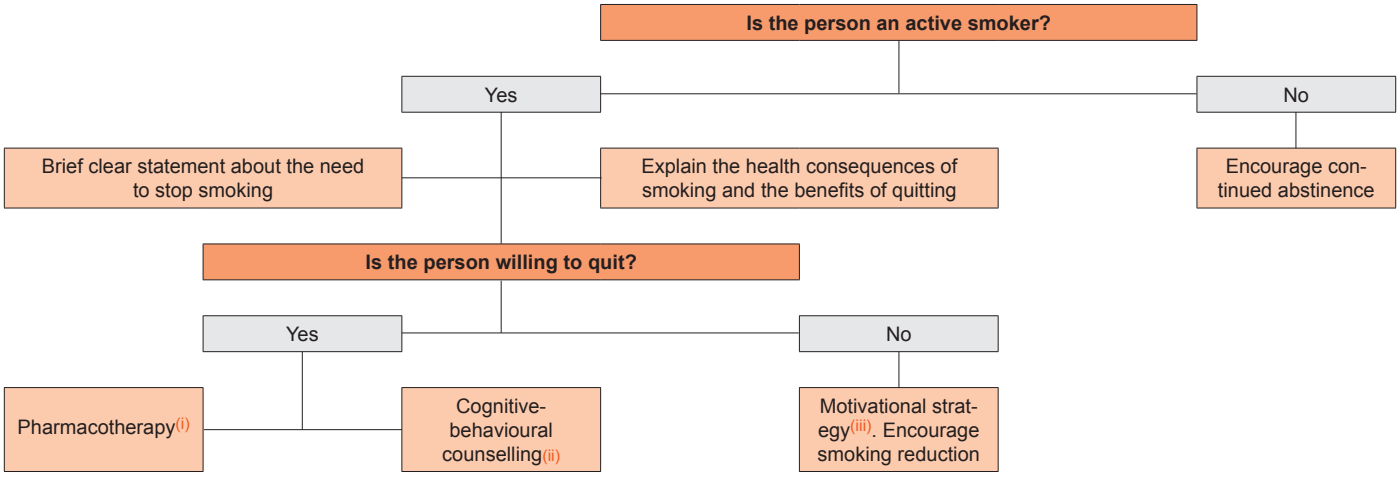
Adults who adhere to Guidelines which promote a healthy diet and physical activity have lower rates of cardiovascular morbidity and mortality than those who do not. In adults without overt cardiovascular risk factors counselling interventions result in improvements in health-promoting behaviors and a 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. Dietary and exercise counselling is recommended for all individuals[(i) (ii)]. A summary of healthy diet and impact on risk of CVD can be found in the European Society of Cardiology (ESC) 2021 guidelines.

With regards to dietary counselling, it is recommended to refer to individual national guidelines[(iii) (iv)].

i Use of diet, nutritional supplements and exercise in HIV-infected patients receiving combination antiretroviral therapies: a systematic review. Antivir Ther. 2008;13(2):149-59. Pere Leyes 1, Esteban Martínez, Maria de Talló Forga, PMID: 18505167
ii www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/aha-diet-and-lifestyle-recommendations
iii knowledge4policy.ec.europa.eu/health-promotion-knowledge-gateway/food-based-dietary-guidelines-europe-table-20_en
iv ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies. Rev Esp Cardiol (Engl Ed) . 2022 May;75(5):429. Frank L J Visseren, et al. PMID: 35525570

Smoking cessation

Persons with HIV 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[(iv)] and Calvo-Sanchez M., et al, 2015[(v)]

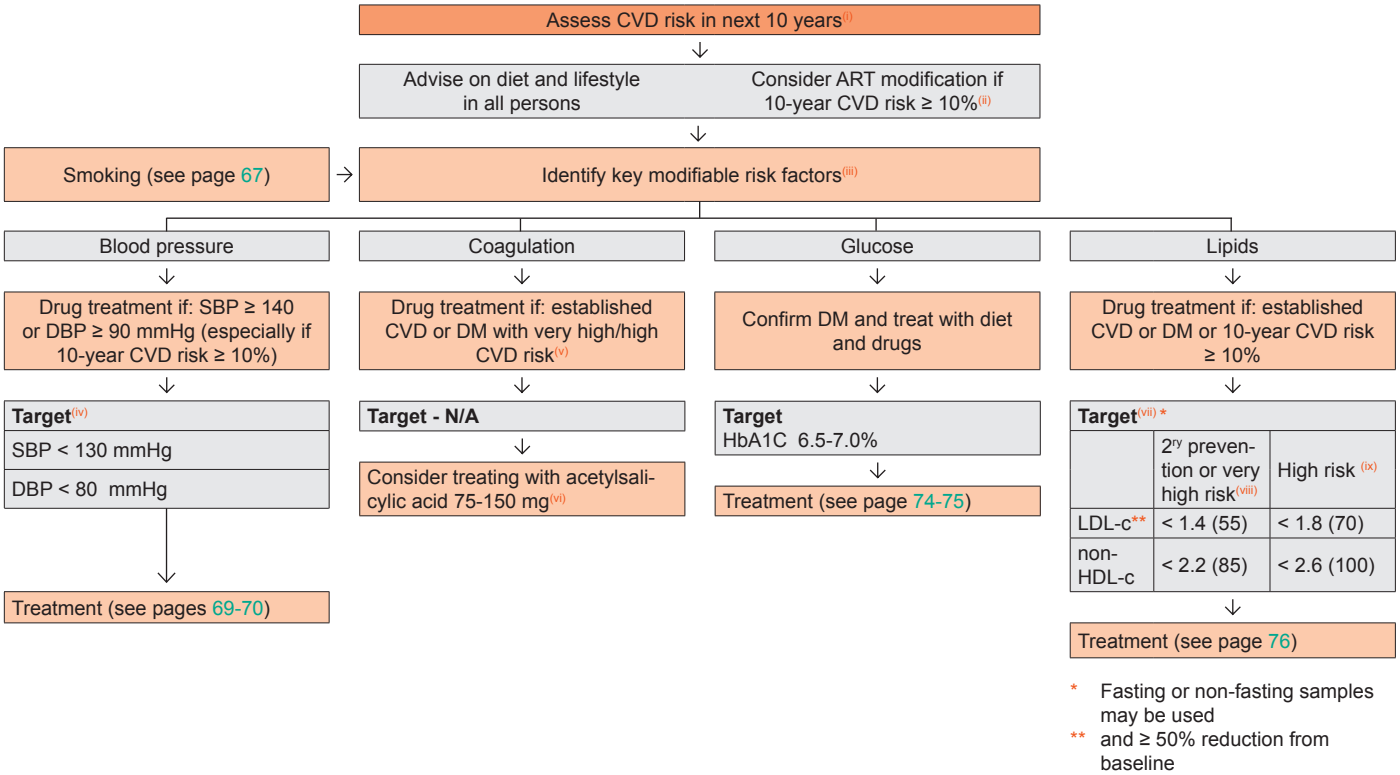
i Pharmacotherapy: Nicotine replacement therapy: nicotine substitution (patch, chewing gum, spray), varenicline and bupropion are approved by the EMA. Bupropion is contraindicated with epilepsy and varenicline may induce depression. Bupropion may interact with PIs and NNRTIs, see Drug-drug Interactions 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
iv ensp.network/european-smoking-cessation-guidelines-and-quality-standards/
v How to address smoking cessation in HIV patients. Calvo-Sánchez M, Martinez E.HIV Med. 2015 Apr;16(4):201-10. doi: 10.1111/hiv.12193. Epub 2014 Oct 9. PMID: 25296689

At this moment, neither EMA nor FDA approve e-cigarettes as a smoking cessation agent. In persons with HIV 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 2022. www.cdc.gov/tobacco/basic_information/e-cigarettes/about-e-cigarettes.html

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.



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

i Use SCORE2 (40-69y) or SCORE2-OP (>70y) as the principal tool for CV risk estimation in primary prevention in "apparently heathy people" (subjects without atherosclerotic cardiovascular disease, diabetes mellitus, chronic kidney disease, or familial hypercholesterolemia). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European Heart Journal, 42 (34): 3227–3337. Frank L J Visseren, et al. This new score includes the non-HDLc (total cholesterol- HDLc) as the lipid biomarker for CVD risk estimation and incorporates different risk score estimations depending on which country in Europe the person comes from (four European risk regions). See link below to access the CV risk estimation calculator. North African and eastern European subjects are considered at very high CVD risk. For other ethnicities: • Southern Asian: multiply the risk by 1.3 for people of Indian and Bangladeshi descent, and 1.7 for people of Pakistani descent. • Other Asian: multiply the risk by 1.1. • Black Caribbean: multiply the risk by 0.85. • Black African and Chinese: multiply the risk by 0.7. This assessment and the associated considerations outlined in this figure should be repeated annually in all persons receiving care, see page 8, to ensure that the various interventions are initiated in a timely manner. SCORE2 has not been validated in people with HIV and likely underestimates CVD risk estimation. HIV has been recognized as a risk enhancer for CVD.

ii Options for ART modification include:
(1) Replace with NNRTI or INSTI 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 Observational studies suggest that smoking cessation results in about 50% less risk of IHD - and this is additive to other interventions. 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.

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

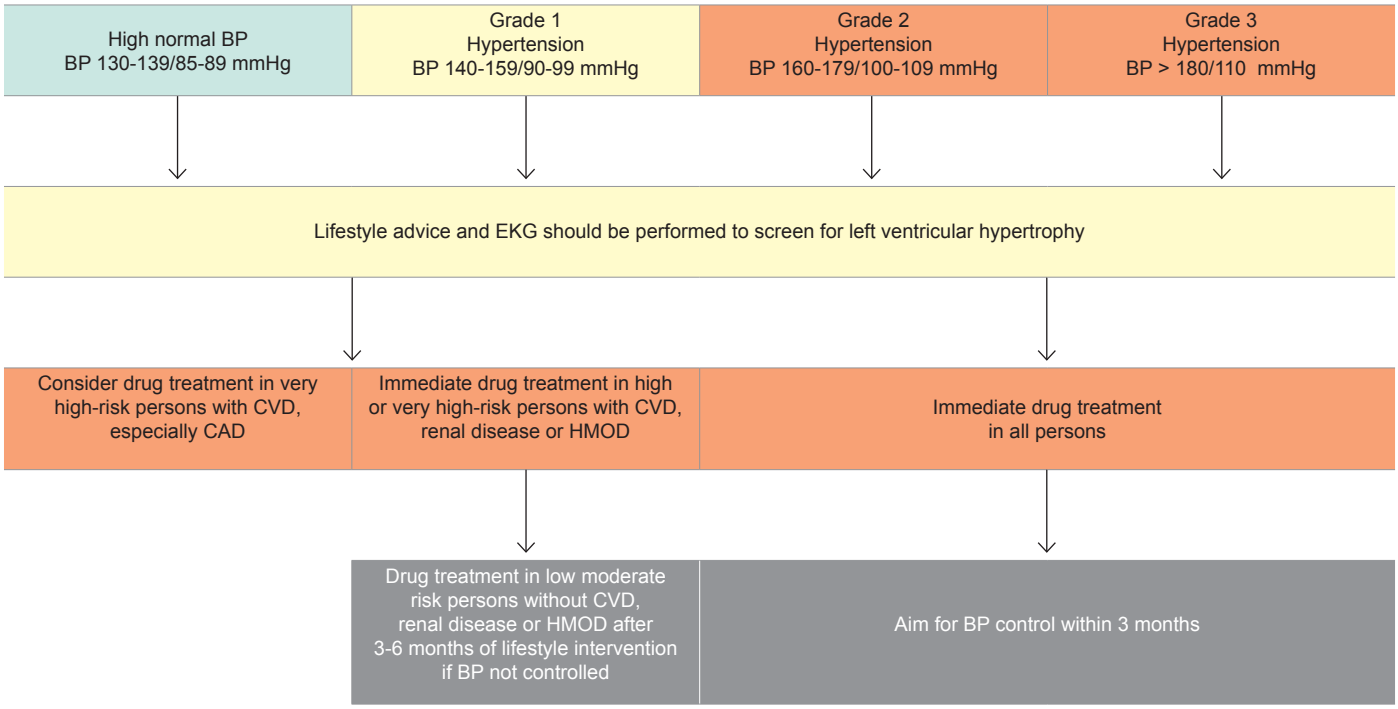
viii Very high-risk persons: Documented atherosclerotic CVD (ASCVD), either clinical [ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease] or unequivocal on imaging [significant 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 high risk calculated via SCORE2 or SCORE2-OP for fatal or non-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, with DM duration ≥ 10 years or another additional risk factor. Moderate CKD (eGFR > 30 - < 60 mL/min).
CV risk estimation calculator: www.heartscore.org/en_GB/

SCORE2 and SCORE2-OP (ESC 2021)

CV risk estimation	< 50y	50-69y	> 70y
Low / moderate	< 2.5%	< 5%	< 7.5%
High	2.5-<7.5%	5-<10%	7.5-<15%
Very high	> 7.5%	>10%	> 15%

Hypertension: Diagnosis, Grading and Management



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

How to measure blood pressure (BP)
Patients should be seated comfortably in a quiet environment for 5 minutes before beginning BP measurements. Three BP measurements should be recorded, 1-2 min apart, and additional measurements only if the first two readings differ by >10 mmHg. BP is recorded as the average of the last two BP readings. Use a standard bladder cuff (12-13 cm wide and 35 cm long) for most patients but have larger and smaller cuffs available for larger (arm circumference > 32 cm) and thinner arms, respectively.
Hypertension in clinic should be confirmed with home BP measurement or 24hr ambulatory BP monitoring if a white coat effect is evoked.

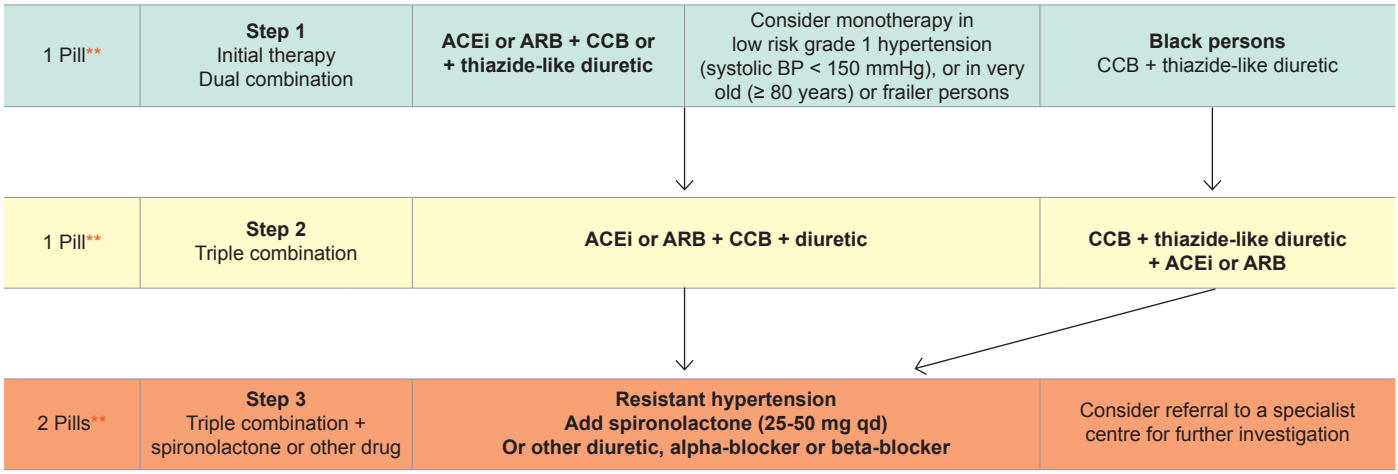
2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement: European Society of Hypertension Council and the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. J Hypertens. 2021 Jul 1;39(7):1293-1302. Stergiou et al.

Comparison of ambulatory blood pressure monitoring (24h ABPM) and home blood pressure monitoring (HBPM)

24h ABPM	HBPM
Advantages • Can identify white coat and masked hypertension • Night time readings • Real life setting • BP variability • Prognosis value (no deeper) • Suspicion of sleep apnea syndrome (no deeper)	**Advantages** • Can identify white coat and masked hypertension • Cheap and widely available • Patient engagement in BP measurement • Easily repeated
Disadvantages • Expensive • Sometimes uncomfortable	**Disadvantages** • Only static BP • Potential measurement error • No nocturnal readings

Where available, please refer to national hypertension guidelines for further information.

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 available, please refer to national guidelines for further information
** Where combination pill is not available, single tablets should be used, considering locally available drugs and fixed drug combinations.

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	LEN	BIC	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	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
β blockers	atenolol	↑c	↔c	↑	↔	↔c	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↑	↑	↔	↔	↔
	bisoprolol	↑c	↑c	↑	↑	↑c	↔	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	carvedilol	↑c	↑↓c	↑	↑↓	↑↓c	↔	↑↓	↑↓	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	labetalol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	metoprolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	nebivolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	oxprenolol	↑c	↓c	↔	↓	↓c	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	pindolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	propranolol	↑c	↑c	↑	↑	↑c	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
Calcium channel blockers	amlodipine	↑d	↑d	↑	↑	↑e	↔	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	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
Diuretics	amiloride	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔
	bendroflu-methiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	chlortalidone	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	eplerenone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	furosemide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	E
	hydrochloro-thiazide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indapamide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑	↔	↔	↔	↑	↔	↔	↔
	torasemide	↔	↓	↔	↓	↓	↔	↑	↑	↔	↔	↑	↔	↔	↔	↔	↔	↓	↔	↔	↔
	xipamide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Others	clonidine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	doxazosin	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	hydralazine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔g	↔	↔	↔	↔	↔	↔	↔	↔h
	methyldopa	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔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 cabotegravir (oral)

None

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.
^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information

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

Type 2 Diabetes: Diagnosis

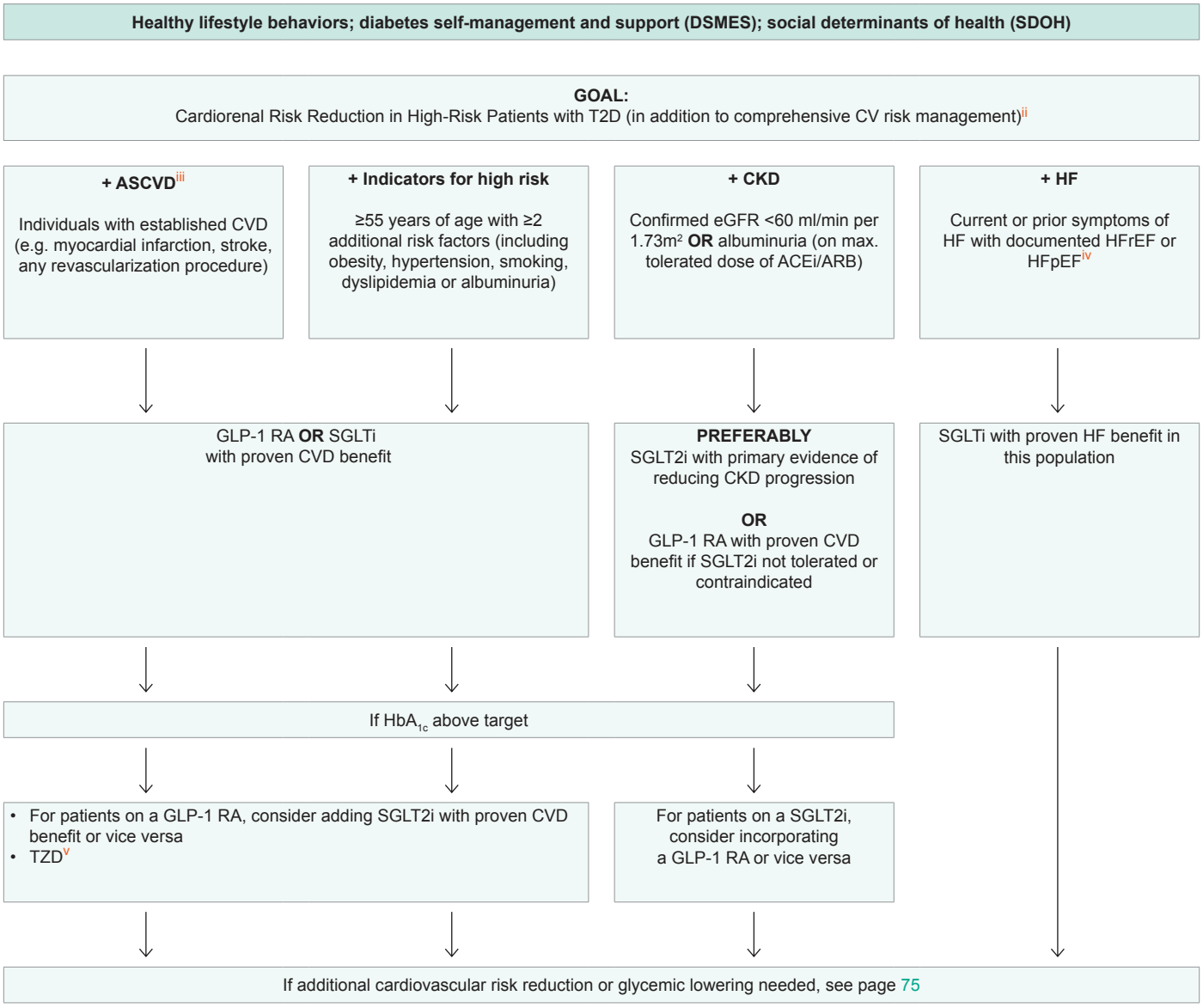
Diagnostic criteria[i]

	Fasting plasma glucose mmol/L (mg/dL)[ii]	Oral glucose tolerance test (OGTT) 2 hours value mmol/L (mg/dL)[iii]	HbA1c[iv] (mmol/mol)
Diabetes	≥ 7.0 (126) OR	≥ 11.1 (200) OR	≥ 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 persons with HIV 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 persons with HIV, 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

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes[i]



i These recommendations are derived from the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) consensus report. Check national guidelines, where available

ii In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use GLP-1 RA or SGLT2i with proven benefit should be independent of the background use of metformin. The benefits of GLP-1 RA and SGLT2i for cardiovascular and renal outcomes have been found to be independent of metformin use, and thus these agents should be considered in people with established or high risk of CVD, HF, or CKD, independent of metformin use

iii Defined differently across trials but all included individuals with established CVD. Variably included: conditions such as transient ischemic attack, unstable angina, amputation, symptomatic or asymptomatic coronary artery disease

iv HFrEF, Heart Failure with reduced Ejection Fraction; HFpEF, Heart Failure with preserved Ejection Fraction

v Low-dose TZD may be better tolerated with similar efficacy

GOAL:
Achievement and Maintenance of Glycemic and Weight Management Goals

Glycemic Management:

Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals

Consider avoidance of hypoglycemia a priori in high-risk individuals

Efficacy for glucose lowering[i]

Very High:
Dulaglutide (high dose), Semaglutide, Tirzepatide

Insulin

Combination Oral, Combination Injectable (GLP-1 RA/Insulin)

High:
GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonyurea, TZD

Intermediate:
DPP-4i

Weight Management:

Set individualized goals

General lifestyle advice: medical nutrition therapy/eating patterns/ physical activity

Intensive evidence-based structured weight management program

Consider medication for weight loss

Consider metabolic surgery

When choosing glucose-lowering therapies: Consider regimen with high-to-very-high dual glucose and weight efficacy

Efficacy for weight loss

Very High:
Semaglutide, Tirzepatide

High:
Dulaglutide, Liraglutide

Intermediate:
GLP-1RA (not listed above), SGLT2i

Neutral:
DPP-4i, Metformin

If HbA_{1c} above target

Identify barriers to goals:

- Consider DSMES referral to support self-efficacy in achievement of goals
- Consider technology (e.g. diagnostic CGM) to identify therapeutic gaps and tailor therapy
- Identify and address SDOH that impact achievement of goals

i In general, higher efficacy approaches have greater likelihood of achieving glycemic goals. Drugs listed may not be available in some countries. Consider referring to diabetologist or endocrinologist.

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. Lipids testing should be performed every year in high or very high risk subjects and every 3-5 years in low and moderate risk subjects.

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 68.

