



**EACS**  
European  
AIDS  
Clinical  
Society

# GUIDELINES

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*English*

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# Introduction to the EACS Guidelines 2019

Welcome to the EACS Guidelines!

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

The EACS Guidelines were first published in 2005, and are currently available in print, online as a pdf and web-based version, and as a free App for both iOS and Android devices. The Guidelines are translated into several different languages and are formally revised at least annually for the electronic version and biennially for the printed version. The electronic version can, however, be updated at any time if the panels consider it necessary.

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

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

The 2019 version of the Guidelines introduces a new drug-drug interaction panel and now consists of six main sections, including a general overview table of all major issues in PLWH, recommendations on antiretroviral treatment, drug-drug interactions, diagnosis, monitoring and treatment of co-morbidities, co-infections and opportunistic diseases.

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do not provide formal grades of evidence, panels make decisions by consensus or by vote when necessary and we do not publish results of the votes or discrepancies if any occur.

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

A list of the main references used to produce the Guidelines is provided as a separate section, see [References](#). Please reference the EACS Guidelines as follows: EACS Guidelines version 10.0, November 2019. Video links to the EACS online course on Clinical Management of HIV are provided throughout the Guidelines, see [Video links](#).

The diagnosis and management of HIV infection and related co-infections, opportunistic diseases and comorbidities continue to require a multidisciplinary effort for which we hope the 2019 version of the EACS Guidelines will provide you with an easily accessible and updated overview.

All comments to the Guidelines are welcome and can be directed to [guidelines@eacsociety.org](mailto:guidelines@eacsociety.org)

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

Enjoy!

Manuel Battegay and Lene Ryom

November 2019

# Summary of Changes from v9.1 to v10.0

## ART section

- What to start with, pages 12-13
  - New recommendation favouring unboosted INSTI with high genetic barrier (DTG or BIC) as third agent for treatment-naïve PLWH initiating treatment
  - 2 NRTIs + DOR included in recommended regimens
  - When indicated, TDF/3TC has been added as a backbone
  - Dual therapy with DTG + 3TC has been upgraded to recommended regimens
- Primary HIV infection, page 14
  - High genetic barrier INSTI or PI/b recommended for initial therapy if resistance testing is not available
- Switch strategies for virologically suppressed persons, page 15
  - DTG + 3TC has been included in dual therapies supported by large clinical trials
  - DRV/b + RPV has been included as dual therapy option supported by small trials
  - Monotherapy with PI/b not recommended
- Treatment of pregnant women living with HIV or women considering pregnancy, page 17
  - Whole section has been updated with treatment guidance regarding different scenarios (Tables 1, 2 and 3)
- ART in TB/HIV co-infection, page 20
  - New tables have been included (ART in TB/HIV co-infection and DDIs)
- Post-exposure prophylaxis (PEP), page 22
  - TAF/FTC, RAL qd and BIC have been included as possible drugs to include in a PEP regimen
- Pre-exposure prophylaxis (PrEP), page 23
  - TAF/FTC has been included as alternative in MSM and transgender women

## DDI section

- All tables have been updated with most recent data on DDIs and the addition of BIC and DOR and removal of older ARVs (including older PIs, ddI and d4T), pages 27, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38 and 39
- Data on DOR and the fixed dose combination TDF/3TC/DOR have been added to the tables on swallowing difficulties and dose adjustment for renal and hepatic insufficiency, pages 40, 42, 43
- A novel table “Dosage Recommendations for Hormone Therapy when Used at High Doses for Gender Transitioning” provides guidance on dosage adjustments to overcome DDIs with ARVs page 49
- Two new tables: “Top 10 Drug Classes to Avoid in Elderly PLWH” and “Non-HIV Drugs Requiring Dosage Adjustment in Renal Insufficiency” have been developed to prevent inappropriate prescribing in elderly PLWH, pages 45, 47, 48

## Co-morbidity section

- All tables have been updated with the addition of BIC and DOR and older ARVs (including older PIs, ddI and d4T) have been removed from all sections apart from that on lipoatrophy, pages 57, 67, 74-76, 78, 87, 90-91 and 94
- A comment has been included on use of e-cigarettes in the lifestyle intervention section, page 53
- Screening for kidney disease recommends the use of albumin/creatinine ratio for glomerular disease and protein/creatinine ratio for screening for and diagnosing ARV-related tubulopathy, pages 64-66
- There are updated targets for lipids and a change in threshold for ART modification from 20% 10-year risk of CVD to 10% 10-year risk of CVD, page 54 and 60
- Blood pressure targets have been updated, pages 54-55
- The medical management of hypertension has been updated to include amended drug sequencing suggestions and recommendations on drugs to use, page 56
- There is an additional 4<sup>th</sup> step in the work-up of liver disease in PLWH to include risk stratification based on risk prediction tools and transient elastography and an updated algorithm for surveillance of varices, page 69
- There is a minor update for the screening guidance for HCC in non-cirrhotic PLWH with HBV, pages 8, 52, 71 and 95
- In the sexual health section, there is a statement about U=U, including how this information affects options for conception for PLWH and their partners and screening for menopause, page 80

- In the section on depression, there is a statement on the impact of depression on overall well-being, page 84
- In the cognitive guidelines, recommendations for modification of ART are based on either CSF resistance testing or on likely ART toxicity, page 88

## Viral Hepatitis Co-infections section

- The chapter has been renamed “Clinical Management and Treatment of Viral Hepatitis Co-infections in PLWH”, page 95
- The structure of the chapter has been reorganised: General recommendations, page 95, Treatment and Monitoring of Persons with HBV/HIV Co-infection, page 96 and Treatment and monitoring of Persons with HCV/HIV Co-infection, page 97
- HCC screening recommendations have been updated with the Co-morbidity panel, pages 8, 52, 71 and 95
- Practical points on diagnosing hepatic fibrosis have been updated and a table on cut-off values of non-invasive tests for the detection of significant fibrosis and cirrhosis has been added, pages 95 and 102
- The section on HBV reactivation has been updated, page 96
- Recommendations for persons with failure to DAA treatment have been updated, page 97
- The DAA table has been updated and split into two parts. One with preferred regimens and one with alternatives, pages 98 and 99
- The figure on management of recently acquired HCV infection has been updated, page 101
- The sections on HEV and HDV have been updated, pages 95 and 103

## Opportunistic Infections section

- The table on when to start ART in the presence of opportunistic infections has been added, page 104
- A table on clinical presentation and management of Immune Reconstitution Inflammatory Syndrome (IRIS) has been added, page 104
- Treatment of the following OIs has been updated: CMV, HSV, VZV, histoplasmosis, cryptococcosis, pages 108-111
- Treatment details of Initial and recurrent genital/mucocutaneous HSV has been removed from the OIs section. A cross reference to the Sexual and Reproductive Health of Women and Men Living with HIV section was made instead, page 110
- Treatment of talaromycosis has been added, page 110
- Details on management of MDR-TB have been added to the TB section, page 115, as well as a table detailing doses for all TB drugs, major side effects and caution when using with ART, page 117

For more detailed summary of changes made from v9.1 to v10.0, please see <http://www.eacsociety.org/guidelines/Details.from-version-9.1to10>

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

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# Abbreviations

Antiretroviral drug (ARV) abbreviations		Other abbreviations	
<b>3TC</b>	lamivudine	<b>MVC</b>	maraviroc
<b>ABC</b>	abacavir	<b>NRTI</b>	nucleos(t)ide reverse transcriptase inhibitors
<b>ATV</b>	atazanavir	<b>NNRTI</b>	non-nucleoside reverse transcriptase inhibitors
<b>BIC</b>	bictegravir	<b>NVP</b>	nevirapine
<b>COBI</b>	cobicistat (used as booster= <i>c</i> )	<b>PI</b>	protease inhibitors
<b>d4T</b>	stavudine	<b>PI/b</b>	protease inhibitors pharmacologically boosted with cobicistat or ritonavir
<b>ddI</b>	didanosine	<b>PI/c</b>	protease inhibitor pharmacologically boosted with cobicistat
<b>DOR</b>	doravirine	<b>PI/r</b>	protease inhibitors boosted with ritonavir
<b>DRV</b>	darunavir	<b>RAL</b>	raltegravir
<b>DTG</b>	dolutegravir	<b>RPV</b>	rilpivirine
<b>EFV</b>	efavirenz	<b>RTV</b>	ritonavir (used as booster= <i>r</i> )
<b>EVG</b>	elvitegravir	<b>SQV</b>	saquinavir
<b>ENF</b>	enfuvirtide (T20)	<b>TAF</b>	tenofovir alafenamide
<b>ETV</b>	etravirine	<b>TDF</b>	tenofovir disoproxil fumarate
<b>FI</b>	fusion inhibitor	<b>TPV</b>	tipranavir
<b>FPV</b>	fosamprenavir	<b>ZDV</b>	zidovudine
<b>FTC</b>	emtricitabine		
<b>IDV</b>	indinavir		
<b>INSTI</b>	integrase strand transferinhibitor		
<b>LPV</b>	lopinavir		
		<b>ACE</b>	angiotensin converting enzyme
		<b>AFP</b>	alpha-fetoprotein
		<b>ALP</b>	alkaline phosphatase
		<b>ALT</b>	alanine aminotransferase
		<b>aMDRD</b>	abbreviated modification of diet in renal disease formula
		<b>ART</b>	antiretroviral therapy
		<b>AST</b>	aspartate aminotransferase
		<b>bid</b>	twice daily
		<b>BMD</b>	bone mineral density
		<b>BMI</b>	body mass index
		<b>BP</b>	blood pressure
		<b>CAPD</b>	continuous ambulatory peritoneal dialysis
		<b>cART</b>	combination antiretroviral treatment
		<b>CKD</b>	chronic kidney disease
		<b>CKD-EPI</b>	CKD epidemiology collaboration formula
		<b>CMV</b>	cytomegalovirus
		<b>CNS</b>	central nervous system
		<b>COPD</b>	chronic obstructive pulmonary disease
		<b>CSF</b>	cerebrospinal fluid
		<b>CVD</b>	cardiovascular disease
		<b>CXR</b>	chest X-ray
		<b>DAA</b>	direct acting antiviral drug
		<b>DDI</b>	drug-drug interaction
		<b>DXA</b>	dual energy X-ray absorptiometry
		<b>ECG</b>	electrocardiogram
		<b>eGFR</b>	estimated glomerular filtration rate
		<b>ESLD</b>	end stage liver disease
		<b>FBC</b>	full blood count
		<b>FRAX</b>	fracture risk assessment tool
		<b>GDR</b>	genotypic drug resistance test
		<b>GT</b>	genotype
		<b>HAV</b>	hepatitis A virus
		<b>HAD</b>	HIV-associated dementia
		<b>HBV</b>	hepatitis B virus
		<b>HCC</b>	hepatocellular carcinoma
		<b>HCV</b>	hepatitis C virus
		<b>HDL-c</b>	HDL-cholesterol
		<b>HDV</b>	hepatitis D virus
		<b>HEV</b>	hepatitis E virus
		<b>HIVAN</b>	HIV-associated nephropathy
		<b>HIV-VL</b>	HIV viral load (HIV-RNA)
		<b>HPV</b>	human papillomavirus
		<b>HRS</b>	hepatorenal syndrome
		<b>HSR</b>	hypersensitivity reaction
		<b>HSV</b>	herpes simplex virus
		<b>IFN</b>	interferon
		<b>IGRA</b>	interferon-gamma release assay
		<b>ICS</b>	inhaled corticosteroids
		<b>IHD</b>	ischaemic heart disease
		<b>im</b>	intramuscular
		<b>IRIS</b>	immune reconstitution inflammatory syndrome
		<b>iv</b>	intravenous
		<b>IVDU</b>	intravenous drug use
		<b>LABA</b>	long-acting $\beta$ 2-agonist
		<b>LAMA</b>	long-acting muscarinic antagonist
		<b>LDL-c</b>	LDL-cholesterol
		<b>LGV</b>	lymphogranuloma venereum
		<b>LOQ</b>	limit of quantification
		<b>MDR-TB</b>	multidrug resistant TB
		<b>Mg</b>	magnesium
		<b>MND</b>	mild neurocognitive disorder
		<b>MRI</b>	magnetic resonance imaging
		<b>MSM</b>	men who have sex with men
		<b>MTCT</b>	mother to child transmission
		<b>MX</b>	methylxanthines
		<b>NAFLD</b>	non-alcoholic fatty liver disease
		<b>NASH</b>	non-alcoholic steatohepatitis
		<b>NP</b>	neuropsychological
		<b>OIs</b>	opportunistic infections
		<b>OLTx</b>	orthotopic liver transplantation
		<b>PAP</b>	papanicolaou test
		<b>PD4</b>	phosphodiesterase 4 inhibitors
		<b>PEP</b>	post-exposure prophylaxis
		<b>PLWH</b>	people living with HIV
		<b>PREP</b>	pre-exposure prophylaxis
		<b>PEG-IFN</b>	pegylated-interferon
		<b>PHI</b>	primary HIV infection
		<b>po</b>	per oral
		<b>PPD</b>	purified protein derivative
		<b>PPI</b>	proton pump inhibitor
		<b>PRT</b>	proximal renal tubulopathy
		<b>PSA</b>	prostate specific antigen
		<b>PTH</b>	parathyroid hormone
		<b>qd</b>	once daily
		<b>qid</b>	four times daily
		<b>RAS</b>	resistance-associated substitutions
		<b>RBV</b>	ribavirin
		<b>RCT</b>	randomized controlled trial
		<b>SABA</b>	short-acting $\beta$ 2-agonist
		<b>SAMA</b>	short-acting muscarinic antagonist
		<b>sc</b>	subcutaneous
		<b>SOT</b>	solid organ transplant
		<b>SSRI</b>	selective serotonin-reuptake inhibitor
		<b>STI</b>	sexually transmitted infection
		<b>SVR</b>	sustained virological response
		<b>TC</b>	total cholesterol
		<b>TDM</b>	therapeutic drug monitoring
		<b>TG</b>	triglycerides
		<b>tid</b>	three times daily
		<b>TMP-SMX</b>	trimethoprim-sulfamethoxazole
		<b>UA/C</b>	urine albumin/creatinine ratio
		<b>UP/C</b>	urine protein/creatinine ratio
		<b>US</b>	ultrasound
		<b>VL</b>	viral load (HIV-RNA)
		<b>VZV</b>	varicella-zoster virus
		<b>WB</b>	western blot
		<b>Zn</b>	zinc



# Part I Assessment of PLWH at Initial & Subsequent Visits

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
<b>HISTORY</b>						
<b>Medical</b>	Complete medical history including:	+	+	First visit	On transfer of care repeat assessment	
	• Family history (e.g. premature CVD, diabetes, hypertension, CKD)	+		First visit	Premature CVD: cardiovascular events in a first degree relative (male < 55, female < 65 years)	54, 55-56
	• Concomitant medicines <sup>(i)</sup>	+	+	Every visit		
	• Past and current co-morbidities	+	+	Every visit		
	• Vaccination history	+		Annual	Measure antibody titres and offer vaccinations where indicated, see <a href="#">Vaccination</a>	
<b>Psychosocial</b>	Current lifestyle (alcohol use, smoking, diet, exercise, drug use)	+	+	6-12 months	Adverse lifestyle habits should be addressed more frequently	53
	Employment	+	+	Every visit	Provide advice and support if needed	
	Social and welfare	+	+		Provide counselling if needed	
	Psychological morbidity	+	+			
Partner and children	+			Test partner and children if at risk		
<b>Sexual and Reproductive Health</b>	Sexual history	+		6-12 months	Address issues concerning sexual dysfunction	80-83
	Safe sex	+			Risk of sexual transmission should be addressed	
	Partner status and disclosure	+			Recommend starting ART in serodifferent couples	
	Conception issues	+	+			
	Hypogonadism (including menopause)	+	+	As indicated	Persons with complaints of sexual dysfunction	80, 82
<b>POST-REPRODUCTIVE HEALTH</b>						
<b>Menopause</b>		+	+	Annual/as indicated	Screen for perimenopause symptoms in women ≥ 40 years.	80
<b>HIV DISEASE</b>						
<b>Virology</b>	Confirmation of HIV Ab pos	+		3-6 months	More frequent monitoring of HIV-VL at start of ART Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection	11-13
	Plasma HIV-VL	+	+			
	Genotypic resistance test and sub-type	+	+/-	At virological failure	Screen if considering R5 antagonist in regimen	
	R5 tropism (if available)		+/-			
<b>Immunology</b>	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 <sup>(ii)</sup> CD4/CD8 ratio is a stronger predictor of serious outcomes	11-13
	HLA-B*57:01 (if available)	+	+/-		Screen before starting ABC containing ART, if not previously tested, pages <a href="#">11-12</a> , <a href="#">24</a>	
<b>CO-INFECTIONS</b>						
<b>STIs</b>	Syphilis serology	+		Annual/ as indicated	Consider more frequent screening if at risk	14, 80
	STI screen	+		Annual/ as indicated	Screen if at risk and during pregnancy	

	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
<b>Viral Hepatitis</b>	HAV screen	+		Annual/ as indicated	Screen at risk (e.g. MSM); vaccinate if non-immune	79, 95-97
	HBV screen	+	+		Annual screen in susceptible persons; vaccinate if non-immune. Use ART containing TDF or TAF in vaccine non-responders	
	HCV screen	+			Annual screen if ongoing risk (e.g. MSM, IVDU) Measure HCV-RNA if HCV Ab pos or if acute infection suspected	
	HDV screen			As indicated	All Persons with positive HBs-Ag should also be screened for HDV co-infection	95, 103
	HEV screen			As indicated	Screen persons with symptoms consistent with acute hepatitis, unexplained flares of aminotransferases or elevated liver function tests, neuralgic amyotrophy, Guillain-Barré, encephalitis or proteinuria. Include anti-HEV IgG and IgM and NAT for HEV-RNA in blood and if possible in stool	103
<b>Tuberculosis</b>	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 <a href="#">Diagnosis and Treatment of TB in PLWH</a>	20, 114
	PPD	+				
	IGRA in selected high-risk populations (if available)	+				
<b>Others</b>	Varicella zoster virus serology	+			Offer vaccination where indicated	79
	Measles/Rubella serology	+			Offer vaccination where indicated	
	Toxoplasmosis serology	+				
	CMV serology	+				79
	Cryptococcus antigen	+/-			Consider screening for cryptococcus antigen in serum in persons with CD4 count < 100 cells/μL	
	Leishmania serology	+/-			Screen according to travel history/origin	
	Tropical screen (e.g. Schistosoma serology)	+/-			Screen according to travel history/origin	
	Influenza virus	+		Annual	In all PLWH, see <a href="#">Vaccination</a>	79
	<i>Streptococcus pneumoniae</i>	+			No recommendations available regarding the need for a booster dose, see <a href="#">Vaccination</a>	79
Human papilloma virus	+		As indicated	Vaccinate all PLWH with 3 doses between ages 9 and 40. If HPV infection is established, efficacy of vaccine is questionable, see <a href="#">Vaccination</a>	79	
<b>CO-MORBIDITIES</b>						
<b>Haematology</b>	FBC	+	+	3-12 months		
	Haemoglobinopathies	+			Screen at risk persons	
	G6PD	+			Screen at risk persons	
<b>Body Composition</b>	Body-mass index	+	+	Annual		53
<b>Cardiovascular Disease</b>	Risk assessment (Framingham score <sup>(iii)</sup> )	+	+	2 years	Should be performed in all men > 40 years and women > 50 years without CVD	54
	ECG	+	+/-	As indicated	Consider baseline ECG prior to starting ARVs associated with potential conduction problems	
<b>Hypertension</b>	Blood pressure	+	+	Annual		55-56
<b>Lipids</b>	TC, HDL-c, LDL-c, TG <sup>(iv)</sup>	+	+	Annual	Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake)	60
<b>Glucose</b>	Serum glucose	+	+	Annual	Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL)	58-59
<b>Pulmonary Disease</b>	Respiratory symptoms and risk factors <sup>(xii)</sup>	+	+	Annual	If severe shortness of breath is reported with preserved spirometry, echocardiography may be performed to rule out heart failure and/or pulmonary hypertension	89
	Spirometry			As indicated	Spirometry <sup>(xii)</sup> should be performed in all symptomatic persons	
<b>Liver Disease</b>	Risk assessment <sup>(v)</sup>	+	+	Annual		69-72
	ALT/AST, ALP, Bilirubin	+	+	3-12 months	More frequent monitoring prior to starting and on treatment with hepatotoxic drugs	
	Staging of liver fibrosis			12 months	In HCV and/or HBV co-infected persons (e.g. FibroScan, serum fibrosis markers)	69-72
	Hepatic ultrasound			6 months	Persons with liver cirrhosis <sup>(xiii)</sup>	69-72



	Assessment	At HIV diagnosis	Prior to starting ART	Follow-up frequency	Comment	See page
<b>Renal Disease</b>	Risk assessment <sup>(vi)</sup>	+	+	Annual	More frequent monitoring if eGFR < 90mL/min, CKD risk factors present <sup>(vi)</sup> and/or prior to starting and on treatment with nephrotoxic drugs <sup>(ix)</sup>	64-65
	eGFR (CKD-EPI) <sup>(vii)</sup>	+	+	3-12 months		
	Urine dipstick analysis <sup>(viii)</sup>	+	+	Annual		
<b>Bone Disease</b>	Bone profile: calcium, PO <sub>4</sub> , ALP	+	+	6-12 months	Consider DXA in specific persons (see page 61 for details)	61-63
	Risk assessment <sup>(x)</sup> (FRAX® <sup>(xi)</sup> in persons > 40 years)	+	+	2 years		
<b>Vitamin D</b>	25(OH) vitamin D	+		As indicated	Screen at risk persons	62
<b>Cognitive impairment</b>	Screening questionnaire	+	+	As indicated	Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 88 for further assessment.	88
<b>Depression</b>	Questionnaire	+	+	As indicated	Screen at risk persons	84-85
<b>Cancer</b>	Mammography			1-3 years	Women 50-70 years	52
	Cervical PAP or liquid based cytology			1-3 years	HIV-positive women > 21 years	
	Rectal exam and anoscopy			1-3 years	MSM and persons with HPV-associated dysplasia. Evidence of benefit not known	
	Ultrasound and alpha-foe-toprotein			6 months	Controversial; persons with cirrhosis and persons with HBV co-infection at high risk of HCC <sup>(xiii)</sup>	
	Others				Controversial	

If PLWH have been stable on ART for 6 months or more, with no other significant issues, clinicians could consider using alternative modalities such as email/phone/or other electronic means (Graduate partnership programme, GPP).

This form of consultation can have the same validity as a face-to-face consultation if properly instituted in a clinical protocol.

The European Union funded EmERGE project is currently looking at such interventions <https://www.emergeproject.eu>

- i Review all concomitant medicines which may potentially interact with ARVs or increase co-morbidities, see [Drug-drug Interactions between Antidepressants and ARVs](#), [Drug-drug Interactions between Antihypertensives and ARVs](#), [Drug-drug Interactions between Analgesics and ARVs](#), [Drug-drug Interactions between Anticoagulants/Antiplatelet Agents and ARVs](#), [Drug-drug Interactions between Antimalarial Drugs and ARVs](#), [Drug-drug Interactions between Bronchodilators \(for COPD\) and ARVs](#), [Drug-drug Interactions between Immunosuppressants \(for SOT\) and ARVs](#), [Drug-drug Interactions between Pulmonary Antihypertensives and ARVs](#), [Drug-drug Interactions between Corticosteroids and ARVs](#), [Drug-drug Interactions between Contraceptives and ARVs](#), [Drug-drug Interactions between DAAs and ARVs](#) and <http://www.hiv-druginteractions.org>
- ii If stable on ART with undetectable HIV-VL and CD4 count > 350 cells/μL, suggest annual CD4 count
- iii A risk equation developed from HIV populations is available, see <https://www.chip.dk/Tools-Standards/Clinical-risk-scores>. Of note, if an individual receives medicines to control dyslipidaemia and/or hypertension, the estimation should be interpreted with caution
- iv A calculator for LDL-cholesterol in cases where TG is not high can be found at <https://www.mdcalc.com/ldl-calculated>
- v Risk factors for chronic liver disease include alcohol, viral hepatitis, obesity, diabetes, insulin resistance, hyperlipidaemia and hepatotoxic drugs.
- vi Risk factors for CKD: hypertension, diabetes, CVD, family history, black African ethnicity, viral hepatitis, low current CD4 count, smoking, older age, concomitant nephrotoxic drugs
- vii eGFR: use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated > 60 mL/min. The abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative, see <https://www.chip.dk/Tools-Standards/Clinical-risk-scores>

- viii Some experts recommend UA/C (urinary albumin creatinine ratio) or UP/C (urinary protein creatinine ratio) as a screening test for proteinuria in all persons. UA/C predominantly detects glomerular disease. Use in persons with diabetes. UP/C detects total protein secondary to glomerular and tubular disease and can be used for screening for ARV toxicity, page 64
- ix Different models have been developed for calculating a 5-year CKD risk score while using different nephrotoxic ARVs, integrating HIV independent and HIV-related risk factors [12], [13]
- x Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m<sup>2</sup>), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (> 3 units/day), steroid exposure (minimum 5 mg for > 3 months)
- xi WHO fracture risk assessment (FRAX®) tool: <http://www.shef.ac.uk/FRAX>
- xii Respiratory symptoms: shortness of breath, chronic cough and sputum. Risk factors: tobacco, occupation, in- and outdoor pollution and host factors including previous PCP or TB, recurrent pneumonia and Alpha-1 antitrypsin deficiency. A diagnosis of COPD should be considered in persons over the age of 35 years who have a risk factor (current or ex-smoker) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze
- xiii HCC screening is indicated in all cirrhotic HBV or HCV co-infected persons (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in persons with F3 fibrosis\* is uncertain, surveillance may be considered based on an individual risk assessment (<https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/>). In HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines. Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH, see pages 52, 71 and 95
- \* See table on cut-off values of non-invasive tests for the detection of significant fibrosis and cirrhosis, page 102. The combination of blood biomarkers, the combination of liver stiffness measurement and blood tests or repeated assessments may improve accuracy, see <https://easl.eu/publication/easl-recommendations-treatment-of-hepatitis-c/>

## Part II ART of PLWH

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

### Assessing PLWH's Readiness to Start and Maintain ART<sup>(ix)</sup>

Goal: to help persons start and/or maintain ART	
<p>Starting ART is recommended for all PLWH regardless of CD4 count to reduce the morbidity and mortality associated with HIV infection, and to prevent HIV transmission (START trial, HPTN 052, PARTNER Study [1-3]. Evidence is accumulating that starting ART on the same day after establishing a diagnosis of HIV infection is feasible and acceptable to PLWH. Nevertheless, assessment of the readiness to start ART is essential to enable PLWH to express their preference and not feel pressured to start ART immediately, unless clinically indicated</p> <p>Given the need for lifelong treatment, successful ART requires a person's readiness to start and adhere to the regimen in a sustained manner. The trajectory from problem awareness to maintenance on ART can be divided into five stages. Knowing a person's stage, health care providers use appropriate techniques to assist them to start and maintain ART</p>	<p>Identify the person's stage of readiness using WEMS<sup>(i)</sup> techniques, and start discussion with an open question/invitation: "I would like to talk about HIV medicines." &lt;wait&gt; "What do you think about them?"</p> <p>Based on the person's response, identify his/her stage of readiness and intervene accordingly<sup>(ii)</sup></p> <p>Immediate (i.e. same day) start of ART should be considered, especially in the following situations:</p> <ul style="list-style-type: none"> <li>- 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</li> <li>- The wish of a PLWH to start ART immediately</li> <li>- In a setting where loss-to-follow-up is more likely if ART is not started the same day</li> </ul>
Stages of readiness to start ART	
<p><b>Precontemplation:</b> "I don't need it, I feel good" "I don't want to think about it"</p>	<p><b>Support:</b> Show respect for the person's attitude. / Try to understand the person's health and therapy beliefs. / Establish trust. / Provide concise, individualised information. / Schedule next appointment</p>
<p><b>Contemplation:</b> "I am weighing things up and feel torn about what to do about it"</p>	<p><b>Support:</b> Allow ambivalence. / Support the person in weighing pros and cons. / Assess the person's information needs and support his/her information seeking. / Schedule the next appointment</p>
<p><b>Preparation:</b> "I want to start, I think the drugs will allow me to live a normal life"</p>	<p><b>Support:</b> Reinforce the person's decision. / Decide with the person which is the most convenient regimen. / Educate the person on adherence, resistance and side effects. / Discuss integration into daily life. / Assess self-efficacy</p> <p><b>Ask:</b> How confident are you that you can take your medicines as we discussed (specify) once you have started?</p> <p><b>Consider skills training:</b></p> <ul style="list-style-type: none"> <li>• Medicines-taking training, possibly Medication Event Monitoring System, e.g. electronic pill boxes</li> <li>• Directly observed therapy with educational support</li> <li>• Use aids: mobile phone alarm, pillboxes</li> <li>• Involve supportive tools/persons where appropriate</li> </ul>
<p><b>Action:</b> "I will start now"</p>	<p><b>'Final check':</b> With a treatment plan established, is the person capable of taking ART and is ART available?</p>
<p><b>Maintenance:</b> "I will continue." or "I have difficulties continuing over the long run"</p> <p>Caveat: A person can relapse to an earlier stage, even from "maintenance" to "precontemplation"</p>	<p><b>Assess:</b> Adherence every 3-6 months<sup>(iii)</sup></p> <p><b>Evaluate adherence:</b> For persons with good adherence: show respect for their success</p> <p><b>Assess:</b> The person's own perception of ability to adhere to and continue treatment</p> <p><b>Ask:</b> In the next 3-6 months, how confident are you that you can take your medicines?</p> <p>For a person without sufficient adherence: use mirroring techniques<sup>(iv)</sup> on problems, ask open questions to identify dysfunctional beliefs</p> <p><b>Assess:</b> Stage of readiness and provide stage-based support</p> <p><b>Assess:</b> Barriers and facilitators<sup>(v)</sup></p> <p>Schedule next appointment and repeat support</p>

Several barriers are known to influence ART decision making and adherence to ART	
Screen for and talk about problems and facilitators	
Consider systematic assessment of: <ul style="list-style-type: none"> <li>• Depression<sup>(vi)</sup>, see pages 84-85</li> <li>• Cognitive problems<sup>(vi)</sup>, see page 88</li> <li>• Harmful alcohol<sup>(viii)</sup> or recreational drug use, see page 51</li> </ul>	Consider talking about: <ul style="list-style-type: none"> <li>• Social support and disclosure</li> <li>• Health insurance and continuity of drug supply</li> <li>• Therapy-related factors</li> </ul>
Recognise, discuss and reduce problems wherever possible in a multi-disciplinary team approach	

- i WEMS: Waiting (> 3 sec), Echoing, Mirroring, Summarising [4]
- 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/ $\mu$ L), the initiation of ART should not be delayed. The person should be closely followed and optimally supported. Schedule the next appointment within a short time, i.e. 1-2 weeks
- 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?" [5]

- 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 [6]
- vi PHQ-2 or PHQ-9 [7]. Meta-analysis shows a consistent relationship between depression and ART non-adherence that is not limited to those with clinical depression. Therefore, assessment and intervention aimed at reducing depressive symptom severity, even at subclinical level is important. Ask: "Over the last two weeks, how often have you been bothered by any of the following problems? 1. Little interest or pleasure in doing things; 2. Feeling down, depressed or hopeless." Answers: Not at all (0) / Several days (1) / More than half the days (2) / Nearly every day (3). If the person scores 2 or more, seven additional questions, see [8]
- vii Ask: "Do you feel having problems to concentrate in your daily life?" / "Do you feel slowed in your thinking?" / "Do you feel having problems with your memory?" / "Did relatives or friends express that they feel you have problems with your memory or difficulty concentrating?" [9]
- viii FAST-alcohol use, ask: How often have you had 6 or more units if female, or 8 or more units if male, on a single occasion in the last year? Never=0, Less than monthly=1, Monthly=2, Weekly=3, Daily or almost daily=4. Stop if the answer is 0 (Never). Ask more questions if the answer is 1, 2, 3 or 4. See [10]
- ix Algorithm adapted from [11]

## Recommendations for Initiation of ART in PLWH with Chronic Infection without prior ART Exposure<sup>(i)</sup>

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

**ART is recommended in all adult PLWH, irrespective of CD4 counts<sup>(i)</sup>**

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

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

# Initial Combination Regimen for ART-naïve Adult PLWH

Before selecting an ART regimen, it is critical to review:

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

## A) Recommended regimens (one of the following to be selected)\*\*

Out of the recommended regimens in PLWH starting ART, we favour the use of an unboosted INSTI with a high genetic barrier (DTG or BIC) as preferred third agent. Tailoring antiretroviral regimens for each individual is essential as other classes of third agents (e.g. PI/b) might be indicated in the presence of resistance

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

\*\* An increasing number of generic HIV drugs are now available, and their use can lead to large cost savings. The use of generic forms of drugs included in recommended regimens should therefore be encouraged, even if single tablet regimens are not used, as recent studies have shown similar virologic outcomes in ART-naïve PLWH receiving either a single pill or two pills qd

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

2 NRTIs + PI/r or PI/c		
ABC/3TC + ATV/c or ATV/r	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL Not on proton pump inhibitor With food	I (ABC: HLA-B*57:01, cardiovascular risk) X (ATV/b & renal toxicity)
ABC/3TC + DRV/c or DRV/r	HLA-B*57:01 negative HBsAg negative With food	I (ABC: HLA-B*57:01, cardiovascular risk) VII (DRV/r and cardiovascular risk)
TAF/FTC or TDF/FTC or TDF/3TC + ATV/c or ATV/r	Not on proton pump inhibitor With food	II (TDF: prodrug types. Renal and bone toxicity. TAF dosing) X (ATV/b: renal toxicity)
Other combinations		
RAL 400 mg bid + DRV/c or DRV/r	HBsAg negative HIV-VL < 100,000 copies/mL CD4 > 200 cells/ $\mu$ L With food	VII (DRV/r: cardiovascular risk)

#### Additional Guidance

- I ABC contraindicated if HLA-B\*57:01 positive. Even if HLA-B\*57:01 negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk (> 20%)
  - II In certain countries, TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate). There are available generic forms of TDF, which instead of fumarate use phosphate, maleate, and succinate salts. They can be used interchangeably.  
When available, combinations containing TDF can be replaced by the same combinations containing TAF. TAF is used at 10 mg when coadministered with drugs that inhibit P-gp, and at 25 mg when coadministered with drugs that do not inhibit P-gp  
The decision whether to use TDF or TAF depends on individual characteristics as well as availability. So far, there are only limited long-term data on TAF. If the ART regimen does not include a booster, TAF and TDF have a similar short-term risk of renal adverse events leading to discontinuation and bone fractures. TAF\*\*\* should be considered as a first choice\*\*\*\* over TDF in individuals with:
    - established or high risk of CKD, see page 64;
    - coadministration of medicines with nephrotoxic drugs or prior TDF toxicity, see page 65;
    - osteoporosis / progressive osteopenia, high FRAX score or risk factors, see page 61;
    - history of fragility fracture, see pages 61 and 63
  - III Two randomized controlled trials (performed in South Africa and Cameroon) showed that, in comparison with EFV, treatment with DTG in naive persons was associated with increased weight gain when combined with TAF/FTC, TDF/FTC or TDF/3TC. The effect on increased weight was more important for women under treatment containing both DTG and TAF [12], [13]
  - 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 DOR is not active against HIV-2
  - VI RPV is not active against HIV-2
  - VII A single study has shown increase in CVD risk with cumulative use of DRV/r [14]
  - VIII TDF/FTC/EVG/c to be used only if eGFR  $\geq$  70 mL/min. It is recommended that TDF/FTC/EVG/c is not initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment
  - IX EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains
  - X Potential renal toxicity with ATV/b
- \*\*\* There are limited data on use of TAF with eGFR < 30 mL/min  
\*\*\*\* Expert opinion pending clinical data



# Primary HIV Infection (PHI)

## Definition of PHI<sup>(i-iv)</sup>

- 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<sup>(i-iv)</sup>

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

## Starting treatment<sup>(v)</sup>

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

### Circumstances where immediate treatment initiation should be advised

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

The recommendation is based on:

- Improvement of clinical symptoms of PHI, when present, especially severe general symptoms and/or neurological disease
- Demonstrated 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. Since PrEP will increase the early diagnosis, it will be very important in order to decrease transmission to treat these persons as soon as possible
- Reduced anxiety and facilitated disclosure to contacts  
The PLWH should be counselled on indications and benefits of starting treatment as soon as possible, despite absence of demonstrated improved long-term clinical benefits<sup>(vi)</sup>  
Once treatment is started, it should be continued. A subsequent interruption is not recommended

## Treatment selection

- The PLWH should preferably be recruited into a clinical trial or studies investigating HIV curative strategies
- Any use of PrEP or PEP should be identified and taken into account when choosing the initial regimen
- A drug resistance test is recommended in all cases as soon as possible after diagnosis. A genotypic test is recommended
- Therapy may have to start before the results of resistance testing become available. In such cases, preference should be given to starting a PI/b or an INSTI with high genetic barrier (DTG or BIC), in order to increase the barrier to resistance of the overall regimen. A potential advantage for selecting DTG or BIC is the faster VL suppression. The benefit of combining PI/r with INSTI has not been shown. A combination of TDF or TAF, FTC, and either DRV/b, DTG or BIC, should therefore be considered, and the regimen adjusted, if needed, once the resistance test becomes available and viral load suppression is achieved. Where such a regimen is not available, national epidemiological data on prevalence and patterns of transmitted drug resistance (where available and sufficiently representative) may assist with the treatment selection process

## Other considerations

- All PLWH should undergo investigations to diagnose sexually transmitted infections (e.g. syphilis, gonorrhoea, chlamydia), HBV, HCV and HPV, pages 7-8. Antibody seroconversion can be delayed and tests to identify the viral RNA are required in order to identify a recent HCV infection, page 101
  - All women living with HIV of reproductive age should have a pregnancy test
  - All PLWH should be counselled about the high risk of transmission, preventive measures, and importance of notifying partners
- 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
  - Where available, Western Blot (WB) or Immunoblot patterns of reactivity can be used to stage the infection as follows:
    - Stage I: HIV-RNA positive only (average duration 5 days). HIV-VL levels are median 2,000 copies/mL (IQR 300-20,000 copies/ml), and are < 100 copies/mL in approximately 10% of PLWH. Low HIV-VL levels should be interpreted with caution due to the risk of false positivity
    - Stage II: HIV-RNA and p24 Ag positive only (average duration 5.3 days)  
NB: HIV-VL levels are usually > 10,000 copies/mL
    - Stage III: HIV-RNA, p24 Ag and anti-HIV antibody positive by immune assay, no specific WB bands (average duration 3.2 days)
    - Stage IV: as Stage III but indeterminate WB pattern (5.6 days)
    - Stage V: as Stage III, but reactive WB pattern lacking p31 reactivity (average duration 69.5 days)
    - Stage VI: as stage III but full WB reactivity including a p31 band (indefinite)
  - 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
  - Some centres may have access to sero-incidence markers (e.g., anti-body avidity testing) that identify an infection acquired within the previous 3-6 months. Assay reliability varies and results should be interpreted with caution when they are the sole indicators of a recent infection
  - Potential disadvantage of treatment: firm, controlled evidence that treatment of PHI results in clinical benefit in the long-term (relative to starting therapy past the PHI stage) is currently lacking  
A small subset of PLWH can spontaneously control the infection without treatment (elite controllers)

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

# Switch Strategies for Virologically Suppressed Persons

## Definition of virologically suppressed

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

## Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. Examples of these reactive switches: lipotrophy (d4T, AZT), central nervous system adverse events (EFV, DTG), diarrhoea (PI/r) and jaundice (ATV), proximal renal tubulopathy and low bone mineral density (TDF), see [Adverse Effects of ARVs and Drug Classes](#)
2. **Prevention of long-term toxicity.** Example of this proactive switch: prevention of lipotrophy in persons receiving d4T or AZT and prevention of proximal renal tubulopathy with TDF, see [Adverse Effects of ARVs and Drug Classes](#). This may include person's concerns about safety
3. **Avoidance of drug-drug interactions**, page 26. This includes ART switch when starting HCV treatment to avoid DDIs, see [Drug-drug Interactions between DAAs and ARVs](#)
4. **Planned pregnancy or women wishing to conceive**, see [Antiretroviral Drugs Not Recommended in Women who Wish to Conceive or Become Pregnant while on ART](#)
5. **Ageing and/or comorbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters
6. **Simplification:** to reduce pill burden, adjust food restrictions, improve adherence and reduce monitoring needs
7. **Protection from HBV** infection or reactivation by including tenofovir in the regimen
8. **Regimen fortification:** Increasing the genetic barrier of a regimen in order to prevent resistance (e.g. in persons with reduced adherence)
9. **Cost reduction:** switching to the generic form of their current regimen, if available

## Principles

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

1. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of comorbid conditions, and improve quality of life. The primary concern when switching should be to sustain and not to jeopardize virological suppression. In persons without prior virological failures and no archived resistance, switching regimens entail a low risk of subsequent failure if clinicians select one of the recommended combinations for first-line therapy. The majority of clinical trials showing non-inferiority of the new regimen after the switch have actively excluded persons with prior virological failures and historical resistance
2. The complete ARV history with HIV-VL, tolerability issue, cumulative genotypic resistance history and/or phases of viremia on previous regimens with the potential of resistance development should be evaluated prior to any drug switch
3. Switches within the same drug class (e.g. TDF/FTC -> TAF/FTC, EFV -> RPV) are usually virologically safe if equal potency and in the absence of resistance
4. Cross-class switches of single drugs with the same genetic resistance barrier (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 genetic resistance barrier of the regimen. A PI/b may only be switched to unboosted ATV, an NNRTI, INSTIs RAL and EVG if full activity of the 2 NRTIs in the new regimen can be assumed based on resistance data, ARV history and HIV-VL results before switching (see 2.) Due to the higher genetic barrier of DTG and BIC, it is currently unclear if a switch to DTG- or BIC-based regimens also requires full activity of 2 NRTIs in the combination

6. Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. This requires knowledge about the resistance selection profile of the switch regimen. For example, some mutations (e.g. K65R or M184I/V) might affect the activity of most currently available STRs and preclude their future use. Especially, when reducing the number of drugs in a regimen or its genetic barrier to resistance, the chances of composing a fully suppressive regimen after potential failure following switch should be considered
7. Proviral DNA genotyping may be useful in persons with multiple virological failures, unavailable resistance history or low-level viremia at the time of switch. Results ought to be taken cautiously as proviral DNA genotype may not detect previous resistance mutations and can also detect clinically irrelevant mutations. Therefore, routine proviral DNA genotyping is currently not recommended
8. When selecting a new regimen, clinicians should carefully review the possibility of new drug-drug interactions with antiretroviral and concomitant medication leading to suboptimal drug exposure or toxicity, as well as the lag time for hepatic enzyme induction or blockade following discontinuation of the offending drug. Examples are: increased TDF toxicity with a PI/b or an increase in metformin exposure with DTG
9. If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV and HBV vaccination status. TDF or TAF should not be discontinued in persons with chronic HBV
10. PLWH should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity or tolerability issues of the new regimen
11. If a PLWH receives and tolerates a regimen that is no longer a preferred option, and none of the other reasons for change applies, there is no need to change. Example: persons tolerating EFV-containing regimens
12. See online video lecture [How to Change ART](#) from the EACS online course Clinical Management of HIV

## Dual therapies

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

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

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

### Dual therapy options supported only by small trials:

DRV/b+ RPV

In persons with suppression of HIV-VL < 50 copies/mL for the past 6 months these dual therapy strategies should only be given if there is

- a) no historical resistance and
- b) absence of chronic HBV co-infection

## Strategies not recommended

- a. Monotherapy with a PI/b
- b. Monotherapy with DTG
- c. Dual or triple NRTIs combinations
- d. Specific two-drug combination, i.e. 1 NRTI + 1 NNRTI or 1 NRTI + 1 unboosted PI, 1 NRTI + RAL, MVC + RAL, PI/b + MVC, ATV/b + RAL
- e. Intermittent therapy, sequential or prolonged treatment interruptions

## Virological Failure

<b>Definition</b>	<b>INCOMPLETE SUPPRESSION:</b> HIV-VL > 200 copies/mL at 6 months <sup>(i)</sup> after starting therapy in PLWH not previously on ART <b>REBOUND:</b> confirmed HIV-VL > 50 copies/mL in PLWH with previously undetectable HIV-VL
<b>General measures</b>	Review expected potency of the regimen Evaluate adherence, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels > 200-500 copies/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations Tropism testing if considering MVC Consider TDM Review ART history Identify treatment options, active and potentially active drugs/combinations
<b>Management of virological failure (VF)</b>	<b>If HIV-VL &gt; 50 and &lt; 200 copies/mL:</b> Check for adherence Check HIV-VL 1 to 2 months later <sup>(ii)</sup> If genotype not possible, consider changing regimen based on past treatment and resistance history <b>If HIV-VL confirmed &gt; 200 copies/mL:</b> Change regimen as soon as possible. What to change will depend on the resistance testing results: If no resistance mutations found: re-check for adherence, perform TDM If resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary expert discussion advised Goal of new regimen: HIV-VL < 50 copies/mL within 6 months

<b>In case of demonstrated resistance mutations</b>	<b>General recommendations:</b> Use at least 2 and preferably 3 active drugs in the new regimen (including active drugs from previously used classes) based on resistance mutations present in current and earlier genotypic analyses Any regimen should use at least 1 fully active PI/b (e.g. DRV/r) plus 1 drug from a class not used previously e.g. INSTI, FI, or CCR5 antagonist (if tropism test shows R5 virus only), or 1 NNRTI (e.g. ETV), assessed by genotypic testing Alternatively, a regimen can be constructed with DTG (when fully active) plus 2 NRTIs, of which at least 1 NRTI is fully active Defer change if < 2 active drugs available, based on resistance data, except in PLWH with low CD4 count (< 100 cells/ $\mu$ L) or with high risk of clinical deterioration for whom the goal is the preservation of immune function through partial reduction of HIV-VL (> 1*log10 reduction) by recycling If limited options, consider experimental and new drugs, favouring clinical trials (but avoid functional monotherapy). New drugs with promising results include humanised CD4+-binding antibody ibalizumab and attachment inhibitor fostemsavir (currently not licensed by the EMA) Treatment interruption is not recommended Consider continuation of 3TC or FTC in particular situations even if documented resistance mutation (M184V/I) If many options are available, criteria of preferred choice include: simplicity of the regimen, toxicity risks evaluation, drug-drug interactions, and future salvage therapy
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- i In PLWH with very high baseline HIV-VL (> 100,000-500,000 copies/mL), achieving viral suppression may take longer than 6 months.
- ii In the absence of resistance and in persons fully adherent to treatment, consider non-suppressible viremia due to cellular proliferation [15]

See online video lecture [Adherence and Prevention of HIV Drug Resistance](#) from the EACS online course Clinical Management of HIV

# Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy

Scenarios for pregnant women or women who wish to conceive

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

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

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

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

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

**Table 3. Antiretroviral regimen for ART-naïve pregnant women**

Pregnant women should be monitored monthly or bimonthly (depending on prior adherence and length of prior virological suppression) and as close as possible to the predicted delivery date. HIV-VL should be tested every two months of pregnancy and including 36 weeks of gestation.