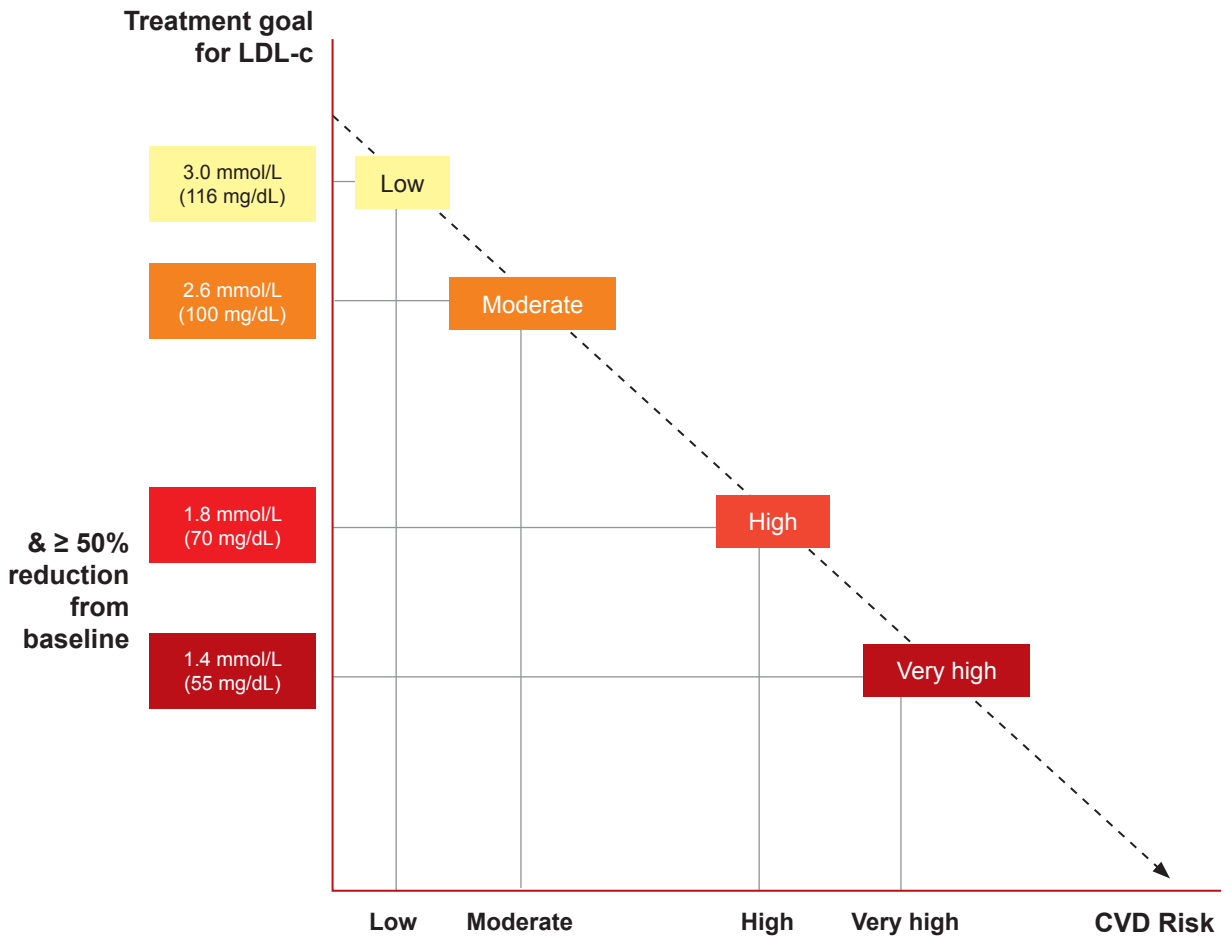
Statins should be used by all those with established vascular disease and in persons who are not at LDL-c goals considering their level of CVD risk, irrespective of lipid levels, see Treatment Goals for LDL-c to reduce cardiovascular risk depending on CV risk estimation. In high risk persons with statin 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 and/or bempedoic acid should be considered.
Icosapent ethyl (EPA) should be discussed in adjunct to statin in very high risk patients (post MI and diabetics with another CV risk factor with TGs > 150mg/dL or > 1.7 mmol/L.

Drugs used to reduce cardiovascular risk by lowering LDL-c and triglycerides

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	
Adenosine triphosphate citrate lyase inhibitor*	Bempedoic acid	180 mg qd	Gout, cholelithiasis	No interaction expected. Contraindicated with simvastatin > 40mg qd	
Intestinal cholesterol absorption inhibitor↓(i,ix)	Ezetimibe(iv)	10 mg qd	Gastrointestinal symptoms	No interaction expected	
PCSK9-inhibitors(x) Monoclonal antibodies	Evolocumab	140 mg 2 weekly or 420 mg monthly	Nil	No interaction expected	
	Alirocumab	75 mg or 150 mg 2 weekly or 300 mg monthly			
Fish oil, Omega-3	Icosapent ethyl(xi)	2 g bid	Atrial fibrillation, bleeding	No interaction expected	

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 77. In persons 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 persons intolerant of statins or added to a statin when LDL-c reduction is inadequate despite maximally tolerated statin
x Data in persons with HIV available for evolocumab
xi Icosapent ethyl, a pure ester of eicosapentaenoic acid (EPA) from the omega-3 family, is indicated to reduce cardiovascular risk as an adjunct to statin therapy in subjects with myocardial infarction and/or people with diabetes at high cardiovascular disease risk with elevated triglycerides (< 10mg:dL or 1.7 mmol/L).

Treatment Goals for LDL-c to Reduce Cardiovascular Risk Depending on CV Risk Estimation*



Treatment algorithm for pharmacological low-density lipoprotein cholesterol lowering*
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.

SCORE2 and SCORE2-OP Cardiovascular disease risk estimation stratified by age*

CV risk estimation	< 50y	50-69y	> 70y
Low / moderate	< 2.5%	< 5%	< 7.5%
High	2.5-<7.5%	5-<10%	7.5-<15%
Very high	> 7.5%	> 10%	> 15%

* For the cardiovascular risk definitions, please refer to the 2019 ESC/EAS Guidelines for the management of dyslipidaemia: lipid modification to reduce cardiovascular risk.

Bone Disease: Screening and Diagnosis

Condition	Characteristics	Risk factors	Diagnostic tests
Osteoporosis • Postmenopausal women and men age ≥ 50 years with BMD T-score ≤ -2.5 at hip or lumbar spine • Premenopausal women and men age < 50 years with BMD Z-score ≤ -2 at hip or lumbar spine and fragility fracture	• Reduced bone mass and altered bone quality • Increased risk of fractures in persons with HIV • Asymptomatic until fractures occur • Aetiology multifactorial • Loss of BMD observed with ART initiation (mainly during 1st year) • Greater loss of BMD with initiation of certain ARVs[i]	Consider classic risk factors[ii] and estimate fracture risk using FRAX in people ≥ 40 years Consider DXA in any person with ≥ 1 risk of:[iii] 1. Postmenopausal women 2. Men ≥ 50 years 3. High risk for falls[iv] 4. Those with high fracture risk (> 20% 10-year major osteoporotic fracture risk based on FRAX assessment without DXA) 5. History of low impact fracture 6. Clinical hypogonadism (symptomatic, see Sexual Dysfunction) 7. Oral glucocorticoid use (minimum 5 mg/d prednisone equivalent for > 3 months)	**DXA scan** In those with classic risk factors who require DXA, where feasible consider DXA scan prior to ART initiation or soon after initiation. Add DXA result to FRAX® to refine fracture risk prediction (www.shef.ac.uk/FRAX) • May underestimate risk in persons with HIV • Consider 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. **Rule out causes of secondary osteoporosis if BMD low**[vi] Vertebral fracture assessment on lateral DXA images or 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)
Osteomalacia	• Defective bone mineralisation • Associated with vitamin D deficiency • Increased risk of fractures and bone pain • Vitamin D deficiency may cause proximal muscle weakness	• Dark skin • Dietary deficiency • Avoidance of sun exposure • Malabsorption • Obesity • Renal phosphate wasting[vii]	Measure serum calcium, phosphate, alkaline phosphatase and 25(OH) vitamin D, see page 79. If deficient or insufficient, check PTH levels and consider vitamin D replacement if clinically indicated, see page 79 ng/mL / nmol/L Deficiency: < 10 / < 25 Insufficiency: < 20 / < 50
Osteonecrosis	• Infarct of epiphyseal plate of long bones resulting in acute bone pain • Rare but increased prevalence in persons with HIV	**Risk factors:** • Low CD4 count • Glucocorticoid exposure • IVDU • Alcohol • Blood coagulation disorders	**MRI**

i Greater loss of BMD observed with initiation of regimens containing TDF and some PIs.* Additional loss and gains in BMD observed with switch to and away from TDF-containing ARV regimens, respectively. Clinical relevance to fracture risk not determined. TAF is associated with less bone loss than TDF
Consider replacing TDF 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/m^2), 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 www2.health.vic.gov.au/about/publications/policiesandguidelines/falls-risk-assessment-tool

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

vi Causes of secondary osteoporosis include hyperparathyroidism, vitamin D deficiency, hyperthyroidism, malabsorption, hypogonadism or amenorrhoea, diabetes mellitus, and chronic liver disease

vii Use of tenofovir disoproxil fumarate (TDF) is associated with cases of renal phosphate wasting. 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 78 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 is prevalent (>80%) in some cohorts of populations with and without HIV – may not be directly associated with HIV **Factors associated with lower vitamin D:** • Dark skin • Dietary deficiency • Avoidance of sun exposure • Malabsorption • Obesity • Chronic kidney disease • Some ARVs[v]	Check vitamin D status in persons with history of: • low bone mineral density and/or fracture • high risk for fracture Consider assessment of vitamin D status in persons with other factors associated with lower vitamin D levels (see left column)	Replacement and/or supplementation of vitamin D is recommended for persons with both vitamin D insufficiency[vi] and one of the following: • osteoporosis • osteomalacia • increased PTH (once the cause has been identified) Consider re-testing after 6 months of vitamin D intake

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

ii 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 83. A combination of low calcium + low phosphate +/- high alkaline phosphatase may indicate osteomalacia and vitamin D deficiency

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

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

Reducing risk of fractures **Persons at high risk of fractures:** • Frail or sarcopenic persons • Previous fracture, particularly if recent • Low BMD • High FRAX score (refer to national guidelines) • High falls risk	• Aim to decrease falls by addressing frailty and fall risks[i] • Consider bisphosphonate[ii] – 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] – No significant interactions between bisphosphonates and ARVs • Optimal management of frailty includes optimising nutrition, exercise (aerobic and resistance training), see section on frailty, page 123 • 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

i Falls Risk Assessment Tool (FRAT), See page 79 for diagnosis and management of vitamin D deficiency 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 79 for diagnosis and management of vitamin D deficiency

iv See page 78; 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			• 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 persons with HIV and ESRD consider transplantation evaluation, see page 113
	UA/C[iii] 3-30	• Check risk factors for CKD, use of nephrotoxic medicines including ART and potential artificial decline in eGFR[iv, viii, ix] • Discontinue or adjust drug dosages where appropriate[v] • Perform renal ultrasound • If haematuria present with any level of proteinuria refer to nephrologist • Refer to nephrologist if new CKD or progressive decline in eGFR			
	UA/C[iii] > 30				

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

Management of HIV-associated kidney disease[vi]

Prevention of progressive renal disease	Comment
1. ART	Start ART immediately where HIV-associated nephropathy (HIVAN)[vii] or HIV immune complex disease strongly suspected. Immunosuppressive therapy may have a role in immune complex diseases. Renal biopsy to confirm histological diagnosis recommended **Consider discontinuing or replacing TDF** by non-tenofovir drug or by TAF*** if:** • UP/C 15-50 mg/mmol (see tubulopathy section) • eGFR > 60 mL/min, but decrease in eGFR by 5 mL/min per year for at least 3 consecutive years or confirmed 25% eGFR decline from baseline • co-morbidities with a high risk of CKD (i.e. diabetes and hypertension) • body weight < 60 kg • use of a PI/b as a third agent **Discontinue or Replace TDF** by non-tenofovir drug or by TAF*** if:** • eGFR ≤ 60 mL/min • UP/C > 50 mg/mmol • nephrotoxic comedication • previous TDF toxicity (proximal renal tubulopathy) ** Expert opinion pending clinical data ***There are limited data on use of TAF with low eGFR, particularly eGFR ≤ 10 mL/min
2. Start ACE inhibitors or angiotensin-II receptor antagonists if: a. Hypertension, see page 70, and/or b. Proteinuria	**Monitor eGFR and K^+ level closely on starting treatment or increasing dose** a. Blood pressure target: < 130/80 mmHg
3. General measures: a. Avoid nephrotoxic drugs including NSAID b. Lifestyle measures (smoking, weight, diet) c. Treat dyslipidaemia, see page 76-77 and diabetes, see page 74-75 d. Adjust drug dosages where necessary, see page 84 e. Aspirin to be considered in those with DM and proteinuria and/or eGFR<30, see page 68	CKD and proteinuria are independent risk factors for CVD

i For eGFR: Use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated > 60 mL/min. The abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative www.chip.dk/Tools-Standards/Clinical-risk-scores.
Definition CKD: eGFR ≤ 60 mL/min for ≥ 3 months (see 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 persons 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. NICE Guidelines recommend UACR values 3-70 mg/mmol are confirmed using early morning urine test, whereas an UACR>70 does not need confirmation. For persistent microscopic haematuria NICE guidelines recommend ultrasound, investigating of urological cancer in age-appropriate groups, and that isolated microscopic haematuria is monitored annually with urinalysis for haematuria and proteinuria, eGFR and blood pressure (See www.nice.org.uk/guidance/ng203/chapter/Recommendations#investigations-for-chronic-kidney-disease).

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 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

ix As acute kidney injury (AKI) predisposes to CKD, NICE guidelines recommend to monitor those with AKI for incident CKD/CKD progression for at least three years, longer in case of more severe AKI (>grade 3), even if eGFR has normalised

ARV-associated Nephrotoxicity

Renal abnormality*	ARV	Management
Proximal tubulopathy with any combination of: 1. Proteinuria: urine dipstick ≥ 1, or confirmed increase in UP/C > 15 mg/mmol(i) 2. Progressive decline in eGFR and eGFR ≤ 90 mL/min(ii) 3. Phosphaturia(iii): confirmed hypophosphataemia secondary to increased urine phosphate leak 4. Glucosuria in non-diabetics	**TDF****	**Assessment:** • Tests for proximal renal tubulopathy/renal Fanconi syndrome(iii) (less frequent in Black persons with HIV) • Consider renal bone disease if hypophosphataemia of renal origin: measure 25(OH) vitamin D, PTH, DXA **Replace TDF by non-tenofovir drug or TAF*** if:** • Documented tubular proteinuria and/or glucosuria • Progressive decline in eGFR and no other cause • Confirmed hypophosphataemia of renal origin and no other cause • Osteopenia/osteoporosis in the presence of increased urine phosphate leak
Nephrolithiasis: 1. Crystalluria 2. Haematuria(iv) 3. Leukocyturia 4. Loin pain 5. Acute renal insufficiency	**ATV (DRV)**	**Assessment:** • Urinalysis for crystalluria/stone analysis • Exclude other cause for nephrolithiasis • Renal tract imaging including CT scan **Consider stopping ATV if:** • Confirmed renal stones • Recurrent loin pain +/- haematuria
Interstitial nephritis: 1. Progressive decline in eGFR(ii) 2. Tubular proteinuria(iii)/ haematuria 3. Eosinophiluria (if acute) 4. Leukocyte casts	**ATV**	**Assessment:** • Renal ultrasound • Refer to nephrologist **Consider stopping ATV if:** • Progressive decline in eGFR and no other cause
Progressive decline in eGFR, but none of the above(ii)	**TDF**** **PI/r(vi)**	**Complete assessment:** • Risk factors for CKD(v) (see Kidney Disease: Definition, Diagnosis and Management) • PRT, UA/C, UP/C (see Kidney Disease: Definition, Diagnosis and Management and Indications and Tests for Proximal Renal Tubulopathy (PRT) • Renal tract ultrasound, see page 81 **Consider stopping ARVs with potential nephrotoxicity if:** • Progressive decline in eGFR and no other cause(v)

In persons with ART-associated nephrotoxicity some data to suggest eGFR improvement may take time after discontinuation of the offending agent, and the potentials for improvement are higher the shorter duration of nephrotoxic ART use, the higher eGFR at discontinuation and the younger the age.

* 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 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:
• Progressive decline in eGFR[i] & eGFR ≤ 90 mL/min & no other cause and/or • Confirmed hypophosphataemia[ii] and/or • Confirmed increase in UP/C[iii] • Renal insufficiency even if stable (eGFR ≤ 60 mL/min) • Tubular proteinuria[v]	• Blood phosphate and urinary phosphate excretion[vi] • Blood glucose and glucosuria • Serum bicarbonate and urinary pH[vii] • Blood uric acid level and urinary uric acid excretion[viii] • Serum potassium and urinary potassium excretion	• Confirmed proximal renal tubulopathy with no other cause

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

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

iii UP/C in spot urine, detects total urinary protein, including protein of glomerular or tubular origin. The urine dipstick analysis primarily detects albuminuria as a marker of glomerular disease and is inadequate to detect tubular disease

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

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

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

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

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

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

Dose Adjustment of ARVs for Impaired Renal Function

	eGFR[ii] (mL/min)				Haemodialysis[iii]
	≥ 50	30-49	10-29	< 10	
NRTIs					
Individual agents					
ABC[iii]	300 mg q12h or 600 mg q24h	No dose adjustment required			
FTC[v]	200 mg q24h		200 mg q72h	200 mg q96h	200 mg q24h[iv]
3TC[v]	300 mg q24h	150 mg q24h	100 mg q24h[vi]	50 mg q24h[vi]	25 mg q24h[iv, vi]
TDF[vii]	300[viii] mg q24h	300[viii] mg q48h	Not recommended (300[viii] mg q72-96h, if no alternative	Not recommended (300[viii] mg q7d, if no alternative)	300[viii] mg q7d[iv]
TAF[ix,x]	25[xi] mg q24h			No data	25 mg q24h[iv]
ZDV	300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h[iv]
Combinations					
ABC[iii]**/3TC**[v]	600/300 mg q24h	Use individual drugs			
ZDV/3TC	300/150 mg q12h				
ABC/3TC/ZDV	300/150/300 mg q12h				
TAF[ix]**/FTC**[v]	25[xi]/200 mg q24h		Use individual drugs[xv]		25/200 mg q24[iv]
TDF[vii]**/FTC**[v]	300[viii]/200 mg q24h	300[viii]/200 mg q48h	Use individual drugs		
NNRTIs					
EFV	600 mg q24h	No dose adjustment required			
ETV	200 mg q12h	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**[v]**/RPV**	25[xi]/200/25 mg q24h		Use individual drugs[xv]		25/200/25 mg q24h[iv]
TDF[vii]**/FTC**[v]**/RPV**	300[viii]/200/25 mg q24h	Use individual drugs			
DOR	100 mg q24h	No dose adjustment required; < 10: no PK data[xix]			
TDF[vii]**/3TC**[v]**/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**[v]**/DRV/c**	10/200/800/150 mg q24h		Use individual drugs		
LPV/r	400/100 mg q12h	No dose adjustment required[xiii]			
Other ART					
RAL	1 x 400 mg tablet q12h or 2 x 600 mg tablets q24h	No dose adjustment required[xiii]			
DTG	50 mg q24h	No dose adjustment required[xiii]			
3TC[v]**/DTG**	300/50 mg q24h	Use individual drugs			
ABC[iii]**/3TC**[v]**/DTG**	600/300/50 mg q24h	Use individual drugs[xvi]			
RPV/DTG	25/50 mg q24h	No dose adjustment required[xiii]			
TAF[ix]**/FTC**[v]**/BIC**	25/200/50 mg q24h	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**[v]**/EVG/c**	10/200/150/150 mg q24h		Not recommended[xii]		10/200/150/150 mg q24h[iv]
TDF[vii]**/FTC**[v]**/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
LEN	600 mg q24h on days 1 & 2, 300 mg q24h on day 8, 927 mg sc on day 15 followed by maintenance dose: 927 mg sc every 6 months (26 weeks +/- 2 weeks)	No dose adjustment required[XX]

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 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; 50 mg loading dose for haemodialysis

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 persons with end-stage renal disease on chronic dialysis. However, TAF/FTC/EVG/c may be used with caution if the potential benefits are considered to outweigh potential risks. One clinlical study has demonstrated safety of TAF/FTC/EVG/c for persons 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 persons 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 persons 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 persons on chronic dialysis, however these findings need to be confirmed in a larger trial

xvii In persons 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

xix Doravirine is modestly removed by heamodialysis so that no dosage adjustment is needed

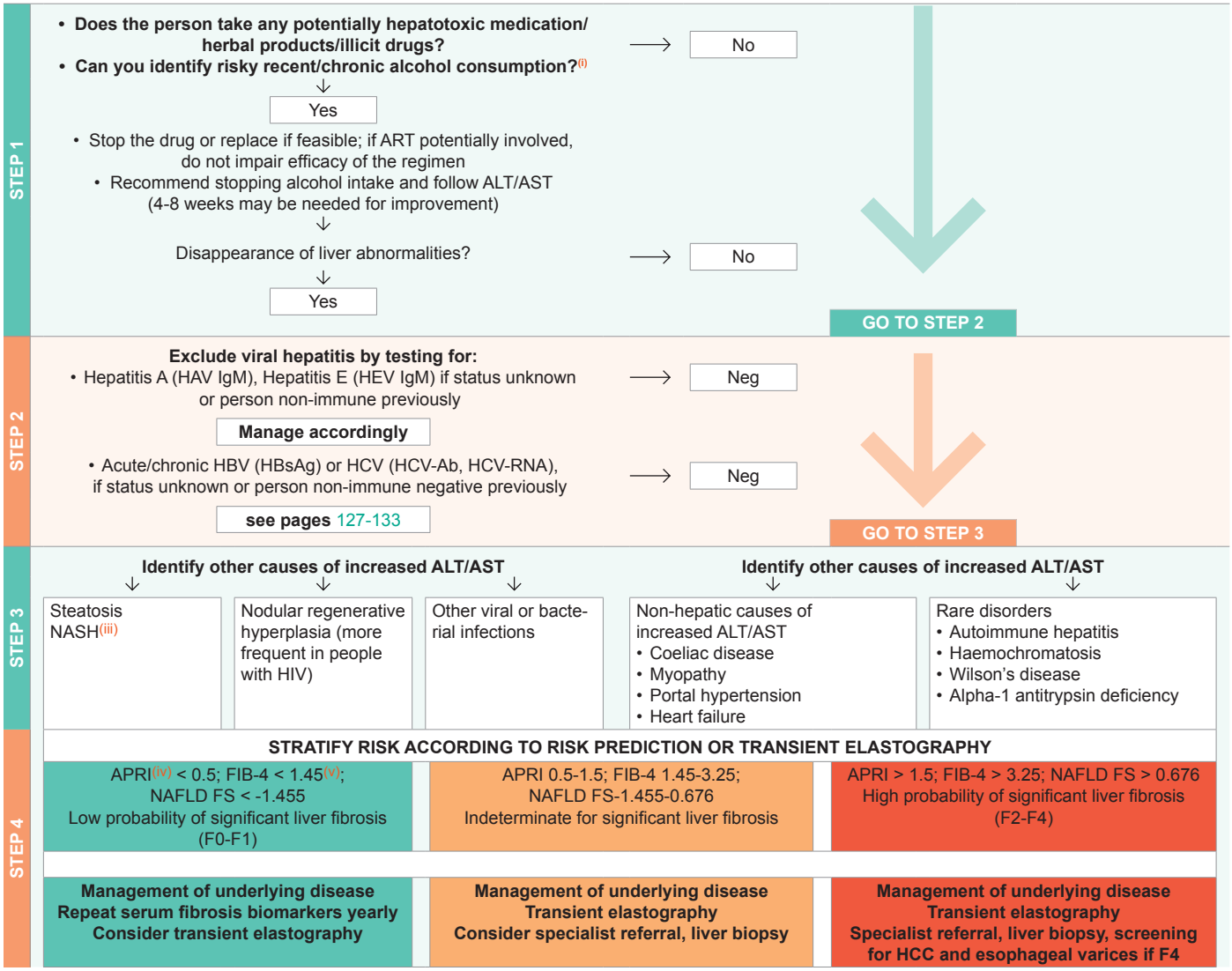
xx LEN has not been studied in individuals with end stage renal disease (CrCL <15 mL/min or on renal replacement therapy and therefore should be used with caution in these individuals)

* Due to lack of COBI data in persons with HIV with renal impairment

For recommendations on ART use in persons with HIV undergoing renal transplantation, see Solid Organ Transplantation, page 125

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

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



See pages 87-90 and 93

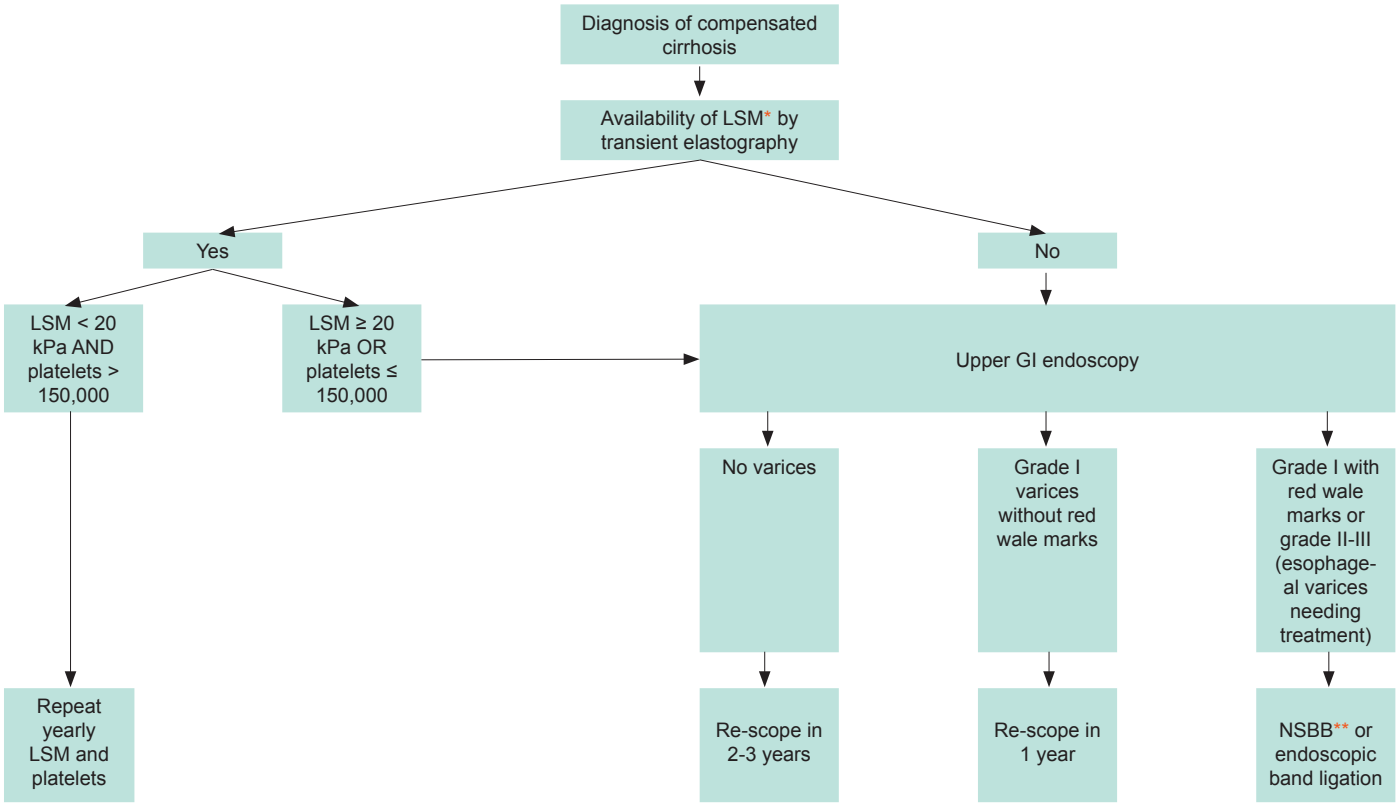
i > 20 g in women, > 30 g in men
ii Reflex anti-Hepatitis delta (HDV) testing if a patient is HBsAg positive
iii Non-Alcoholic Steatohepatitis, see NAFLD
iv APRI, AST to Platelet Ratio Index = (AST in IU/L) / (AST Upper Limit of Normal in IU/L)/ (Platelets in 10^9/L)
v FIB-4 = Age [years] x AST [U/L])/([platelet [10^9/L]) x ALT$^{1/2}$ [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 VII consensus (EASL)
* LSM, liver stiffness measurement;
** NSBB, non-selective beta-blocker: prefer carvedilol 6.25-25 mg/day
Persons with compensated cirrhosis without varices on screening endoscopy should have endoscopy repeated every 2 years with ongoing liver injury, overweight 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, is the gold standard and 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: sinusoidal portal
HVPG ≥ 10 mmHg: clinically significant portal hypertension
In primary and secondary prophylaxis for variceal bleeding HVPG measurement allows to monitor efficacy of beta-blockers
LSM by TE ≤15 kPa plus platelet count ≥150x109/L rules out clinically significant portal hypertension (sensitivity and negative predictive value >90%) in patients with compensated liver cirrhosis.
In patients with ascites and low-risk varices (small, no red signs, not Child-Pugh C), traditional NSBBs or carvedilol may be used to prevent first variceal haemorrhage. Carvedilol is the preferred NSBB in compensated cirrhosis, since it is more effective at reducing HVPG.