Regimen	Main requirements	Additional guidance (footnotes)
<b>Recommended regimens</b>		
<b>2 NRTIs + INSTI (PREFERRED)</b>		
ABC/3TC + DTG ABC/3TC/DTG	Initiate after 8 weeks of pregnancy HLA-B*57:01 negative HBsAg negative	I (ABC: HLA-B*57:01, may delay starting ART) II (DTG: neural tube defects risk during periconception)
TDF/FTC or TDF/3TC + DTG	Initiate after 8 weeks of pregnancy	III (Tenofovir salts) II (DTG: neural tube defects risk during periconception)
TDF/FTC or TDF/3TC + RAL 400 mg bid		III (Tenofovir salts) IV (RAL in pregnancy, bid dosing)
<b>2 NRTIs + PI/r</b>		
TDF/FTC or TDF/3TC + DRV/r 600 mg/100 mg bid	With food	III (Tenofovir salts) V (DRV dosing) VI (COBI boosting)

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

#### Additional guidance

- I: ABC contraindicated if HLA-B\*57:01 positive. Even if HLA-B\*57:01 negative, counselling on HSR risk still mandatory. If testing for HLA-B\*57:01 results in delay of ART initiation, consider other recommended backbone
- II: Data from the Tsepamo observational cohort showed neural tube defects occurred in 3 per 1000 deliveries among women on DTG from conception, a small but significant increase compared with all other antiretroviral exposures [16]
- III: Some generic forms of TDF use phosphate, maleate, and succinate salts instead of fumarate. They may be used interchangeably. In certain countries, TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)
- IV: 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
- V: DRV/r 800/100 mg qd not recommended during pregnancy due to decreased levels. DRV/c is not recommended during pregnancy due to significant lower exposures of DRV and COBI in the second and third trimester of pregnancy
- VI: Boosting with COBI is not recommended after the second trimester of pregnancy (insufficient drug levels)
- VII: EFV not active against HIV-2 and HIV-1 group O strains
- VIII: Lower RPV exposure during second and third trimesters; Consider monitoring VL more frequently. RPV is not active against HIV-2
- IX: 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
- X: ATV/r may produce maternal hyperbilirubinemia, no evidence for neonatal hyperbilirubinemia
- XI: In countries with limited access to drugs listed in recommended and alternative regimens, treatment with 2 NRTIs + LPV/r or including AZT as part of the NRTI backbone are acceptable choices for pregnant women
- XII: AZT may cause maternal anaemia, consider monitoring for haematological toxicity
- XIII: LPV/r has higher toxicity than other PIs (nausea)

## Labour

### Scenarios:

#### 1) Women whose HIV-VL is > 50 copies/mL at week 34-36:

- Elective cesarean section to be planned at week 38
- iv ZDV: During labor and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery
  - Scheduled cesarean delivery: start iv ZDV 3 hours before surgery
  - Unscheduled cesarean delivery: consider administering loading dose then proceed to delivery

#### 2) Women diagnosed with HIV during labour:

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

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

## Breastfeeding

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



# ART in TB/HIV Co-infection

## Principles

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

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

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

< 50 cells/μL\*: As soon as TB treatment is tolerated and whenever possible within 2 weeks  
 ≥ 50 cells/μL: Can be deferred up to 8 weeks of TB treatment, especially when there are difficulties with DDIs, adherence and toxicities  
 Although a RCT showed that early ART (within 2 weeks) did not reduce mortality in TB meningitis, recommendations on ART initiations should be based on the CD4 count in PLWH with TB co-infection [17]

\* Be aware of IRIS reaction in persons starting ART at low CD4 count levels and with early initiation of ART. Prophylactic prednisone for 4 weeks at the time of ART initiation (prednisone 40 mg qd for 14 days, then 20 mg qd for 14 days) can prevent paradoxical TB-associated IRIS in persons with CD4 < 100 cells/μL receiving TB treatment [18]  
 Corticosteroids should be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response

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

These recommendations are for PLWH initiating ART with susceptible Mycobacterium tuberculosis infection. When treating MDR-TB or XDR-TB, careful review of DDIs and potential toxicities is mandatory before initiating ART

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

## Additional guidance

- I There are available generic forms of TDF, which instead of fumarate use phosphate, maleate, and succinate salts. They can be used interchangeably. In certain countries, TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)
- II EFV: not to be given if history of suicide attempts or mental illness; not active against HIV-2 and HIV-1 group O strains
- III ABC contraindicated if HLA-B\*57:01 positive. Even if HLA-B\*57:01 negative, counselling on HSR risk still mandatory. ABC should be used with caution in PLWH with a high CVD risk (> 20%)
- IV DTG should be dosed 50 mg bid when given with rifampicin
- V RAL 400 or 800 mg bid. With RAL 400 bid a large phase 3 study showed non-inferiority at week 24 but failed to show non-inferiority at week 48. With 800 mg bid only limited data from a phase 2 study with potential increases in liver toxicity [19]
- VI See table 2 for guidance on antiretroviral and rifabutin dosing page 21

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

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

**Non-rifamycin regimens**

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

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

In countries where neither DTG nor rifabutin are available, 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
<b>Blood</b>	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
<b>Genital secretions</b>	Anal or vaginal sex and not on PrEP or low PrEP adherence	Viraemic HIV-positive or serostatus unknown but presence of HIV risk factors. If source person is on ART, PEP should be started, HIV-VL should be repeated, and, if undetectable, PEP can be stopped
	Receptive oral sex with ejaculation and not on PrEP or low PrEP adherence	Viraemic HIV-positive
<b>Intravenous drug use</b>	Exchange of syringe, needle, preparation material or any other material	HIV-positive

- Rapid testing of the source person for HCV and HIV (if HIV-status unknown) recommended
- If source person HIV-positive on ART, order resistance testing if HIV-VL detectable
- Individualise PEP according to the source's treatment history and previous resistance tests
- For sexual exposure, if HIV-positive source has documented undetectable HIV-VL, PEP is no longer recommended
- PEP to be started ideally < 4 hours after the exposure, and no later than 48/72 hours
- Duration of PEP: 4 weeks (unless discontinued due to lack of indication)
- PEP regimens: TDF/FTC or TAF/FTC (alternative: ZDV/3TC) + RAL bid or qd, or + DRV/r qd. TDF/FTC or TAF/FTC+ DTG qd or TAF/FTC/BIC may be also considered as alternatives
- Full sexual health screen in case of sexual exposure
- Emergency contraception counselling for sexual exposure
- Follow-up:
  - HIV serology + HBV and HCV, pregnancy test (women) within 48 hours of exposure
  - Re-evaluation of PEP indication by HIV expert within 48-72 hours
  - Assess tolerability of PEP regimen
  - Transaminases, HCV-PCR and HCV serology at month 1 if source person HCV-positive (observed or suspected)
  - HIV serology at the end of PEP and one month later
  - Discuss opportunity to start PrEP

# Pre-exposure Prophylaxis (PrEP)

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

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

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

### The following procedures are recommended:

- Documented negative fourth generation HIV test a week prior to starting PrEP. In case of suspicion of acute HIV-infection, an RNA test on plasma should also be performed, page 14. During PrEP, a fourth generation HIV test should be repeated at one month and then every 3 months. PrEP should be stopped immediately in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test and the person referred for evaluation to an HIV unit

- Before PrEP is initiated, HBV serology status should be documented. If HBsAg positive, see [Clinical Management and Treatment of HBV and HCV Co-infection in PLWH](#)
- Counsel that PrEP does not prevent other types of STIs; screen for STI (syphilis, chlamydia, gonorrhoeae, HAV, HCV) when starting PrEP and regularly during use of PrEP, pages 6-8
- Counsel that PrEP may impact renal and bone health, see pages 61 and 63-65. Check renal function before starting PrEP and check renal function and bone mineral density during PrEP according to guidelines on TDF use
- Counsel that PrEP, like other prevention methods, only works when it is taken. Adherence counselling is recommended
- Counsel that PrEP can be prescribed long-term but that each consecutive PrEP prescription should be for a period of maximum 3 months (90 tablets) to ensure appropriate monitoring

See online video lectures [PrEP-Part 1](#) and [PrEP-Part 2](#) from the EACS online course Clinical Management of HIV

3. PrEP regimen

- TDF/FTC 300\*/200 mg 1 tablet qd. In both men and women PrEP should be taken for 7 days before the first exposure and stopped 7 days after the last exposure
- A trial with daily TAF/FTC in MSM and transgender women has shown non inferiority to daily TDF/FTC. No data are available in other high risk groups [20]
- For MSM only, PrEP may be dosed 'on demand' (double dose of TDF/FTC 2-24 hours before each sexual intercourse, followed by two single doses of TDF/FTC, 24 and 48 hours after the first drug intake). There are no efficacy data with on demand PrEP with TDF/FTC in women
- Use of generic formulations of TDF/FTC, if and where available, may help to improve the cost-effectiveness of PrEP, which is essential for its use as public health approach

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

## Adverse Effects of ARVs and Drug Classes

	Skin	Digestive	Liver	CV	Musculo-skeletal	Genito-urinary	Nervous	Body fat	Metabolic	Other
<b>NRTIs</b>										
ABC	Rash	Nausea* Diarrhoea*		IHD						*Systemic hypersensitivity syndrome (HLA B*57:01 dependent)
ZDV <sup>(vi)</sup>	Nail pigmentation	Nausea	Steatosis		Myopathy, Rhabdomyolysis			Lipoatrophy	Dyslipidaemia, Hyperlactataemia	Anaemia
3TC										
FTC										
TDF <sup>(vi)</sup>			Hepatitis		↓ BMD, Osteomalacia ↑ Fractures risk	↓ eGFR, Fanconi syndrome		↓ plasma lipids		
TAF <sup>(vii)</sup>									Weight increase	
<b>NNRTIs</b>										
EFV	Rash		Hepatitis				Depression, Sleep disturbance, Headache, Suicidal ideation		Dyslipidaemia, Gynaecomastia	↓ plasma 25(OH) vitamin D
ETV	Rash									
NVP	Rash*		Hepatitis*							*Systemic hypersensitivity (CD4 count and gender dependent)
RPV	Rash		Hepatitis			↓ eGFR <sup>(iv)</sup>	Depression, Sleep disturbance, Headache			
DOR										
<b>PIs</b>										
ATV <sup>(v)</sup>		Nausea and Diarrhoea <sup>(vii)</sup>	Hyperbilirubinaemia, Jaundice, Cholelithiasis			↓ eGFR, Nephrolithiasis			Dyslipidaemia	
DRV <sup>(vi)</sup>	Rash		IHD			Nephrolithiasis			Dyslipidaemia	
LPV			IHD			↓ eGFR			Dyslipidaemia	
<b>Boosting</b>										
RTV		Nausea and diarrhoea				↓ eGFR <sup>(iv)</sup>			Dyslipidaemia	
COBI		Nausea and diarrhoea				↓ eGFR <sup>(iv)</sup>			Dyslipidaemia	

FI										
ENF	Injection nodules									Hypersensitivity
INSTI										
RAL		Nausea			Myopathy, Rhabdomyolysis		Sleep disturbance, Headache			Systemic hypersensitivity syndrome <sup>(viii)</sup> Weight increase
DTG	Rash	Nausea				↓ eGFR <sup>(iv)</sup>	Sleep disturbance, Headache			Systemic hypersensitivity syndrome (< 1%) Weight increase
EVG/c		Nausea, Diarrhoea				↓ eGFR <sup>(iv)</sup>	Sleep disturbance, Headache			Weight increase
BIC						↓ eGFR <sup>(iv)</sup>	Sleep disturbance, Headache			Weight increase
CCR5 inhibitor										
MVC			Hepatitis							

- i **"Frequent effects" (events expected in at least 10% of treated PLWH), in bold**  
**"Severe effects" (events that can put a person's life at risk and represent a medical emergency), in red**  
 "Neither frequent nor severe effects", in black
- ii Still available, but generally not recommended due to toxicity
- iii TDF has been the classical prodrug of tenofovir. TAF has lower tenofovir-related kidney and bone adverse effects, but long-term experience is lacking, see pages 61, 64-65
- iv Due to inhibition of renal tubular creatinine secretion without affecting glomerular filtration itself
- v ATV can be used unboosted, or boosted with low-dose RTV or COBI. ATV-related adverse effects are more common with boosting. DRV can be used boosted with low-dose RTV or COBI. Both low-dose RTV and COBI as boosters may cause minor digestive problems and lipid increases (low-dose RTV more than COBI). IHD reported with ritonavir-boosted DRV only (no data with cobicistat-boosted DRV, although lipid effects lower)
- vi Still available but seldom used. Requires RTV-boosting
- vii Frequency and severity differs between individual ARVs
- viii DRESS syndrome reported, but currently in only 6 cases
- \* Refers to effects seen in relation to hypersensitivity reactions

Notes:

- 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
- D4T, ddI, FPV, IDV, SQV and TPR removed. Please refer to EACS v9.1 for details, [http://www.eacsociety.org/files/2018\\_guidelines-9.1-english.pdf](http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf)

See online video lecture [Adverse Effects and Monitoring of ART](#) from the EACS online course Clinical Management of HIV



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

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

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

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





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

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

# Drug-drug Interactions between ARVs and non-ARVs

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

### Colour legend

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

### Comment

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

### Legend

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

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

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

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

\* This table summarises the drug-drug interactions between HIV therapy and some commonly prescribed co-medicines as well as the drug-drug interactions of particular clinical relevance. This table is not exhaustive.

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

### Interactions with ZDV

Clarithromycin, rifampicin (decrease in ZDV exposure)

Fluconazole, methadone (increase in ZDV exposure)

Carbamazepine (increase in carbamazepine exposure)

Phenytoin (decrease in phenytoin exposure)

### Comments

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

# Drug-drug Interactions between Antidepressants and ARVs

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

## Colour legend

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

## Legend

- ↑ Potential elevated exposure of the antidepressant
- ↓ Potential decreased exposure of the antidepressant
- ↔ No significant effect
- D Potential decreased exposure of ARV drug
- E Potential elevated exposure of ARV drug
- ATV/c ATV co-formulated with COBI (300/150 mg qd)
- DRV/c DRV co-formulated with COBI (800/150 mg qd)

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and antidepressants

## Comments

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

## Further Information

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

# Drug-drug Interactions between Antihypertensives and ARVs

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

## Colour legend

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

## Legend

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

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and anti-hypertensives

## Comments

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

## Further Information

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

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

# Drug-drug Interactions between Analgesics and ARVs

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

## Colour legend

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

## Legend

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

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

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

## Interactions with ZDV

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

## Comments

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

## Further Information

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



# Drug-drug Interactions between Anticoagulants/Antiplatelet Agents and ARVs

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

## Colour legend

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

## Legend

- ↑ Potential elevated exposure of the anticoagulant/antiplatelet agent
- ↓ Potential decreased exposure of the anticoagulant/antiplatelet agent
- ↔ No significant effect
- D Potential decreased exposure of ARV drug
- E Potential elevated exposure of ARV drug

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

## Interactions with ZDV

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

## Comments

- a** US label suggests to use apixaban at a reduced dose (2.5 mg twice daily) if needed
- b** Unboosted ATV predicted to increase the anticoagulant, monitor INR and adjust the anticoagulant dosage accordingly
- c** Decreased conversion to active metabolite leading to non-responsiveness to clopidogrel. An alternative to clopidogrel should be considered.
- d** Increase in amount of active metabolite via induction of CYP3A4 and CYP2B6
- e** No pharmacokinetic interaction is expected, however, abacavir has been shown to potentiate platelet activation in vitro and may reduce the pharmacodynamic effect of clopidogrel
- f** Unboosted ATV predicted to increase dipyridamole exposure due to UGT1A1 inhibition
- g** Reduced active metabolite, but without a significant reduction in prasugrel activity

## Further Information

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

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

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

## Colour legend

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

## Legend

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

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

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

- ICS** inhaled corticosteroids
- LABA** long-acting β<sub>2</sub> agonists
- LAMA** long-acting muscarinic antagonists
- MX** methylxanthines
- PD4** phosphodiesterase 4 inhibitors
- SABA** short-acting β<sub>2</sub> agonists
- SAMA** short-acting muscarinic antagonists

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and bronchodilators

## Comments

- a** Caution as both drugs can induce QT interval prolongation
- b** Exposure can be increased up to 2-fold however this increase does not raise any concerns based on indacaterol's safety data
- c** ECG monitoring is recommended
- d** Increase in concentration of active metabolite observed with RTV 100 mg bid alone but without significant effect on adrenal function. Caution is still warranted, use the lowest possible corticosteroid dose and monitor for corticosteroid side effects

## Further Information

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

# Drug-drug Interactions between Contraceptives and ARVs

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

## Colour legend

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

## Legend

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

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

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

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and contraceptives

## Comments

- a** Alternative or additional contraceptive measures are recommended or, if used for hormone replacement therapy, monitor for signs of oestrogen deficiency

- b** Unboosted ATV increased ethinylestradiol AUC by 48%. Use no more than 30 µg of ethinylestradiol if co-administered with unboosted ATV and at least 35 µg of ethinylestradiol if co-administered with ATV/r
- c** Depending on the contraceptive method, ethinylestradiol concentrations are either not significantly changed (COC) or significantly decreased (VR). Levels of co-administered progestin are markedly decreased. Use with EFV is not recommended as it may impair contraceptive efficacy
- d** European SmPC states a hormonal contraceptive should contain at least 30 µg ethinylestradiol
- e** When used in a combination pill, the estrogen component is reduced to a small extent
- f** When used in a combination pill, the estrogen component is significantly reduced, caution is recommended and additional contraceptive measures should be used
- g** EFV is expected to decrease the progestin exposure and thereby impair the efficacy of the contraceptive method. A reliable method of barrier contraception must be used in addition to hormonal contraceptives
- h** Used in combination with ethinylestradiol (0.015 mg/day) which is predicted to be decreased. Since there is no possibility to adjust ethinylestradiol, caution is recommended and additional contraceptive measures should be used
- i** Unboosted ATV increased ethinylestradiol AUC by 48% and norethisterone AUC by 110%. Use no more than 30 µg of ethinylestradiol if co-administered with unboosted ATV and at least 35 µg of ethinylestradiol if co-administered with ATV/r
- j** Unlikely to have clinical consequences as hormone is administered as single dose
- k** Use 3 mg as a single dose for emergency contraception. Of note, the doubling of the standard dose is outside the product license and there is limited evidence in relation to efficacy
- l** Not recommended, non-hormonal emergency contraception (Cu-IUD) should be considered

## Further Information

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

# Drug-drug Interactions between Corticosteroids and ARVs

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

## Colour legend

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

## Legend

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

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

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and corticosteroids

## Comments

- a** Co-administration of RTV (100 mg bid) increased the concentrations of the active metabolite (beclometasone-17-monopropionate) but no significant effect on adrenal function was seen. Caution is still warranted, use the lowest possible corticosteroid dose and monitor for corticosteroid side effects
- b** DRV/r decreased the exposure of active metabolite (beclometasone-17-monopropionate), no significant effect on adrenal function was seen
- c** Risk of having elevated corticosteroid levels, Cushing's syndrome and adrenal suppression. This risk is present for oral and injected corticosteroid but also for topical, inhaled or eye drops administration
- d** No dose adjustment required but monitor closely, especially for signs of Cushing's syndrome when using a high dose or prolonged administration
- e** The extent of percutaneous absorption is determined by many factors such as degree of inflammation and alteration of the skin, duration, frequency and surface of application, use of occlusive dressings
- f** Use the lowest possible flunisolide dose with monitoring for corticosteroid side effects

## Further Information

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

# Drug-drug Interactions between Antimalarial Drugs and ARVs

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

## Colour legend

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

## Legend

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

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

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

## Interactions with ZDV

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

## Comments

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

## Further Information

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

## Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

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

### Colour legend

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

### Legend

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

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

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

**ERA** endothelin receptor antagonists

**IP<sup>r</sup>** IP receptor agonists

**PA** prostacyclin analogues

**PDE5** phosphodiesterase type 5 inhibitors

**sGC** soluble guanylate cyclase stimulators

### Interactions with ZDV

No clinically relevant interactions expected with ZDV and pulmonary antihypertensives

### Comments

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

### Further Information

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

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

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

## Colour legend

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

## Legend

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

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

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

\* available as prolonged release formulation

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

- AM** antimetabolite
- CNI** calcineurin inhibitors
- CS** corticosteroids
- mTOR** mTOR inhibitors

## Interactions with ZDV

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

## Comments

- a** TDM of immunosuppressant is recommended
- b** Monitor renal function

## Further Information

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



# Drug-drug Interactions between DAAs and ARVs

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

## Colour legend

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

## Legend

- ↑ Potential elevated exposure of DAA
- ↓ Potential decreased exposure of DAA
- ↔ No significant effect
- D Potential decreased exposure of ARV drug
- E Potential elevated exposure of ARV drug

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

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

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

First/second/third numbers refer to AUC changes for SOF/VEL/VOX

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and DAAs

## Comments

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

## Further Information

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

# Administration of ARVs in Persons with Swallowing Difficulties

Drug	Formulation	Crush tablets	Open capsules	Comment
<b>NRTIs</b>				
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) <sup>(vi)</sup>	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 <sup>(i)</sup> mg)	yes		Better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste)
ZDV	capsule (250 mg) syrup (10 mg/mL)	no	no	Sticky, bitter taste Better: use syrup or iv 6 mg/kg per day in glucose 5%
TAF/FTC	tablet (25/200 mg and 10/200 mg) <sup>(v)</sup>	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) <sup>(vii)</sup>
TDF/FTC	tablet (300 <sup>(i)</sup> /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
<b>NNRTIs</b>				
DOR	tablet (100 mg)	no		Tablet must be swallowed whole
TDF/3TC/DOR	tablet (300/300/100 mg)	no		Tablet must be swallowed whole
EFV	tablet (600 mg)	yes		Difficult to dissolve; solution has lower bioavailability; if > 40 kg use 720 mg
	capsule (50, 100, 200 mg) solution (30 mg/mL)	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 (200, 400 mg) <sup>(ii)</sup> suspension (10 mg/mL)	yes <sup>(ii)</sup>		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 <sup>(i)</sup> /200/600 mg)	no		
TAF/FTC/RPV	tablet (25/200/25 mg) <sup>(v)</sup>	no		Tablets should be swallowed whole and should not be chewed, crushed or split
TDF/FTC/RPV	tablet (300 <sup>(i)</sup> /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.
<b>PIs</b>				
ATV	capsule (150, 200, 300 mg)	no	no	Do not open the capsule, swallow whole
ATV/c	tablet (300/150 mg)	no		Tablets should be swallowed whole and should not be chewed, broken, cut or crushed
DRV	tablet (75,150, 400, 600, 800 mg) solution (100 mg/mL)	yes		Take with food. Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately
DRV/c	tablet (800/150 mg)	yes		Crushing of tablets is not recommended in the product information. However, based on data with the fixed-dose combination tablet (TAF/FTC/ DRV/c), crushing of tablets does not impact significantly DRV/c pharmacokinetics <sup>(viii)</sup>
LPV/r	tablet (200/50 mg) solution (80/20 mg/mL)	no		42% alcohol, do not dilute with water (risk of precipitation), rinse with milk (no water); take with food, bitter taste: dilute with chocolate milk
RTV	tablet (100 mg) solution (80 mg/mL)	no		43% alcohol, do not dilute solution (risk of precipitation), rinse with milk (no water); bitter taste; take with food
TAF/FTC/DRV/c	tablet (10/200/800/150 mg) <sup>(v)</sup>	yes		Crushing of tablets has no significant effect on the pharmacokinetics of the components of the tablet (of note: TAF bioavailability is reduced by 20% (crushing) but this decrease is unlikely to be clinically significant. TAF bio-availability is not changed when splitting the pill) <sup>(viii)</sup>
<b>Others</b>				
DTG	tablet (50 mg)	yes		Tablets may be split or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately
MVC	tablet (150, 300 mg)	yes		While the company does not have any specific kinetic information, crushing the tablet is not expected to negatively affect the bioavailability
RAL <sup>(iii)</sup>	tablet (400 mg) chewable tablets (25, 100 mg)	yes		The bioavailability of the chewable tablet is higher: 300 mg chewable tablet (= 400 mg film-coated tablet)
RPV/DTG	tablet (25/50 mg)	no		Tablets should be swallowed whole and should not be chewed, crushed or split

Drug	Formulation	Crush tablets	Open capsules	Comment
TAF/FTC/BIC	tablet (25/200/50 mg) <sup>(vi)</sup>	no		Tablets should be swallowed whole and should not be chewed, crushed or split
TAF/FTC/EVG/c	tablet (10/200/150/150 mg) <sup>(vi)</sup>	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) <sup>(vii)</sup> . Similarly, crushing of /TDF/FTC/EVG/c did not have a significant effect of the pharmacokinetics of EVG/c <sup>(iv)</sup>
TDF/FTC/EVG/c	tablet (300 <sup>(i)</sup> /200/150/150 mg)	yes		Crushing of tablets does not significantly modify the pharmacokinetic profiles <sup>(iv)</sup>
ABC/3TC/DTG <sup>(iii)</sup>	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
<b>Prophylaxis/treatment of opportunistic infections</b>				
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) capsule (150, 300 mg) suspension (20 mg/mL)	yes no	 yes	 Take on empty stomach
rifabutin	capsule (150 mg)	no	yes	Mix with apple sauce, syrup (insoluble in water)
isoniazid	tablet (100, 150 mg)	yes		Take on empty stomach
pyrazinamide	tablet (500 mg)	yes		
ethambutol	tablet (100, 400 mg)	yes		Difficult to dissolve Better: use iv solution
rifampicin/isoniazid	tablet (150/100, 150/75 mg)	yes		Take on empty stomach
Rifater (rifampicin, isoniazid, pyrazinamide)	tablet (120/50/300 mg)	yes		Take on empty stomach
Rimstar (rifampicin, isoniazid, pyrazinamide, ethambutol)	tablet (150/75/400/275 mg)	yes		Take on empty stomach
ribavirin	capsule (200 mg)	no	yes	Disperse in orange juice, take with food

For recommendations on prophylaxis/treatment of opportunistic infections, see [Part VI Opportunistic Infections](#)

- i In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)
- ii Extended release effect lost. Note: NVP 400 mg qd (immediate release) can lead to sub-therapeutic trough levels in individuals with higher body weight ( $\geq 90$  kg) compared to NVP 200 mg bid. Therefore, NVP bid administration should be preferred in individuals with higher body weight
- iii Crushing tablets is not recommended in the product information, however absorption of RAL was not compromised when the drug was crushed, dissolved in 60 mL warm water and administered by gastrostomy tube [2]. In addition, RAL drug absorption has been shown to be higher in PLWH taking RAL 400 mg bid by chewing the tablets as compared to swallowing the intact tablets [3]
- iv Crushing tablets is not recommended in the product information however the pharmacokinetic profiles of TDF/FTC/EVG/c were not significantly modified when the fixed-dose combination tablet (Stribild) was crushed and administered with food or with drip feed compared to the administration of the whole tablet [4]
- v TAF is used at 10 mg when co-administered with drugs that inhibit P-gp. TAF is used at 25 mg when co-administered with drugs that do not inhibit P-gp
- vi The pharmacokinetic profiles of ABC/3TC/DTG were not modified to a clinically significant extent when the fixed-dose combination tablet (Trimeq) was crushed and administered suspended in water or in enteral nutrition (of note: crushing leads to a 26% increase in DTG exposure) [5]
- vii The bioavailability of 3TC solution has been shown to be significantly reduced in a dose dependent manner by sorbitol present in other liquid formulations (e.g. ABC, NVP, cotrimoxazole) [6]
- viii Crushing of tablets is not recommended in the product information, however the individual pharmacokinetic profiles of TAF/FTC/ DRV/c were not significantly modified when the fixed-dose combination tablet (Symtuza) was administered crushed or split compared to the whole tablet [7]

## Dose Adjustment of ARVs for Impaired Hepatic Function

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

PIs	
<b>ATV</b>	Child-Pugh Class A: no dose adjustment Child-Pugh Class B: 300 mg qd (unboosted) Child-Pugh Class C: not recommended
<b>ATV/c</b>	Child-Pugh Class A: no dosage adjustment Child-Pugh Class B or C: not recommended
<b>COBI</b>	Refer to recommendations for the primary PI
<b>DRV</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: not recommended
<b>DRV/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: not recommended
<b>TAF/FTC/DRV/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: not recommended
<b>LPV/r</b>	No dosage recommendation; use with caution in persons with hepatic impairment
<b>RTV</b>	Refer to recommendations for the primary PI
FI	
<b>ENF</b>	No dosage adjustment
CCR5 Inhibitor	
<b>MVC</b>	No dosage recommendations. Concentrations will likely be increased in persons with hepatic impairment
INSTI	
<b>RAL</b>	No dosage adjustment
<b>EVG</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>DTG</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>BIC</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data, not recommended
<b>TAF/FTC/EVG/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>TDF/FTC/EVG/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>ABC/3TC/DTG</b>	Use separate compounds and refer to those adjustments
<b>TAF/FTC/BIC</b>	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 <sup>(i)</sup> (mL/min)				Haemodialysis <sup>(ii)</sup>
		≥ 50	30-49	10-29	< 10	
<b>NRTIs</b>						
<b>Individual agents</b>						
<b>ABC<sup>(iii)</sup></b>		300 mg q12h or 600 mg q24h	No dose adjustment required			
<b>FTC<sup>(iv)</sup></b>		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h <sup>(iv)</sup>
<b>3TC<sup>(v)</sup></b>		300 mg q24h	150 mg q24h	100 mg q24h <sup>(vi)</sup>	50-25 mg q24h <sup>(vi)</sup>	50-25 mg q24h <sup>(iv, vi)</sup>
<b>TDF<sup>(vii)</sup></b>		300 <sup>(viii)</sup> mg q24h	300 <sup>(viii)</sup> mg q48h	Not recommended (300 <sup>(viii)</sup> mg q72-96h, if no alternative)	Not recommended (300 <sup>(viii)</sup> mg q7d, if no alternative)	300 <sup>(viii)</sup> mg q7d <sup>(iv)</sup>
<b>TAF<sup>(ix,x)</sup></b>		25 <sup>(xi)</sup> mg q24h			no data	limited data
<b>ZDV</b>		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h <sup>(iv)</sup>
<b>Combinations</b>						
<b>ABC<sup>(iii)</sup>/3TC<sup>(v)</sup></b>		600/300 mg q24h	Use individual drugs			
<b>ZDV/3TC</b>		300/150 mg q12h				
<b>ABC/3TC/ZDV</b>		300/150/300 mg q12h				
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup></b>		25 <sup>(xi)</sup> /200 mg q24h	Use individual drugs <sup>(xv)</sup>			
<b>TDF<sup>(viii)</sup>/FTC<sup>(iv)</sup></b>		300 <sup>(viii)</sup> /200 mg q24h	300 <sup>(viii)</sup> /200 mg q48h	Use individual drugs		
<b>NNRTIs</b>						
<b>EFV</b>		600 mg q24h	No dose adjustment required			
<b>ETV</b>		200 mg q12h				
<b>NVP</b>		200 mg q12h				
<b>RPV</b>		25 mg q24h				
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/RPV</b>		25 <sup>(xi)</sup> /200/25 mg q24h	Use individual drugs <sup>(xv)</sup>			
<b>TDF<sup>(viii)</sup>/FTC<sup>(iv)</sup>/RPV</b>		300 <sup>(viii)</sup> /200/25 mg q24h	Use individual drugs			
<b>DOR</b>		100 mg q24h	No dose adjustment required; < 10: no PK data			
<b>TDF<sup>(viii)</sup>/3TC<sup>(v)</sup>/DOR</b>		300 <sup>(viii)</sup> /300/100 mg q24h	Use individual drugs			
<b>PIs<sup>(vii)</sup></b>						
<b>ATV/c</b>		300/150 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>ATV/r</b>		300/100 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>DRV/r</b>		800/100 mg q24h 600/100 mg q12h	No dose adjustment required <sup>(xiii)</sup>			
<b>DRV/c</b>		800/150 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/DRV/c</b>		10/200/800/150 mg q24h	Use individual drugs			
<b>LPV/r</b>		400/100 mg q12h	No dose adjustment required <sup>(xiii)</sup>			
<b>Other ART</b>						
<b>RAL</b>		1 x 400 mg tablet q12h or 2 x 600 mg tablets q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>DTG</b>		50 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>3TC<sup>(v)</sup>/DTG</b>		300/50 mg q24h	Use individual drugs			
<b>ABC<sup>(iii)</sup>/3TC<sup>(v)</sup>/DTG</b>		600/300/50 mg q24h	Use individual drugs <sup>(xvi)</sup>			
<b>RPV/DTG</b>		25/50 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/BIC</b>		25/200/50 mg q24h	Not recommended (no PK data for BIC for eGFR < 15 mL/min)			
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/EVG/c</b>		10/200/150/150 mg q24h	Not recommended <sup>(xii)</sup>			
<b>TDF<sup>(viii)</sup>/FTC<sup>(iv)</sup>/EVG/c</b>		300 <sup>(viii)</sup> /200/150/150 mg q24h Do not initiate if eGFR < 70 mL/min	Not recommended			
<b>MVC: co-administered without CYP3A4 inhibitors<sup>(xiv)</sup></b>		300 mg q12h	No dose adjustment required <sup>(xiii)</sup>			
<b>MVC: co-administered with CYP3A4 inhibitors<sup>(xiv)</sup></b>		If eGFR < 80 mL/min 150 mg q24h <sup>(xiv)</sup>				

- i eGFR: Use CKD-EPI formula; the abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see [https:// www.chip.dk/Tools-Standards/ Clinical-risk-scores](https://www.chip.dk/Tools-Standards/Clinical-risk-scores)
- ii For Continuous Ambulatory Peritoneal Dialysis (CAPD) dosing for hemodialysis may be used. However, elimination of drugs in CAPD varies depending on CAPD conditions. TDM therefore is recommended
- iii Potential cardiovascular risk of ABC may increase cardiovascular risk associated with renal failure
- iv After dialysis
- v Large bodily accumulation in impaired renal function. Although affinity for mitochondrial DNA polymerase is low and clinical toxicity in patients with severe renal impairment is rare, long-term mitochondrial toxicity is possible and must be monitored (polyneuropathy, pancreatitis, lactate acidosis, lipodystrophy, metabolic disturbances)
- vi 150 mg loading dose
- vii TDF and (boosted) PIs are associated with nephrotoxicity; consider alternative ART if pre-existing CKD, risk factors for CKD and/or decreasing eGFR, see [ARV-associated Nephrotoxicity](#) and [Kidney Disease: Definition, Diagnosis and Management](#)
- viii In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)
- ix Limited clinical data documented limited accumulation in hemodialysis. However, there is no long-term data on residual kidney function and bone toxicity. No data for eGFR < 10 mL/min but no dialysis
- x Only licenced for hepatitis B
- xi 10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)
- xii TAF/FTC/EVG/c as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, TAF/FTC/EVG/c may be used with caution if the potential benefits are considered to outweigh potential risks. One clinical study has demonstrated safety of TAF/FTC/EVG/c for PLWH on chronic dialysis [27]
- 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  $\leq$  30 mL/min/10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)
- xv TAF/FTC and TAF/FTC/RPV single tablet regimens should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, these combinations may be used with caution if the potential benefits are considered to outweigh potential risks
- xvi ABC/3TC/DTG as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic haemodialysis. A recent case series study found that use of ABC/3TC/DTG appears to be a safe and effective option in PLWH on chronic dialysis [28]

## Selected Non-ARV Drugs Requiring Dosage Adjustment in Renal Insufficiency

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



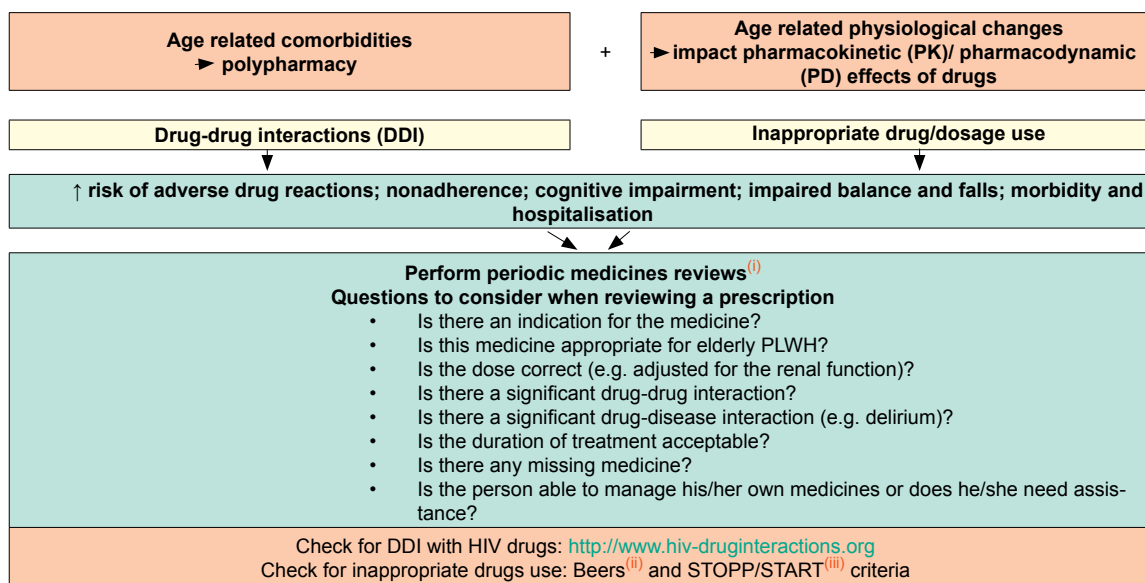
<b>DPP4-inhibitors</b>		
Alogliptin	≤ 50 mL/min	
Saxagliptin	< 45 mL/min	
Sitagliptin	< 45 mL/min	
Vildagliptin	< 50 mL/min	
<b>SGLT2-inhibitors</b>		
Canagliflozin	< 60 mL/min	Should not be initiated if CL <sub>CRT</sub> < 60 mL/min. Dose adjustment if CL <sub>CRT</sub> falls below 60 mL/min during treatment, and stop if CL <sub>CRT</sub> < 45 mL/min (lack of efficacy)
Dapagliflozin	-	Should not be initiated if CL <sub>CRT</sub> < 60 mL/min. Stop if CL <sub>CRT</sub> < 45 mL/min (lack of efficacy)
Empagliflozin	< 60 mL/min	Should not be initiated if CL <sub>CRT</sub> < 60 mL/min. Dose adjustment if CL <sub>CRT</sub> falls below 60 mL/min during treatment, and stop if CL <sub>CRT</sub> < 45 mL/min (lack of efficacy)
<b>GOUT MEDICATION</b>		
Allopurinol	≤ 50 mL/min	
Colchicine	≤ 50 mL/min	Dose dependent toxicity. Routine monitoring of colchicine adverse reactions recommended
<b>ANTIPARKINSON DRUG</b>		
Pramipexole	≤ 50 mL/min	Dose adjustment depends on indication
<b>ANALGESICS</b>		
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
<b>ANTIEPILEPTICS</b>		
Gabapentin	< 80 mL/min	
Levetiracetam	< 80 mL/min	
Pregabalin	< 60 mL/min	
<b>PSYCHOLEPTIC</b>		
Lithium	< 90 mL/min	Reduced dose and slow titration. TDM recommended. Avoid if CL <sub>CRT</sub> < 30 mL/min
<b>DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)</b>		
Methotrexate (low dose)	< 60 mL/min	Dose dependent toxicity. Contraindicated if CL <sub>CRT</sub> < 30 mL/min

#### Legend

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

[1], [8], [9]

# Prescribing in Elderly PLWH



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

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

## Selected Top 10 Drug Classes To Avoid in Elderly PLWH

Drug class	Problems/alternatives
<b>First generation antihistamines</b> 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
<b>Tricyclic antidepressants</b> e.g., amitriptyline, clomipramine, doxepin, imipramine, trimipramine	Strong anticholinergic properties, risk of impaired cognition, delirium, falls, peripheral anticholinergic adverse reactions (dry mouth, constipation, blurred vision, urinary retention). Alternatives: citalopram, escitalopram, mirtazapine, venlafaxine
<b>Benzodiazepines</b> 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.
<b>Atypical antipsychotics</b> e.g., clozapine, olanzapine, quetiapine	Anticholinergic adverse reactions, increased risk of stroke and mortality (all antipsychotics). Alternatives: aripiprazole, ziprasidone
<b>Urological spasmolytic agents</b> 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).
<b>Stimulant laxatives</b> e.g., senna, bisacodyl	Long-term use may cause bowel dysfunction. Alternatives: fibres, hydration, osmotic laxatives
<b>NSAIDs</b> 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
<b>Digoxin</b> Dosage > 0.125 mg/day	Avoid doses higher than 0.125 mg/day due to risk of toxicity. Alternatives for atrial fibrillation: beta-blockers
<b>Long acting sulfonylureas</b> e.g., glyburide, chlorpropamide	Can cause severe prolonged hypoglycemia. Alternatives: metformin or other antidiabetic classes
<b>Cold medications</b> Most of these products contain antihistamines (e.g., diphenhydramine) and decongestants (e.g., phenylephrine, pseudoephedrine)	First generation antihistamines can cause central and peripheral anticholinergic adverse reactions as described above. Oral decongestants can increase blood pressure. Avoid

### Legend

NSAID nonsteroidal anti-inflammatory drug

[1]

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

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

## Comments

- <sup>a</sup> ARVs with no predicted effect: DOR, RPV, MVC, BIC, DTG, RAL, ABC, FTC, 3TC, TAF, TDF, ZDV
- <sup>b</sup> ARVs predicted to inhibit estrogen metabolism: ATV alone, ATV/c, DRV/c, EVG/c
- <sup>c</sup> ARVs predicted to induce estrogen metabolism: ATV/r, DRV/r, LPV/r, EFV, ETV, NVP
- <sup>d</sup> ARVs predicted to inhibit androgen blocker and androgen metabolism: ATV alone, ATV/c, DRV/c, EVG/c, ATV/r, DRV/r, LPV/r
- <sup>e</sup> ARVs predicted to induce androgen blocker and androgen metabolism: EFV, ETV, NVP
- \* Matrix type transdermal patch can be cut in order to reduce the amount of hormone delivered/day
- † Conjugated estrogen is associated with high thromboembolic risk and therefore should be avoided

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

## Recommendations for dose changes

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

# Part IV Prevention and Management of Co-morbidities in PLWH

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

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

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

Conversely, many HIV doctors are not specialists in managing co-morbidities and should seek expert advice where appropriate in the prevention and management of such conditions. Situations where consultation is generally recommended are indicated elsewhere in this document.

In particular, as individuals with treated HIV age, some individuals may experience multiple co-morbidities, which may contribute to frailty and disability. Such circumstances may require a comprehensive “geriatric-type” multidimensional, multidisciplinary assessment aimed at appropriately capturing the composite of medical, psychosocial and functional capabilities and limitations of elderly PLWH. Suggesting for this approach are included in this version of the Guidelines. One area that requires further exploration is how co-morbidities impact on overall quality of life and an appropriate approach to mitigate this. This issue will be a focus of the Guidelines panel going forward.

Depending on future clinical research findings, these recommendations will be regularly updated as required. The online versions at <http://www.eacsociety.org> and the EACS Guidelines App contain more detailed information and links to other relevant websites; these will be regularly updated.

The current recommendations highlight co-morbidities that are seen frequently in the routine care of PLWH and those for which specific issues should be considered.