The Baveno VII consensus (EASL) mentions the term compensated advanced chronic liver disease (cACLD), which encompasses both advanced liver fibrosis and cirrhosis (www.journal-of-hepatology.eu/article/S0168-8278%2821%2902299-6/fulltext)

Surveillance and management for hepatocellular carcinoma should be conducted according to the EASL guidelines*.
See also "Screening for complications" section in the Viral Hepatitis Coinfections section.

* EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma (J Hepatol 2018, vol. 69, 182-236) DOI: 10.1016/j.jhep.2018.03.019

Liver Cirrhosis: Management

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

Management of hypervolaemic hyponatreaemia (Na^+ concentracion≤130 mmol/L)	Management strategy of hepatic encephalopathy (HE)
1. Fluid restriction: 1000-1500 mL/day 2. Hold diuretics 3. Consider albumin infusion 4. At present, the use of vaptans should be limited to controlled clinical studies	**General management** 1. Identify and treat precipitating factor (GI haemorrhage, infection, pre-renal azotaemia, constipation, sedatives) 2. In patients with severe hyperacute disease with HE and highly elevated arterial ammonia who are at risk of cerebral oedema, nutritional protein support can be deferred for 24-48 h until hyperammonemia is controlled 3. Recommend enteral or parenteral nutritional support in critically ill patients **Specific therapy** Lactulose 30 cm^3 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 cm^3 po bid) Lactulose enemas (300 cm^3 in 1L of water) in persons who are unable to take it po. Lactulose can be discontinued once the precipitating factor has resolved Rifaximin 550 mg po bid is an effective add-on therapy to lactulose for prevention of overt hepatic encephalopathy recurrence

Management strategy in uncomplicated ascites	
General management	• 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) 1) Persons with cirrhosis and gastrointestinal bleeding 2) 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%) 3) Persons in which ascitic fluid protein is < 1.5 g/dL along with • 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	• Salt restriction: 1-2 g/day. Liberalise if restriction results in poor food intake • Large volume paracentesis as initial therapy only in persons with tense ascites • Administer iv albumin (= 6-8 g/L ascites removed)
Follow-up and goals	• Adjust diuretic dosage every 4-7 days • Weigh the person at least weekly and BUN, 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

Caloric requirements
- Nonobese at least 35 kcal/kg body weight/day; obese 25-35 kcal/kg/day if BMI 30-40, and 20-25 kcal/kg/day if BMI>40

Protein requirements
- Protein restriction is not recommended
- Protein intake of 1.2-1.5 g/kg/day of normal body weight
- Type: rich in branched chain (non-aromatic) amino acids

Micronutrients
- Vitamin A, D, E, K; vitamin B1, B3, B6, B9, B12, C, magnesium, zinc, selenium, copper
- Micronutrient deficiencies should be assessed at least annually

Physical activity
Recommended to improve muscle contractile function and muscle mass in patients with cirrhosis.
Personalized activity prescription:
- Frequency – Aerobic (4-7 d/week)
- Resistance (2-3 d/week)
- Intensity – Use the talk test (be short of breath but can still speak a full sentence); 3 sets of 10-15
- Time – Start slow and build up
  - Aerobic: 150 min per week
  - Resistance: ≥1 day per week
- Type – aerobic, resistance, flexibility and balance

Personalized activity prescription (guided by a certified exercise physiologist or physical therapist)

Analgesia in persons with hepatic failure

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

Screening for HepatoCellular Carcinoma (HCC)

- HCC screening is indicated in all cirrhotic persons with HBV or HCV co-infection (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 easl.eu/publications/clinical-practice-guidelines/
- In HBV-positive non-cirrhotic persons, HCC screening should follow current EASL guidelines. 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, see pages 8, 65 and 127. Table on fibrosis cut-offs, page 132
- Ultrasound (US), with or without alpha-foetoprotein (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
Best to refer early as disease progresses rapidly

= MELD(i) score 12 (listing at 15)
Decompensated cirrhosis (at least one of the following complications at its first occurrence)
- Ascites
- Hepatic encephalopathy
- Variceal bleeding
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- NASH cirrhosis(ii)
- HCC

See Solid Organ Transplantation (SOT)

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 www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/

ii Particularly with metabolic decompensations

Consideration of malnutrition, frailty and sarcopenia in persons with cirrhosis*:

1) All persons with cirrhosis should be assessed for frailty with a standardized tool both at baseline and longitudinally.
2) Given the strong association between muscle mass and outcomes in persons with cirrhosis, objective measures of muscle loss should be considered to assess risk for poor outcomes.
3) All persons with cirrhosis (regardless of a diagnosis of malnutrition) should receive educational resources and counseling regarding the association between nutritional status and outcomes and to optimize nutritional status.

For hepatorenal syndrome, please refer to version 11.1 of the EACS guidelines.

* Hepatology 74(3):p 1611-1644, September 2021. | DOI: 10.1002/hep.32049

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: overweight, type 2 diabetes, dyslipidemia and hypertension. However, NAFLD can occur in lean patients (BMI<25). NAFLD may affect 25% of lean people with HIV. Experts proposed redefining NAFLD as metabolic-associated fatty liver disease (MAFLD) to provide a positive rather than exclusionary diagnosis. However, the role of contemporary ART on MAFLD (in particular regarding an association with weight gain) remains unknown.

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 persons with HIV (30 - 40%) than in the general population. Nearly half of the persons with HIV 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 (≥ F2) or advanced (≥ 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

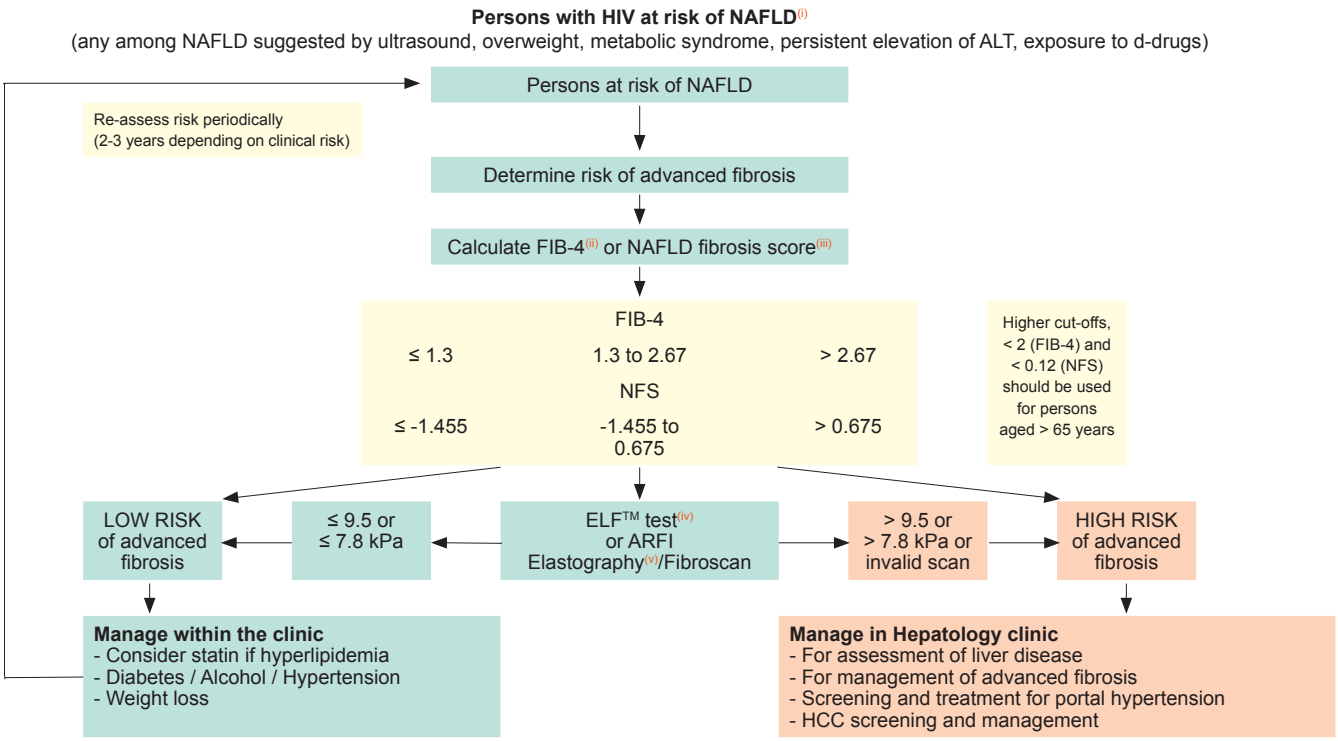
Consideration of ARV drugs

- 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
- A Mediterranean diet should be advised to improve steatosis and insulin sensitivity
- Pharmacotherapy should be reserved for individuals with NASH, particularly for those with significant fibrosis ≥ F2 and individuals with less severe disease, but at high risk of faster disease progression (i.e. with diabetes, metabolic syndrome, persistently increased ALT, high necroinflammation)
- Management 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 persons with HIV 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 x age (years) + 0.094 x BMI (kg/m^2) + 1.13 x impaired fasting glucose/diabetes mellitus(iv) (yes = 1/ no = 0) + 0.99 x AST/ALT ratio-0.013 x platelet (x10^9)-0.66 x albumin(g/dL)

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

v ARFI elastography, Acoustic Radiation Force Impulse

Diagnosis and Management of Hepatorenal Syndrome / Acute Kidney Injury (HRS-AKI)

Diagnosis	• Cirrhosis; acute liver failure; acute-on-chronic liver failure • Increase in serum creatinine ≥ 0.3 mg/dl (≥ 26.5 µmoL/L) within 48 h or ≥ 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 89-90). If person is on transplant list, MELD score should be updated daily and communicated to transplant centre, see Solid Organ Transplantation (SOT)		
Alternative (bridging therapy)	Vasoconstrictors	terlipressin	0.5-2.0 mg iv every 4-6 hours
		or octreotide	100-200 µg sc tid → Goal to increase mean arterial pressure by 15 mmHg
		+ midodrine	5-15 mg po tid
	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: use with caution
	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
Capsid Inhibitor	
LEN	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
INSTI	
RAL	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
EVG	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
DTG	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
DTG/3TC	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, use with caution
DTG/RPV	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
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, not recommended
TDF/FTC/EVG/c	Child-Pugh Class A or B: no dosage adjustment
	Child-Pugh Class C: no data, not recommended
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, not recommended
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: Prevention and Management

Lipoatrophy	Lipohypertrophy[i]
Prevention • Avoid d4T and ZDV or pre-emptively switch. No evidence of benefit by switching other antiretrovirals • Avoid excessive weight loss due to diet and exercise • In ART-naïve persons, limb fat usually increases with initiation of ART not containing d4T or ZDV, reflecting "return-to-health" type of response	**Prevention** • No proven strategy • No contemporary ART has been specifically associated with increased visceral adiposity • An excess of visceral fat has been reported in people with HIV compared with non-HIV persons for the same BMI (even in the absence of obesity) • 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 • Modification of ART: Switch away from d4T or ZDV – Increase in total limb fat ~400-500 g/year (in the first two years) – Risk of toxicity from new drug, see Adverse Effects of ARVs & Drug Classes • Surgical intervention – Offered for cosmetic relief of (facial) lipoatrophy – Autologous fat (whenever possible) or resorbable facial filler (if autologous fat not available) should be preferred against non-resorbable filler	**Management** • Diet and exercise may reduce visceral adiposity – No prospective trials in persons with HIV to indicate degree of diet and/or exercise needed to reduce visceral fat • Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects • Surgical therapy can be considered for localised lipomas/buffalo humps – 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

For "Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management" see page 96

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. An increase > 5% of weight may be considered to define weight gain potentially associated with insulin resistance	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, dyslipidemia, 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 increases weight as part of a return-to-health phenomenon INSTI and TAF may induce greater weight gain than other ARVs´ Switching from INSTI and/or TAF may have a small weight loss effect in overweight/obese people with HIV		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: • ↑ 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, semaglutide). 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 PWH with obesity. Obesity alone doesn't ↑ risk of virological failure with long-acting CAB/RPV; other factors are required
Bariatric surgery		Medical devices or endoscopic procedures (e.g intragastric balloon, aspiration therapy, endoscopic sleeve gastroplasty) 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.	Bariatric surgery may impact ARVs absorption*. Consider therapeutic drug monitoring and drug dose adjustment post-bariatric surgery

* https://liverpool-hiv-hep.s3.amazonaws.com/prescribing_resources/pdfs/000/000/227/original/Gastric_Surgery_2022_Oct.pdf?1665583467

Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management

Risk factors	Prevention/Diagnosis	Symptoms
• HCV/HBV co-infection • Use of ribavirin • Liver disease • Low CD4 count • Pregnancy • Female sex • Obesity	• Routine monitoring of serum lactate levels not recommended - does not predict risk of lactic acidosis • Measurement of serum lactate, bicarbonate & arterial blood gases + pH indicated in case of symptoms suggestive of hyperlactataemia • Close monitoring for symptoms if > 1 risk factor	• Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, elevated ALT and/or AST, weight loss • Acidaemia: asthenia, dyspnoea, arrhythmias • Guillain-Barré-like syndrome

Management

Serum lactate (mmoL/L)	Symptoms	Action
> 5(i)	Yes / No	• Repeat test under standardised conditions to confirm & obtain arterial pH and bicarbonate(i) • If confirmed, exclude other causes – Arterial pH ↓ and/or bicarbonate ↓(i): Stop NRTIs – Arterial pH and/or bicarbonate normal: Consider switch from high to low-risk NRTI & monitor carefully OR stop NRTIs
2-5	Yes	Exclude other causes; if none found: watchfully follow up OR consider switch from high to low-risk NRTI, OR stop NRTI
2-5	No	Repeat test If confirmed, watchfully follow up
< 2		None

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

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

Admit the person.
Stop NRTIs.
Provide iv fluids.
Vitamin supplementation can be used (vitamin B complex forte 4 mL bid, riboflavin 20 mg bid, thiamine 100 mg bid; L-carnitine 1000 mg bid), although benefit is not proven

Travel

General precautions	• Delay travel until clinically stable and treatment established • Provide drug prescription / letter listing ART and concomitant medications for comorbidities 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	• If possible, maintain hours of medicines (e.g., 23.00 local time) when switching time zones, shortening the interval to the next dose when flying east • For those on oral ART ensure sufficient supply • For those on an injectable LA regimen, consider when next injections are due, see Part III: Drug-drug Interactions and Other Prescribing Issues
Acknowledge increased susceptibility[i] of persons with HIV	**1. Observe food, respiratory and hand hygiene** • Particularly important for travellers visiting friends and relatives (VFR) • Bacterial enterocolitis e.g. diarrhoeagenic E. coli, Salmonella, Shigella, Campylobacter • Opportunistic intestinal parasitosis: Cryptosporidium, Cyclospora, Cystoisospora, Microsporidia • Consider respiratory hygiene including mask wearing if circulating respiratory viruses **2. Prevent insect bites** • Repellents (DEET ≥ 30%), spray clothing with insecticide (permethrin) • Sleep under insecticide-treated bednet • Wear long pants and long-sleeved clothes **3. Vaccination and prophylaxis** • Ensure routine, standard of care vaccinations are up to date (see page 99) • Check if travel related vaccines are required (including SARS-CoV-2) and ensure there are no contraindications (eg. Yellow Fever), see page 99 and wwwnc.cdc.gov/travel/page/travel-vaccines • Malaria chemoprophylaxis (consider carrying emergency stand-by treatment[ii] **4. Sun safety** • Caution if on drugs associated with photosensitivity (eg. doxycycline, voriconazole, hydrochlorothiazide, amiodorone)

Advice on travel restrictions, see www.hivtravel.org or consular office of destination country

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	LEN	BIC	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	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	↔	↑ E	↔	↔ 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	↔	↑ E	↔	↔ 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	↔ v	↔	↑ 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 cabotegravir (oral)

None

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.
^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information

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

Vaccination

- Vaccinate according to national guidelines for healthy population, preferably after having achieved suppressed viraemia and immune reconstitution (CD4 count ≥200 cells/μL or ≥15%)
- Consider repeating vaccinations performed at CD4 count <200 cells μL (or <15%) or unsuppressed viraemia once adequate immune reconstitution is achieved (HIV VL undetectable and CD4 count ≥200 cells/μL or ≥15%
- As vaccine responses may be significantly lower in persons with HIV (i.e. lower seroconversion rates, faster titre 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 (<15%) or unsuppressed viremia (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 www.bhiva.org/vaccination-guidelines.aspx and www.cdc.gov/vaccines/schedules/downloads/adult/adult-combined-schedule.pdf

- For attenuated live vaccines[i] (in addition to restrictions for general population):
  - ***Varicella, measles, mumps, rubella, yellow fever**
    Contraindicated if CD4 count <200 cells/μL (<15%) 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 (≥15%). Contraindicated if CD4 count < 200 cells/μL (<15%): then give inactivated parenteral polysaccharide vaccine
  - **Mpox (Jynneos, Imvamune® or Imvanex®)**
    This live but attenuated non-replicating modified vaccinia Ankara (MVA) strain vaccine is safe in persons with HIV, although effectiveness may be lower if CD4 count <200 cells/μL (<15%) and/or people living with unsuppressed HIV

Infection	Vaccination rationale	Comment
Influenza Virus	Higher rate of pneumonia. Explicitly recommended in all persons with HIV	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 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) or use more immunogenic vaccines in particular with low CD4 count and high HIV VL. No benefit for intradermal application. See page 127
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 persons at high risk. Weaker immune response expected with HAV/HBV co-vaccine. See page 127
Neisseria meningitidis	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. Vaccinate against Meningococcus serotype B according to national guidelines
Streptococcus pneumoniae	Higher rate and severity of invasive disease. Vaccine explicitly recommended for all persons with HIV	One dose of a conjugated vaccine: PCV-13, PCV-15 or PCV-20a for all persons according to availability and national guidelines, also if pre-vaccinated with PPV-23 polysaccharide vaccine. For patients vaccinated with PCV-13 or PCV-15, one dose of PPV-23 at least 2 months after the conjugate vaccine may be considered in some national guidelines for all persons with HIV
Varicella Zoster Virus (VZV)	Higher rate and severity of both chickenpox and zoster	Perform serology if exposure history negative. Vaccinate if seronegative. For contraindications, see*. To prevent shingles, 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 every 10 years
Rabies		If pre-exposure rabies vaccination is administered in persons with CD4 ≥ 200 cells/μL, 2-dose (days 0 and 7) IM schedule is recommended. For persons with CD4 count <200 cells/μL or detectable viremia, consider pre-exposure vaccination with 3 doses (0, 7, 21 or 28 days) and antibody titre measurement 14 days later. In case of rabies postexposure prophylaxis (PEP) in unvaccinated persons, perform immediate wound cleaning, infiltration of human rabies immunoglobulin (HRIG) within and around the wound and days 0, 3, 7 and 14 IM administration of rabies vaccine in people with HIV with CD4≥200 cells/μL. In people with HIV with CD4 <200 cells/μL or detectable viremia, PEP should comprise a 5-dose vaccination regimen (days 0, 3, 7, 14, and 28), with one dose of HRIG and additional vaccine dose is recommended if rabies serology demonstrates inadequate titers during the follow-up (antibody levels <0.5 IU/mL). In vaccinated people with HIV, the PEP recommendation for a 2/3-dose vaccination series has not changed

Severe Acute Respiratory Syndrome 2 (SARS-CoV-2)	Low CD4 count and non-suppressed HIV VL may increase the risk of acquiring SARS-CoV-2 infection and/or progressing to severe COVID-19	In a pandemic situation, all persons with HIV should be vaccinated according to the national guidelines irrespective of CD4 count and HIV VL. Advanced HIV infection (CD4 count < 200 cells/μL) and persons with detectable HIV viraemia have poorer humoral immune responses and are candidates for COVID-19 booster doses. Bivalent COVID-19 vaccines are authorized for use only in people with HIV who have received at least primary vaccination against COVID-19
Mpox, See Management of Mpox in persons with HIV	Mpox can be a life-threatening opportunistic infection in people with HIV with CD4 count <200 cells/μL (<15%) and/or detectable HIV viraemia	Two doses administered 28 days (4 weeks) apart by subcutaneous (0.5 mL) route. Intradermal route also effective using one fifth of the standard dose. Primary mpox vaccination should be offered to all people using HIV PrEP and people with HIV at high-risk for mpox exposure[iv]. In case of vaccine shortage, people with HIV with advanced disease (CD4 T-cells<350/uL) or detectable HIV viraemia should be prioritised, according to the WHO and CDC guidelines. Post-exposure prophylaxis with mpox vaccination should be given as soon as possible and ideally within four days of exposure. Administration 4 to 14 days after exposure may still provide some protection. People with HIV with advanced disease (CD4 T-cells<350/uL or detectable HIV viraemia should be prioritised for post-exposure vaccination (if available) according to local and international WHO, CDC 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
iv Gay, bisexual, and other men who have sex with men, and transgender or nonbinary people (including adolescents who fall into any of the aforementioned categories) who in the past 6 months have had:
- A new diagnosis of one or more sexually transmitted diseases (e.g., chlamydia, gonorrhea, syphilis); or
- More than one sexual partner; or
- People who have had any of the following in the past 6 months:
  - Sex at a commercial sex venue; or
  - Sex in association with a large public event in a geographic area where mpox transmission is occurring; or
  - Sexual partners of people with the above risks; or
  - People with HIV or other causes of immunosuppression who have had recent or anticipate potential mpox exposure

Sexual and Reproductive Health

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 partner living with HIV	• When the partner with HIV is virologically suppressed on ART for >6 months, there is no risk of transmission to the partner without HIV • Undetectable equals untransmissible (U=U) • Consider in e.g. sero-different couples(i)
Pre-exposure prophylaxis (PrEP)	• Effective in persons without HIV at risk of acquiring HIV, see Pre-exposure prophylaxis (PrEP)
Post-exposure prophylaxis (PEP)	• Consider after unprotected anal or vaginal intercourse, if one partner has a detectable HIV-VL and the other partner is HIV seronegative • Start as soon as possible and within 72 hours post-sexual exposure. See Post-exposure prophylaxis (PEP)
Male condom or female condom use	• Effective in reducing the sexual transmission of HIV

U=U should be discussed with all persons with HIV, at diagnosis and when starting/switching ART. The evidence is clear that persons with undetectable VL do not transmit HIV sexually. In large studies of sexual HIV transmission among thousands of sero-different couples, (one partner living with HIV and one not), no cases of linked sexual transmission of HIV from a virally suppressed person with HIV on ART to their HIV-negative partner were observed. Within these studies, all HIV transmissions seen were not phylogenetically linked to within-couple transmission.

i see page 12

Reproductive health

All persons should be asked about their reproductive goals at HIV diagnosis and during follow-up and should 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

Intercourse without condom use is recommended as a preferred method of conception. In cases where the partner is living with HIV and is not on effective treatment or treatment adherence remains uncertain, the following should be considered:

- 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 there is uncertainty about partner living with HIV adherence to ART, 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 persons with HIV 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, 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

Treatment for menopausal women

i Topical (vaginal) hormone replacement therapy (HRT) should be considered in all women given the positive effects on sexual health and urogenital symptoms
ii Systemic HRT should be considered in women experiencing vasomotor, mood or urogenital symptoms.
iii 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
iv 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 should be sought
- 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

Prophylaxis for bacterial STIs

Recent studies have shown high efficacy in preventing bacterial STIs such as chlamydia, gonorrhoea and syphilis in men on doxycycline as PrEP and PEP.
Discussion on the use of doxycycline PrEP and PEP should be undertaken in men with HIV with recent bacterial STI and offered if locally available and following local guidance.
See Pre-exposure prophylaxis, page 23

STI screening and treatment

STI screening should be offered to all sexually active persons 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 persons 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 iusti.org/treatment-guidelines/