# Drug Dependency and Drug Addiction

## Characteristics of drugs used as opioid substitution therapy (OST)<sup>(i)</sup>

Feature	Methadone	Buprenorphine
Dose required to prevent withdrawal symptoms according to degree of opioid dependency	Linear relationship (from 10-300 mg per day)	Linear relationship for persons with less opioid dependency only – ceiling effect (max daily dose 24 mg)
Interaction with ARVs	Methadone plasma concentrations are reduced if used together with NNRTIs or PIs: <ul style="list-style-type: none"> <li>• NVP &amp; EFV: ↓ 50%</li> <li>• ETV: ↓ &lt; 10%<sup>(ii)</sup></li> <li>• LPV/r: ↓ 50%</li> <li>• SQV/r, DRV/r, FPV/r: ↓ 15-25%</li> <li>• ATV, IDV: ↓ &lt; 10%</li> </ul>	Buprenorphine (B) and active metabolite norbuprenorphine (N) plasma concentrations are reduced if combined with NNRTIs and increased if combined with some PIs or INSTIs <ul style="list-style-type: none"> <li>• EFV: ↓ up to 50% (B) and 70% (N)</li> <li>• ETV: ↓ 25% (B)</li> <li>• ATV/r, IDV, SQV/r: ↑ 50-100% (B&amp;N)</li> <li>• DRV/r: ↑ 50% (N)</li> <li>• <b>CAVE:</b> B reduces ATV; do not use without RTV or COBI boosting</li> <li>• EVG/c, ↑ 35-42% (B&amp;N)</li> </ul> (BIC, DTG, RAL, RPV & LPV/r do not affect B & N metabolism)
	<b>CAVE:</b> withdrawal symptoms if combined with ARV that decreases plasma concentration and risk of drug toxicity if such ARVs are interrupted – reverse if ARVs increase plasma concentration	
Risk of overdose	Yes	No, if used as a co-formulation with naloxone
Causing QT prolongation on ECG	Yes (dose-response relationship) <sup>(iii)</sup>	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

<sup>i</sup> See [Drug-drug Interactions between Analgesics and ARVs](#)

<sup>ii</sup> Note that despite ETV causes a decrease in the plasma concentration of methadone, the active methadone enantiomer is in fact increased 6% by ETV

<sup>iii</sup> ECG recommended for daily methadone doses exceeding 50 mg; special caution with concomitant use of other drugs known to cause QT prolongation (e.g. certain PIs such as SQV/r as well as albuterol (USAN) or salbutamol (INN), amiodarone, amitriptyline, astemizole, chloroquine, clomipramine and moxifloxacin)

## Cancer: Screening Methods<sup>(i)</sup>

Problem	Persons	Procedure	Evidence of benefit	Screening interval	Additional comments
<b>Anal cancer</b>	MSM and persons with HPV-associated dysplasia <sup>(i)</sup>	Digital rectal exam ± anal cytology	Unknown; advocated by some experts	1-3 years	If anal cytology abnormal, anoscopy
<b>Breast cancer</b>	Women 50-70 years	Mammography	↓ Breast cancer mortality	1-3 years	
<b>Cervical cancer</b>	HIV-positive women > 21 years	PAP smear or liquid based cervical cytology test	↓ Cervical cancer mortality	1-3 years	HPV genotype testing may aid PAP/liquid based cervical screening
<b>Colorectal cancer</b>	Persons 50-80 years with a life expectancy > 10 years	Faecal occult blood test annually or sigmoidoscopy every 5 years or colonoscopy every 10 years	↓ Colorectal cancer mortality	1-3 years	
<b>HepatoCellular Carcinoma (HCC)</b>	Persons with HCV and HBV with cirrhosis & in HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines* see pages 7, 71 and 95 <sup>(iii)</sup>	Ultrasound (and alpha-fetoprotein)	Earlier diagnosis allowing for improved ability for surgical eradication	Every 6 months	* Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH
<b>Prostate cancer</b>	Men > 50 years with a life expectancy >10 years	PSA <sup>(iv)</sup>	Use of PSA is controversial	2-4 years	Pros: ↑ early diagnosis and modest ↓ prostate cancer specific mortality. Cons: overtreatment, adverse effects of treatment on quality of life

- i** Screening recommendations derived from the general population. These screenings should preferably be done as part of national general population-screening programmes. Careful examination of skin should be performed regularly to detect cancers such as Kaposi's sarcoma, basal cell carcinoma and malignant melanoma
- ii** Includes Anal Intraepithelial Neoplasia (AIN), Penile Intraepithelial Neoplasia (PIN), Cervical Intraepithelial Neoplasia (CIN), Vaginal Intraepithelial Neoplasia (VAIN) and Vulval Intraepithelial Neoplasia (VIN)
- iii** HCC screening is indicated in all cirrhotic HBV or HCV co-infected persons (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in persons with F3 fibrosis is uncertain, surveillance may be considered based on an individual risk assessment (<https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/>). In HBV-positive non-cirrhotics, HCC screening should follow current EASL guidelines. Risk factors for HCC in this population include family history of HCC, ethnicity (Asians, Africans), HDV and age > 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH, see pages 71 and 95
- iv** Whilst prostate cancer screening with PSA can reduce prostate cancer specific mortality, the absolute risk reduction is very small. Given limitations in the design and reporting of the randomized trials, there remain important concerns that the benefits of screening are outweighed by the potential harms to quality of life, including the substantial risks for over-diagnosis and treatment complications. See online video lectures [Epidemiology of cancers and HIV-Part 1](#), [Epidemiology of cancers and HIV-Part 2](#), [Clinical Management of cancers and HIV-Part 1](#) and [Clinical Management of cancers and HIV-Part 2](#) from the EACS online course Clinical Management of HIV



## Lifestyle Interventions<sup>(i)</sup>

<b>Dietary counselling</b>	<ul style="list-style-type: none"> <li>• Dietary intervention should not interfere with the dietary requirements necessary for appropriate absorption of ART drugs (e.g. maintaining sufficient calorie intake for RPV).</li> <li>• Keep caloric intake balanced with energy expenditure</li> <li>• Limit intake of saturated fat, cholesterol and refined carbohydrates</li> <li>• Reduce total fat intake to &lt; 30% and dietary cholesterol to &lt; 300 mg/day</li> <li>• Emphasise intake of vegetables, fruit and grain products with fibre</li> <li>• Cut back on beverages and foods with added sugar</li> <li>• Choose and prepare foods with little or no salt. Adequate intakes of sodium in adults have been estimated mostly around 1.5 g/day (corresponding to 3.8 g salt/day<sup>(ii)</sup>)</li> <li>• Emphasise consumption of fish, poultry (without skin) and lean meat</li> <li>• Consider referral to dietician, one-week food and drink diary to discover 'hidden' calories</li> <li>• Avoid binge eating ('yo-yo dieting')</li> <li>• In persons with HIV-related wasting and dyslipidaemia, address wasting first and consider referral to dietician</li> <li>• Persons who are obviously overweight should be motivated to lose weight. Starvation diets are not recommended (immune defence mechanisms potentially decreased). Malnutrition has to be addressed where observed. Normal BMI range: 18.5-24.9; Overweight: 25.0-29.9, Obesity: &gt; 30.0 kg/m<sup>2</sup></li> </ul>
	<ul style="list-style-type: none"> <li>• The following questions are helpful to determine average alcohol intake <ol style="list-style-type: none"> <li>1. How often do you drink alcohol: never, ≤ 1/month, 2-4x/month, 2-3x/week, &gt; 4x/week</li> <li>2. If you drink alcohol, how much typically at a time: 1-2, 3-4, 5-6, 7-9, &gt; 10 drinks</li> <li>3. How many times do you have 6 or more alcoholic drinks at one occasion: never, &lt; 1/month, 1x/month, 1x/week, more or less daily</li> </ol> </li> <li>• Intake of alcohol should be restricted to no more than one drink per day for women and two drinks per day for men (&lt; 20-40 g/day)</li> <li>• In particular, persons with hepatic disease, see <a href="#">NAFLD</a>, adherence problems, inadequate CD4 count increase, tumours, past tuberculosis, diarrhoea and other conditions associated with high alcohol intake should be motivated to decrease or stop alcohol intake</li> </ul>
	<p><b>Exercise promotion</b></p> <ul style="list-style-type: none"> <li>• Promote active lifestyle to prevent and treat obesity, hypertension and diabetes</li> <li>• Encourage self-directed moderate level physical activity (take the stairs, cycle or walk to work, cycling, swimming, hiking, etc.)</li> <li>• Emphasise regular moderate-intensity exercise rather than vigorous exercise</li> <li>• Achieve cardiovascular fitness (e.g. 30 minutes brisk walking &gt; 5 days a week)</li> <li>• Maintain muscular strength and joint flexibility</li> </ul>

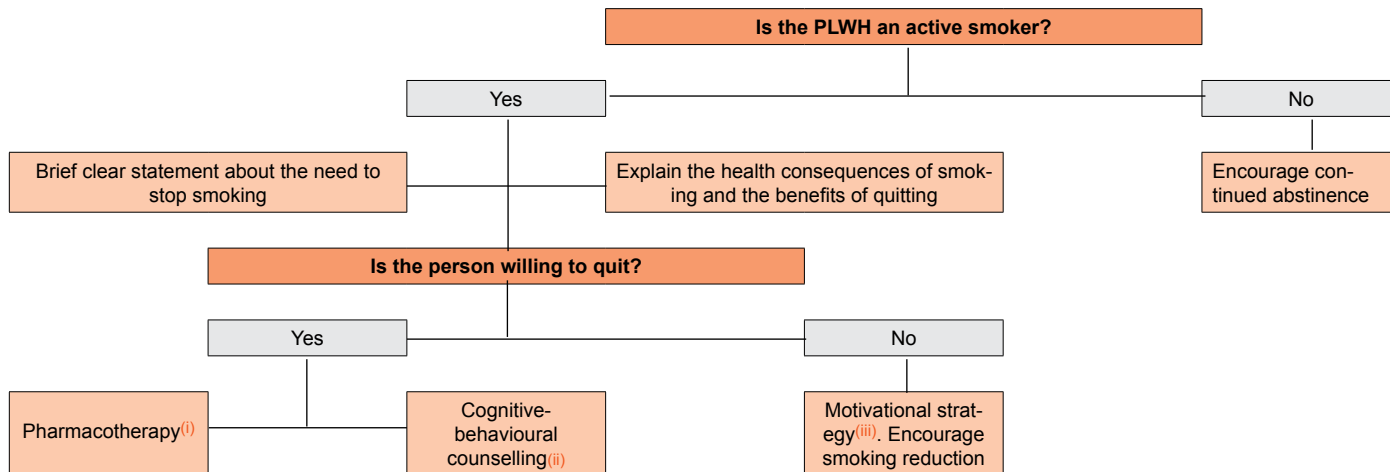
i Based on recommendations by the US Preventive Services Task Force

ii [1]

## Smoking cessation

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

Regularly consider the following algorithm with two major questions:



Adapted from [2] and [3]

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

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

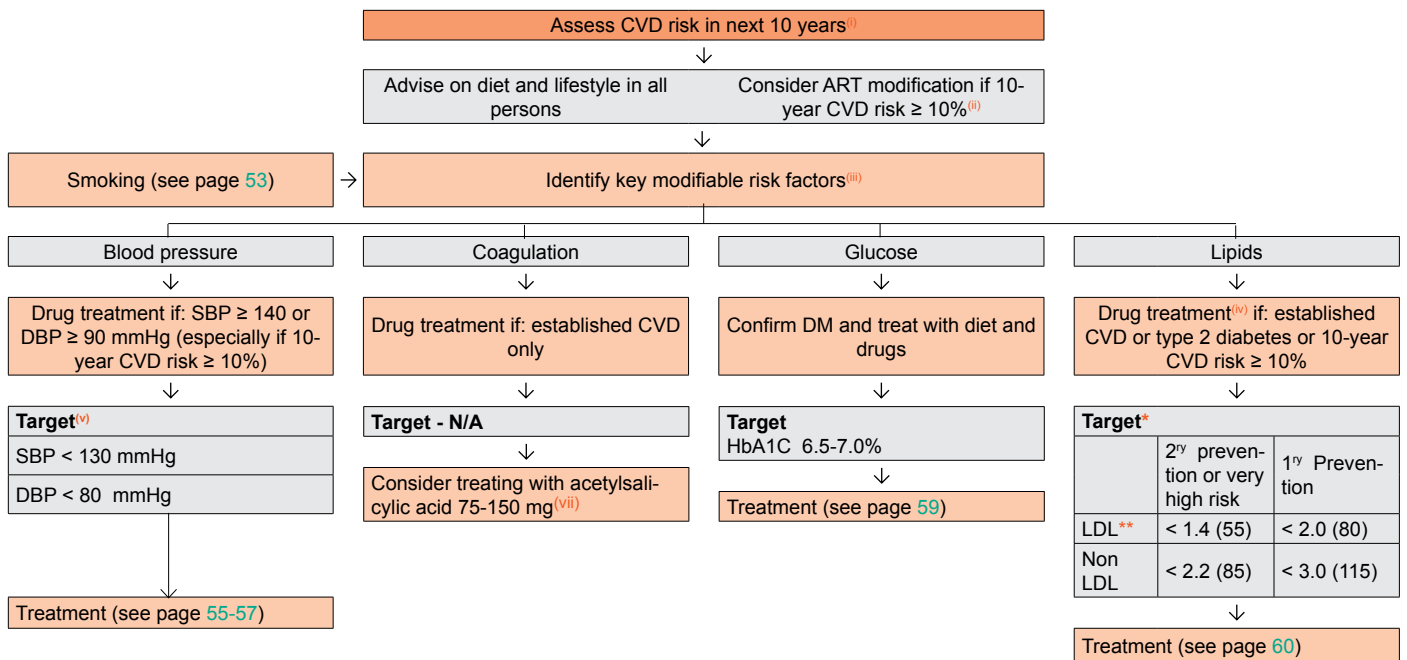
iii Motivational strategy: Identify potential health risks of the smoker and to stratify both acute (e.g. exacerbations of COPD) and long-term (e.g. infertility, cancer) risks. Show the PLWH the personal benefits of stopping smoking. Identify the barriers or obstacles that might impede the success of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

At this moment, neither EMA nor FDA approve e-cigarettes as a smoking cessation agent. In PLWH there is no data on long term outcomes and it is not possible to add any more specific recommendations. EACS follows the statement issued by the CDC in 2018 [4]

- E-cigarettes have the potential to benefit adult smokers who are not pregnant if used as a complete substitute for regular cigarettes and other smoked tobacco products
- E-cigarettes are not safe for people who do not currently use tobacco products
- E-cigarettes have the potential to benefit some people and harm others, however, whether e-cigarettes are effective for quitting smoking has not been definitively established
- E-cigarettes should not be recommended in persons who never smoked or used other tobacco products or e-cigarettes.
- E-cigarettes may have a potential benefit if used as a complete substitution for tobacco, but are not considered safe if not currently using tobacco products

# Prevention of Cardiovascular Disease (CVD)

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



\* Fasting or non-fasting samples may be used

\*\* and ≥ 50% reduction from baseline

- i Use the Framingham equation or whatever system local National Guidance recommends; a risk equation developed from HIV populations is available: see <https://www.chip.dk/Tools-Standards/Clinical-risk-scores>. This assessment and the associated considerations outlined in this figure should be repeated annually in all persons under care, see page 7, to ensure that the various interventions are initiated in a timely way
- ii Options for ART modification include:
  - (1) Replace with NNRTI, INSTI or another PI/r known to cause less metabolic disturbances and/or lower CVD risks, see page 11
  - (2) Consider replacing ZDV or ABC with TDF or use an NRTI-sparing regimen
- iii Of the modifiable risk factors outlined, drug treatment is reserved for certain subgroups where benefits are considered to outweigh potential harm. Of note, there is a combined benefit of various interventions in target groups identified. Per 10 mmHg reduction in systolic blood pressure, per 1 mmol/L (39 mg/dL) reduction in TC and with use of acetylsalicylic acid, each reduces risk of IHD by 20-25%; the effect is additive. Observational studies suggest that smoking cessation results in about 50% less risk of IHD – and this is additive to other interventions
- iv See discussion on drug treatment of persons with lower CVD risk at ESC/EAC Guidelines for the Management of Dyslipidaemias EHJ September 2019 [5]

- v Age 65+: Target 130-139 SBP  
Age 18-65: 120-129 SBP
- vi Target levels are to be used as guidance and are not definitive – expressed as mmol/L with mg/dL in parenthesis. In case LDL cannot be measured or calculated because of high triglyceride levels, the non-HDL-c (TC minus HDL-c) target should be used. Target levels for TG are usually < 1.7 (65) but the independent contribution from TG to CVD risk is uncertain
- vii In acute settings (Post-MI, ischemic, stroke or stent insertion) dual anticoagulation is recommended for up to 1 year

See online video lecture [CVD, CKD, Endocrinology](#) from the EACS online course [Clinical Management of HIV](#)

# Hypertension: Diagnosis, Grading and Management

Other risk factors, asymptomatic organ damage or disease	Blood pressure (mmHg)	Blood pressure (mmHg)	Blood pressure (mmHg)	Blood pressure (mmHg)
	High normal SBP 130-139 or DBP 85-89	Grade 1 hypertension SBP 140-159 or DBP 90-99	Grade 2 hypertension SBP 160-179 or DBP 100-109	Grade 3 hypertension SBP ≥ 180 or DBP ≥ 110
<b>No other risk factors</b>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>No BP drug intervention</li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup> for several months</li> <li>Then add BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup> for several weeks</li> <li>Then add BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>Immediate BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>
<b>1-2 risk factors</b>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>No BP drug intervention</li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup> for several weeks</li> <li>Then add BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup> for several weeks</li> <li>Then add BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>Immediate BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>
<b>≥ 3 risk factors</b>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>i.e. no BP drug intervention</li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup> for several weeks</li> <li>Then add BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>Immediate BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>
<b>Organ damage, CKD stage 3 or diabetes</b>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>Consider blood pressure drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>Immediate BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>
<b>Symptomatic CVD, CKD stage ≥ 4 or diabetes with organ damage/risk factors</b>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>Consider blood pressure drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Lifestyle changes<sup>(i)</sup></li> <li>Immediate BP drugs targeting &lt; 130/80<sup>(ii)</sup></li> </ul>

**BP** blood pressure  
**DBP** diastolic blood pressure  
**SBP** systolic blood pressure

Repeated blood pressure measurements should be used for stratification

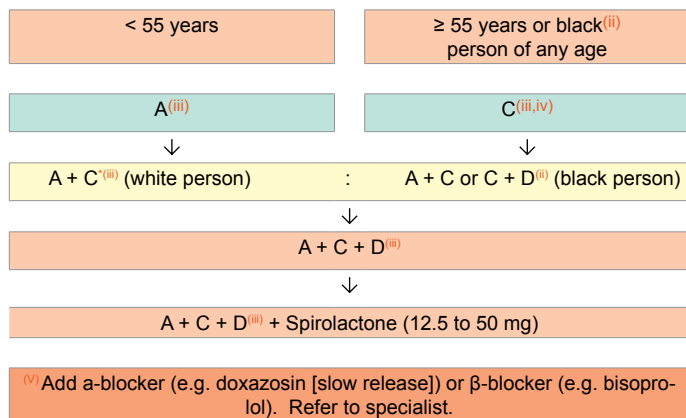
i Recommended lifestyle interventions, see page 53

ii Age 18-65: 120-129  
 Age 65+: Target 130-139

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

# Hypertension: Drug Sequencing Management

## Choosing drugs<sup>(i)</sup> for persons newly diagnosed with hypertension



- A ACE inhibitor (e.g. perindopril, lisinopril or ramipril) or angiotensin receptor blockers (ARB) (e.g. losartan, candesartan)
  - C Dihydropyridine calcium-channel blocker (e.g. amlodipine). If not tolerated or if deemed at high risk of heart failure, 'D' drugs can be used instead. Where a C drug is preferred but not tolerated, verapamil or diltiazem may be used (note: dose with caution with PIs as these may increase plasma concentrations of these calcium-channel blockers, potentially leading to toxic reactions)
  - D Thiazide-type diuretic. e.g. indapamide or chlorthalidone as a first choice. This excludes thiazides (e.g. hydrochlorothiazide (HCTZ), bendroflumethiazide etc.). However, if thiazide-type diuretics are not available low-dose thiazides may be used as a treatment alternative
- i Two antihypertensive drugs (ideally administered as single tablet combinations, where available) are increasingly recommended both as first-line therapy (A + C or A + D) and second-line therapy particularly if the initial pre-treatment SBP is ≥ 160 mmHg
  - ii Black persons are those of African or Caribbean descent, and not mixed race, Asian or Chinese persons. Either A+C or C+D can be used for this
  - iii Wait 4-6 weeks to assess whether target, see page xx, is achieved; if not, go to next step
  - iv Some calcium-channel blockers interact marginally with the pharmacokinetics of ARVs, see [Drug-drug Interactions between Antihypertensives and ARVs](#)
  - v Requirement of 4-5 drugs to manage hypertension needs specialist advice
- \* Use A+D if C not tolerated

# Drug-drug Interactions between Antihypertensives and ARVs

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

## Colour legend

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

## Legend

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

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and anti-hypertensives

## Comments

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

## Further Information

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

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

## Type 2 Diabetes: Diagnosis

### Diagnostic criteria<sup>(i)</sup>

	Fasting plasma glucose mmol/L (mg/dL) <sup>(ii)</sup>	Oral glucose tolerance test (OGTT) 2-h value mmol/L (mg/dL) <sup>(iii)</sup>	HbA1c <sup>(iv)</sup> (mmol/mol)
<b>Diabetes</b>	≥ 7.0 (126) OR→	≥ 11.1 (200)	≥ 6.5% (≥ 48)
<b>Impaired glucose tolerance (IGT)</b>	< 7.0 (126) AND→	7.8 – 11.0 (140-199)	Prediabetes 5.7-6.4% (39-47)
<b>Impaired fasting glucose (IFG)</b>	5.7– 6.9 AND (100-125)	< 7.8 (140)	

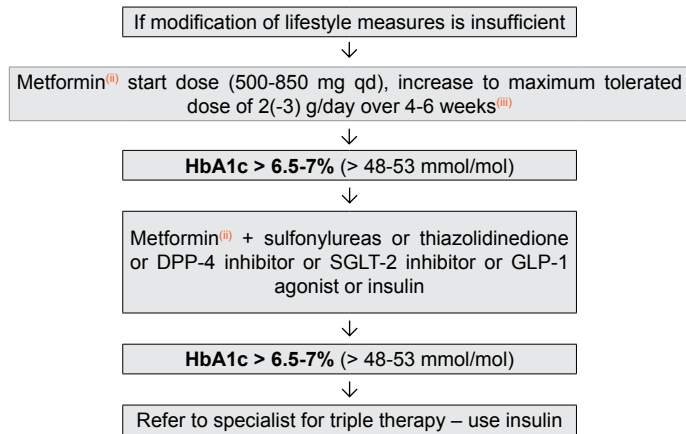
<sup>i</sup> As defined by WHO, [8] and [9]

<sup>ii</sup> An abnormal finding should be repeated before confirming the diagnosis

<sup>iii</sup> Recommended in PLWH with fasting blood glucose of 5.7 - 6.9 mmol/L (100-125 mg/dL) as it may identify persons with overt diabetes

<sup>iv</sup> Do not use HbA1c in presence of haemoglobinopathies, increased erythrocyte turnover and severe liver or kidney dysfunction. Falsely high values are measured under supplementation with iron, vitamin C and E as well as older age (age > 70: HbA1c + 0.4%). HbA1c values in treated PLWH, particularly when on ABC, tend to underestimate type 2 diabetes. Both IGT and IFG increase CVD morbidity and mortality and increase the risk of developing diabetes by 4-6-fold. These persons should be targeted for lifestyle intervention, and their CVD risk factors must be evaluated and treated

## Type 2 Diabetes<sup>(i)</sup>: Management



### Treatment goals:

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

- Normal blood lipids, see page 60, and blood pressure < 130/80 mmHg, see page 55
- Acetylsalicylic acid (75-150 mg qd) should be considered in those with elevated underlying CVD risk, see page 54
- Nephropathy, polyneuropathy and retinopathy screening and podiatry review should be performed as in diabetic persons without HIV
- Consultation with a specialist in diabetology is recommended

- i Type 1 diabetes should be treated according to national guidelines
- ii Metformin may worsen lipoatrophy.  
No data for any oral anti-diabetic agents in terms of CVD prevention in PLWH. Incretins (DPP-4 inhibitors [e.g. linagliptin, saxagliptin (reduce dose when given with a booster), sitagliptin and vildagliptin], GLP-1 agonists [liraglutide, exenatide], and SGLT-2 inhibitors [e.g. dapagliflozin, canagliflozin, empagliflozin] have not been evaluated in PLWH, but some (e.g. empagliflozin, canagliflozin, dapagliflozin, liraglutide) have shown to reduce mortality from CVD; choice of drugs dependent on a variety of individual- & disease-specific factors; no clinically significant drug-drug-interaction or adverse effects on CD4 counts expected; clinical use of pioglitazone questioned by its side effects; HbA1c targets up to 7.5% can be considered for older PLWH with long-standing type 2 diabetes and evidence of CVD
- iii Consider lower dose in PLWH with mild to moderate CKD or individuals receiving DTG



## Dyslipidaemia

**Principles:** Higher LDL-c levels increase risk of CVD and reduction diminishes this risk (see table below for drugs used on this indication); the reverse is probably true for HDL-c but trial data are less compelling. The CVD risk implications from higher than normal TG levels are even less clear, as TG has not consistently been shown to independently predict the risk of CVD. Furthermore, the clinical benefit of treating moderate hypertriglyceridaemia is uncertain; very high TG (> 10 mmol/L or > 900 mg/dL) increase risk of pancreatitis

Less calories, more exercise, reducing bodyweight, and stopping smoking tend to improve (increase) HDL. Eating fish, reducing calories, saturated fat and alcohol intake reduce triglyceride levels. Reducing dietary saturated fat intake improves LDL-levels; if not effective, consider change of ART, then consider lipid-lowering medicine, see page 54. Statins should be used by all those with established vascular disease and among those with type 2 diabetes or at high risk of CVD, irrespective of lipid levels

### Drugs used to lower LDL-c

Drug class	Drug	Dose	Side effects	Advise on use of statin together with ART	
				use with PI/r	use with NNRTIs
Statin <sup>(i,ix)</sup>	atorvastatin <sup>(ii)</sup>	10-80 mg qd	Gastrointestinal symptoms, headache, insomnia, rhabdomyolysis (rare) and toxic hepatitis	Start with low dose <sup>(v)</sup> (max: 40 mg)	Consider higher dose <sup>(vi)</sup>
	fluvastatin <sup>(iii)</sup>	20-80 mg qd		Consider higher dose <sup>(vi)</sup>	Consider higher dose <sup>(vi)</sup>
	pravastatin <sup>(iii)</sup>	20-80 mg qd		Consider higher dose <sup>(vi,vii)</sup> (max: 20 mg)	Consider higher dose <sup>(vi)</sup>
	rosuvastatin <sup>(ii)</sup>	5-40 mg qd		Start with low dose <sup>(v)</sup> (max: 20 mg)	Start with low dose <sup>(v)</sup>
	simvastatin <sup>(ii)</sup>	10-40 mg qd		Contraindicated	
Intestinal cholesterol absorption inhibitor <sup>(i,viii)</sup>	ezetimibe <sup>(iv)</sup>	10 mg qd	Gastrointestinal symptoms	No known drug-drug interactions with ART	
PCSK9-inhibitor <sup>(x)</sup>	evolocumab	140 mg 2 weekly or 420 mg monthly	Nil	No drug-drug interactions anticipated	

- i** A statin is preferred first-line therapy; different statins have variable intrinsic LDL-c lowering ability
- ii, iii, iv** Target levels for LDL-c, see page 54. In PLWH where LDL-c targets are difficult to achieve, consult/refer to specialist  
Expected range of reductions of LDL-c: **ii** 1.5-2.5 mmol/L (60-100 mg/dL), **iii** 0.8-1.5 mmol/L (35-60 mg/dL), **iv** 0.2-0.5 mmol/L (10-20 mg/dL)
- v, vi** The ARV may **v** inhibit (statin toxicity, ↓ dose) or **vi** induce (=less effect of statin, ↑ dose gradually to achieve expected benefit **ii, iii**) the excretion of the statin
- vii** **Exception:** If used with DRV/r, start with lower dose of pravastatin
- viii** This agent can be used for PLWH intolerant of statins or added to a statin when LDL reduction is inadequate despite maximally tolerated statin
- ix** Pitavastatin has as yet no morbidity/mortality trial data to support its use but may have advantages of reducing immune activation and arterial inflammation, fewer drug-drug interactions, more HDL increase and less adverse glucose effect than other statins
- x** Consider for highest risk individuals inadequately controlled on top statin dose or for statin intolerant individuals

## Bone Disease: Screening and Diagnosis

Condition	Characteristics	Risk factors	Diagnostic tests									
<b>Osteoporosis</b> <ul style="list-style-type: none"> <li>Postmenopausal women and men age ≥ 50 years with BMD T-score ≤ -2.5 at hip, femur or lumbar spine</li> <li>Premenopausal women and men age &lt; 50 years with BMD Z-score ≤ -2 and fragility fracture</li> </ul>	<ul style="list-style-type: none"> <li>Reduced bone mass</li> <li>Increased incidence of osteoporosis and fractures in PLWH</li> <li>Asymptomatic until fractures occur</li> <li>Aetiology multifactorial</li> <li>Loss of BMD observed with ART initiation (mainly during 1<sup>st</sup> year)</li> <li>Greater loss of BMD with initiation of certain ARVs<sup>(i)</sup></li> </ul>	<p>Consider classic risk factors<sup>(ii)</sup> and estimate fracture risk using FRAX in people &gt; 40 years</p> <p>Consider DXA in any person with ≥ 1 risk of:<sup>(iii)</sup></p> <ol style="list-style-type: none"> <li>1. Postmenopausal women</li> <li>2. Men ≥ 50 years</li> <li>3. High risk for falls<sup>(iv)</sup></li> <li>4. Those between 40-50 years with high fracture risk (&gt; 20% 10-year major osteoporotic fracture risk based on FRAX assessment without DXA)</li> <li>5. History of low impact fracture</li> <li>6. Clinical hypogonadism (symptomatic, see <a href="#">Sexual Dysfunction</a>)</li> <li>7. Oral glucocorticoid use (minimum 5 mg/d prednisone equivalent for &gt; 3 months)</li> </ol>	<p><b>DXA scan</b></p> <p>Preferably perform DXA in those with previous risk factors prior to ART initiation</p> <p>Add DXA result to FRAX® to refine fracture risk prediction (<a href="http://www.shef.ac.uk/FRAX">http://www.shef.ac.uk/FRAX</a>)</p> <ul style="list-style-type: none"> <li>May underestimate risk in PLWH</li> <li>Consider using HIV as a cause of secondary osteoporosis<sup>(v)</sup></li> </ul> <p><b>Rule out causes of secondary osteoporosis if BMD low<sup>(vi)</sup></b></p> <p><b>Lateral spine X-rays</b> (lumbar and thoracic) if low spine BMD, osteoporosis on DXA, or significant height loss or kyphosis develops. (DXA-based vertebral fracture assessment can be used as an alternative to lateral spine X-ray)</p>									
<b>Osteomalacia</b>	<ul style="list-style-type: none"> <li>Defective bone mineralisation</li> <li>Associated with vitamin D deficiency</li> <li>Increased risk of fractures and bone pain</li> <li>Vitamin D deficiency may cause proximal muscle weakness</li> <li>High prevalence (&gt; 80%) of vitamin D insufficiency in some HIV cohorts and in the general population</li> </ul>	<ul style="list-style-type: none"> <li>Dark skin</li> <li>Dietary deficiency</li> <li>Avoidance of sun exposure</li> <li>Malabsorption</li> <li>Obesity</li> <li>Renal phosphate wasting<sup>(vii)</sup></li> </ul>	<p>Measure 25(OH) vitamin D in all PLWH at presentation. If deficient or insufficient, check PTH levels and consider vitamin D replacement if clinically indicated, see page 62</p> <table border="1"> <thead> <tr> <th></th> <th>ng/mL</th> <th>nmol/L</th> </tr> </thead> <tbody> <tr> <td>Deficiency</td> <td>&lt; 10</td> <td>&lt; 25</td> </tr> <tr> <td>Insufficiency</td> <td>&lt; 20</td> <td>&lt; 50</td> </tr> </tbody> </table> <p><b>X-rays and bone biopsy can also help in the diagnosis</b></p>		ng/mL	nmol/L	Deficiency	< 10	< 25	Insufficiency	< 20	< 50
	ng/mL	nmol/L										
Deficiency	< 10	< 25										
Insufficiency	< 20	< 50										
<b>Osteonecrosis</b>	<ul style="list-style-type: none"> <li>Infarct of epiphyseal plate of long bones resulting in acute bone pain</li> <li>Rare but increased prevalence in PLWH</li> </ul>	<p><b>Risk factors:</b></p> <ul style="list-style-type: none"> <li>Low CD4 count</li> <li>Glucocorticoid exposure</li> <li>IVDU</li> <li>Alcohol</li> <li>Blood coagulation disorders</li> </ul>	<p><b>MRI</b></p>									

- i Greater loss of BMD observed with initiation of regimens containing TDF and some PIs.\* Additional loss and gains in BMD observed with switch to and away from TDF-containing ARV regimens, respectively. Clinical relevance to fracture risk not determined. TAF is associated with less bone loss than TDF
- Consider replacing TDF\*\* by non-tenofovir drug or TAF\*\*\* if:
- Osteoporosis / progressive bone loss
  - History of fragility fracture
  - FRAX score for major osteoporotic fracture > 10%
- \* There is limited data on use of PIs and changes after their replacement.
- \*\* Expert opinion, pending clinical data
- \*\*\* There is limited data on use of TAF with eGFR ≤ 30 mL/min and longer term outcomes are unknown
- ii Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m<sup>2</sup>), vitamin D deficiency, smoking, physical inactivity, history of low trauma fracture, alcohol excess (> 3 units/day), glucocorticoid exposure (minimum prednisone 5 mg/qd or equivalent for > 3 months)
- iii If T-score normal, repeat after 3-5 years in risk groups 1, 2 and 3; no need for re-screening with DXA in risk groups 4 and 5 unless risk factors change and only rescreen group 6 if glucocorticoid use ongoing
- iv Falls Risk Assessment Tool (FRAT), see <https://www2.health.vic.gov.au/ageing-and-aged-care/wellbeing-and-participation/healthy-ageing/falls-prevention/falls-prevention-tools>

- v If including BMD within FRAX, entering yes in the secondary cause box will not be considered in the FRAX algorithms, as it is assumed that secondary osteoporosis affects fracture risk solely through BMD. However, if the contribution of HIV infection to fracture risk is partially independent of BMD, fracture probability may be underestimated by FRAX
- vi Causes of secondary osteoporosis include hyperparathyroidism, vitamin D deficiency, hyperthyroidism, malabsorption, hypogonadism or amenorrhoea, diabetes mellitus, and chronic liver disease
- vii For diagnosis and management of renal phosphate wasting, see [Indications and Tests for Proximal Renal Tubulopathy \(PRT\)](#)

## Vitamin D Deficiency: Diagnosis and Management

Vitamin D	Test	Therapy <sup>(i)</sup>
<b>Deficiency:</b> < 10 ng/mL (< 25 nmol/L) <sup>(ii)</sup> <b>Insufficiency:</b> < 20 ng/mL (< 50 nmol/L)	Serum 25-hydroxy vitamin D (25(OH) vitamin D) If deficient, consider checking parathyroid hormone (PTH), calcium, phosphate <sup>(iii)</sup> , alkaline phosphatase	If vitamin D deficient, replacement recommended. Various regimens suggested <sup>(iv)</sup> Consider re-checking 25(OH) vitamin D levels 3 months after replacement. After replacement, maintenance with 800-2,000 IU vitamin D daily
<b>Vitamin D insufficiency prevalent in both HIV-positive and HIV-negative populations – may not be directly associated with HIV.</b>  <b>Factors associated with lower vitamin D:</b> <ul style="list-style-type: none"> <li>• Dark skin</li> <li>• Dietary deficiency</li> <li>• Avoidance of sun exposure</li> <li>• Malabsorption</li> <li>• Obesity</li> <li>• Chronic kidney disease</li> <li>• Some ARVs<sup>(v)</sup></li> </ul>	Check vitamin D status in persons with history of: <ul style="list-style-type: none"> <li>• low bone mineral density and/or fracture</li> <li>• high risk for fracture</li> </ul> Consider assessment of vitamin D status in persons with other factors associated with lower vitamin D levels (see left column)	Replacement and/or supplementation of vitamin D is recommended for PLWH with both vitamin D insufficiency <sup>(vi)</sup> and one of the following: <ul style="list-style-type: none"> <li>• osteoporosis</li> <li>• osteomalacia</li> <li>• increased PTH (once the cause has been identified)</li> </ul> Consider re-testing after 6 months of vitamin D intake

- i Can be provided according to national recommendations/availability of preparations (oral and parenteral formulations). Combine with calcium where there is insufficient dietary calcium intake. Consider that in some countries food is artificially fortified with vitamin D
- ii Some experts consider a value of  $\leq 30$  ng/mL as vitamin D deficiency. Low vitamin D has a prevalence of up to 80% in HIV cohorts and was associated with increased risk for osteoporosis, type 2 diabetes, mortality and AIDS events. However, causal association not proven for all outcomes. Consider seasonal differences (in winter approximately 20% lower than in summer)
- iii Consider that hypophosphataemia can be associated with TDF therapy. This phosphate loss through proximal renal tubulopathy may be independent of low vitamin D, see page 66. A combination of low calcium + low phosphate +/- high alkaline phosphatase may indicate osteomalacia and vitamin D deficiency
- iv Expect that 100 IU vitamin D daily leads to an increase in serum 25(OH) vitamin D of approximately 1 ng/mL. Some experts prefer a loading dose of e.g. 10,000 IU vitamin D daily for 8-10 weeks in PLWH with vitamin D deficiency. The principal goal is to achieve a serum level > 20 ng/mL (50 nmol/L) and to maintain normal serum PTH levels. Combine with calcium where potential for insufficient dietary calcium intake. The therapeutic aim is to maintain skeletal health; vitamin D supplementation has not been proven to prevent other co-morbidities in PLWH
- v The role of HIV-therapy or specific drugs remains unclear. Some studies suggest an association of EFV with reductions in 25(OH)D but not 1,25(OH)D. PIs may also affect vitamin D status by inhibiting conversion of 25(OH)D to 1,25(OH)D
- vi The implications of vitamin D levels that are below the physiological reference range but not markedly reduced and the value of supplementation are not completely understood

## Approach to Fracture Reduction in PLWH

<p><b>Reducing risk of fractures</b></p> <p><b>Subjects at high risk of fractures:</b> -Frail or sarcopenic subjects -Low BMD</p>	<ul style="list-style-type: none"> <li>• Aim to decrease falls by addressing fall risks<sup>(i)</sup></li> <li>• Ensure sufficient dietary calcium (1-1.2 g daily) and vitamin D (800-2,000 IU daily) intake<sup>(ii)</sup></li> <li>• Consider screening by DXA scan<sup>(iii)</sup></li> <li>• Rule out causes of secondary osteoporosis if BMD low</li> <li>• Where appropriate, screen for osteoporosis<sup>(iii)</sup> and refer to national/regional guidelines on treatment of osteoporosis             <ul style="list-style-type: none"> <li>– If no guidelines available, consider bisphosphonate<sup>(iv)</sup></li> <li>– Treatment based on FRAX score (see section on <a href="#">Bone Disease Screening and Diagnosis</a>).</li> <li>– Ensure adequate calcium and vitamin D intake</li> <li>– No significant interactions between bisphosphonates and antiretrovirals</li> <li>– If diagnosed with osteoporosis and requiring therapy, optimize vitamin D status and consider using ART that preserves or improves BMD<sup>(v)</sup></li> </ul> </li> <li>• Optimal management of frailty and sarcopenia includes optimising nutrition, exercise (aerobic and resistance training) and hormone replacement in cases of deficiency, see section on frailty, page 92</li> <li>• In complicated cases (e.g. young men, premenopausal women, recurrent fracture despite bone protective therapy), refer to osteoporosis specialist</li> <li>• If on bisphosphonate treatment, repeat DXA after 2 years and reassess need for continued treatment after 3-5 years</li> </ul>	<ul style="list-style-type: none"> <li>i Falls Risk Assessment Tool (FRAT), see <a href="https://www2.health.vic.gov.au/ageing-and-aged-care/wellbeing-and-participation/healthy-ageing/falls-prevention/falls-prevention-tools">https://www2.health.vic.gov.au/ageing-and-aged-care/wellbeing-and-participation/healthy-ageing/falls-prevention/falls-prevention-tools</a></li> <li>ii See page 62 for diagnosis and management of vitamin D deficiency</li> <li>iii See page 61 for screening and diagnosis of bone disease in HIV</li> <li>iv Bisphosphonate treatment with either of: alendronate 70 mg once weekly po; risedronate 35 mg once weekly po; ibandronate 150 mg po once a month or 3 mg iv every 3 months; zoledronic acid 5 mg iv once yearly</li> <li>v BMD loss is greatest in the first year after ART initiation, with more BMD loss with ART regimens containing TDF and some PIs. Switch away from TDF can lead to increases in BMD. Consider relative risk/benefit of using these agents in persons with high fracture risk. Vitamin D supplementation can reduce bone loss with ART initiation</li> </ul>
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# Kidney Disease: Definition, Diagnosis and Management

## Diagnosis of kidney disease

		eGFR <sup>(i)</sup>			
		> 60 mL/min	> 60 mL/min, but accelerated decline of eGFR*	> 30 - ≤ 60 mL/min	≤ 30 mL/min
Proteinuria (mg/mmol) <sup>(ii)</sup>	UA/C <sup>(iii)</sup> < 3	Regular follow-up	<ul style="list-style-type: none"> <li>Check risk factors for CKD<sup>(x)</sup> and nephrotoxic medicines including ART<sup>(iv, x)</sup></li> <li>Discontinue or adjust drug dosages where appropriate<sup>(v)</sup></li> <li>Perform renal ultrasound</li> <li>If haematuria present with any level of proteinuria refer to nephrologist</li> <li>Refer to nephrologist if new CKD or progressive decline in eGFR</li> </ul>		
	UA/C <sup>(iii)</sup> 3-30				
	UA/C <sup>(iii)</sup> > 30		<ul style="list-style-type: none"> <li>Check risk factors for CKD and nephrotoxic medicines including ART<sup>(iv)</sup></li> <li>Discontinue or adjust drug dosages where appropriate<sup>(v)</sup></li> <li>Perform renal ultrasound</li> <li>Urgent referral to nephrologist</li> </ul>		

\* 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<sup>(vi)</sup>

Prevention of progressive renal disease	Comment
1. ART	<p>Start ART immediately where HIV-associated nephropathy (HIVAN)<sup>(vii)</sup> or HIV immune complex disease strongly suspected. Immunosuppressive therapy may have a role in immune complex diseases. Renal biopsy to confirm histological diagnosis recommended</p> <p><b>Consider replacing TDF** by non-tenofovir drug or TAF*** if:</b></p> <ul style="list-style-type: none"> <li>UP/C 15-50 mg/mmol (see <a href="#">tubulopathy section</a>)</li> <li>eGFR &gt; 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</li> <li>co-morbidities with a high risk of CKD (i.e. diabetes and hypertension)</li> <li>body weight &lt; 60 kg</li> <li>use of a PI/r as a third agent</li> </ul> <p><b>Replace TDF** by non-tenofovir drug or TAF*** if:</b></p> <ul style="list-style-type: none"> <li>eGFR ≤ 60 mL/min</li> <li>UP/C &gt; 50 mg/mmol</li> <li>nephrotoxic comedication</li> <li>previous TDF toxicity (proximal renal tubulopathy)</li> </ul> <p>** Expert opinion pending clinical data</p> <p>***There are limited data on use of TAF with eGFR ≤ 30 mL/min, and longer term outcomes are unknown</p>
2. Start ACE inhibitors or angiotensin-II receptor antagonists if: a. Hypertension and/or b. Proteinuria	<p><b>Monitor eGFR and K<sup>+</sup> level closely on starting treatment or increasing dose</b></p> <p>a. Blood pressure target: &lt; 130/80 mmHg</p>
3. General measures: a. Avoid nephrotoxic drugs b. Lifestyle measures (smoking, weight, diet) c. Treat dyslipidaemia <sup>(viii)</sup> and diabetes <sup>(ix)</sup> d. Adjust drug dosages where necessary <sup>(v)</sup>	<p>CKD and proteinuria are independent risk factors for CVD</p>

- i For eGFR: Use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated > 60 mL/min. The abbreviated modification of diet in renal disease (AMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative <https://www.chip.dk/Tools-Standards/Clinical-risk-scores>. Definition CKD: eGFR ≤ 60 mL/min for ≥ 3 months (see [https://kdigo.org/wp-content/uploads/2017/02/KDIGO\\_2012\\_CKD\\_GL.pdf](https://kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf)). If not previously known to have CKD, confirm pathological eGFR within 2 weeks. Use of DTG, RPV, COBI and RTV boosted PIs is associated with an increase in serum creatinine/reduction of eGFR (10-15 mL/min/1.73m<sup>2</sup>) due to inhibition of proximal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1-2 months
- ii Urinalysis: use urine dipstick to screen for haematuria. To screen for proteinuria, use urine dipstick and if ≥ 1+ check urine albumin/creatinine (UA/C) to screen for glomerular disease or protein/creatinine (UP/C) to screen for both glomerular and tubular disease, see [iii](#) and [ARV-nephrotoxicity](#). Proteinuria is defined as persistent if confirmed on ≥ 2 occasions > 2-3 weeks apart
- iii UA/C largely detects glomerular disease and can be used for screening for HIV-associated renal disease and in diabetics but is not appropriate for screening for tubular proteinuria secondary to drug nephrotoxicity (e.g. TDF), where UP/C should be used (see [Indications and Tests for Proximal Renal Tubulopathy and ARV-nephrotoxicity](#)). KDIGO screening values for UA/C are: < 3, 3-30 and > 30 mg/mmol and for UP/C: < 15, 15-50, > 50 mg/mmol [10], [11]. UA/C and UP/C ratio are calculated as urine protein albumin (or protein) (mg/L) / urine creatinine (mmol/L); may also be expressed as mg/mg. Conversion factor for mg to mmol creatinine is x 0.000884
- iv Repeat eGFR and urinalysis as per screening table, see page 8
- v See [Dose Adjustment of ARVs for Impaired Renal Function](#)
- vi Joint management with a nephrologist
- vii HIVAN suspected if black ethnicity & UAP/C > 30 mg/mmol & no haematuria
- viii See page 60
- ix See page 58-59
- x Different models have been developed for calculating a 5-years CKD risk score while using different nephrotoxic ARVs integrating HIV-independent and HIV-related risk factors [12], [13]