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

	Therapy	Comment
Chlamydia infection including lymphogranuloma venereum (LGV)	**Preferred treatment:** Doxycycline (100 mg po bid 7-10 days, contraindicated in pregnancy) for urethritis and cervicitis[i] **Alternatives:** Azithromycin 1 g po followed by 500mg once daily for two days or Erythromycin (500 mg po qid[ii] for 10-14 days) or levofloxacin (500 mg po qd for 7 days) If rectal infection, a test of cure (TOC) should be performed **For LGV:** **Preferred treatment:** Doxycycline (100 mg po bid for 21 days) **Alternatives:** Erythromycin (500 mg po qid[ii] for 21 days)	• May cause therapy-resistant proctitis in HIV-positive MSM • Screening recommended at genital, rectal and pharyngeal sites according to exposure • Pharyngeal infections is usually asymptomatic • Consider co-infections with *Neisseria gonorrhoeae* • Avoid sexual activity for 7 days post-treatment initiation • Individuals should only resume having sex after symptoms have resolved and sex partners have been treated • The same treatment for LGV is recommended for asymptomatic individuals and contacts of individuals with LGV
Gonorrhoea	Ceftriaxone (1 g im as a single dose)[i]	• Can cause proctitis, prostatitis and epididymitis • Screening recommended at genital, rectal and pharyngeal sites according to exposure • Rectal and pharyngeal infections may be 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 BASHH recommendations, www.bashhguidelines.org/current-guidelines/urethritis-and-cervicitis/gonorrhoea-2018/. IUSTI Guidelines recommend 500 mg im with azithromycin 2 g as a single dose, however these recommendations have not been updated in several years, iusti.org/regions/guidelines/
HBV infection **HCV infection**	See detailed information on HIV/HCV or HIV/HBV co-infections, pages 128-129	• Interruption of TDF, 3TC or FTC can lead to HBV reactivation • Clusters of acute HAV and HCV infection in HIV-positive MSM across Europe • See Vaccination
HPV infection	There are several treatment modalities for the management of genital warts with no evidence to suggest one approach is better than another approach. Consider operative removal by laser surgery, infrared coagulation, cryotherapy, etc. Management of both pre-invasive cervical lesions as well as peri- and intra-anal lesions should follow local or national guidelines	• Infection is mostly asymptomatic; relapse of genital warts is frequent • Cervical PAP smear test recommended in all HIV-positive women • Anal HPV screening and cytology should be considered in all persons with HIV practicing anal sex • Consider high resolution anoscopy (See Cancer: Screening Methods) Rectal palpation or external inspection is not sufficient • See Vaccination
HSV infection	**Primary infection**: aciclovir (400-800 mg po tid), famciclovir (250-500 mg po tid) or valaciclovir (1000 mg po bid) for 7-10 days **Recurrent episodes**: aciclovir (400 mg po tid) or valaciclovir (500 mg po bid) for 5-10 days **Suppressive management**: Chronic suppressive therapy is usually offered to persons who experience six or more clinical episodes per year or who experience significant anxiety or distress related to their clinical recurrences. Chronic suppression: aciclovir (400-800 mg bid or tid) or famciclovir 500 mg bid or valaciclovir 500 mg po bid	• Treatment of HSV2 alone does not prevent HIV-transmission and only modestly prevents HIV disease progression
Mpox	For information on the diagnosis and management of mpox, see Part VI: Opportunistic Infections and COVID-19 section	
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). Alternative regimen include doxycyline (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 and ocular syphilis:** penicillin G (6 x 3 - 4 million IU iv for at least 2 weeks) 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 28 days is also an alternative approach but should be reserved for exceptional circumstances. This regimen has very limited supporting data[i] **Adjunctive therapy with prednisolone:** adjunctive treatment with prednisolone (20-60 mg po daily for 3 days) may be considered in optic neuritis, uveitis, pregnancy and neurosyphilis	• 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 • Consider cerebrospinal fluid examination if a four-fold reduction in VDRL test is not achieved

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 www.fertstert.org/article/S0015-0282%2809%2902741-1/fulltext	
Check for endocrine causes:	Signs of hypogonadism	**Men** - Look for signs of testosterone insufficiency (main: decreased or absent nocturnal erections, decrease in testes size, decreased volume of ejaculate, hot flushes, sweats, reduction of body hair and beard; others: reduced sexual arousal and libido, decreased frequency of sexual thoughts and fantasies, decreased genital sensitivity, erectile dysfunction, loss of vitality; fatigue; loss of muscle mass and muscle strength) - If signs or symptoms of hypogonadism are present ask for hormonal assessment: lutropin hormone (LH), follicle stimulating hormone (FSH), total testosterone; sex hormone-binding globulin evaluation to calculate free testosterone, see 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

Men	Women
Treatment of erectile dysfunction	**Sexual pain**
Primarily oral PDE5-inhibitors (sildenafil, tadalafil, vardenafil). • All at least 30 minutes before initiation of sexual activity • Use lower dose if on PI/b - sildenafil (25 mg every 48 hours) - tadalafil 5 mg initial dose with maximum dose 10 mg in 72 hours - vardenafil 2.5 mg maximum dose in 72 hours Poppers have a synergistic effect with PD5-blockers which can lead to profound hypotension thus concurrent use is not recommended • Tadalafil also licensed for use as an everyday ongoing therapy	Counselling Local hormone therapy Pelvic physiotherapy Vaginal/rectal suppositories Topical lidocaine Capsaicin Vestibulectomy
Treatment of premature ejaculation	**Low desire**
• 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	Counselling Hormonal therapy Bupropion Flibanserin (contraindicated with boosted ARVs due to risk of hypotension)
	Low arousal
	Counselling Hormonal therapy PDE5 inhibitors (e.g., sildenafil)
	Orgasmic dysfunction
	Mindfulness, sex therapy Hormonal therapy Bupropion PDE inhibitors (e.g., sildenafil) Yohimbine hydrocholoride (concomitant use of boosted ARVs may increase BP)

Mental Health: Depression and Anxiety Disorders

Depression: Screening and Diagnosis

Significance

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

Screening and diagnosis of depression

Who?	How to screen?	How to diagnose?
Consider screening at each routine HIV clinic visit, in view of the high prevalence of depression **Populations at particularly high risk** • Positive history of depression in family • Depressive episode in personal history • Older age • Adolescence • Persons with history of drug addiction, psychiatric, neurologic or severe somatic co-morbidity • Use of EFV • Use of neurotropic and recreational drugs • As part of investigation of neurocognitive impairment, see page 114 • Socially isolated	• Two questions: 1. Have you often felt depressed, sad or without hope in the last few months? 2. Have you lost interest in activities that you usually enjoy? • Rule out other medical conditions (such as hypothyroidism, hypogonadism, Cushing's syndrome, vitamin B12 deficiency) • Rule out depressive symptoms associated with ART (such as EFV) and non-ART medication (such as corticosteroids)	**Symptoms – evaluate regularly** **A.** At least 2 weeks of depressed mood OR **B.** Loss of interest OR **C.** Diminished sense of pleasure + **4 out of 7 of the following:** 1. Weight change of ≥ 5% in one month or a persistent change of appetite 2. Insomnia or hypersomnia on most days 3. Changes in speed of thought and movement 4. Fatigue 5. Feelings of guilt and worthlessness 6. Diminished concentration and decisiveness 7. Suicidal ideation or a suicide attempt(i) Assessment of the risk of suicide should be done with the following questions: • 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?

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

Depression: Management

Degree of depression	Number of symptoms (see page 106: A, B or C + 4/7)	Treatment	Consultation with expert
No	< 4	No	
Mild	4	• Problem-focused consultation • Consider antidepressant treatment(i) • Recommend physical activity	• Always, if treating doctor is unfamiliar with use of antidepressants • If depression not responding to treatment • If person has suicidal ideation or psychotic symptoms (delusions or hallucinations) • 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[ii]	Sedation	Nausea or GI effects	Sexual dysfunction	Weight gain
	mg/day							
Selective serotonin-reuptake inhibitors (SSRIs)[i]								
paroxetine	10-20	20-40	No (unless if combined with other CNS drugs)	++	++	+++	+++	++
sertraline	25-50	50-150	Low	+	- / +	+	+	+[iii]
citalopram	10-20	20-40	No	+++	+++	+++	++	+[iii]
escitalopram	5-10	10-20	No (unless if combined with other CNS drugs)	++	++	+++	++	+[iii]
Mixed or dual-action reuptake inhibitors								
duloxetine	30	30-60	Yes (at > 1000 mg)	++	+++	+++	++	+
venlafaxine	37.5-75	75-225	Yes	+++	+++	+++	++	++
Mixed-action newer agents								
mirtazapine	30	30-60	Low	- / +	++	- / +	- / +	++

- none / + moderate / ++ severe / +++ very severe

i For many persons, SSRI induction may be associated with adverse effects (sexual dysfunction, 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 or other 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	LEN	BIC	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	E	↔	↑	↔	↔	↔
	phenelzine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	reboxetine	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
	St John's wort	Dd	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 cabotegravir (oral)
None

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.
- # At least a 2-week (moderate inducers) or 4-week (strong inducers) cessation period is recommended prior to initiation of LEN due to the persisting inducing effect after discontinuation of an inducer.

Further Information
For additional drug-drug interactions and for more detailed pharmacokinetic interaction data and dosage adjustments, please refer to:
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 persons with HIV[i]
- Specific anxiety disorders include the following:
  - panic disorder (10% in persons with HIV)
  - generalized anxiety disorder (5.6% persons with HIV)
  - social anxiety disorder (9% persons with HIV)
  - 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

Screening and diagnosis of anxiety		
Who?	**How to screen?**	**How to diagnose?**
Consider screening all persons with HIV at each routine clinic visit (in view of the high prevalence of anxiety) **Populations at particularly high risk** • Positive history of anxiety disorders in family • Anxious personality • Alcohol excess • As part of investigation of cognitive impairment, see page 114 • Multiple stressful life events (particular relevance during COVID-19 pandemic)	**Generalised Anxiety Disorder-2 (GAD-2) Screening tool[i]:** "Over the last 2 weeks, how often have you been bothered by the following problems?" • Feeling nervous, anxious or on edge • Not being able to stop or control worrying **Score each question and calculate sum:** 0. Not at all 1. Several days 2. More than half the days 3. Nearly every day	**If GAD-2 cut-off score of ≥ 3**, ask the following questions to diagnose General Anxiety Disorder: • 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 **Rule out hyperthyroidism, hypoglycemia and hyperadrenocorticism. Exclude caffeine excess and use of stimulants (such as cocaine, crystal meth, amphetamines)** **Seek expert advice to diagnose panic disorders, social phobia and PTSD**

i GAD-2 score is a validated screening tool in persons with HIV, 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	• 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:
		  • Cognitive Behavioral Therapy
		  • Cognitive Behavioral Stress Management
		  • Mindfulness-based Cognitive Therapy
		  • Peer Support Counseling
			• Always, if treating doctor is unfamiliar with use of antidepressants
			• If anxiety not responding to treatment
			• If person has suicidal ideation
			• In case of complex situations such as drug addiction, personality disorders, 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 and Other Medications used to Treat Anxiety

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								
citalopram	10 mg qd	10-20 mg	no	+++	+++	+++	++	+
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	12.5-25 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	LEN	BIC	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 cabotegravir (oral)
None

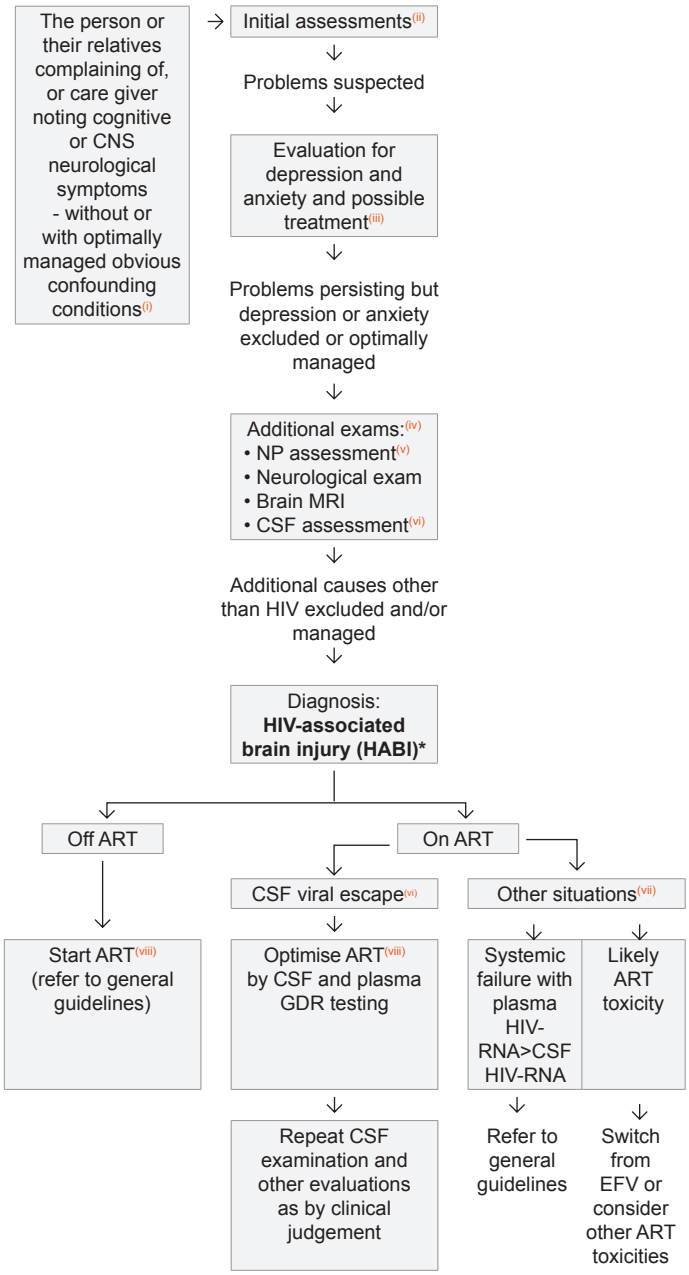
Interactions with ibalizumab
None

Comments

- a ECG monitoring is recommended.
- b Caution as both drugs can induce QT interval prolongation.
- ^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

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

Algorithm for Diagnosis and Management of Cognitive and Central Nervous System Neurological Symptoms



Abbreviations

CSF	cerebrospinal fluid
CNS	central nervous system
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 drugs that can impair cognitive function, such as anticholinergic (e.g. amitriptyline, chlorpromazine) or psychotropic drugs
3. Alcohol abuse
4. Sequelae from previous CNS-OIs, pre-treatment cognitive disease or other neurological diseases
5. Current CNS-OIs or other neurological diseases

ii **The following questions may be used to guide initial assessments of cognitive symptoms (other screening assessments are also 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 assessment, neurological exam, brain MRI and CSF assessment** are required to diagnose other pathologies (consultation with neurologist specialist may be required) and to further characterise possible HIV-associated brain injury (HABI)

v **NP assessment** should be considered where cognitive symptoms are present and ideally 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. Cognitive impairment is defined by impairment in cognitive function on the above neuropsychological test where performance is compared to age- and education-matched appropriate controls and is considered clinically significant

vi **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*

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

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

* Moving on From HAND: Why We Need New Criteria for Cognitive Impairment in Persons Living With Human Immunodeficiency Virus and a Proposed Way Forward. Clin Infect Dis. 2021 Sep 15;73(6):1113-1118. doi: 10.1093/cid/ciab366. Sam Nightingale, Anna J Dreyer, Deanna Saylor, Magnus Gisslén, Alan Winston, John A Joska. PMID: 33904889 DOI: 10.1093/cid/ciab366

The use of Patient Reported Outcome Measures (PROMs) in HIV Clinical Care

Patient reported outcome measures (PROMs) are being increasingly used in clinical care to directly measure patient symptomatology and quality of life. EACS guidelines recommend utilization of PROM tools annually in every individual to facilitate the dialogue between care providers and the patient, improve patient and physicians' awareness of their own health, introduce patient-centered care and to empower patients in this conversation.

What to collect?

PROMs pertain multidimensional domains including (but not limited to): physical, mental and sexual health, pain, stigma, family/community support, social isolation, loneliness, food security, housing, financial and migration status.
Domains should be chosen according to local and regional requirements, age, socio-economic background and environmental characteristics in consultation with local patient representatives.

How to choose PROMs?

Prioritize PROMs which are:
- designed and validated for a specific outcome(i)
- available in multiple languages
- short and concise (consider using computer adaptive testing if available)
- formulated in understandable way
- are supported by local guidelines or healthcare providers.
- validated in people with HIV (if available)

Who should be assessed?

All persons with HIV in particular prior to or during a healthcare encounter with a care provider including telemedicine encounters. Whichever approach is chosen the purpose of collecting PROMs is to evaluate them.
Therefore, PROM results should always be discussed.

How to collect?

PROMs are generally self-completed questionnaires (EACS guideline recommend some screening tools for anxiety, depression and sexual function). In addition, a widely used and important PROM are those to assess Health Related Quality of Life (HRQoL) for example EQ-5D-5L or SF36 or HIV specific PROMs for HRQoL (for example WHOQoL).

Ideally PROMs should be integrated within electronic patients records and collected using electronic tools, including websites, tablets or apps. However, people with technological or language barriers may have higher burdens of unmet needs and may require assistance to complete PROMs.

i PROMIS website has numerous examples of validated questionnaires: www.healthmeasures.net/explore-measurement-systems/promis, or www.healthmeasures.net/explore-measurement-systems/promis/intro-to-promis/list-of-adult-measures

Chronic Lung Disease

PWH have faster lung function decline than the background population. Age and smoking are the main risk factors, but even never-smokers have faster lung function decline than never-smokers in the background population.*

Screen for chronic lung disease. This is especially relevant in ever smokers and persons aged 50 years and older:
Do you have ANY of the following on a regular basis:
a) shortness of breath when walking up a slight hill or hurrying on flat ground
b) cough and/or sputum
c) recurrent wheezing

"Yes"
to any of the three questions

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

"No"
Repeat questions annually

Assess for airflow limitation with Spirometry[i]

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

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

Post-bronchodilator FEV1 / FVC < 0.70 Diagnose COPD

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

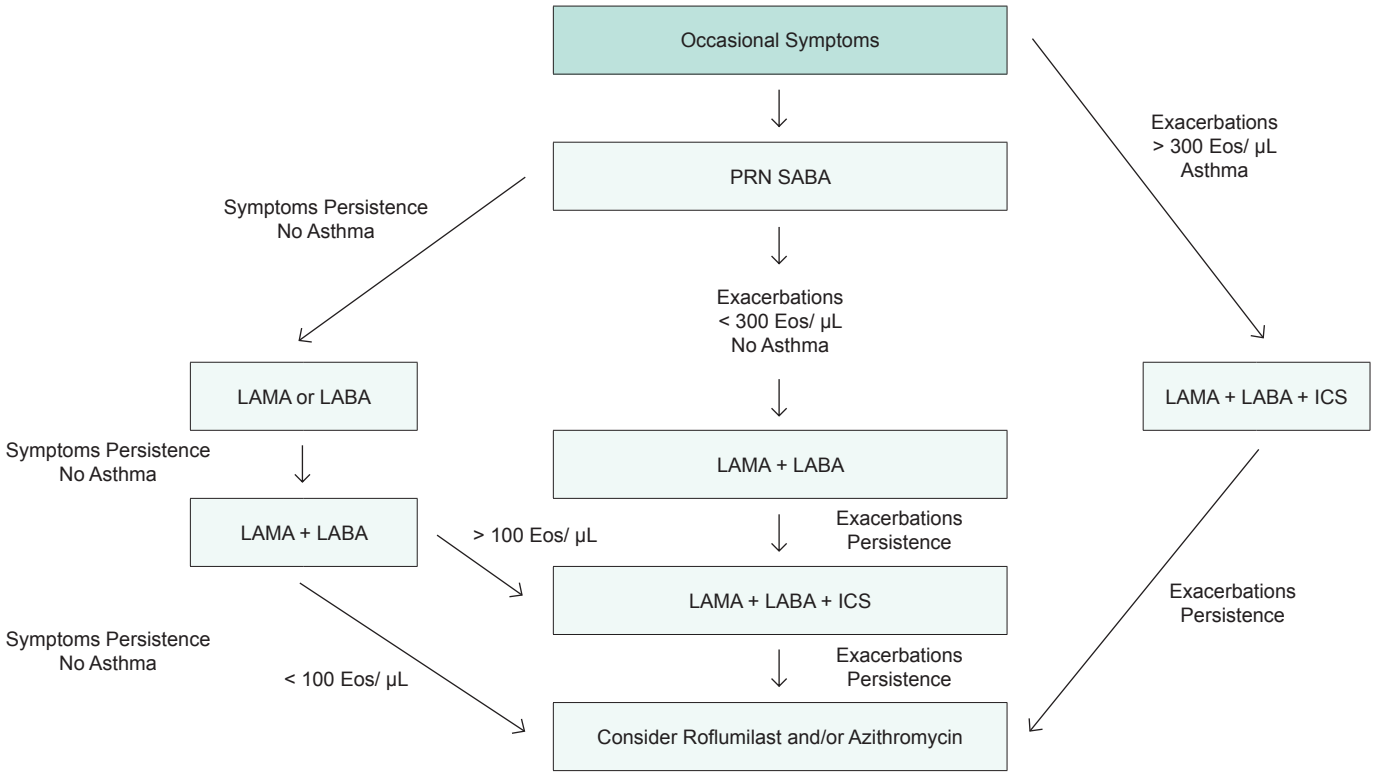
Assessment of symptoms/risk of exacerbations[iii]

Assessment of concomitant chronic diseases[iv]

There are 3 lifesaving interventions in COPD:	1. Smoking cessation 2. Chronic oxygen when stable (non-exacerbated) resting $SpO_2 \leq 88\%$ (or $PaO_2 \leq 55$ mmHg) 3. Non-invasive ventilation (NIV) in individuals with persistent hypercapnia

* Thudium, Ronit, Afzal et al. Faster lung function decline in people living with HIV despite adequate treatment: a longitudinal matched cohort study: COCOMO, INSIGHT START Pulmonary Substudy and CGPS Study Groups. Thorax. 2023 Jan 13;thoraxjnl-2022-218910. PMID: 36639241
Verboeket, Boyd, Wit, et al. Changes in lung function among treated HIV-positive and HIV-negative individuals: analysis of the prospective AGEhIV cohort study. Lancet Healthy Longev. 2021 Apr;2(4):e202-e211. PMID: 36098121

Pharmacological treatment of COPD [v][vi]



Eos: eosinophils
LABA: Long Acting Beta2 Agonist
LAMA: Long Acting AntiMuscarinic
ICS: Inhaled Corticosteroid
SABA: Short Acting Beta2 Agonist

Reassess and adjust regularly according to the response to treatment in terms of symptoms and/or acute exacerbations.
Adapted from GOLD 2023 (www.goldcopd.org)

i Risk assessment for spirometry should be undertaken in the setting of COVID-19
ii Based on expert opinion, also consider interstitial lung disease, CT scan may help to identify people with interstitial lung disease and lung cancer
iii Assessment of either dyspnoea using mMRC, see www.verywellhealth.com/guidelines-for-the-mmrc-dyspnea-scale-914740 or symptoms using CAT™, see www.catestonline.org/ and history of exacerbations (including prior hospitalisations)
iv COPD may have significant extra-pulmonary (systemic effects) including weight loss, nutritional abnormalities, frailty and skeletal mass dysfunction, and is almost invariably associated with one or more chronic comorbidities, mainly cardiovascular, respiratory and metabolic
v 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 (> 300/µL), or in individuals not adequately controlled by LAMA/LABA combinations. 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). Long-term azithromycin may also be considered in non-smokers, not well controlled with maximal inhaled drug dosage
vi LAMA/LABA/ICS are now available in a fixed dose combination. This drug combination improves clinical control of COPD and increases life expectancy. goldcopd.org/2023-gold-report-2/

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	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
LAMA	aclidinium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	glycopyrronium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tiotropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	umeclidinium bromide	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔
SAMA	Ipratropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
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	↔	↔	↔	↑ e	↔	↔	↔
	ciclesonide	↑ f	↑ f	↑ f	↑ f	↑ f	↔	↔	↔	↔	↔	↔	↔	↑ f	↔	↔	↔	↑ f	↔	↔	↔
	fluticasone	↑ e	↑ e	↑ e	↑ e	↑ e	↔	↓	↓	↓	↔	↔	↔	↑ e	↔	↔	↔	↑ e	↔	↔	↔
	mometasone	↑ e	↑ 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 cabotegravir (oral)
None

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:
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	LEN	BIC	CAB/ RPV	DTG	EVG/c	RAL	TAF	TDF
ERA	ambrisentan	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
	bosentan	↑a	↑a	↑a	↑a	↑a	D	↓	↓	↓b	D	↑	D	D #	D	D	D	↑a	↔	↔	↔
	macitentan	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
PDE5	sildenafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↓3%	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	tadalafil	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
sGC	riociguat	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↑	↔	↑	↔	↔	↔	↑	↔	↔	↔
PA	epoprostenol	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	iloprost	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	treprostinil	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
IPr	selexipag	↔c	↔c	↔c	↔c	↑120%d	↔	↔	↔	↔	↔	↔	↔	↔c	↔	↔	↔	↔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
Ipr	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 cabotegravir (oral)

None

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.

^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

At least a 2-week (moderate inducers) or 4-week (strong inducers) cessation period is recommended prior to initiation of LEN due to the persisting inducing effect after discontinuation of an inducer.

Further Information

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

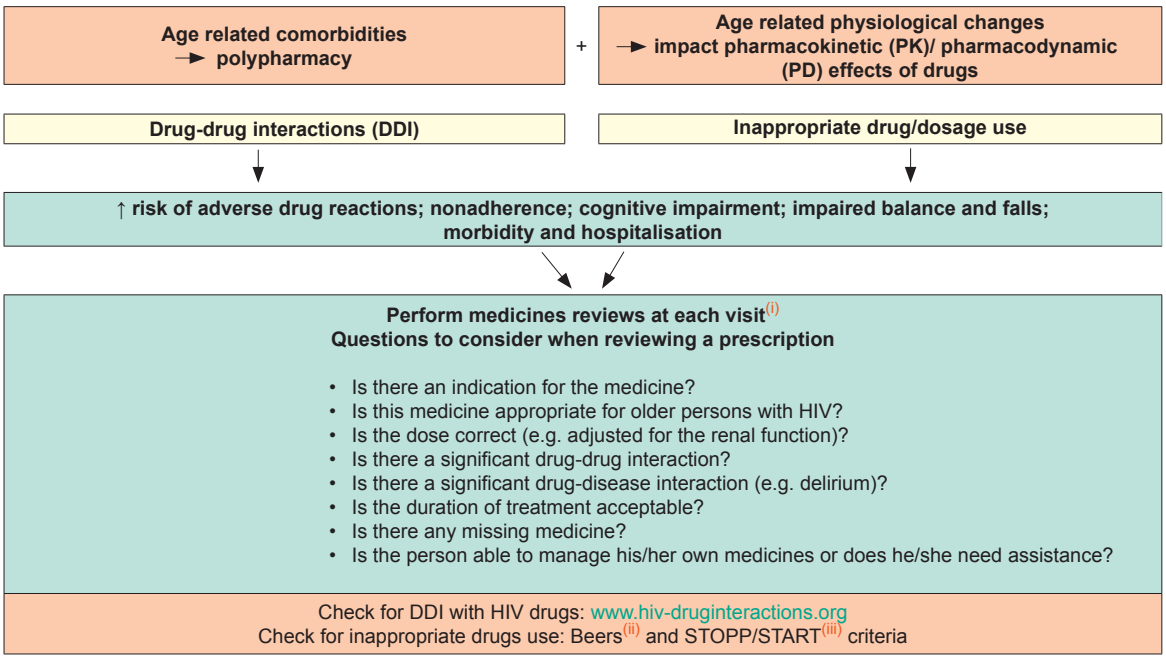
Managing Older Persons with HIV

This section focuses on important issues for older persons with HIV: polypharmacy, frailty and falls that have shown to be better predictors of survival and quality of life among older people in the general population than co-morbidity alone.

Polypharmacy

Polypharmacy is defined as the concurrent use of > 5 drugs and refers to non-HIV medications given in addition to ARVs. Deprescribing or the planned and supervised process of dose reduction or stopping of medication that may cause harm, or no longer provide benefit should be incorporated in the assessment of older persons with HIV. A freely accessible resource to help deprescribe can be found at medstopper.com.

Prescribing in Older Persons with HIV



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 Persons with HIV

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

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 syndrome is more prevalent than expected in persons with HIV compared to lifestyle-similar persons without HIV and may occur at an earlier age.
Early identification and management of frailty is a priority since it is potentially reversible.

Screening for Frailty

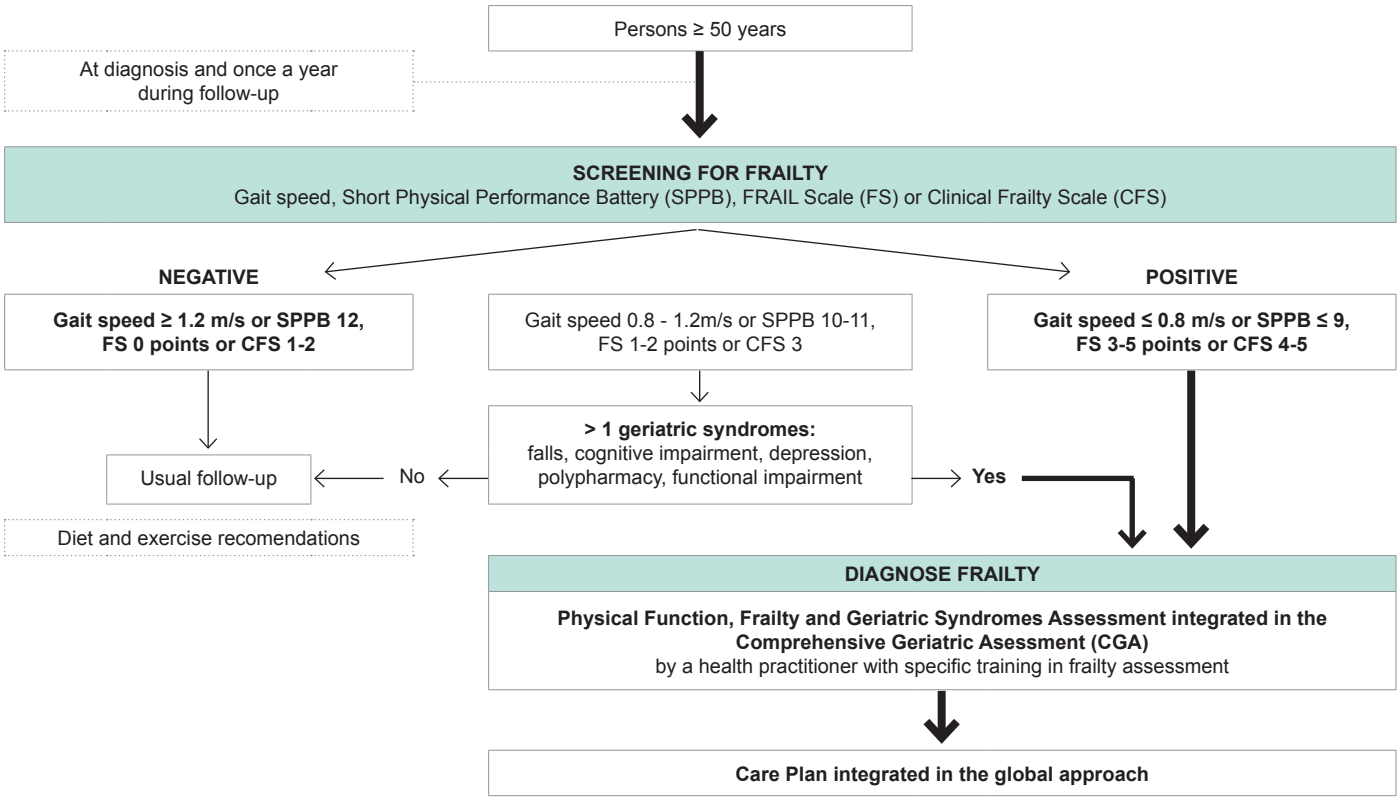
Screening for frailty in persons with HIV above 50 years of age should be considered. The age cut-off was chosen as the incidence of frailty in persons with HIV has been shown to increase above this age. Evidence of benefit is still unknown. It is advocated by some experts.
Screening has to be performed using validated tools for this purpose and can be provided by any trained health staff (nurses, general practitioners, etc.).
The instruments available for screening frailty are gait speed measurement, Short Physical Performance Battery (SPPB), Clinical Frailty Scale (CFS) and FRAIL Scale (FS). In the absence of a gold standard, the choice of one tool over another will depend on the available resources.

Frailty Screening Tools

Tools	Description	Measure	Time	Equipment	Setting
Gait speed[1]	Mark a 4-metre distance on the floor. Ask the patient to walk at usual pace from a standing start and stop the watch once they cross the 4-metre line without stopping (metres/second)	Objective	Quick (< 2 min)	Stopwatch 4m space	Clinic
Short Physical Performance Battery (SPPB)[2]	Test for standing balance: side by side stands, semi-tandem, and tandem plus 4-metre gait speed test plus testing the ability to rise from a chair and sit down again five times (seconds).	Objective Ceiling effects	Takes 5 min	Stopwatch 4m space A chair	Clinic
FRAIL Scale[3]	Short 5-question assessment of fatigue, resistance, aerobic capacity, illnesses, and loss of weight	Subjective	Quick (< 2 min)	None	Clinic Hospitalisation
Clinical Frailty Scale (CFS)[4]	A judgement-based frailty tool that evaluates comorbidity, function, and cognition to generate a frailty score ranging from 1 (very fit) to 9 (terminally ill)	Subjective	Quick (< 2 min)	None	Hospitalisation Emergency

1) Studenski S. JAMA. 2011;305(1):50-58. 2) Guralnik JM. J Gerontol. 1994 Mar;49(2):M85-94. 3) Morley JE, JAMDA 2013;14:392–7. 4) Rockwood K. CMAJ. 2005 Aug 30;173(5):489–495.

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

Recommendations

In persons with HIV who are frail:
1. Promote Comprehensive Geriatric Assessment (CGA)
2. Sustain and recover physical function impairment and sarcopenia by prescribing physical exercise with a resistance training component
3. Address polypharmacy by reducing or deprescribing any inappropriate/superfluous medications, see Prescribing in older persons with HIV
4. Screen for, and address modifiable causes of fatigue
5. For persons exhibiting unintentional weight loss, screen for reversible causes and consider food fortification and protein/caloric supplementation
6. Prescribe vitamin D for individuals deficient in vitamin D, see page 79

(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’

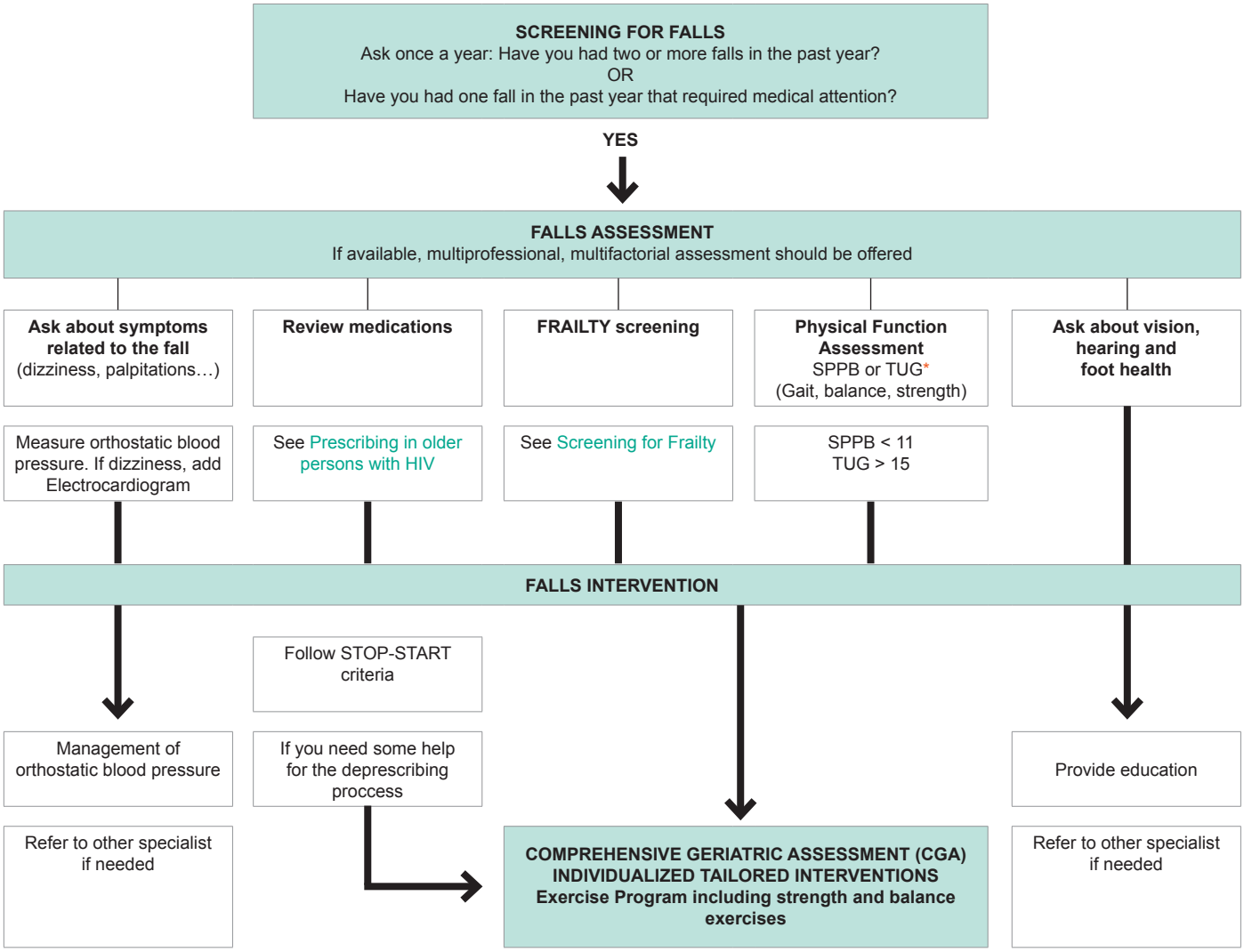
(c) **Low physical activity** as considered present if the participant’s physical activity is lower than 383 kcal/week in men and 270 kcal/week in women which is equivalent to < 2.5 hours/week in men and < 2 hours/week in women using the Minnesota Leisure Time Activity Questionnaire

(d) **Walk speed time** is measured by a 4-metre 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 with the mean value of three consecutive measurements of the dominant hand (adjusted by sex and BMI quartile based on the Cardiovascular Health Study (CHS) population) as follows:
- 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. The prevalence of falls among older adults with HIV is estimated to be between 25% and 30%, affects independent movement and mobility and should be considered a warning sign of potentially unidentified underlying conditions.



* SPPB: Short Physical Performance Battery. TUG: Timed Up and Go Test

Solid Organ Transplantation (SOT)

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

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

Organ donation
- Persons with HIV 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, persons with HIV 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 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 127-133. 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 persons with HIV, see page 150, 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
- There is no experience with LEN, FTR, ibalizumab and long-acting CAB and RPV in people with HIV with SOT
  see Drug-drug Interactions between Immunosuppressants (for SOT) and ARVs

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 150

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 as people who are HIV-negative

Screening for co-morbidities and frailty

Persons with HIV 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 transplant recipients who are HIV-negative. The risk of acute rejection is however double of that of SOT recipients who are HIV-negative and, therefore, requires close monitoring. Recipients with a pretransplant CD4/CD8 ratio ≥0.5 have the highest risk of acute rejection*
- 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 require 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

* Arrieta SS, Serrano L, Rafecas A, Manzardo C, Fortun J, Blanes M, Salcedo M, Bilbao I, Cordero E, Del Campo S, Moreno A, Rimola A, Brander C, Miro JM. CD4/CD8 Ratio ≥0.5 is a risk factor of acute rejection in HIV infected LT recipients. Poster presented at: 29th Conference on Retroviruses and Opportunistic Infections (CROI); February 12-16, 2022; Virtual meeting. Poster number 00551. www.croiconference.org/wp-content/uploads/sites/2/resources/2022/croi2022-abstract-ebook.pdf

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

Immuno-suppressants		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	FTR	MVC	LEN	BIC	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	↑a ^	E	E	↔	↑a	↔	E	Eb
	tacrolimus*	↑a,c	↑a,c	↑a	↑a	↑a,c	↓a	↓a	↓a	↓a	↔c	↔c	↔	↑a ^	↔	↔c	↔	↑a	↔	↔	↔b
mTOR	everolimus	↑	↑	↑	↑	↑	↔	↓a	↓a	↓a	↔	↔	↔	↑ ^	↔	↔	↔	↑	↔	↔	↔
	sirolimus	↑	↑	↑	↑	↑	↓a	↓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 haematoxicity with azathioprine.
ZDV: potential alteration in mycophenolate exposure, monitor plasma concentrations.

Interactions with cabotegravir (oral)

None

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.
- ^ LEN causes moderate inhibition of CYP3A4 and, when discontinued, remains in the circulation for prolonged periods. Residual concentrations of LEN may affect the exposure of sensitive CYP3A4 substrates and/ or narrow therapeutic index drugs that are initiated within 9 months after the last subcutaneous dose of LEN.

Further Information

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

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

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. HCV should be screened for at time of 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. Persons engaging in activities associated with increased risk of HCV transmission[iv] should be tested for HCV infection every 3 to 6 months. Persons 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 persons with ongoing risk behavior for HCV re-infection after successful treatment or spontaneous clearance at 3 to 6-monthly intervals
2. All persons should be screened for HAV and HBV. Persons who are anti-HBc positive and HBsAg negative, in particular those with elevated liver transaminases, should be screened for HBV-DNA in addition to HBsAg to rule out occult HBV infection with detectable viremia
3. HDV antibodies should be screened for in all HBsAg positive persons
4. Persons 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 persons 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). Staging of fibrosis should identify patients with compensated advanced chronic liver disease (cACLD) and among them those with clinically significant portal hypertension (CSPH) see page 87-88
6. Treatment with non selective Beta blockers (NSBBs propranolol, nadolol or carvedilol) should be considered for the prevention of decompensation in patients with CSPH.Carvedilol is the preferred NSBB in compensated cirrhosis, since it is more effective at reducing hepatic venous pressure gradient (HVPG)

Screening for complications

7. HCC screening is indicated in
   a) all cirrhotic patients (irrespective of viral clearance for HCV or viral suppression for HBV)
   b) non-cirrhotic HBV (irrespective of HBV suppression) in persons with one of the following: family history of HCC; Asian/African ethnicity, HDV-co-infection, age >45 years, Caucasian patients with PAGE-B score ≥10
   c) consider HCC screening for non-cirrhotic F3 patients, regardless of etiology, based on individual risk assessment (e.g. family history of HCC)

End Stage Liver Disease (ESLD)

8. Persons with HIV and liver cirrhosis require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative persons, see page 87-90 and 92
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 persons improves overall survival
10. Persons 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 (OLTX), see Solid Organ Transplantation (SOT)
11. Renal complications are frequent, see page 81 and Diagnosis and Management of Hepatorenal Syndrome / Acute Kidney Injury (HRS-AKI)

Vaccination, see page 99

12. Persons lacking anti-HAV IgG antibodies or anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4 count. The response to the HBV vaccine is influenced by the CD4 count and level of HIV-VL. In persons with low CD4 count (< 200 cells/µL) and ongoing HIV replication, ART should be initiated first, prior to respective vaccination. The use of the more immunogenic vaccine Heplisav B should be evaluated where available. Heplisav B may be used for primary immunization to reach better responses. Because of the lack of randomized data on the impact of immunisation in isolated anti-HBc IgG positive persons (HBsAg negative, anti-HBc positive and anti-HBs negative profile), vaccination should be discussed on an individual level. However, if anti-HBc results are not available, HBV vaccination is recommended in all HBs-Ag negative persons
13. In persons vaccinated for HBV with insufficient response (anti-HBs < 10 IU/L), re-vaccination should be considered. The use of the more immunogenic vaccine Heplisav B should be evaluated where available (off-label). 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)[iv], should be provided and risk reduction should be discussed
17. In women of childbearing age, HCV treatment should be initiated prior to conception because of limited safety data in pregnancy, and to reduce the risk of MTCT of HCV. 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 132

vi MELD calculation, see page 89-90

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

Treatment indication

1. All persons 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 persons with no prior 3TC exposure and together with fully active ART
4. Persons with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes (for management of cirrhotic persons, see pages 87-93). 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-pretreated cirrhotic persons as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir. Therefore, HBV-DNA and transaminases should be checked regularly
6. Prior to ART simplification with a regimen without TDF/TAF, HBV status should be re-checked. In PLWH with isolated anti-HBc, relapse of HBV-DNA is possible, therefore transaminases and HBV-DNA should be checked regularly. PLWH with positive HBsAg should remain on TDF or TAF containing ART
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 78-83

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 persons with liver cirrhosis, stopping of effective anti-HBV treatment is not recommended, in order to avoid liver decompensation due to flares of liver enzymes

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(i)

HBV reactivation

11. In HBs-Ag negative, anti-HBc positive persons 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 persons 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 GT[i], 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 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 for 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 SVR_{12} defined as undetectable HCV-RNA 12 weeks after the end of therapy (evaluated using sensitive molecular tests) or HCV core antigen levels where HCV-RNA assays are not available or not affordable. SVR_{12} corresponds to a definitive cure of HCV infection in the vast majority of cases

Treatment monitoring

8. In persons 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 persons with positive anti-HBc, monitoring of ALT and HBV-DNA in case of ALT elevation is recommended
9. In persons 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 persons 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 persons 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, 65, 87-88 and 89-90
13. All persons 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 94

Treatment of recently acquired HCV infection

15. IFN-containing HCV regimens are no longer recommended
16. HCV treatment immediately after diagnosis is recommended in all persons particularly in those 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 130
17. 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

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 from the EACS online course Management of HIV and Co-infections

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 persons with GT1a with baseline HCV-RNA < 800,000 IU/mL and/or absence of NS5A RASs, as well as in treatment-naïve persons with GT4 with HCV-RNA < 800,000 IU/mL In GT 1b treatment-naïve persons with F0-F2 fibrosis 8 weeks can be considered
ii 8 weeks treatment can be considered in treatment naïve persons
iii 8 weeks treatment without RBV only in treatment-naïve persons with F < 3 and baseline HCV-RNA < 6 million IU/mL
iv RBV can be omitted in treatment-naïve or -experienced persons 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 persons 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 naive people with compensated cirrhosis
viii In treatment experienced (exposure to IFN/RBV/SOF) persons, 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	LEN	BIC	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 cabotegravir (oral)
None

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:
www.hiv-druginteractions.org (University of Liverpool)

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 Infection

Hepatitis Delta Virus (HDV)

1. HDV antibodies should be screened for in all HBsAg positive persons
2. In persons with positive HDV antibodies, HDV-RNA should be measured in order to assess activity of the disease
3. In persons with chronic HDV co-infection and significant liver fibrosis (≥ F2), long-term (at least 12 months) treatment with PEG-IFN might be considered in association with TDF-based ART
4. Non-invasive fibrosis markers (transient elastography and serum markers) should be used with caution in HIV/HBV co-infected persons 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 (2mg/d; s.c.) in combination with TDF/TAF is recommended in HDV-RNA positive persons with compensated liver disease and should be used where available. The optimal duration of treatment remains unclear. Treatment should be performed in centers with sufficient experience
7. People with HIV and HDV infection 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 persons. Histological remission of liver disease is a less ambitious but more likely achievable goal
10. In persons 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 persons with symptoms consistent with acute hepatitis, unexplained flares of aminotransferases (even if sus- pected drug induced liver injury), unexplained elevated liver function tests, neuralgic amyotrophy, Guillain-Barrè, 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 persons 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 persons 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 persons with HIV in Europe
- Overview of management of COVID-19 in persons with HIV
- Overview of management of Mpox in persons with HIV
- Please note that additional infections presented in other sections of these guidelines (e.g. sexually-transmitted infections) may be more severe and/or have atypical presentations in people with advanced HIV infection. Please refer to the appropriate sections for management and treatment

See online videos for selected opportunistic infections in the EACS online course https://iversity.org/en/courses/management-of-hiv-and-co-infections

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

	Initiation of ART	Comments
General recommendation	As soon as possible within 2 weeks after starting treatment for the opportunistic infection	
TB meningitis	In persons with CD4 < 50 cells/μL, ART should be initiated within the first 2 weeks after initiation of TB treatment, if close monitoring and optimal TB treatment can be ensured ART initiation should be delayed for 4 weeks in all other cases	Corticosteroids are recommended as adjuvant treatment Where very close monitoring and optimal treatment are available, ART could be initiated early in selected cases
Cryptococcal meningitis	Defer initiation of ART for at least 4 weeks	Corticosteroids are not recommended as adjuvant treatment Where very close monitoring and optimal treatment are available, earlier ART start could be considered in selected cases

Immune Reconstitution Inflammatory Syndrome (IRIS)

Definition	
Paradoxical worsening ("Paradoxical IRIS") or new onset ("Unmasking IRIS") 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 4-6 weeks
unmasking IRIS	Determine serum cryptococcal antigen in persons newly HIV-diagnosed or unsuccessfully treated with CD4 counts < 100 cells/μL. If cryptococcal antigen is detected, 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	Prophylactic prednisone (40 mg qd po for 2 weeks, followed by 20 mg qd po for 2 weeks) may be considered as it reduced the risk of TB-IRIS by 30% in persons with CD4 cell count < 100 cells/μL and no TB meningitis or rifampin resistance who started anti-TB treatment within 30 days prior to ART
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 life-threatening or other 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	**Prednisone** 1.5 mg/kg/day po for 2 weeks, then 0.75 mg/kg/day for 2 weeks
PML-IRIS	**Methylprednisolone** 1 g/day iv for 3-5 days or dexamethasone 0.3 mg/kg/day iv for 3-5 days, then oral tapering

Primary Prophylaxis of OIs According to Stage of Immunodeficiency

CD4 count threshold / indication			
CD4 count < 200 cells/µL, CD4 percentage < 14%, recurrent oral thrush, or relevant concomitant immunosuppression*			
Prophylaxis against *Pneumocystis jirovecii* Pneumonia (PcP) & *Toxoplasma gondii* infection **Stop:** if CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months * e.g. use of corticosteroids > 20 mg prednisone equivalent per day for > 2 weeks, cancer chemotherapy, biological agents such as rituximab and others. Decisions on installation and discontinuation in these situations have to be taken individually			
	Drug	**Dose**	**Comments**
Positive or negative serology for Toxoplasmosis	**trimethoprim-sulfamethoxazole (TMP-SMX)**	80/400 mg qd po or 160/800 mg qd po or 160/800 mg x 3/week po	In case of non-severe TMP-SMX allergy and if other therapeutic options are not available/not clinically appropriated, desensitization can be attempted*
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL sterile water x 1 inhalation/month	Does not prevent the rare extrapulmonary manifestations of *P. jirovecii*
Negative serology for toxoplasmosis	**dapsone**	100 mg qd po	Check for G6PD-deficiency
Negative serology for toxoplasmosis	**atovaquone suspension**	1500 mg qd (with food)	
Positive serology for toxoplasmosis	**dapsone** **+ pyrimethamine** **+ folinic acid**	200 mg/week po 75 mg/week po 25-30 mg/week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	**atovaquone suspension** **+/- pyrimethamine** **+ folinic acid**	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	
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) *(M. avium* complex, *M. genavense, M. kansasii)* Prophylaxis is not recommended if ART is started Prophylaxis may be considered for persons with CD4 counts < 50 cells/µL who remain viremic 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 Anti-infective and ART interactions table
	or **clarithromycin**	500 mg bid po	
	or **rifabutin**	300 mg qd po	Check for interactions with ARVs, see Anti-infective and ART interactions table Active TB should be ruled out before starting **rifabutin**

* for protocols see: J. Allerg. Clin. Immunol 1994; 93:1001-1005; J Infect Dis 2001 Oct 15;184(8):992-7

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

Pneumocystis jirovecii Pneumonia (PcP)

Primary prophylaxis

Start: if CD4 count < 200 cells/µL, CD4 percentage < 14%, oral thrush or relevant concomitant immunosuppression, see Primary Prophylaxis of OIs
Stop: if CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months

	Drug	Dose	Comments
Negative or positive serology for toxoplasmosis	**TMP-SMX**	80/400 mg qd po or 160/800 mg qd po or 160/800 mg x 3/week po	In case of non-severe TMP-SMX allergy and if other therapeutic options are not available/not clinically appropriated, desensitization can be attempted *
Negative serology for toxoplasmosis	**pentamidine**	300 mg in 6 mL sterile water x 1 inhalation/month	Does not prevent the rare extrapulmonary manifestations of *P. jirovecii*
Negative serology for toxoplasmosis	**dapsone**	100 mg qd po	Check for G6PD-deficiency
Negative serology for toxoplasmosis	**atovaquone suspension**	1500 mg qd po (with food)	
Positive serology for toxoplasmosis	**dapsone**	200 mg/week po	Check for G6PD-deficiency
	+ pyrimethamine	75 mg/week po	
	+ folinic acid	25-30 mg/week po	
Positive serology for toxoplasmosis	**atovaquone suspension** **+/- pyrimethamine** **+ folinic acid**	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	

Diagnosis and treatment

Diagnosis:
Definitive diagnosis: Cough and dyspnea on exertion AND microorganism identification by cytology / histopathology of induced sputum (sensitivity up to 80%), broncho-alveolar lavage (sensitivity > 95%) or bronchoscopic tissue biopsy (sensitivity > 95%)

Presumptive diagnosis: CD4 count < 200 cells/µL AND dyspnea / 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.