See online video lecture [CVD, CKD and Endocrinology](#) from the EACS online course Clinical Management of HIV

## ARV-associated Nephrotoxicity

Renal abnormality*	ARV	Management
<b>Proximal tubulopathy with any combination of:</b> <ol style="list-style-type: none"> <li>1. Proteinuria: urine dipstick <math>\geq 1</math>, or confirmed increase in UP/C <math>&gt; 15</math> mg/mmol<sup>(i)</sup></li> <li>2. Progressive decline in eGFR and eGFR <math>\leq 90</math> mL/min<sup>(ii)</sup></li> <li>3. Phosphaturia<sup>(iii)</sup>: confirmed hypophosphataemia secondary to increased urine phosphate leak</li> <li>4. Glucosuria in non-diabetics</li> </ol>	TDF**	<b>Assessment:</b> <ul style="list-style-type: none"> <li>• Tests for proximal renal tubulopathy/renal Fanconi syndrome<sup>(iii)</sup></li> <li>• Consider renal bone disease if hypophosphataemia of renal origin: measure 25(OH) vitamin D, PTH, DXA</li> </ul> <b>Replace TDF by non-tenofovir drug or TAF*** if:</b> <ul style="list-style-type: none"> <li>• Documented tubular proteinuria and/or glucosuria</li> <li>• Progressive decline in eGFR and no other cause</li> <li>• Confirmed hypophosphataemia of renal origin and no other cause</li> <li>• Osteopenia/osteoporosis in the presence of increased urine phosphate leak</li> </ul>
<b>Nephrolithiasis:</b> <ol style="list-style-type: none"> <li>1. Crystalluria</li> <li>2. Haematuria<sup>(iv)</sup></li> <li>3. Leukocyturia</li> <li>4. Loin pain</li> <li>5. Acute renal insufficiency</li> </ol>	IDV ATV (DRV)	<b>Assessment:</b> <ul style="list-style-type: none"> <li>• Urinalysis for crystalluria/stone analysis</li> <li>• Exclude other cause for nephrolithiasis</li> <li>• Renal tract imaging including CT scan</li> </ul> <b>Consider stopping IDV/ATV if:</b> <ul style="list-style-type: none"> <li>• Confirmed renal stones</li> <li>• Recurrent loin pain +/- haematuria</li> </ul>
<b>Interstitial nephritis:</b> <ol style="list-style-type: none"> <li>1. Progressive decline in eGFR<sup>(ii)</sup></li> <li>2. Tubular proteinuria<sup>(iii)</sup>/ haematuria</li> <li>3. Eosinophiluria (if acute)</li> <li>4. Leukocyte casts</li> </ol>	IDV ATV	<b>Assessment:</b> <ul style="list-style-type: none"> <li>• Renal ultrasound</li> <li>• Refer to nephrologist</li> </ul> <b>Consider stopping IDV/ATV if:</b> <ul style="list-style-type: none"> <li>• Progressive decline in eGFR and no other cause</li> </ul>
<b>Progressive decline in eGFR, but none of the above<sup>(v)</sup></b>	TDF** PI/r	<b>Complete assessment:</b> <ul style="list-style-type: none"> <li>• Risk factors for CKD<sup>(v)</sup> (see <a href="#">Kidney Disease: Definition, Diagnosis and Management</a>)</li> <li>• PRT, UA/C, UP/C (see <a href="#">Kidney Disease: Definition, Diagnosis and Management</a> and <a href="#">Indications and Tests for Proximal Renal Tubulopathy (PRT)</a>)</li> <li>• Renal tract ultrasound, see page 64</li> </ul> <b>Consider stopping ARVs with potential nephrotoxicity if:</b> <ul style="list-style-type: none"> <li>• Progressive decline in eGFR and no other cause<sup>(v)</sup></li> </ul>

- \* Use of DTG, RPV, COBI and PI/r is associated with an increase in serum creatinine/reduction of eGFR (10–15 mL/min/1.73m<sup>2</sup>) due to inhibition of proximal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1–2 months
- \*\* TAF has shown lower tenofovir-related renal adverse effects due to lower systemic tenofovir exposure. Switch-studies from TDF to TAF and certain PIs suggest potential reversion of renal toxicity, however, long-term experience with TAF is lacking
- \*\*\* Particularly if eGFR  $> 30$  mL/min, as there are limited data to on use of TAF with eGFR  $\leq 30$  mL/min, and longer term outcomes are unknown
- i UP/C in spot urine detects total urinary protein including protein of glomerular or tubular origin. The urine dipstick analysis primarily detects albuminuria as a marker of glomerular disease and is inadequate to detect tubular disease
- ii For eGFR: use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated  $> 60$  mL/min. The abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see <https://www.chip.dk/Tools-Standards/Clinical-risk-scores>
- iii See [Indications and Tests for Proximal Renal Tubulopathy \(PRT\)](#)
- iv Microscopic haematuria is usually present
- v Different models have been developed for calculating a 5-years CKD risk score while using different nephrotoxic ARVs integrating HIV-independent and HIV-related risk factors [12], [13]

## Indications and Tests for Proximal Renal Tubulopathy (PRT)

Indications for proximal renal tubulopathy tests	Proximal renal tubulopathy tests <sup>(iv)</sup> , including	Replace TDF by non-tenofovir drug or TAF* alternative drug if:
<ul style="list-style-type: none"> <li>Progressive decline in eGFR<sup>(i)</sup> &amp; eGFR ≤ 90 mL/min &amp; no other cause and/or</li> <li>Confirmed hypophosphataemia<sup>(ii)</sup> and/or</li> <li>Confirmed increase in UP/C<sup>(iii)</sup></li> <li>Renal insufficiency even if stable (eGFR ≤ 60 mL/min)</li> <li>Tubular proteinuria<sup>(v)</sup></li> </ul>	<ul style="list-style-type: none"> <li>Blood phosphate and urinary phosphate excretion<sup>(vi)</sup></li> <li>Blood glucose and glucosuria</li> <li>Serum bicarbonate and urinary pH<sup>(vii)</sup></li> <li>Blood uric acid level and urinary uric acid excretion<sup>(viii)</sup></li> <li>Serum potassium and urinary potassium excretion</li> </ul>	<ul style="list-style-type: none"> <li>Confirmed proximal renal tubulopathy with no other cause</li> </ul>

- i** For eGFR: use CKD-EPI formula. The abbreviated MDRD (Modification of Diet in Renal Disease) or the Cockcroft-Gault (CG) equation may be used as an alternative, see <https://www.chip.dk/Tools-Standards/Clinical-risk-scores>
- ii** Serum phosphate < 0.8 mmol/L or according to local thresholds; consider renal bone disease, particularly if alkaline phosphatase increased from baseline: measure 25(OH) vitamin D, PTH
- iii** UP/C in spot urine, detects total urinary protein, including protein of glomerular or tubular origin. The urine dipstick analysis primarily detects albuminuria as a marker of glomerular disease and is inadequate to detect tubular disease
- iv** It is uncertain which tests discriminate best for TDF renal toxicity. Proximal tubulopathy is characterised by: proteinuria, hypophosphataemia, hypokalaemia, hypouricaemia, renal acidosis, glucosuria with normal blood glucose level. Renal insufficiency and polyuria may be associated. Most often, only some of these abnormalities are observed
- v** Tests for tubular proteinuria include retinol binding protein, α1- or β2-microglobulinuria, urine cystatin C, aminoaciduria
- vi** Quantified as fractional excretion of phosphate (FEPHos):  $(PO_4(\text{urine}) / PO_4(\text{serum})) / (Creatinine(\text{urine}) / Creatinine(\text{serum}))$  in a spot urine sample collected in the morning in fasting state. Abnormal > 0.2 (> 0.1 with serum phosphate < 0.8 mmol/L)
- vii** S-bicarbonate < 21 mmol/L and urinary pH > 5.5 suggests renal tubular acidosis
- viii** Fractional excretion of uric acid (FEUricAcid):  $(UricAcid(\text{urine}) / UricAcid(\text{serum})) / (Creatinine(\text{urine}) / Creatinine(\text{serum}))$  in a spot urine sample collected in the morning in fasting state; abnormal > 0.1
- \* Particularly if eGFR > 30 mL/min, as there are limited data on use of TAF with eGFR ≤ 30 mL/min



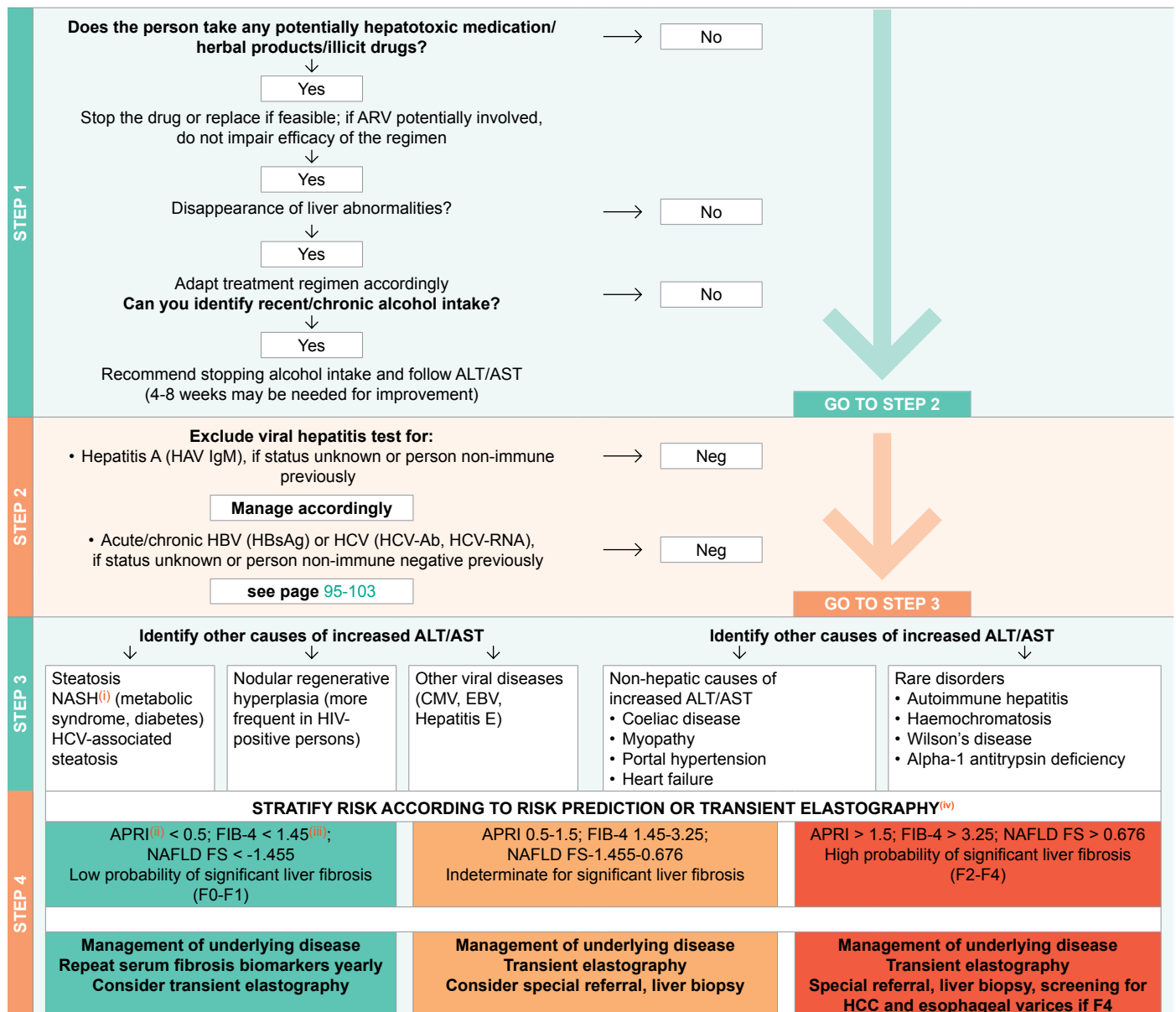
## Dose Adjustment of ARVs for Impaired Renal Function

		eGFR <sup>(i)</sup> (mL/min)				Haemodialysis <sup>(ii)</sup>
		≥ 50	30-49	10-29	< 10	
<b>NRTIs</b>						
<b>Individual agents</b>						
<b>ABC<sup>(iii)</sup></b>		300 mg q12h or 600 mg q24h	No dose adjustment required			
<b>FTC<sup>(iv)</sup></b>		200 mg q24h	200 mg q48h	200 mg q72h	200 mg q96h	200 mg q96h <sup>(iv)</sup>
<b>3TC<sup>(v)</sup></b>		300 mg q24h	150 mg q24h	100 mg q24h <sup>(vi)</sup>	50-25 mg q24h <sup>(vi)</sup>	50-25 mg q24h <sup>(iv, vi)</sup>
<b>TDF<sup>(vii)</sup></b>		300 <sup>(viii)</sup> mg q24h	300 <sup>(viii)</sup> mg q48h	Not recommended (300 <sup>(viii)</sup> mg q72-96h, if no alternative)	Not recommended (300 <sup>(viii)</sup> mg q7d, if no alternative)	300 <sup>(viii)</sup> mg q7d <sup>(iv)</sup>
<b>TAF<sup>(ix,x)</sup></b>		25 <sup>(xi)</sup> mg q24h			no data	limited data
<b>ZDV</b>		300 mg q12h	No dose adjustment required		100 mg q8h	100 mg q8h <sup>(iv)</sup>
<b>Combinations</b>						
<b>ABC<sup>(iii)</sup>/3TC<sup>(v)</sup></b>		600/300 mg q24h	Use individual drugs			
<b>ZDV/3TC</b>		300/150 mg q12h				
<b>ABC/3TC/ZDV</b>		300/150/300 mg q12h				
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup></b>		25 <sup>(xi)</sup> /200 mg q24h	Use individual drugs <sup>(xv)</sup>			
<b>TDF<sup>(viii)</sup>/FTC<sup>(iv)</sup></b>		300 <sup>(viii)</sup> /200 mg q24h	300 <sup>(viii)</sup> /200 mg q48h	Use individual drugs		
<b>NNRTIs</b>						
<b>EFV</b>		600 mg q24h	No dose adjustment required			
<b>ETV</b>		200 mg q12h				
<b>NVP</b>		200 mg q12h				
<b>RPV</b>		25 mg q24h				
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/RPV</b>		25 <sup>(xi)</sup> /200/25 mg q24h	Use individual drugs <sup>(xv)</sup>			
<b>TDF<sup>(viii)</sup>/FTC<sup>(iv)</sup>/RPV</b>		300 <sup>(viii)</sup> /200/25 mg q24h	Use individual drugs			
<b>DOR</b>		100 mg q24h	No dose adjustment required; < 10: no PK data			
<b>TDF<sup>(viii)</sup>/3TC<sup>(v)</sup>/DOR</b>		300 <sup>(viii)</sup> /300/100 mg q24h	Use individual drugs			
<b>PIs<sup>(vii)</sup></b>						
<b>ATV/c</b>		300/150 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>ATV/r</b>		300/100 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>DRV/r</b>		800/100 mg q24h 600/100 mg q12h	No dose adjustment required <sup>(xiii)</sup>			
<b>DRV/c</b>		800/150 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/DRV/c</b>		10/200/800/150 mg q24h	Use individual drugs			
<b>LPV/r</b>		400/100 mg q12h	No dose adjustment required <sup>(xiii)</sup>			
<b>Other ART</b>						
<b>RAL</b>		1 x 400 mg tablet q12h or 2 x 600 mg tablets q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>DTG</b>		50 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>3TC<sup>(v)</sup>/DTG</b>		300/50 mg q24h	Use individual drugs			
<b>ABC<sup>(iii)</sup>/3TC<sup>(v)</sup>/DTG</b>		600/300/50 mg q24h	Use individual drugs <sup>(xvi)</sup>			
<b>RPV/DTG</b>		25/50 mg q24h	No dose adjustment required <sup>(xiii)</sup>			
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/BIC</b>		25/200/50 mg q24h	Not recommended (no PK data for BIC for eGFR < 15 mL/min)			
<b>TAF<sup>(ix)</sup>/FTC<sup>(iv)</sup>/EVG/c</b>		10/200/150/150 mg q24h	Not recommended <sup>(xii)</sup>			
<b>TDF<sup>(viii)</sup>/FTC<sup>(iv)</sup>/EVG/c</b>		300 <sup>(viii)</sup> /200/150/150 mg q24h Do not initiate if eGFR < 70 mL/min	Not recommended			
<b>MVC: co-administered without CYP3A4 inhibitors<sup>(xiv)</sup></b>		300 mg q12h	No dose adjustment required <sup>(xiii)</sup>			
<b>MVC: co-administered with CYP3A4 inhibitors<sup>(xiv)</sup></b>		If eGFR < 80 mL/min 150 mg q24h <sup>(xiv)</sup>				

- i eGFR: Use CKD-EPI formula; the abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see [https:// www.chip.dk/Tools-Standards/ Clinical-risk-scores](https://www.chip.dk/Tools-Standards/Clinical-risk-scores)
- ii For Continuous Ambulatory Peritoneal Dialysis (CAPD) dosing for hemodialysis may be used. However, elimination of drugs in CAPD varies depending on CAPD conditions. TDM therefore is recommended
- iii Potential cardiovascular risk of ABC may increase cardiovascular risk associated with renal failure
- iv After dialysis
- v Large bodily accumulation in impaired renal function. Although affinity for mitochondrial DNA polymerase is low and clinical toxicity in patients with severe renal impairment is rare, long-term mitochondrial toxicity is possible and must be monitored (polyneuropathy, pancreatitis, lactate acidosis, lipodystrophy, metabolic disturbances)
- vi 150 mg loading dose
- vii TDF and (boosted) PIs are associated with nephrotoxicity; consider alternative ART if pre-existing CKD, risk factors for CKD and/or decreasing eGFR, see [ARV-associated Nephrotoxicity](#) and [Kidney Disease: Definition, Diagnosis and Management](#)
- viii In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoproxil fumarate)
- ix Limited clinical data documented limited accumulation in hemodialysis. However, there is no long-term data on residual kidney function and bone toxicity. No data for eGFR < 10 mL/min but no dialysis
- x Only licenced for hepatitis B
- xi 10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)
- xii TAF/FTC/EVG/c as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, TAF/FTC/EVG/c may be used with caution if the potential benefits are considered to outweigh potential risks. One clinical study has demonstrated safety of TAF/FTC/EVG/c for PLWH on chronic dialysis [27]
- 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  $\leq$  30 mL/min 10 mg if co-administered with a boosting agent (inhibition of P-glycoprotein, P-gp)
- xv TAF/FTC and TAF/FTC/RPV single tablet regimens should generally be avoided in PLWH with end-stage renal disease on chronic dialysis. However, these combinations may be used with caution if the potential benefits are considered to outweigh potential risks
- xvi ABC/3TC/DTG as a single tablet regimen should generally be avoided in PLWH with end-stage renal disease on chronic haemodialysis. A recent case series study found that use of ABC/3TC/DTG appears to be a safe and effective option in PLWH on chronic dialysis [28]

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

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



See pages 70-71 and 73-74

i Non-Alcoholic Steatohepatitis, see NAFLD

ii APRI, AST to Platelet Ratio Index = (AST in IU/L) / (AST Upper Limit of Normal in IU/L) / (Platelets in 10<sup>9</sup>/L)

iii FIB-4 = Age ([years] x AST [U/L]) / ((platelet [10<sup>9</sup>/L]) x ALT [U/L]). For NAFLD aetiology FIB4 cut offs are as follows: < 1.30 (low risk), >2.67 high risk. FIB4 cut off < 2.0 should be considered in persons aged > 65 years

iv [14]

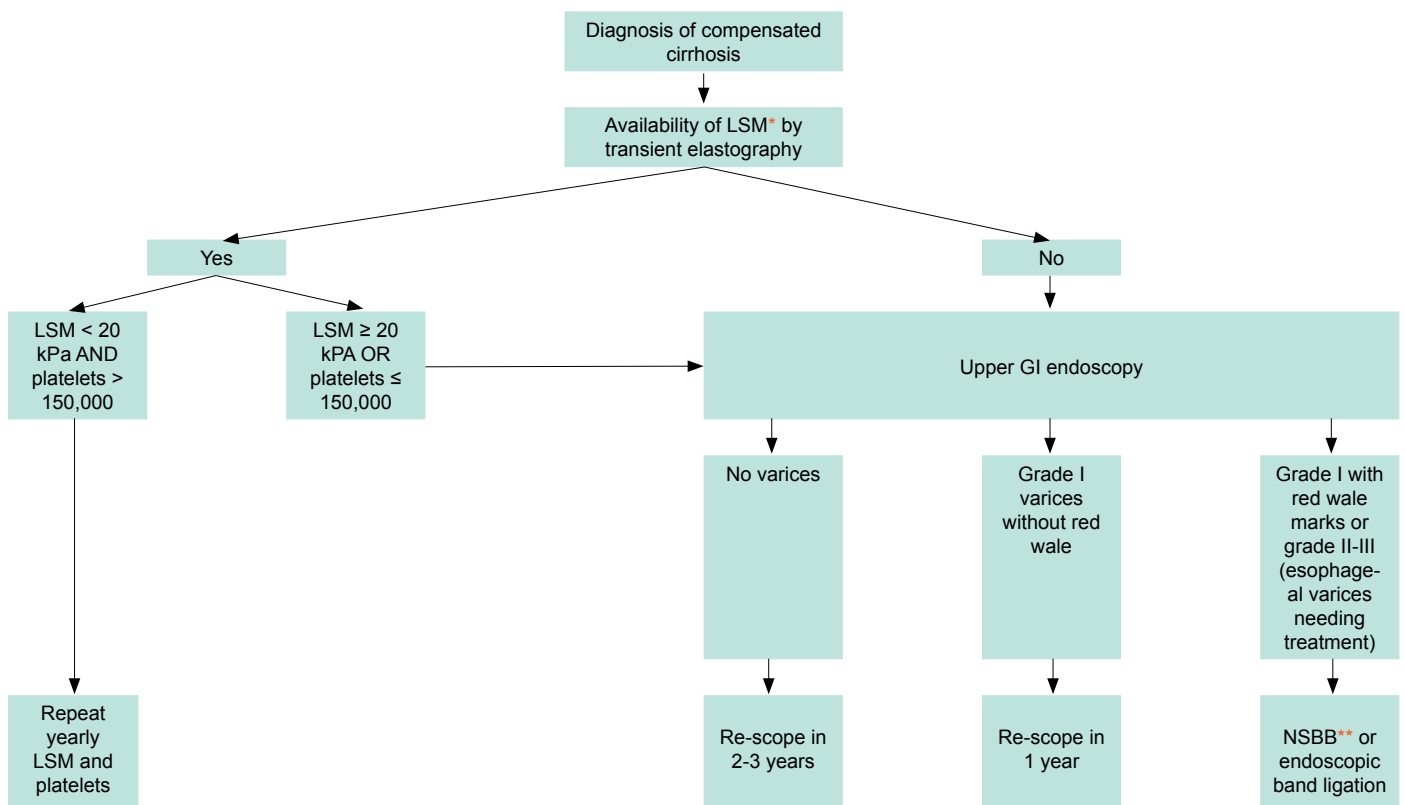
# Liver Cirrhosis: Classification and Surveillance

## Child-Pugh classification of the severity of cirrhosis

	Points <sup>(i)</sup>		
	1	2	3
Total bilirubin, mg/dL (μmol/L)	< 2 (< 34)	2-3 (34-50)	> 3 (> 50)
Serum albumin, g/L (μmol/L)	> 35 (> 507)	28-35 (406-507)	< 28 (< 406)
INR	< 1.7	1.7-2.20	> 2.20
Ascites	None	Mild/Moderate (diuretic responsive)	Severe (diuretic refractory)
Hepatic encephalopathy	None	Grade I-II (or suppressed with medicine)	Grade III-IV (or refractory)

- i 5-6 points: Class A
- 7-9 points: Class B
- 10-15 points: Class C

## Algorithm for surveillance for varices and primary prophylaxis



Based on Baveno VI consensus (EASL) and guideline on portal hypertension (AASLD) [15], [16]

\* LSM, liver stiffness measurement;

\*\* NSBB, non-selective beta-blocker e.g. propranolol 80-160 mg/day or carvedilol 6.25-50 mg/day

Persons with compensated cirrhosis without varices on screening endoscopy should have endoscopy repeated every 2 years (with ongoing liver injury or associated conditions, such as obesity and alcohol use) or every 3 years (if liver injury is quiescent, e.g., after viral elimination, alcohol abstinence)

Hepatic Venous Pressure Gradient (HVPG) when available, allows a direct measure of portal hypertension and prognostic stratification of persons with compensated cirrhosis

HVPG < 6 mmHg: no portal hypertension

HVPG 6-9 mmHg: portal hypertension non clinically significant

HVPG ≥ 10 mmHg: clinically significant portal hypertension

In primary and secondary prophylaxis for variceal bleeding HVPG measurement allows to monitor efficacy of beta-blockers

# Liver Cirrhosis: Management

Management of PLWH with cirrhosis should be done in collaboration with experts in liver diseases. More general management guidance is described below

For dosage adjustment of antiretrovirals, see [Dose Adjustment of ARVs for Impaired Hepatic Function](#)

In end-stage liver disease (ESLD), use of EFV may increase risk of CNS symptoms

ART, if otherwise indicated, also provides net benefit to cirrhotic persons.