Notes on treatment:
Treat at least 21 days, then secondary prophylaxis until CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months. See also anti-infective/ART interaction table for treatment optimization

	Drug	Dose	Comments
Preferred therapy	**TMP-SMX**	5 mg/kg tid TMP iv/po + 25 mg/kg tid SMX iv/po	Monitor myelotoxicity (mainly neutropenia), kidney function and electrolytes (mainly high potassium)
	+ prednisone if PaO_2 < 10 kPa or < 70 mmHg, or alveolar/arterial O_2 gradient > 35 mmHg. Start prednisone preferentially 15-30 min before treatment	40 mg bid po 5 days 40 mg qd po 5 days 20 mg qd po 10 days	Benefit of corticosteroids if started within 72 hours after start of treatment
Alternative therapy for *moderate to severe* PcP	**primaquine**	30 mg (base) qd po	Check for G6PD deficiency
	+ clindamycin	600-900 mg tid iv/po	
	or **pentamidine**	4 mg/kg qd iv (infused over 60 min.)	
	For each regimen: **+ prednisone** if PaO_2 < 10 kPa or < 70 mmHg, or alveolar/ arterial O_2 gradient > 35 mmHg. Start prednisone preferentially 15-30 min before TMP/SMX	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 *mild to moderate* PcP	**primaquine**	30 mg (base) qd po	Check for G6PD deficiency
	+ clindamycin	600-900 mg tid po	
	or		
	atovaquone suspension	750 mg bid po (with food)	
	or		
	dapsone	100 mg qd po	Check for G6PD deficiency In case of rash: reduce dose of TMP (50%), use antihistamines
	+ trimethoprim	5 mg/kg tid po	

* for protocols see: J. Allerg. Clin. Immunol 1994; 93:1001-1005; J Infect Dis 2001 Oct 15;184(8):992-7

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**	80/400 mg qd po or 160/800 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 *P. jirovecii*
Negative serology for toxoplasmosis	**dapsone**	100 mg qd po	Check for G6PD-deficiency
Negative serology for toxoplasmosis	**atovaquone suspension**	1500 mg qd po (with food)	
Positive serology for toxoplasmosis	**dapsone** **+ pyrimethamine** **+ folinic acid**	200 mg/week po 75 mg/week po 25-30 mg/week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	**atovaquone suspension** **+/- pyrimethamine** **+ folinic acid**	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	

Toxoplasma gondii Encephalitis

Primary prophylaxis			
Start: if CD4 count < 200 cells/µL, or CD4 percentage < 14%, oral thrush, or relevant concomitant immunosuppression (see above) **Stop:** if CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months			
	Drug	**Dose**	**Comments**
Preferred prophylaxis	**TMP-SMX**	80/400 mg qd po or 160/800 mg qd po or 160/800 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	
Diagnosis and treatment			
Diagnosis: **Definitive diagnosis:** clinical symptoms, typical focal lesions neuroradiology AND cytological / histological detection of organism in brain tissue. Toxoplasma PCR in CSF has high specificity (95-100%) but low sensitivity (50%) **Presumptive diagnosis:** clinical symptoms, serum Ig G toxoplasma Ab, typical focal lesions neuroradiology AND response to empirical treatment. This is the standard in most clinical settings **Notes on treatment:** - Treat 6 weeks, then secondary prophylaxis until CD4 count > 200 cells/µL and HIV-VL undetectable over 6 months - In patients with cerebral lesions (or surrounding edema) causing mass effect, corticosteroids (dexamethasone) could be used as adjunctive therapy. Corticosteroids should be discontinued as soon as clinically feasible to prevent immunosuppression - See also anti-infective/ART interaction table for treatment optimization			
	Drug	**Dose**	**Comments**
Preferred therapies	**pyrimethamine** **+ sulfadiazine** **+ folinic acid**	Day 1: 200 mg qd po, **then** • If ≥ 60 kg; 75 mg qd po • If < 60 kg: 50 mg qd po • If ≥ 60 kg: 3000 mg bid po/iv • If < 60 kg: 2000 mg bid po/iv 10-15 mg qd po	Monitor for myelotoxicity of **pyrimethamine**, mostly neutropenia **Sulfadiazine** is associated with crystalluria and may lead to renal failure and urolithiasis. Good hydration is essential. Check renal function and urine sediment for microhematuria and crystalluria
	TMP-SMX	5 mg TMP/kg bid iv/po + 25 mg SMX/kg bid iv/po	Preferred intravenous regimen if oral route not possible A recent meta-analysis showed that this regimen is as effective and possibly safer than pyrimethamine-based regimens. Furthermore, in countries where there are supply shortages for pyrimethamine or it cannot be administered due to its high price, TMP-SMX should be the preferred therapeutic option. Monitor myelotoxicity (mainly neutropenia), kidney function and electrolytes (mainly high potassium)

Alternative therapies	**pyrimethamine** **+ clindamycin** **+ folinic acid**	Day 1: 200 mg qd po, **then** • If ≥ 60 kg: 75 mg qd po • If < 60 kg: 50 mg qd po 600-900 mg qid po/iv 10-15 mg qd po	Monitor for myelotoxicity of **pyrimethamine**, mostly neutropenia Additional PcP prophylaxis is necessary
	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**	2000-4000 mg daily po in 2-4 doses 25-50 mg qd po 10-15 mg qd po	
	or **TMP-SMX**	160/800 mg bid 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)	

Cryptococcosis – disease caused by *Cryptococcus neoformans*

Diagnosis and 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: not recommended systematically in the European context

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 HIV-diagnosed persons with CD4 counts < 100 cells/μL. See Pre-emptive therapy below

Notes on treatment:
Treat cryptococcal meningitis and disseminated cryptococcosis for 14 days (induction therapy), then 8 weeks (consolidation therapy), then secondary prophylaxis for at least 12 months. Stop secondary prophylaxis if CD4 count > 100 cells/μL and HIV-VL undetectable over 3 months.
See also Anti-infective/ART interaction table for treatment optimization

	Drug	Dose	Comments
Pre-emptive therapy	**fluconazole**	800 mg qd po for 2 weeks followed by 400 mg qd po for 8 weeks	In case of: - positive cryptococcal serum antigen - asymptomatic individual with CD4 < 100 cells/μL - cryptococcal meningitis, pulmonary or other site infection ruled out
Induction therapy	**liposomal amphotericin B** **+ flucytosine**	3 mg/kg qd iv 25 mg/kg qid po	**14 days** - Perform repeated lumbar puncture (LP), until opening pressure is < 20 cm H_20: - If CSF culture is sterile, switch to oral regimen - Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure which is associated with better survival - Corticosteroids have no effect in reducing increased intracranial pressure, could be detrimental and are contraindicated - **Flucytosine** dosage must be adapted to renal function - Defer start of ART for at least 4 weeks, since early initiation of ART has been associated with decreased survival. Where very close monitoring and optimal treatment are available, earlier ART start can be considered in selected, low-risk cases - 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
	or **amphotericin B deoxycholate** **+ flucytosine**	0.7 mg/kg qd iv 25 mg/kg qid po	
	or **single-dose liposomal amphotericin B** **+ flucytosine** **+ fluconazole**	10 mg/kg IV single-dose 25 mg/kg qid po for 2 weeks 1200 mg/die for 2 weeks	- Preferred WHO-2022 regimen in resource limited settings - In resource-limited settings, alternative induction regimens may include: i) one week of **amphotericin B** + **flucytosine** followed by one week of **fluconazole** 1200 mg qd (the 2018 WHO-recommended treatment) or ii) two weeks of **fluconazole** 1200 mg qd plus **flucytosine**
Consolidation therapy	**fluconazole**	400 mg qd po (single loading dose of 800 mg on 1st day)	8 weeks See Drug-drug Interactions between ARVs and Non-ARVs

Secondary prophylaxis / Maintenance therapy

At least 12 months
Consider to stop: if CD4 count >100 cells/μL and HIV-VL undetectable over 3 months

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

Candidiasis

Diagnosis and treatment

Diagnosis:
- **Oropharyngeal candidiasis:** typical clinical appearance.
- **Oesophagitis:**
  - definitive diagnosis: evidence of disease at macroscopic inspection during endoscopy, OR histology of biopsy, OR cytology of specimen from the mucosal surface.
  - presumptive diagnosis: recent onset of dysphagia AND oropharyngeal candidiasis

Notes on treatment:
see Drug-drug Interactions Between ARVs and Non-ARVs and Anti-infective/ART interaction table for all azole therapies

Disease	Drug	Dose	Comments
Oropharyngeal candidiasis	**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	**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*)

Diagnosis and 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. *Aspergillus* galactomannan assays may be helpful to diagnose disseminated infections as cross reactivity occurs

Note: CSF, which shows typically a lymphatic pleocytosis, is usually microscopy and culture negative. Detection of histoplasma antigen or antibody is more sensitive. A clinical diagnosis is possible, if disseminated histoplasmosis is present and CNS infection is not explained by another cause

Notes on treatment:
- **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 and Anti-infective/ART interaction table
- 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** **Consolidation therapy:** **itraconazole**	 3 mg/kg qd iv 200 mg tid po for 3 days, then 200 mg bid po	 For 2 weeks or until clinical improvement For at least 12 months
Moderate disseminated histoplasmosis	**itraconazole**	200 mg tid po for 3 days, then 200 mg bid po	For at least 12 months
Histoplasma meningitis	**Induction therapy:** **liposomal amphotericin B** **Consolidation therapy:** **itraconazole**	 5 mg/kg qd iv 200 mg bid - tid po	For 4-6 weeks For at least 12 months and until resolution of abnormal CSF findings
Secondary prophylaxis / Maintenance therapy			
Stop: if CD4 count > 150 cells/µL and HIV-VL undetectable over 6 months, negative fungal blood cultures, histoplasma serum antigen < 2 µg/L or negative PCR, if available, and > 1 year treatment **Consider long-term suppressive** therapy in severe cases of meningitis and in cases of relapse despite adequate treatment			
	itraconazole	200 mg qd po	

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

Diagnosis and treatment

Consider diagnosis in persons with HIV 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.
Next generation sequencing may provide rapid diagnosis

Notes on treatment:
see Anti-infective/ART interaction table for treatment optimization

	Drug	Dose	Comments
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)
			A recent trial suggested that **voriconazole** (6 mg/kg bid day 1, then 4 mg/kg bid for 2 weeks) may be an alternative therapy for induction phase

Secondary prophylaxis / Maintenance therapy

Secondary prophylaxis: itraconazole 200 mg qd po
Stop: if CD4 count > 100 cells/µL and HIV-VL undetectable over 6 months, negative fungal blood cultures or negative PCR/ negative antigen

Herpes simplex virus (HSV) infections

Diagnosis and treatment

Diagnosis:
Identification of HSV-DNA by nucleic acid amplification techniques (NAT) in skin lesions is useful to confirm clinical diagnosis and enables differentiation of HSV-1 vs. HSV-2 vs. VZV. **Identification of HSV-DNA** in CSF, aqueous humor or tissue biopsy is recommended for diagnosis of infection of specific sites. Tissue antigen detection may be used when NAT is not available

Notes on treatment:
for treatment optimization, see Anti-infective/ART interaction table

Disease	Drug	Dose	Comments
Initial and recurrent genital / mucocutaneous HSV			See Sexual and Reproductive Health section, page 101
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, retinitis or infection of other sites (e.g., GI)	**aciclovir**	10 mg/kg tid iv	14-21 days If retinitis, consult ophthalmologist
Aciclovir resistant 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

Diagnosis and treatment

Diagnosis:
Identification of VZV-DNA by nucleic acid amplification techniques (NAT) in skin lesions is useful to confirm clinical diagnosis and enables differentiation of VZV vs. HSV-1 vs. HSV-2 when lesion distribution is not typical. **Identification of VZV-DNA** in CSF, aqueous humor or tissue biopsy is recommended for diagnosis of infection of specific sites. Tissue antigen detection may be used when NAT is not available.

Notes on treatment:
monitor renal function and adjust drug dose in renal impairment. See also Anti-infective/ART interaction table

	Drug	Dose	Comments
Primary Varicella infection (Chickenpox) and Herpes Zoster (Shingles): Not disseminated	**valaciclovir**	1000 mg tid po	Chickenpox: 5-7 days, Shingles: 7-10 days
	or **famciclovir** or **aciclovir**	500 mg tid po 800 mg x 5/day po	
Herpes Zoster: Disseminated	**aciclovir**	10 mg/kg tid iv	10-14 days (or until lesion resolution)
Encephalitis (including vasculitis), retinitis or infection of other sites	**aciclovir**	10-15 mg/kg tid iv	14-21 days If retinitis, consult ophthalmologist

Cytomegalovirus (CMV) infections

Diagnosis and treatment			
Diagnosis: **Retinitis:** typical retinal lesions at ophthalmological examination AND response to therapy. Identification of CMV-DNA by NAT in of aqueous and vitreous humor optional **Esophagitis/colitis:** endoscopic presence of ulcerations AND typical histopathological picture (cellular / nuclear inclusion bodies) with identification of CMV antigens **Encephalitis/polyradiculomyelitis:** clinical appearance AND Identification of CMV-DNA by NAT in CSF **Identification of CMV-DNA** in blood supportive, but not diagnostic of end-organ disease **Notes on treatment:** monitor renal function and adjust drug dose in renal impairment. See also Anti-infective/ART interaction table			
Disease	**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**. Most 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 **ganciclovir**	5 mg/kg bid iv	
	or **foscarnet**	90 mg/kg bid iv	If adverse reactions or ineligibility to **ganciclovir/valganciclovir**
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** **foscarnet**	5 mg/kg bid iv 90 mg/kg bid iv	Treat until symptoms resolved with clearance of CMV-DNA in CSF, then secondary prophylaxis Some experts recommend **ganciclovir** combined with **foscarnet** especially in progressive or relapsing cases
Secondary Prophylaxis / Maintenance therapy: Cytomegalovirus (CMV) Retinitis			
Stop: Inactive lesions treated for at least 3 months AND CD4 count > 100 cells/µL with HIV-VL undetectable over 3 months			
Regimens	**valganciclovir** (preferred regimen)	900 mg qd po (with food)	
	or **ganciclovir**	5 mg/kg qd iv (x 5 days/ week)	
	or **foscarnet**	90-120 mg/kg qd iv (x 5 days/ week)	
Cidofovir (+ probenecid) may be considered as a therapeutic option for patients unable to tolerate the other treatments listed			

Progressive Multifocal Leukoencephalopathy (PML)

Diagnosis and treatment	
Definitive diagnosis: compatible clinical-radiological picture, with either evidence of JCV-DNA in CSF or typical histological findings with in situ evidence of JCV-DNA or antigen **Probable 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	
Off-ART	Initiate ART immediately (following general guidelines for treatment, see Initial Combination Regimen for ART-naïve Adults, 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
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
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. There is no recommendation to use the following drugs which previously or occasionally were used in PML: alpha-IFN, cidofovir, cytarabine, mefloquine, mirtazapine, corticosteroids (except for treatment of IRIS-PML, see IRIS section), iv immunoglobulins. Newer immune-based approaches have shown some efficacy, including Interleukin-7, infusion of polyomavirus-specific HLA-matched T-cells, PD1 inhibitors (pembrolizumab, nivolumab). Results from large retrospective cohorts did not show a benefit of IL-7 or PD1 inhibitors on survival, but no data from clinical trials are currently supporting recommending for or against their clinical use. If used, participation in treatment protocols is strongly encouraged

Bacillary Angiomatosis *(Bartonella henselae, Bartonella quintana)*

Diagnosis and treatment			
Diagnosis: typical histology on biopsies from clinically suspect lesions **Notes on treatment:** treat until clinical improvement and for at least 3 months. For possible interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs and Anti-infective and ART interactions table			
	Drug	**Dose**	**Comments**
	doxycycline	100 mg bid po	Until improvement (at least 3 months)
	or **clarithromycin**	500 mg bid po	

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

Diagnosis and treatment			
Diagnosis: immunofluorescence, acid fast stain, cryptosporidium antigen or PCR detection on stools or tissues in persons with chronic diarrhea, mostly with CD4 count < 100 cells/µL. If the diarrhea lasts > 4 weeks, the diagnosis of cryptosporidiosis is an AIDS defining illness **Notes on treatment:** mainstay of therapy is the initiation 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 reconstitution			
	Drug	**Dose**	**Comments**
	nitazoxanide	500-1000 mg bid po	14 days
	or **paromomycin**	500 mg qid po	14-21 days

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

	Drug	Dose	Comments
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 viremic 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**
Diagnosis and treatment			
Diagnosis: clinical appearance and cultures of blood, lymph nodes, bone marrow or other usually sterile specimen. **Notes on treatment:** for any treatment regimen, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs and Anti-infective and ART interactions table **Active TB should be ruled out before starting anti-TB drugs (rifampicin, rifabutin, ethambutol, isoniazid)**			
***Mycobacterium avium-intracellulare* complex (MAC)**			
Preferred therapy	**clarithromycin** **+ ethambutol** **+/- rifabutin** **rifabutin** can be replaced by: **+ levofloxacin/ moxifloxacin** or **+ amikacin**	500 mg bid po 15-20 mg/kg qd po 300 mg qd po (or 150 mg qd if PI/b) 500 mg qd po/400 mg qd po 10-15 mg/kg qd iv	12 months, then secondary prophylaxis **rifabutin** can be considered in case of severe disease, if resistance to macrolides or **ethambutol** is suspected, or in case of high bacterial load (> 2*log of CFU/mL of blood). **rifabutin** is indicated if ART is not given **levofloxacin/ moxifloxacin** or **amikacin** can be considered as a 4th drug for disseminated or severe/refractory disease (no data on additional clinical benefit)
	azithromycin **+ ethambutol**	500 mg qd po 15-20 mg/kg qd po	Consider additional drugs as above
Mycobacterium kansasii			
	rifampicin **+ isoniazid** **+ ethambutol**	600 mg qd po (or **rifabutin** 300 mg qd po) 300 mg qd po 15-20 mg/kg qd po	12 months after negative culture
	or **rifampicin** **+ clarithromycin** **+ ethambutol**	600 mg qd po (or **rifabutin** 300 mg qd po) 500 mg bid po 15-20 mg qd po	12 months after negative culture
Secondary prophylaxis / Maintenance therapy for MAC			
Stop: if CD4 count > 100 cells/µL and HIV-VL undetectable over 6 months and MAC treatment for at least 12 months			
Mycobacterium avium (MAC) infection **Regimens listed are alternatives**	**clarithromycin** **+ ethambutol**	500 mg bid po 15-20 mg/kg qd po	
	or **azithromycin** **+ ethambutol**	500 mg qd po 15-20 mg/kg qd po	

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

Diagnosis and treatment			
Diagnosis: detection of oocysts by UV fluorescence or microscopy of stools, duodenal aspirates or intestinal tissue biopsy in persons with chronic, mostly watery diarrhea. If the diarrhea lasts > 4 weeks, the diagnosis of cystoisosporiasis is an AIDS defining illness **Notes on treatment:** besides antiprotozoal treatment, additional measures are symptomatic treatment, rehydration and electrolyte management. see also Anti-infective/ART interaction table for treatment optimization			
	Drug	**Dose**	**Comments**
Preferred therapy	**TMP-SMX**	320/1600 mg bid po or 160/800 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**	160/800 mg x 3/week po or 160/800 mg qd po or 320/1600 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**

Visceral Leishmaniasis

Diagnosis and treatment			
Diagnosis: microscopy or PCR in smears, body fluids or tissue **Notes on treatment:** see also Anti-infective/ART interaction table for treatment optimization			
	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 **liposomal amphotericin B** **+Milltefosine**	5 mg/kg every other day (days 1, 3, 5, 7, 9, 11) 50 mg bid for 14 days	The efficacy of this regimen has not been assessed in regions where *L. infantum* is prevalent (i.e. Europe, Mediterranean basin)
	or **pentavalent antimonium salt (Glucantime®)**	20 mg/kg qd iv or im	4 weeks
	or **miltefosine**	1.5-2.5 mg/kg qd po	4 weeks Efficacy of miltefosine can vary in different Leishmania spp. and has been reported to be lower in *L. infantum*
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 Persons with HIV

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

Disease	Drug	Dose[i]	Comments*
Susceptible *Mycobacterium tuberculosis*			
Initial phase	**rifampicin** **+ isoniazid (+ pyridoxine)** **+ pyrazinamide** **+ ethambutol**	Weight based	**Initial phase** for 2 months. Possibility to omit **ethambutol**, if *M. tuberculosis* is known to be fully drug sensitive. Preventive steroid therapy may be considered to avoid IRIS, see IRIS section Corticosteroids are recommended as adjuvant treatment in TB meningitis and TB with CNS involvement
Alternative Initial phase	**rifabutin** **+ isoniazid (+ pyridoxine)** **+ pyrazinamide** **+ ethambutol**	Weight based	**Initial phase** for 2 months. Possibility to omit **ethambutol**, if *M. tuberculosis* 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 (only in patients with CD4>100) 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 (see WHO Guidelines, 2022) Evidence on efficacy of this regimen in extrapulmonary TB is limited.

* Intermittent regimens (2 or 3 times per week) are contraindicated in persons with HIV. Missed doses can lead to treatment failure, relapse or acquired drug resistance.
Insufficient evidence is available to recommend any ultra-short (<4 months) regimens in HIV patients.

i For dose details, please see separate table TB drug doses, page 150

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

MDR/XDR-TB should be suspected in case of:

- Previous or incomplete 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 - since 2021: 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 optimizing treatment

Treatment of resistant TB

Isoniazid-resistant TB
- **rifampicin/rifabutin** + **pyrazinamide** + **ethambutol** + **levofloxacin or moxifloxacin** for 6 months, (WHO 2020 recommendations)

Rifampicin-resistant (RR) and MDR-TB
- Treatment of MDR/XDR-TB is a specialist area. WHO has published new Guidelines (2022)

- Currently recommended all-oral regimen:
Can be used in persons with confirmed RR/MDR-TB who have not been exposed to **bedaquiline**, **pretomanid**, **linezolid** for > 1 month

- 6 months of **bedaquiline**, **pretomanid**, **linezolid** (600 mg qd) and **moxifloxacin (BPaLM)**. This regimen may be used without moxifloxacin if resistance to fluoroquinolones (pre-XDR-TB) is documented **(BPaL)**. In this case consider extension of 3 months. Data on the effectiveness of this regimen in extensive pulmonary TB disease or severe extra-pulmonary TB are currently not available (see WHO Guidelines 2022)

- Alternative all oral regimen:
Can be used in persons with MDR/RR-TB without resistance to fluoroquinolones and without previous exposure to second-line drugs and without extensive pulmonary TB or severe extra-pulmonary TB

- 4-6 months **bedaquiline** (6 months) + **levo-/ moxifloxacin** + **ethionamide**** + **ethambutol** + **isoniazid** (high-dose) + **pyrazinamide** + **clofazimine** followed by
- 5 months **levo-/ moxifloxacin** + **ethambutol** + **pyrazinamide** + **clofazimine**

4 months of **ethionamide can be replaced by 2 months of **linezolid** (600 mg qd)

Longer TB treatment regimens (>18 months)

Patients with XDR-TB and those not eligible to or failing all-oral short regimens may benefit from individualized longer treatment.
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.
The duration of longer regimens must be individualized. For details, see WHO Guidelines 2022
Treatment compliance is crucial. If needed, each dose of medicines 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-TB

Drug choices

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

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

Pretomanid is recommended but not yet included in Group A drugs

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 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	To be used with clavulanic acid
Meropenem	1000 mg tid iv	To be used with clavulanic acid
Amikacin 30-35 kg 36-45 kg 46-55 kg > 55 kg	 625 mg qd iv 750 mg qd iv 750-1000 mg qd iv 1000 mg qd iv	After initial period can be reduced to trice weekly Baseline audiometry should be performed Caution: monitor renal function, audiometry and drug levels
Streptomycin	12-18 mg/kg qd iv	Max 1000 mg qd iv
Ethionamide or prothionamide 30-45 kg 46-70 kg > 70 kg	 500 mg qd 750 mg qd 1000 mg qd	Caution: gastrointestinal toxicity; add **pyridoxine**, up to 50 mg/250 mg **prothionamide**
Para-aminosalycilic acid	4000 mg bid	In weight > 70 kg can be increased to 4000-6000 mg bid Caution: gastrointestinal toxicity
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 Persons with HIV

Introduction

Epidemiology of SARS-CoV-2 in persons with HIV

- Incidence of SARS-CoV-2 infection in persons with HIV seems to be similar to that reported in the general population
- Higher rates of SARS-CoV-2 breakthrough infections have been reported in fully vaccinated persons with HIV when compared to the general population

Risk factors for severe COVID-19 outcomes

- More adverse COVID-19 outcomes (hospitalization, disease severity, mortality) have been reported in persons with HIV and CD4 count < 200-350 cells/μL when compared to the general population and to persons with HIV with higher CD4 count, and in persons with untreated HIV infection and/or with detectable viremia when compared to those with controlled HIV infection, with a possible increasing association of COVID-19 severity with higher HIV-VL
- An increased incidence of severe COVID-19 has been described in persons with concomitant OIs (especially TB and PcP) and associated comorbidities. Among hospitalized COVID-19 patients, studies reported a younger age and higher rates of comorbidities in people with HIV when compared to the general population

Management of HIV infection during COVID-19 infection

- In case of lockdown or home isolation, it is important to ensure continuum of HIV-care. Consider teleconsultation and phone visits for stable persons, not requiring changes in ART or co-medications. Retain in-person visits for persons recently diagnosed with HIV and initiating ART, or complaining of acute problems, adverse effects due to ART, virological failure, STIs or other complains/ co-morbidities requiring clinical evaluation. Consider tele-pharmacy, and ensure continuous ART supply
- New development or worsening of mental health problems (anxiety, depression, increased loneliness and stigma) have been very common following social distancing and lockdowns; psychological/psychiatric and social support should be actively offered, and well-being general measures (e.g. diet/ exercise) should be recommended
- ART should neither be stopped nor modified due to recently diagnosed SARS-CoV-2 infection, unless strictly necessary (no ARV drug has proved to be clinically effective against SARS-CoV-2 infection). The ART regimen should be adapted in persons who are unable to swallow their ARV drugs (e.g., those on mechanical ventilation or ECMO therapy). see Administration of ARVs in Persons with Swallowing Difficulties
- Total lymphocytes, CD4 and CD8 subpopulations may decrease during acute 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 unknown
- Co-morbidities and co-infections should be managed as indicated in specific sections of the Guidelines, see Prevention and Management of Co-morbidities, Viral hepatitis co-infections, Opportunistic infections

Management of COVID-19

Diagnostic approach and differential diagnosis:

- The same approach, as for general population, should be applied, according to the national or international recommendations. For details, see WHO recommendations
- For persons with poor immune status, other respiratory diseases (e.g., PcP, and TB) should be considered as differential diagnosis. Appropriate diagnostic workup should follow current recommendations, see Opportunistic infections
- Isolation precautions should be the same as for the general population, although persons with uncontrolled HIV infection may show long-term viral shedding, relevance or risk for transmission are unknown

Treatment approach:

- Treatment of COVID-19 should be the same as for general population. As treatment guidelines and prescription requirements for COVID-19 might vary between countries, refer to national guidelines. In absence of those, follow international recommendations: NIH; WHO
- Several early treatments with anti-SARS-CoV-2 antiviral agents are available to prevent COVID-19 progression to severe disease. People with HIV may be eligible for such treatments, according to local guidelines, and those with AIDS, poor immune responses to ART and/or ART-untreated HIV infection should be preferentially considered for early anti-SARS-CoV-2 treatment initiation.
- Check for drug-drug interactions and overlapping toxicities between COVID-19 treatments (particularly nirmatrelvir/ritonavir or other anti-SARS-CoV-2 directed agents, corticosteroids, and anticoagulants) and ARV drugs, see table Drug-drug Interactions between COVID-19 Therapies and ARVs, Drug-drug Interactions and Other Prescribing Issues, Drug-drug Interactions between Corticosteroids and ARVs

Management of long-term symptoms and sequelae of COVID-19 (Post-acute COVID-19 syndrome, PACS)

- A substantial proportion of COVID-19 patients may show progressive or newly presenting symptoms, involving the lungs or other organs, weeks to months after COVID-19 (post-acute COVID-19 syndrome, PACS); studies addressing whether frequency of PACS is increased in persons with HIV are ongoing, but some preliminary results suggest a higher prevalence of PACS in persons with HIV
- These conditions should be specifically addressed and evaluated; refer to the appropriate specialist consultations following local/national guidelines for persistent COVID-19 sequelae
- Check for drug-drug interactions if any treatment for post- COVID-19 complications is initiated, see Drug-drug Interactions and Other Prescribing Issues, Drug-drug Interactions between COVID-19 Therapies and ARVs, Drug-drug Interactions between Corticosteroids and ARVs

Prophylaxis of COVID-19 in persons with HIV

Vaccination guidelines as well as prescription requirements for anti-SARS-CoV-2 pharmacological prophylaxis might vary between countries, and the efficacy of specific antiviral agents may differ against different SARS-CoV-2 variants. Please refer to national guidelines and local epidemiology or international recommendations: NIH; WHO

SARS-CoV-2 prevention:

- It is recommended for all persons with HIV to be vaccinated against SARS-CoV-2. There is no data to recommend a specific vaccine and the choice depends on the availability in individual countries. Priority should be given to those with immunosuppression (CD4 count < 350 cells/μL), if access to vaccines is limited, see Vaccination
- Persons with advanced disease (CD4<200 cells/mm^3) and/or detectable VL have poorer humoral and cellular mediated immune responses to vaccination, and are candidates for booster doses following local guidelines (see also Vaccination)
- Other vaccines (particularly S pneumoniae and influenza) should be given as scheduled, see Vaccination
- Links to an overview of available vaccines and information regarding SARS-CoV-2 vaccination in persons with HIV: NIH; BHIVA; WHO; EACS
- Passive immunization with antibodies against SARS-CoV-2 has been considered as pre-exposure prophylaxis (PrEP) in unvaccinated persons or in those with advanced immunodepression. As sensitivity of circulating variants to these agents may vary, please refer to local guidelines and epidemiology

Management of Mpox in Persons with HIV

Epidemiology and prevention

- An outbreak of Mpox (formerly known as Monkeypox) outside West/Central Africa is ongoing since May 2022. In the context of the current outbreak, sexual intercourses have been the major route of transmission. It has disproportionally affected MSM, particularly people with HIV and PrEP users
- Counselling should be offered to these persons to reduce the risk of Mpox transmission
- Close contacts of an individual with Mpox should be identified and monitored according to local guidelines
- See Vaccination for recommendations regarding Mpox preventive and post-exposure vaccination
- Individuals recently diagnosed with Mpox should be tested for concomitant STIs. See also STI

Clinical features and diagnosis

- Fever, lymphadenopathy and enanthema in prodromal phase, followed by cutaneous lesions (most frequently vesiculopustular, but multiple morphologies may occur). Atypical presentations, such as single genital ulcer, proctitis and anorectal involvement, or conjunctival involvement may occur
- Aggressive disseminated infection with large necrotizing skin/mucosal lesions and multisystemic involvement (pulmonary, ocular or central nervous system manifestations; secondary cutaneous or bacteriaemic superinfection) may occur in individuals with immunosuppression, including persons with advanced/uncontrolled HIV infection (CD4 T cells<200 cells/mm^3, having most cases <100 cells/mm^3)
- Definitive diagnosis requires Mpox DNA detection by PCR on cutaneous lesion/crust swab. PCR on oropharyngeal/conjunctival/rectal swab may be useful in atypical presentations. See also WHO guidelines and CDC guidelines

Management and treatment

- All individuals with Mpox should be offered appropriate symptomatic treatment (pain and fever management, care of skin lesions)
- Isolation measures for confirmed cases and effective contact-tracing should be implemented to reduce the risk of Mpox spreading, according to local guidelines
- Non-severe cases without immunosuppression or other high-risk clinical manifestations and able to self-isolate at home may be managed conservatively. Close monitoring of clinical conditions and early recognition of complications (e.g.: bacterial superinfection; difficult breathing; deterioration of general conditions) should be ensured
- Severe cases or cases at high-risk of severe disease, defined as persons with any of the following:
  - CD4 T cells <200 cells/mm^3 (see also CDC guidelines)
  - fulminant disseminated infection (confluent, necrotic skin lesions; pulmonary or CNS complications; sepsis)
  - mucosal or genital lesions with the potential for causing strictures
  - ocular involvement
  - lymphadenopathy causing difficulties in breathing/oral intake
  - skin and deep tissues bacterial superinfection
  - severe, uncontrolled pain
  - pre-existing skin conditions affecting skin integrity
  - pediatric, pregnant or breast-feeding populations
  - other conditions requiring hospitalization

  Should be evaluated for hospitalization and initiation of antiviral treatment (see also WHO guidelines and CDC guidelines)

Therapeutic considerations for severe cases

Severe cases and persons at risk of severe disease should be admitted for close monitoring. In immunocompromised patients, it is critical to optimize immune function to maximize chances of recovery. To date, effectiveness of antiviral therapies in Mpox has not been systematically evaluated, but preliminary data suggest that their use may be beneficial in severe cases. See also MMWR-Interim clinical treatment considerations for Mpox

First-line therapy	Dose	Comments
Tecovirimat	Oral dosing: • 40-120 kg: 600 mg bid • >120 kg: 600 mg tid • To be administered with high-fat meal IV dosing: • 35-120 kg: 200 mg every 12 hours over 6 hours • > 120 kg: 300 mg every 12 hours over 6 hours • Do not administer IV formulation in patients with CrCl< 30mL/min, and use caution in people with milder degrees of renal impairment Treatment duration: 10 to 14 days	• Tecovirimat has been approved for the treatment orthopox viruses infections (including Mpox) based on animal studies. Studies to assess benefit of tecovirimat treatment in people with Mpox are ongoing. Data on special population (pregnant women; pediatric patients) are limited. • Tecovirimat may reduce RPV levels. Consider additional drug-drug interactions when prescribing tecovirimat; See also Anti-infective/ART interaction table

Additional therapeutic options

Several agents have been proposed as adjunctive or alternative therapies for Mpox.

- Brincidofovir and cidofovir are effective against other poxviruses, and anecdotical data suggest that they could be effective against Mpox. The use of these agents may be considered in patients not eligible to or failing first-line therapy with tecovirimat. In addition, either brincidofovir or cidofovir may be considered in combination with tecovirimat as first-line therapy for severely immunocompromised patients.
- Vaccinia immune globulin intravenous (VIGIV) can be considered for severely immunocompromised patients unable to mount an effective immune response. Caution should be applied in administering VIGIV in patients with corneal involvement. See also MMWR-Interim clinical treatment considerations for Mpox
- Topical application of trifluridine could be considered in patients with ocular involvement

Considerations for ART start

- Cases of clinical deterioration attributable to immune reconstitution inflammatory syndrome (IRIS) have been observed in persons with advanced HIV infection antiretroviral-naïve or re-initiating ART. Monitor carefully for signs of IRIS after ART introduction

Part VII Paediatric HIV Treatment and Prevention of Vertical Transmission

Initiation of ART in Children and Adolescents

- 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 with HIV and urgent initiation of treatment for 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 a motivational message to enhance adherence and prevent onward HIV transmission

Initial Combination Regimen for Children and Adolescents who are ART Naive 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 (anchor drug)
- 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 availability of ART formulations is limited or for individuals at particular risk of specific toxicity or DDIs
- Whenever possible, first line anchor drugs with high barrier to resistance have been selected in view of potential difficulties with adherence in children and adolescents
- When choosing a regimen, potential transmitted resistance, including from maternal or infant ART exposure after failed prevention of vertical transmission, should always be considered
- Dual therapy as first line is not generally recommended outside of a clinical trial but DTG plus 3TC can be considered following discussion with a multi-disciplinary team (MDT)/paediatric virtual clinic (PVC)
- In infants under 4 weeks and/or under 3 kg, when NVP has been used in pregnancy or there is a risk of transmitted NVP resistance, non-NNRTI-based ART, including RAL from birth or LPV/r from 2 weeks are preferred. Once over 4 weeks and 3kg, we recommend switching to DTG based ART as soon as possible to provide a once daily, highly effective, low toxicity, anchor drug with a high barrier to resistance
- RAL has a relatively low barrier to resistance. If commenced on RAL under 2 weeks of age and DTG is not likely to be available in an appropriate formulation during infancy, then we recommend an interim switch to LPV/r to remove the risk of developing INSTI resistance. It should be noted that LPV/r can also bring challenges with adherence due to poor palatability and this should be taken into account when considering the risk/benefit of this approach

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 ART in high prevalence setting, options should be discussed within an MDT or 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
- Support from 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 are also included in the licensing of ARVs in children
- Detailed guidance on paediatric dosing is available from the Penta website
- Long acting injectable CAB/RPV is not currently licensed for treatment of HIV in individuals aged less than 18 years of age in Europe and although it is not yet recommended as an option for children and adolescents, it may be considered on a case by case basis following discussion at an MDT/PVC and following the same general principles as outlined for adults, see page 16
- TDF/FTC is licensed in Europe for PrEP in adolescents over 12 years and over 35 kg. When other agents are approved for use in the adolescent age range, these agents can also be considered. The same principles should be followed as discussed on page 23 (EACS PrEP in adults guidance) with additional prioritisation of safeguarding assessments and social as well as medical support for adolescents at significant risk of HIV transmission.

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

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

Notes:

Toxicities as listed in the table on page 24 and 25 should be considered. Additional toxicity considerations specific to paediatrics are described in the footnotes below

i In view of potential long-term toxicity, any child on ZDV should be switched to ABC or TAF (preferred for younger children) or TDF (alternative for younger children, with renal/bone toxicity monitoring) once increase in age and/or weight makes licensed formulations available. When ABC and TAF are contraindicated or unavailable for young children it is recommended that treatment options are discussed at MDT to decide between ZDV or TDF on a case by case basis

ii 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

iii LPV/r should not be routinely 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 appropriate INSTI formulations are unavailable. In these circumstances the neonate should be monitored closely for LPV/r related toxicity (cardiac, metabolic, endocrine)

iv If starting a non-DTG anchor drug in the neonatal period it is acceptable to continue this option. However, when over 4 weeks and 3 kg, a switch to second generation INSTI (DTG or BIC) is recommended if and when an appropriate licensed formulation is available. If initially commenced on RAL and appropriate DTG or BIC formulations are not predicted to be available in a suitable timeframe then an interim switch to LPV/r could be considered in order to remove risk of developing INSTI resistance while awaiting availability of DTG (or BIC)

v At HIV-VL > 100,000 copies/mL ABC + 3TC should not be combined with EFV as anchor drug

vi TAF is currently licensed in Europe for children and adolescents in a number of FDC's including: TAF/FTC (10/200 mg or 25/200 mg when administered with or without a booster (cobicistat or ritonavir) respectively) from 12 years 35 kg, TAF/FTC/EVG/c (10/200/150/150 mg) from 2 years and 14 kg, TAF/FTC/BIC (25/200/50 mg) from 25 kg, TAF/FTC/BIC (15/120/30 mg) from 2 years and between 14 kg and 25 kg, TAF/FTC/DRV/c (10/200/800/150 mg) from 12 years 40 kg, TAF/FTC/RPV (25/200/25 mg) 12 years 35 kg. When TAF becomes licensed in younger ages and lower weights it should be included as a preferred option. TAF has been associated with excessive weight gain in adults, especially in combination with DTG. This has not yet been demonstrated in paediatric and adolescent observational studies or trials, however the possibility of this should be considered when TAF is used. Families and young people should be counselled regarding this and weight should be monitored. DTG remains the preferred anchor drug due to superior efficacy

vii XTC indicates circumstances when FTC or 3TC may be used interchangeably

viii If using NVP as an anchor drug in children aged 2 weeks to 3 years, consider using 3 NRTI backbone (ABC + ZDV + 3TC) until VL consistently < 50 copies/mL

ix TDF is only licensed from 2 years of age. In view of concerns about potential impact on bone development and renal toxicity TAF is recommended over TDF at all ages in settings where this is licensed and available

x BIC is currently licensed in Europe for children and adolescents in the following FDC's: TAF/FTC/BIC (25/200/50 mg) from 25 kg, TAF/FTC/BIC (15/120/30 mg) from 2 years and between 14 kg and 25 kg. When BIC becomes licensed in younger ages and weights it can be included as a preferred option

xi DTG is licensed from 4 weeks and 3 kg. When DTG becomes licensed at younger ages and weights it can be included as a preferred option. Dispersible ABC/3TC/DTG tablets have been recently licensed for children between 14 and 25 kg in Europe. **Specific caution should be taken when prescribing dispersible DTG as is not bioequivalent to film coated tablets.** DTG has been associated with excessive weight gain in adults, especially in combination with TAF. This has not yet been demonstrated in paediatric and adolescent observational studies or trials, however the possibility of this should be considered when DTG is used. Families and young people should be counselled regarding this and weight should be monitored

xii Due to predicted poor adherence in adolescence, if preferred anchor drug (BIC or DTG) are not available/appropriate then of the possible alternative anchor drugs, DRV/b is favoured due to a higher barrier to resistance compared to EFV, RAL or RPV

Switch Strategies children and adolescents who are virologically suppressed

- The general indications for switching when virologically suppressed are as for adults, (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 low toxicity profiles and optimal efficacy data. For example, in children aged less than 3 years commenced on liquid LPV/r, consider switching to once daily regimens as dispersible DTG becomes available or pill swallowing is achieved
- If "preferred" options become available for a child as they get older then a switch to this preferred 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
- Switching to dual therapy is not routinely recommended, but is a potential option for simplification and can be considered on a case by case basis in adherent children and adolescents
- Dual therapy as first line is not generally recommended outside of a clinical trial
- Simplification to monotherapy and treatment interruptions are not recommended and are strongly discouraged

Special Situations

- 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 42, and whether the young person is trying to conceive. DTG use at conception is not associated with increased rates of birth defects (including neural tube defects)
- **DDI:** see page 26 for information on avoidance and management of DDI. In addition to the information on interactions in this guideline a further useful resource is provided by University of Liverpool here
- **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 page 128
- **HCV co-infection:** DAAs against HCV are licensed and available in paediatric formulations down to 3 years of age. Seek specialist advice for choice of curative HCV therapy for children and adolescents with HCV co-infection, for recommendation in adults with HCV/HIV co-infection, see page 129
- **TB co-infection:** From 4 weeks of age DTG bid is preferred anchor drug in the context of rifampicin administration. Double dose RAL can be considered as an alternative. Over 3 years of age EFV is also an alternative option if DTG is not available. Super boosted LPV/r can also be considered when paediatric INSTI formulations are not available. 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 on page 17) 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 on ALL previous ART exposure and documented cumulative HIV resistance mutations at all times tested
- TDM may provide additional useful information, especially in very young children
- Second line options should ideally be discussed at a PVC/MDT, ideally including a virologist

Choosing an anchor drug

Failed on first line NNRTI

- Switch to optimised 2 NRTI with either INSTI with a high barrier to resistance (i.e. DTG or BIC) or PI/b
- Consider INSTI or PI with 2 NRTI single tablet regimen to reduce pill burden
- If high VL and substantial NRTI resistance consider using regimen with at least 2 fully active drugs (e.g. INSTI with PI/b and 2 NRTI). This should be discussed at MDT/PVC

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
- Consider switch to INSTI with high barrier to resistance (i.e. DTG or BIC)
- Consider INSTI or PI with 2 NRTI single tablet regimen to reduce pill burden (e.g. DRV/c (only in the absence of significant PI resistance), DTG or BIC where/when licensing allows)
- If substantial NRTI resistance consider initial therapy with DTG + PI/b + optimised 2 NRTI. This should be discussed at MDT/PVC

Failed on first line INSTI

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

Optimising NRTI backbone

- If resistance testing is 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 and availability of formulations. If TAF or TDF are not available or contraindicated then ZDV can be considered (if not used first line) but alternatives to ZDV should be regularly assessed in order to remove from the regimen as soon as possible due to risk of ZDV toxicity over time
- If resistance testing not available, switch to (or continue) TDF or TAF (or ZDV as per above) with 3TC or FTC (see rationale below)
- TDF or TAF are preferred in second line in combination with 3TC or FTC (even if failing on TDF or TAF)
- The M184V mutation 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 viral susceptibility to tenofovir and ZDV

Virological Failure on Second Line Combination

- Subsequent virological failure on second line therapy requires further assessment of adherence and is likely to require resistance testing, even if availability is limited
- 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 (with a robust INSTI or PI/b based regimen including 3TC or FTC) to maintain CD4 count whilst additional adherence support is provided

General Principles of Postnatal Prophylaxis and Infant Feeding (Also see page 18)

Evidence to guide practice in relation to postnatal prophylaxis (PNP) and feeding for infants exposed to HIV during pregnancy and during breastfeeding is mainly from low and middle-income countries and limited in settings with universal access to maternal ART and regular viral load monitoring as well as alternative feeding options. Consequently, guidance and practices vary across Europe and in other high-income settings. Some general principles are consistent across all settings.

- Complex antenatal and PNP cases should be discussed at MDT/PVC. If not available locally referrals are welcome to the Penta paediatric virtual clinic via the Guideline Team
- Recommendations for PNP should be based on risk stratification. The most important factor is maternal HIV VL at the time of delivery. Other important factors determining the risk are duration of ART before or during pregnancy and VL in the weeks leading up to delivery. Other risk factors for transmission may also be taken in to account e.g. mode of delivery, duration of rupture of membranes, prematurity etc.
- If an infant is considered very low risk for transmission, in most settings single agent PNP (most commonly ZDV or NVP) for 2-6 weeks is recommended . In some countries, it is recommended that neonates fulfilling criteria for very low risk do not require PNP
- For infants at higher risk of acquiring HIV, combination PNP is recommended (2 or 3 agents e.g. NVP/ZDV/3TC) for 4 weeks. Maternal treatment history and resistance test results, and the risk of transmitted resistance should be taken into account when deciding on optimal combination PNP components
- Prophylactic doses of ART for PNP are available which differ from standard treatment doses. Some guidelines continue to use these prophylactic doses, but there is a move in several guidelines to use standard treatment doses for PNP to reduce the risk of confusion, and to simplify moving on to treatment in infants who do turn out to be diagnosed with HIV
- For non-breastfed infants, PCR based infant testing should take place at birth, 2 weeks after stopping PNP and at 3 months of age. If high risk of transmission an additional PCR can be done at 2 weeks of age. HIV serology can be done at around 2 years of age to confirm loss of placentally transferred maternal antibody
- Current evidence does not yet demonstrate that “undetectable = untransmissible” in the context of vertical transmission
- Principles of shared decision making should be followed when considering choices around infant feeding. Accessible, clear information relating to low but non-zero risk of transmission during breastfeeding should be provided to all pregnant women, ideally well before delivery
- If specific criteria are met including optimal maternal ART adherence, suppressed VL and availability of regular MDT support and VL monitoring, then the option of supported breastfeeding should be provided
- In some countries, infant pre-exposure prophylaxis is offered for the duration of supported breastfeeding. In others, only the usual post birth regimen is recommended
- During supported breastfeeding, easy access to MDT support should be available throughout and especially during times of complications such as detectable maternal VL, mastitis or other intercurrent illness (mother or infant)
- Regular (1-2 monthly) monitoring of maternal VL is recommended to rapidly identify viral rebound. If maternal VL is detectable during breastfeeding, alternative feeding options should be used, breastfeeding should be interrupted or stopped, and post-exposure prophylaxis should be considered for the infant. Decision making around post-exposure prophylaxis should take in to account the time since most recent potential exposure
- If breastfeeding is stopped abruptly then cabergoline should be provided to help suppress lactation (note that the recommended cabergoline prescription is different for inhibition of lactation at birth compared to cessation of established breastfeeding)
- Infant PCR based HIV testing should take place regularly during breastfeeding and 2-4 weeks after cessation of breastfeeding with follow up PCR testing as per usual practice (e.g. 3 months after stopping breastfeeding)
- The risk of HIV transmission during breastfeeding with an undetectable VL in maternal blood is very low, but not zero, and continues with longer duration of breastfeeding and so as short a duration of breastfeeding as possible should be encouraged with an aim to wean around 6 months of age
- Exclusive breastfeeding is considered lowest risk and in the context of suppressed maternal VL, occasional formula milk can be used (e.g. during periods of mastitis). Mixed feeding (i.e. breastfeeding and solids) especially in very young infants before 6 months of age potentially increases the risk of HIV transmission and should be avoided

References

A comprehensive EACS course on HIV and co-infections can be followed at: https://iversity.org/en/courses/management-of-hiv-and-co-infections

References to All Sections

Part I Assessment of Initial & Subsequent Visits

Please see references for Part IV

Part II ARV Treatment

Cohen MS, Chen YQ, McAuley M et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. N Engl J Med 2016; 375:830-839. DOI:10.1056/NEJMoa1600693

Insight Start study group: Lundgren JD, Babiker AG, Gordin F et al. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015 Aug 27; 373(9):795-807 DOI:10.1056/NEJMoa1506816

Landovitz RJ, Donnell D, Clement ME, et al. HPTN 083 Study Team. Cabotegravir for HIV Prevention in Cisgender Men and Transgender Women.N Engl J Med. 2021 Aug 12;385(7):595-608. doi: 10.1056/NEJMoa2101016. PMID: 34379922
First study to demonstrate the effectiveness of cabotegravir in MSM and TGW

Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2. Lancet. 2021;397(10281):1276-1292. doi:10.1016/S0140-6736(21)00314-7
Randomized trial including HIV-1 pregnant women at 14–28 weeks' gestation, comparing TAF/FTC + DTF vs. TDF/FTC + DTG vs. TDF/FTC/EFV. At delivery, DTG regimens were superior to TDF/FTC/EFV in virological efficacy. TAF/FTC + DTG had the lowest frequency of composite adverse pregnancy outcomes and of neonatal deaths

Luetkemeyer AF, Donnell D, Dombrowski JC, et al. DoxyPEP Study Team. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections N Engl J Med. 2023 Apr 6;388(14):1296-1306. doi: 10.1056/NEJMoa2211934. PMID: 37018493
Study among MSM on PrEP or living with HIV showing the reduction of STI incidence with doxycycline PEP

Molina JM, Squires K, Sax PE, et al for the DRIVE-FORWARD trial group. Doravirine versus ritonavir-boosted darunavir in antiretroviral-naive adults with HIV-1 (DRIVE-FORWARD): 96-week results of a randomised, double-blind, non-inferiority, phase 3 trial. Lancet HIV. 2020;7: e16–e26. doi:10.1016/S2352-3018(19)30336-4
Randomized trial where DOR + 2NRTIs was non-inferior compared to DRV/r + NRTIs in HIV-1 ART-naïve participants at 96 weeks

Molina JM, Ghosn J, Assoumou L, et al. ANRS PREVENIR Study Group. Daily and on-demand HIV pre-exposure prophylaxis with emtricitabine and tenofovir disoproxil (ANRS PREVENIR): a prospective observational cohort study. Lancet HIV. 2022 Aug;9(8):e554-e562. doi: 10.1016/S2352-3018(22)00133-3. Epub 2022 Jun 27. PMID: 35772417
Large cohort of MSM using oral TDF/FTC for PrEP either daily or on demand with a very low and similar HIV incidence

Orkin C, Squires KE, Molina JM, et al for the DRIVE-AHEAD Study Group. Doravirine/Lamivudine/Tenofovir Disoproxil Fumarate (TDF) Versus Efavirenz/Emtricitabine/TDF in Treatment-naive Adults With Human Immunodeficiency Virus Type 1 Infection: Week 96 Results of the Randomized, Double-blind, Phase 3 DRIVE-AHEAD Noninferiority Trial. Clin Infect Dis. 2021;73: 33–42. doi:10.1093/cid/ciaa822
Randomized trial where TDF/3TC/DOR was non-inferior compared to TDF/FTC/EFV in HIV-1 ART-naïve participants at 96 weeks

Overton ET, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection: 152-week results from ATLAS-2M, a randomized, open-label, Phase 3b, non-inferiority study Clin Infect Dis. 2023 May 3;76(9):1646-1654. doi: 10.1093/cid/ciad020
Long-term follow up of long acting CAB/RPV, confirms the long-term efficacy, safety, and tolerability of CAB+RPV LA every two months to maintain viral suppression

Paton NI, Musaazi J, Kityo C, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. Lancet HIV. 2022; S2352301822000923. doi:10.1016/S2352-3018(22)00092-3
Randomized trial where switching to DTG based regimen is non inferior to DRV based regimen 96 weeks after first line treatment failure but is a greater risk of resistance. Tenofovir should be continued rather than being switched to zidovudine

Patel K, Huo Y, Jao J, et al. Pediatric HIV/AIDS Cohort Study; Swiss Mother and Child HIV Cohort Study. Dolutegravir in Pregnancy as Compared with Current HIV Regimens in the United States. N Engl J Med. 2022 Sep 1;387(9):799-809. doi: 10.1056/NEJMoa2200600. PMID: 36053505
No clear differences in adverse birth outcomes with dolutegravir-based ART as compared with non-dolutegravir-based ART, although samples were small

Segal-Maurer S, DeJesus E, Stellbrink HJ et al. CAPELLA Study Investigators. Capsid Inhibition with Lenacapavir in Multidrug-Resistant HIV-1 Infection. N Engl J Med. 2022 May 12;386(19):1793-1803. doi: 10.1056/NEJMoa2115542. PMID: 35544387
First study to demonstrate the antiviral activity of lenacapavir in patients with multiresistant HIV-1

World Health Organization-WHO. Hiv Prevention, Infant Diagnosis, Antiretroviral Initiation and Monitoring Guidelines; 2021
Last 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)

Part III Drug-drug Interactions and Other Prescribing Issues

American Geriatrics Society 2019 Updated AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc 2019;67:674-94

Bettonte S, Berton M, Stader F, et al. Management of drug-drug interactions between long-acting cabotegravir and rilpivirine and comedications with inducing properties: a modelling study, Clin Infect Dis 2023; 76(7):1225-1236

Brown K, Thomas D, McKenney K et al. Impact of splitting or crushing on the relative bioavailability of the darunavir/cobicistat/emtricitabine/tenofovir alafenamide single tablet regimen. Clin Pharmacol Dev 2019; 8(4):541-8

Cerrone M, Alfarisi O, Neary M, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. J Antimicrob Chemother 2019; 74:1670-8
PK study showing that coadministration of TAF 25 mg qd with rifampicin results in lower exposure of TAF but intracellular tenofovir diphosphate levels are still 4.2 fold higher than those observed with TDF even without rifampicin

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal H et al. Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab, 2009, 94(9):3132-54

Hiremath S, Blake PG, Yeung A, et al. Early experience with modified dose nirmatrelvir/ritonavir in dialysis patients with coronavirus disease 2019. Clin J Am Soc Nephrol 2023; 18(4):485-490

Hiremath S, McGuinty M, Argyropoulos C et al. Prescribing nirmatrelvir/ritonavir for COVID-19 in advanced CKD. Clin J Am Soc Nephrol 2022

Hocqueloux L, Lefeuvre S, Bois J, et al. Bioavailability of dissolved and crushed single tablets of bictegravir, emtricitabine, tenofovir alafenamide in healthy adults: the SOLUBIC randomized crossover study. J Antimicrob Chemother 2022; 78(1): 161-8

Hodge D, Back DJ, Gibbons S, et al. Pharmacokinetics and drug-drug interactions of intramuscular cabotegravir and rilpivirine. Clin Pharmacokinet 2021 Jul;60(7):835-853. doi: 10.1007/s40262-021-01005-1. Epub 2021 Apr 8
This review provides insight on the im administration of drugs and summarizes DDI profiles after oral and im administration of CAB and RPV

O'Mahony, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people. Age and Ageing 2015;44:213- 218

Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. Clin Endocrinol (Oxf). 2015, 83(5):597-606

Orkin C et al. Expanded multivariable models to assist patient selection for long-acting cabotegravir + rilpivirine treatment: clinical utility of a combination of patient, drug concentration, and viral factors associated with virological failure over 152 weeks. International Congress on Drug Therapy in HIV Infection (HIV Glasgow) 2022, abstract O44
This analysis pooled data from the ATLAS, FLAIR and ATLAS-2M studies to determine factors that can be used to identify people with HIV at higher risk of experiencing failure of injectable treatment with cabotegravir and rilpivirine

Roskam-Kwint M, Bollen P, Colbers A, et al. Crushing of dolutegravir fixed dose combination tablets increases dolutegravir exposure. J Antimicrob Chemother 2018; 73(9):2430-2334

Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people. Department of Family & Community Medicine, University of California, 2016

Good practice guidelines for the assessment and treatment of adults with gender dysphoria. Royal College of Psychiatrists, London, 2013, Document CR181

Age Ageing 2015. Good practice guidelines for the assessment and treatment of adults with gender dysphoria. Royal College of Psychiatrists, London, 2013, Document CR181 O'Mahony D et al.

www.medicines.org.uk/emc/

Primary health Tasmania. A guide to deprescribing, available at www.primaryhealthtas.com.au

The Renal Drug Handbook. 5th ed. Boca Raton:CRC Press; 2019 Ashley C, Dunleavy A, editors

Part IV Prevention and Management of Co-morbidities

Articles:

Aprahamian I, Lin SM, Suemoto CK, et al. Feasibility and factor structure of the FRAIL scale in older adults. JAMDA. 2017;18(4):367.e11e367.e18 DOI:10.1016/j.jamda.2016.12.067

Arrieta SS, Serrano L, Rafecas A et al. CD4/CD8 ratio ≥0.5 is a risk factor for acute rejection in HIV infected LT recipients. Poster presented at: 29th Conference on Retroviruses and Opportunistic Infections (CROI); February 12-16, 2022; Virtual meeting. Poster number 00551

Boustani MA, Campbell NL, Munger S, Maidment I, Fox GC. Impact of anticholinergics on the aging brain: a review and practical application. Aging Heatlh. 2008;4(3):311-320. DOI:10.2217/1745509X.4.3.311

Bischoff SC, Bernal W, Dasarathy S, et al, ESPEN Practical Guideline: Clinical Nutrition in Liver Disease. Clin Nutr. 2020 Dec;39(12):3533-3562. doi: 10.1016/j.clnu.2020.09.001. Epub 2020 Oct 27

Brandt C, Zvolensky MJ, Woods SP et al. Anxiety symptoms and disorders among adults living with HIV and AIDS: A critical review of and integrative synthesis of the empirical literature. Clin Psychol Rev. 2017;51:164-84 DOI:10.1016/j.cpr/2016.11.005

Brañas F, Ryan P, Troya J et al. Geriatric Medicine: the geriatrician's role. European Geriatric Medicine. 2019;10(2):259-265. DOI: 10.1007/s41999-018-0144-1

Calvo-Sanchez M, Martinez E. How to address smoking cessation in HIV patient HIV Med 2015; 16: 201-210 DOI:10.1111/hiv.12193

Davies MJ, Aroda VR, Collins BS, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care, 2022 Nov 1;45(11):2753-2786. DOI: 10.2337/dci22-0034

De Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension J Hepatol 2022 Apr;76(4):959-974. PMID: 35120736 doi: 10.1016/j.jhep.2021.12.022. Epub 2021 Dec 30

Divo M, Celli BR. Multimorbidity in Patients with Chronic Obstructive Pulmonary Disease. Clin Chest Med. 2020 Sep;41(3):405-419. doi: 10.1016/j.ccm.2020.06.002

Freudenreich O, Goforth HW, Cozza K et al. Psychiatric Treatment of Persons with HIV/AIDS: An HIV-Psychiatry Consensus Survey of Current Practices. Psychosomatics. 2010; 51:480–8. DOI: 10.1016/S0033-3182(10)70740-4

Garakani A, Murrough JW, Freire RC et al. Pharmacotherapy of Anxiety Disorders: Current and Emerging Treatment Options. Front Psychiatry. 2020; 11:595584 DOI: 10.3389/fpsyt.2020.595584

Guralnik JM, Simonsick EM, Ferrucci L, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994 Mar;49(2):M85-94. doi: 10.1093/geronj/49.2.m85

Kooij KW, Wit FW, Schouten J et al. HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls. AIDS. 2016 Jan;30(2):241-50 DOI:10.1097/QAD.0000000000000910
A significantly higher prevalence of frailty among PWH compared to HIV-negative controls was demonstrated in a European cohort

Kroenke K, Spitzer RL, Williams JB et al. Anxiety disorders in primary care: prevalence, impairment, comorbidity, and detection. Ann Intern Med. 2007;146:317-25 DOI:10.7326/0003-4819-146-5-200703060-00004

Lai JC, Tandon P, Bernal W, et al. Malnutrition, Frailty, and Sarcopenia in Patients With Cirrhosis: 2021 Practice Guidance by the American Association for the Study of Liver Diseases. Hepatology. 2021 Sep;74(3):1611-1644. doi: 10.1002/hep.32049. DOI: 10.1002/hep.32049

Manzardo C, Londoño MC, Castells L, et al. Direct-acting antivirals are effective and safe in HCV/HIV-coinfected liver transplant recipients who experience recurrence of hepatitis C: A prospective nationwide cohort study. Am J Transplant. 2018 Oct;18(10):2513-2522. doi: 10.1111/ajt.14996

Morley J, Vellas B, van Kan GA, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013 Jun;14(6):392-7. doi: 10.1016/j.jamda.2013.03.022

Negredo E, Warriner AH: Pharmacologic approaches to the prevention and management of low bone mineral density in HIV-infected patients. Curr Opin HIV AIDS 2016, 11:351-357 DOI:10.1097/COH.0000000000000271
This manuscript describes the most common approaches to treat osteoporosis in persons with HIV; beyond bisphosphonates, there are a few other osteoporosis treatment options that are known to be effective in improving BMD and reducing fracture risk in this population

Nightingale S, Dreyer AJ, Saylor D., et al. Moving on From HAND: Why We Need New Criteria for Cognitive Impairment in Persons Living With Human Immunodeficiency Virus and a Proposed Way Forward. Clin Infect Dis. 2021 Sep 15;73(6):1113-1118. DOI: 10.1093/cid/ciab366

Premaor MO, Compston JE: People living with HIV and fracture risk. Osteoporos Int 2020, 31:1633-1644 DOI:10.1007/s00198-020-05350-y
This recent review covers the epidemiology and pathophysiology of osteoporosis in persons with HIV, addresses approaches to fracture risk assessment and discusses the current evidence-base for pharmacological interventions to reduce fracture risk

Presti RM, Flores SC, Palmer BE, et al. Mechanisms Underlying HIV-Associated Noninfectious Lung Disease. Chest. 2017;152(5):1053-1060. doi:10.1016/j.chest.2017.04.154

Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005 Aug 30;173(5):489-95. doi: 10.1503/cmaj.050051

Rosen RC, Riley A, Wagner G et al. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 49(6):822-830. DOI:10.1016/S0090-4295(97)00238-0

Spithoff S, Kahan M. Primary care management of alcohol use disorder and at-risk drinking: Part 1: screening and assessment. Can Fam Physician. 2015 Jun;61(6):509-14

Spithoff S, Kahan M. Primary care management of alcohol use disorder and at-risk drinking: Part 2: counsel, prescribe, connect. Can Fam Physician. 2015 Jun;61(6):515-21

Stergiou GS, Palatini P, Parati G, et al. 2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement. European Society of Hypertension Council and the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. J Hypertens. 2021 Jul 1;39(7):1293-1302

Studenski S, Perera S, Patel K, et al. Gait speed and survival in older adults. JAMA. 2011 Jan 5;305(1):50-8. doi: 10.1001/jama.2010.1923

Swanepoel CR, Atta MG, D'Agati et al. Kidney disease in the setting of HIV infection: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference Kidney Int. 2018 Mar;93(3):545-559 DOI: 10.1016/j.kint.2017.11.007

Thudium RF, Ronit A, Afzal S, et al; COCOMO, INSIGHT START Pulmonary Substudy and CGPS Study Groups. Faster lung function decline in people living with HIV despite adequate treatment: a longitudinal matched cohort study. Thorax. 2023 Jun;78(6):535-542

Verboeket SO, Boyd A, Wit FW, et al; AGEhIV Cohort Study. Changes in lung function among treated HIV-positive and HIV-negative individuals: analysis of the prospective AGEh IV cohort study. Lancet Healthy Longev. 2021 Apr;2(4):e202-e211

Verheij E, Kirk GD, Wit FW, et al. Frailty is associated with mortality and incident comorbidity among middle-aged HIV-positive and HIV negative participants. J Infect Dis. 2020;222:919–928 DOI: 10.1093/infdis/jiaa010
Authors demonstrated that frailty is a strong predictor of mortality and incident comorbidity with those who were prefrail being at intermediate risk for both outcomes

Verheij E, Wit FW, Verboeket SO, et al. Frequency, Risk Factors, and Mediators of Frailty Transitions During Long-Term Follow-Up Among People With HIV and HIV-Negative AGEhIV Cohort Participants. J Acquir Immune Defic Syndr. 2021 Jan 1;86(1):110-118. DOI:10.1097/QAI.0000000000002532
Distinct factors may contribute to frailty transitions, with many of those factors being potentially preventable and reversible

Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies with the special contribution of the European Association of Preventive Cardiology (EAPC). European Heart Journal, Volume 42, Issue 34, 7 September 2021, Pages 3227–3337 doi.org/10.1093/eurheartj/ehab484

Winston A, Antinori A, Cinque P, Fox HS, Gisslen M, Henrich TJ, Letendre S, Persaud D, Price RW, Spudich S. Defining cerebrospinal fluid HIV RNA escape: editorial review AIDS. AIDS. 2019 Dec 1;33 Suppl 2:S107-S111. doi: 10.1097/QAD.0000000000002252
This manuscript outlines the rationale for the consensus definition of cerebrospinal fluid HIV RNA escape which is utilised in the EACS Guidelines

Guidelines:

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020 Jan 1;41(1):111-188. DOI: 10.1093/eurheartj/ehz455

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323 DOI:10.1093/eurheartj/ehz486

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). European Heart Journal, 42 (34): 3227–3337

2021 European Society of Hypertension practice guidelines for office and out-of-office blood pressure measurement: European Society of Hypertension Council and the European Society of Hypertension Working Group on Blood Pressure Monitoring and Cardiovascular Variability. J Hypertens. 2021 Jul 1;39(7):1293-1302

American Diabetes Association. Glycemic Targets: Standards of Medical Care in Diabetes. Diabetes Care 2020 Jan; 43 (Supplement 1): S66-S76 doi.org/10.2337/dc20-S006

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), American Psychiatric Association, Arlington VA USA 2013

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) European Association for the Study of Obesity (EASO). J Hepatol 2016 Jun;64(6):1388-402 doi: 10.1016/j.jhep.2015.11.004

EASL Clinical Practice Guidelines: Management of Hepatocellular Carcinoma Journal of Hepatology 2018;69:182-236 DOI:10.1016/j.jhep.2018.03.019 easl.eu/publications/clinical-practice-guidelines/

EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis J Hepatol 2018 Aug;69(2):406-460. doi: 10.1016/j.jhep.2018.03.024. Epub 2018 Apr 10

ESPEN Practical Guideline: Clinical Nutrition in Liver Disease. Clin Nutr. 2020 Dec;39(12):3533-3562. doi: 10.1016/j.clnu.2020.09.001. Epub 2020 Oct 27

European Smoking Cessation Guidelines ensp.network/wp-content/uploads/2021/01/ENSP-ESCG_FINAL.pdf DOI:10.1001/jama.2020.21749

International Union against Sexually Transmitted Infections Treatment Guidelines iusti.org/treatment-guidelines/

KDIGO (Kidney Disease Improving Global Outcomes) Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease kdigo.org/guidelines https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf

WHO Guidelines on Integrated Care for Older People (ICOPE) 2017 apps.who.int/iris/bitstream/handle/10665/258981/9789241550109-eng.pdf;j-sessionid=1D2957E0CEEB6271255FBA6F30084771?sequence=1
The recommendations provided in these WHO guidelines on integrated care for older people (ICOPE) offer evidence-based guidance on the appropriate approaches to detect and manage important declines in physical and mental capacities as they are strong predictors of mortality and care dependency in older age

WHO Policy brief. Transgender people and HIV. WHO/HIV/2015.17 apps.who.int/iris/bitstream/handle/10665/179517/WHO_HIV_2015.17_eng.pdf

Online resources:

CHIP Clinical (Kidney) Risk Assessment Tool chip.dk/Resources/Clinical-risk-scores

COPD Assessment Test www.catestonline.org/

Deprescribing Resource Medstopper.com

Female Sexual Functioning Index www.fertstert.org/article/S0015-0282%2809%2902741-1/fulltext

Free and bioavailable testosterone calculator www.issam.ch/freetesto.htm

Generalized Anxiety Disorder – 2 Item Screening Tool (GAD-2) www.hiv.uw.edu/page/mental-health-screening/gad-2
This link provides details on the Generalized Anxiety Disorder 2-item (GAD-2) screening tool for anxiety and validation details in persons with HIV

Global Initiative for Chronic Obstructive Lung Disease (GOLD) goldcopd.org/2023-gold-report-2/

MELD (Model for End-Stage Liver Disease) Score Calculator 12 and older www.mdcalc.com/meld-score-model-end-stage-liver-disease-12-older

Modified Medical Research Council Dyspnea Scale www.verywellhealth.com/guidelines-for-the-mmrc-dyspnea-scale-914740

For previous references, please refer to the archived v11.1 guidelines

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

Guidelines:

AASLD Guidelines for Treatment of Chronic Hepatitis B. February 2018 www.aasld.org/practice-guidelines/chronic-hepatitis-b

AASLD Recommendations for Testing, Managing, and Treating Hepatitis C www.hcvguidelines.org/

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection easl.eu/publication/management-of-hepatitis-b-virus-infection/

EASL Clinical practice guidelines on hepatitis E virus infection 2018 www.journal-of-hepatology.eu/article/S0168-8278(18)30155-7/pdf

EASL recommendations on treatment of hepatitis C: Final update of the series easl.eu/wp-content/uploads/2020/10/EASL-recommendations-on-treatment-of-hepatitis-C.pdf

Recently acquired and early chronic hepatitis C in MSM: Recommendations from the European treatment network for HIV, hepatitis and global infectious diseases consensus panel. AIDS 2020 Oct 1;34(12):1699-1711.

Part VI Opportunistic Infections and COVID-19

Articles:

Absar N, Daneshvar H, Beall G. Desensitization to trimethoprim/sulfamethoxazole in HIV-infected patients. J Allergy Clin Immunol. 1994 Jun;93(6):1001-5. doi: 10.1016/s0091-6749(94)70048-6.

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 overview of SARS-CoV-2 infection in persons with HIV, including risk factors, pathogenesis, clinical manifestation, management, prognostic factors and outcomes

Antinori A, Cicalini S, Meschi S, et al. Humoral and Cellular Immune Response Elicited by mRNA Vaccination Against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in People Living With Human Immunodeficiency Virus Receiving Antiretroviral Therapy Based on Current CD4 T-Lymphocyte Count. Clinical Infectious Diseases 2022:ciac238
Prospective study investigating the immunological responses to SARS-CoV-2 vaccination in persons with HIV

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/μL. 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/μL)

Burza S, Mahajan R, Kazmi S, et al. AmBisome Monotherapy and Combination AmBisome-Miltefosine Therapy for the Treatment of Visceral Leishmaniasis in Patients Coinfected With Human Immunodeficiency Virus (HIV) in India: A Randomized Open-Label, Parallel-Arm, Phase 3 Trial. Clinical Infectious Diseases 2022:ciac127
Randomized, open-label clinical trial documenting similar outcomes in persons with HIV treated for visceral leishmaniasis receiving a combination therapy of oral miltefosine plus liposomal Amphotericin B or current WHO-recommended regimen

Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J. 2021 Apr 15;57(4):2100048. doi: 10.1183/13993003.00048-2021. Yang X, Sun J, Patel RC, et al. Associations between HIV infection and clinical spectrum of COVID-19: a population level analysis based on US National COVID Cohort Collaborative (N3C) data. The Lancet HIV 2021;8:e690–e700

Conradie F, Diacon AH, Ngubane N, 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

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

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

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

Ingle SM, Miro JM, May MT et al. Early antiretroviral therapy not associated with higher cryptococcal meningitis mortality in people with HIV in high-income countries: an international collaborative cohort study. Clin Infect Dis. 2023 Mar 8:ciad122
Large, multicentric retrospective study suggesting that early initiation of ART in cryptococcal meningitis may be possible and safe in high-income countries

Jarvis JN, Lawrence DS, Meya DB, et al. Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis. New England Journal of Medicine 2022;386:1109–1120
Randomized, controlled study documenting non-inferiority of single-dose liposomal Amphotericin B combined with flucytosine and fluconazole against WHO-recommended therapy for cryptococcal meningitis in persons with HIV

Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim- sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for Pneumocystis Carinii pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. J Infect Dis. 2001 Oct 15;184(8):992-7. doi: 10.1086/323353.

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 persons with HIV

Mitjà O, Alemany A, Marks M, et al. Mpox in people with advanced HIV infection: a global case series. Lancet. 2023 Mar 18;401(10380):939-949. doi: 10.1016/S0140-6736(23)00273-8
Global case series illustrating clinical features of Mpox in persons with advanced HIV infection

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

Nomah DK, Reyes-Urueña J, Díaz Y, et al. Sociodemographic, clinical, and immunological factors associated with SARS-CoV-2 diagnosis and severe COVID-19 outcomes in people living with HIV: a retrospective cohort study. The Lancet HIV 2021;8:e701–e710
These three large-sized cohort studies illustrates the clinical features and outcomes of persons with HIV infected with SARS-CoV-2

Prosty C, Hanula R, Levin Y, Bogoch II, McDonald EG, Lee TC. Revisiting the Evidence Base for Modern-Day Practice of the Treatment of Toxoplasmic Encephalitis: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2023 Feb 8;76(3):e1302-e1319
Meta-analysis suggesting the non-inferiority of TMP-SMX when compared to standard regimens for the treatment of toxoplasmic encephalitis

Rao AK, Schrodt CA, Minhaj FS, et al. Interim Clinical Treatment Considerations for Severe Manifestations of Mpox - United States, February 2023. MMWR Morb Mortal Wkly Rep 2023;72:232–243.DOI: http://dx.doi.org/10.15585/mmwr.mm7209a4
Interim clinical guidelines for management of Mpox

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

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: dx.doi.org/10.15585/mmwr.rr6901a1

Sun J, Zheng Q, Madhira V, et al. Association Between Immune Dysfunction and COVID-19 Breakthrough Infection After SARS-CoV-2 Vaccination in the US. JAMA Internal Medicine 2022;182:153–162
A large cohort study identifying a higher rate of SARS-CoV-2 breakthrough infections in fully-vaccinated persons with HIV

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 persons with HIV

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

WHO consolidated guidelines on tuberculosis: module 4: treatment: drug-susceptible tuberculosis treatment
www.who.int/publications/i/item/9789240048126
Updated WHO guidelines for treatment of drug-susceptible TB

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update
www.who.int/publications/i/item/9789240063129
Updated WHO guidelines for treatment of MDR/XDR-TB

Part VII Paediatric HIV Treatment

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

WHO Guidelines
www.who.int/publications/i/item/9789240022232

Paediatric use of ABC
clinicalinfo.hiv.gov/en/guidelines/pediatric-arv/abacavir

University of Liverpool HIV-drug interaction checker
www.hiv-druginteractions.org/checker