See [Diagnosis and Management of Hepatorenal Syndrome \(HRS\)](#)

Management of hypervolaemic hyponatraemia	Management strategy of hepatic encephalopathy (HE)
<ol style="list-style-type: none"> <li>Fluid restriction: 1000-1500 mL/day (consumption of bouillon allowed ad libitum)</li> <li>If fluid restriction is ineffective, consider use of oral tolvaptan               <ol style="list-style-type: none"> <li>To be started in hospital at 15 mg/day for 3-5 days, then titrated to 30-60 mg/day until normal s-Na; duration of treatment unknown (efficacy/safety only established in short-term studies (1 month))</li> <li>S-Na should be monitored closely, particularly after initiation, dose modification or if clinical status changes</li> <li>Rapid increases in s-Na concentration (&gt; 8 mmol/day) should be avoided to prevent osmotic demyelination syndrome</li> <li>Persons may be discharged after s-Na levels are stable and without need to further adjust dose</li> </ol> </li> </ol>	<p><b>General management</b></p> <ol style="list-style-type: none"> <li>Identify and treat precipitating factor (GI haemorrhage, infection, pre-renal azotaemia, constipation, sedatives)</li> <li>Short-term (&lt; 72 hours) protein restriction may be considered if HE is severe</li> </ol> <p><b>Specific therapy</b></p> <p>Lactulose 30 cm<sup>3</sup> po every 1-2h until bowel evacuation, then adjust to a dosage resulting in 2-3 formed bowel movements per day (usually 15-30 cm<sup>3</sup> po bid)</p> <p>Lactulose enemas (300 cm<sup>3</sup> in 1L of water) in PLWH who are unable to take it po. Lactulose can be discontinued once the precipitating factor has resolved</p>

Management strategy in uncomplicated ascites	
<b>General management</b>	<ul style="list-style-type: none"> <li>Treat ascites once other complications have been treated</li> <li>Avoid NSAIDs</li> <li>Norfloxacin prophylaxis (400 mg po, qd) in persons with <b>1</b>) an ascites protein level of &lt; 1.5 mg/dL, <b>2</b>) impaired renal function (serum creatinine level &gt; 1.2 mg/dL, BUN &gt; 25 mg/dL), <b>3</b>) s-Na level &lt; 130mE g/L), or <b>4</b>) severe liver failure (Child-Pugh score &gt; 9 points with s-bilirubin level &gt; 3 mg/dL)</li> </ul>
<b>Specific management</b>	<ul style="list-style-type: none"> <li>Salt restriction: 1-2 g/day. Liberalise if restriction results in poor food intake</li> <li>Large volume paracentesis as initial therapy only in persons with tense ascites</li> <li>Administer iv albumin (= 6-8 g/L ascites removed)</li> </ul>
<b>Follow-up and goals</b>	<ul style="list-style-type: none"> <li>Adjust diuretic dosage every 4-7 days</li> <li>Weigh the person at least weekly and BUN, s-creatinine, and electrolytes measured every 1-2 weeks while adjusting dosage</li> <li>Double dosage of diuretics if: weight loss &lt; 2 kg a week and BUN, creatinine and electrolytes are stable</li> <li>Halve the dosage of diuretics or discontinue if: weight loss ≥ 0.5 kg/day or if there are abnormalities in BUN, creatinine or electrolytes</li> <li>Maximum diuretic dosage: spironolactone (400 mg qd) and furosemide (160 mg qd)</li> </ul>

Nutrition of cirrhotic persons	
<p><b>Caloric requirements</b></p> <ul style="list-style-type: none"> <li>25-30 Kcal/kg/day of normal body weight</li> </ul> <p><b>Protein requirements</b></p> <ul style="list-style-type: none"> <li>Protein restriction is not recommended (see above for exception if HE)</li> </ul>	<ul style="list-style-type: none"> <li>Type: rich in branched chain (non-aromatic) amino acids</li> <li>Some studies support that parenteral proteins carry less risk of encephalopathy since not converted by colonic bacteria into NH<sub>3</sub></li> </ul> <p><b>Micronutrients</b></p> <ul style="list-style-type: none"> <li>Mg and Zn</li> </ul>

Analgesia in PLWH with hepatic failure	
<ul style="list-style-type: none"> <li><b>Acetaminophen</b> can be used; caution on daily dose (max 2 g/day)</li> <li><b>NSAIDs generally avoided;</b> predispose persons with cirrhosis to develop GI bleeding. Persons with decompensated cirrhosis are at risk for NSAID-induced renal insufficiency</li> </ul>	<ul style="list-style-type: none"> <li><b>Opiate</b> analgesics are not contraindicated but must be used with caution in persons with pre-existing hepatic encephalopathy</li> </ul>

Screening for HepatoCellular Carcinoma (HCC)	
<ul style="list-style-type: none"> <li>HCC screening is indicated in all cirrhotic HBV or HCV co-infected PLWH (even if HCV infection has been cured and HBV replication is medically suppressed) in a setting where treatment for HCC is available. Although the cost-effectiveness of HCC screening in PLWH with F3 fibrosis is uncertain, surveillance may be considered based on an individual risk assessment <a href="https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/">https://easl.eu/publication/easl-clinical-practice-guidelines-management-of-hepatocellular-carcinoma/</a></li> <li>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 &gt; 45 years. EASL guidelines propose using the PAGE-B score in Caucasians to assess the HCC risk, however this score has not been validated in PLWH; see pages 8, 52 and 95. <a href="#">Table on fibrosis cut-offs</a>, page 102</li> <li>Ultrasound (US), with or without AFP, every 6 months. Alpha-fetoprotein (AFP) should not be used alone. AFP is a suboptimal surveillance tool because of low sensitivity and specificity</li> </ul>	

When to refer for liver transplantation	
Best to refer early as disease progresses rapidly	
= MELD <sup>®</sup> score 10-12 (listing at 15) Decompensated cirrhosis (at least one of the following complications)	
<ul style="list-style-type: none"> <li>Ascites</li> <li>Hepatic encephalopathy</li> <li>Variceal bleeding</li> <li>Spontaneous bacterial peritonitis</li> <li>Hepatorenal syndrome</li> <li>Hepatopulmonary syndrome</li> <li>NASH cirrhosis<sup>(ii)</sup></li> <li>HCC</li> </ul>	
See <a href="#">Solid Organ Transplantation (SOT) in PLWH</a>	

- i Unit for both s-creatinine and s-bilirubin is mg/dL. MELD score = 10 {0.957 Ln (serum creatinine (mg/dL)) + 0.378 Ln (total bilirubin (mg/dL)) + 1.12 Ln (INR) + 0.643}, see <http://www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/>
- ii Particularly with metabolic decompensations

# Non-Alcoholic Fatty Liver Disease (NAFLD)

The prevalence of NAFLD is higher in PLWH (30 - 40% in the US) than in the general population [17]. Nearly half of the PLWH who undergo evaluation for unexplained liver test abnormalities are found to have NAFLD. The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption  $\geq 30$  g for men and  $\geq 20$  g for women

## Spectrum of NAFLD

Often associated with components of the metabolic syndrome:

### NAFLD is defined as:

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

### Non-Alcoholic SteatoHepatitis (NASH)

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

### Most common concurrent diseases

- AFLD-alcoholic fatty liver disease
- Drug-induced fatty liver disease
- HCV-associated fatty liver (GT 3)

## Consideration on ARV drugs

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

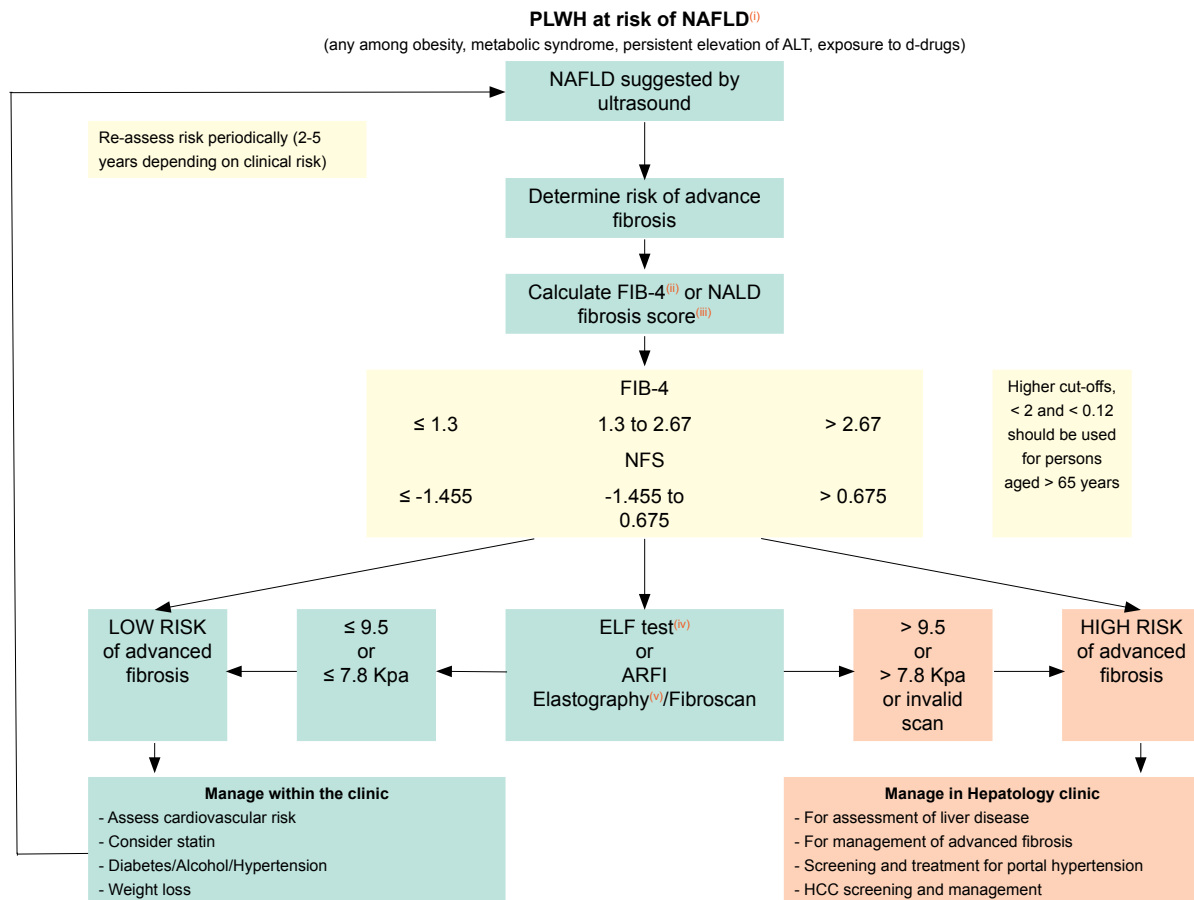
## Diagnosis

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

## Treatment of NAFLD

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

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



These recommendations are largely inspired by the EASL-EASD-EASO Clinical Practice Guidelines for the Management of Non-Alcoholic Fatty Liver Disease: European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity [18]

<sup>i</sup> NAFLD, Non-alcoholic fatty liver disease

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

<sup>iii</sup> NFS, Non-alcoholic fatty liver disease Fibrosis Score =  $-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2) + 1.13 \times \text{impaired fasting glucose/diabetes mellitus}^{\text{iv}}$  (yes=1/no=0) +  $0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (x}10^9) - 0.66 \times \text{albumin(g/dL)}$

<sup>iv</sup> 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)

<sup>v</sup> ARFI elastography, Acoustic Radiation Force Impulse

## Diagnosis and Management of Hepatorenal Syndrome (HRS)

<b>Diagnosis</b>	<p>Consider HRS in PLWH with cirrhosis and ascites and a creatinine level of &gt; 1.5 mg/dL. It is a diagnosis of exclusion. Before making the diagnosis, the following need to be ruled out and treated:</p> <ul style="list-style-type: none"> <li>• Sepsis (person needs to be pancultured)</li> <li>• Volume depletion (haemorrhage, diarrhoea, overdiuresis)</li> <li>• Vasodilators</li> <li>• Organic renal failure (urine sediment; kidney ultrasound)</li> </ul> <p>Diuretics should be discontinued and intravascular volume expanded with iv albumin. If renal dysfunction persists despite above, diagnose HRS</p>		
<b>Recommended therapy</b>	<p>Liver transplant (priority dependent on MELD score, see page 71). If person is on transplant list, MELD score should be updated daily and communicated to transplant centre, see <a href="#">Solid Organ Transplantation (SOT) in PLWH</a></p>		
<b>Alternative (bridging therapy)</b>	Vasoconstrictors	octreotide	100-200 µg sc tid → Goal to increase mean arterial pressure by 15 mmHg
		+ midodrine	5-15 mg po tid
		or terlipressin	0.5-2.0 mg iv every 4-6 hours
	and iv albumin (both for at least 7 days)		

## Dose Adjustment of ARVs for Impaired Hepatic Function

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

PIs	
<b>ATV</b>	Child-Pugh Class A: no dose adjustment Child-Pugh Class B: 300 mg qd (unboosted) Child-Pugh Class C: not recommended
<b>ATV/c</b>	Child-Pugh Class A: no dosage adjustment Child-Pugh Class B or C: not recommended
<b>COBI</b>	Refer to recommendations for the primary PI
<b>DRV</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: not recommended
<b>DRV/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: not recommended
<b>TAF/FTC/DRV/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: not recommended
<b>LPV/r</b>	No dosage recommendation; use with caution in persons with hepatic impairment
<b>RTV</b>	Refer to recommendations for the primary PI
FI	
<b>ENF</b>	No dosage adjustment
CCR5 Inhibitor	
<b>MVC</b>	No dosage recommendations. Concentrations will likely be increased in persons with hepatic impairment
INSTI	
<b>RAL</b>	No dosage adjustment
<b>EVG</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>DTG</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>BIC</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data, not recommended
<b>TAF/FTC/EVG/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>TDF/FTC/EVG/c</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data
<b>ABC/3TC/DTG</b>	Use separate compounds and refer to those adjustments
<b>TAF/FTC/BIC</b>	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no data

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



# Lipoatrophy and Obesity: Prevention and Management

Lipoatrophy	
<p><b>Prevention</b></p> <ul style="list-style-type: none"> <li>• Avoid d4T and ZDV or pre-emptively switch. No evidence of benefit by switching other antiretrovirals</li> <li>• Avoid excessive weight loss due to diet and exercise</li> <li>• In ART-naïve persons, limb fat usually increases with initiation of ART not containing d4T or ZDV, reflecting “return-to-health” type of response</li> </ul>	<p><b>Management</b></p> <ul style="list-style-type: none"> <li>• Modification of ART: Switch away from d4T or ZDV               <ul style="list-style-type: none"> <li>– Increase in total limb fat ~400-500 g/year (in the first two years)</li> <li>– Risk of toxicity from new drug, see <a href="#">Adverse Effects of ARVs &amp; Drug Classes</a></li> </ul> </li> <li>• Surgical intervention               <ul style="list-style-type: none"> <li>– Offered for cosmetic relief of (facial) lipoatrophy only</li> </ul> </li> </ul>

i See online video lecture [CVD, CKD and Endocrinology](#) from the EACS online course Clinical Management of HIV

## Obesity

### Definition:

Body mass index (BMI) > 30 kg/m<sup>2</sup>

Also body fat > 25% (men) or > 33% (women) for persons with low muscle mass

Waist circumference is an indicator of abdominal fat and a useful predictor of cardiometabolic diseases. Cut-off points indicating higher cardiometabolic risks are > 88 cm for women and > 102 cm for men. Naturally, different ethnicities have different body builds and proportions. Asians have a naturally slimmer, petite frame and therefore the waist circumference cut off for Japanese, Chinese and South Asian people is lower than for Caucasians.

Visceral adipose tissue (VAT) area ≥ 130 cm<sup>2</sup> is a validated threshold for increased cardiometabolic risk

### Consequences:

Not only cosmetic concern

Worse outcomes with surgery and acute infections (e.g. pneumonia, influenza)

Increased risk of diabetes mellitus, hypertension, cardiovascular disease, some cancers, obstructive sleep apnea, cholelithiasis, erectile dysfunction, non-alcoholic fatty liver disease, osteoarthritis and depression

### Contributing factors:

Older age

Sedentary lifestyle

Intake of excess or poor quality calories (e.g. saturated fats, processed sugars)

Excess alcohol consumption

Some medications (e.g. psychotropic drugs, steroids, antidiabetic drugs)

Endocrine disorders (e.g. GH deficiency, hypothyroidism, Cushing's syndrome, hypogonadism)

### Assessment:

Weight, waist circumference and BMI, see page [53](#)

Fasting lipids and glucose, see pages [54](#), [58](#) and [60](#)

Dyslipidaemia management, see page [60](#)

Assess NAFLD, see page [72](#)

Prevention of cardiovascular disease, see page [54](#)

### Aim:

An objective of 5% weight loss from initial weight may have a beneficial impact on obesity-related comorbidities

### Management:

Structured exercise

Dietary intervention

No data on ART switch

Treat underlying or associated conditions

There are several drugs approved to treat obesity (e.g. orlistat, phentermine/topiramate, lorcaserin, naltrexone/bupropion, liraglutide) but they should be prescribed by an endocrinologist or obesity expert. All of them may have adverse effects and drug-drug interactions with ART.

Bariatric surgery may be considered in persons with a BMI ≥ 40 kg/m<sup>2</sup> or ≥ 35 kg/m<sup>2</sup> with obesity-related comorbidities refractory to serious attempts at lifestyle changes and should be coordinated through an established, specialist led obesity programme. Consider therapeutic drug monitoring and drug dose adjustment post-bariatric surgery

Surgery can be considered for localised lipomas and dorsocervical fat accumulation for cosmetic purposes only

# Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management

Risk factors	Prevention/Diagnosis	Symptoms
<ul style="list-style-type: none"> <li>• HCV/HBV co-infection</li> <li>• Use of ribavirin</li> <li>• Liver disease</li> <li>• Low CD4 count</li> <li>• Pregnancy</li> <li>• Female sex</li> <li>• Obesity</li> </ul>	<ul style="list-style-type: none"> <li>• Routine monitoring of serum lactate levels not recommended - does not predict risk of lactic acidosis</li> <li>• Measurement of serum lactate, bicarbonate &amp; arterial blood gases + pH indicated in case of symptoms suggestive of hyperlactataemia</li> <li>• Close monitoring for symptoms if &gt; 1 risk factor</li> </ul>	<ul style="list-style-type: none"> <li>• Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, elevated ALT and/or AST, weight loss</li> <li>• Acidaemia: asthenia, dyspnoea, arrhythmias</li> <li>• Guillain-Barré-like syndrome</li> </ul>

## Management

Serum lactate (mmol/L)	Symptoms	Action
> 5 <sup>(i)</sup>	Yes/No	<ul style="list-style-type: none"> <li>• Repeat test under standardised conditions to confirm &amp; obtain arterial pH and bicarbonate<sup>(i)</sup></li> <li>• If confirmed, exclude other causes               <ul style="list-style-type: none"> <li>– Arterial pH ↓ and/or bicarbonate ↓<sup>(i)</sup>: Stop NRTIs</li> <li>– Arterial pH and/or bicarbonate normal: Consider switch from high to low-risk NRTI &amp; monitor carefully OR stop NRTIs</li> </ul> </li> </ul>
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

<sup>i</sup> 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

<b>General precautions</b>	<ul style="list-style-type: none"> <li>• Delay travel until clinically stable and treatment established</li> <li>• Provide drug prescription and referral letter for emergencies</li> <li>• Provide medical certificate for import of personal medicines/syringes</li> <li>• Carry ARVs split between suitcase and hand luggage</li> <li>• Beware of fake drugs</li> </ul>
<b>ART</b>	<ul style="list-style-type: none"> <li>• Maintain hours of medicines (e.g. 23.00 local time) when switching time zones, shortening the interval to the next dose when flying east</li> </ul>
<b>Acknowledge increased susceptibility<sup>(i)</sup> of PLWH</b>	<p><b>1. Observe food hygiene</b></p> <ul style="list-style-type: none"> <li>• Particularly important for travellers visiting friends and relatives (VFR)</li> <li>• Bacterial enterocolitis e.g. diarrhoeagenic <i>E. coli</i>, <i>Salmonella</i>, <i>Shigella</i>, <i>Campylobacter</i></li> <li>• Opportunistic intestinal parasitosis <i>Cryptosporidium</i>, <i>Cyclospora</i>, <i>Cystoisospora</i>, <i>Microsporidia</i></li> </ul> <p><b>2. Prevent insect bites</b></p> <ul style="list-style-type: none"> <li>• Repellents (DEET ≥ 30%), spray clothing with insecticide (permethrin)</li> <li>• Sleep under bednet</li> <li>• Malaria chemoprophylaxis/emergency standby treatment<sup>(ii)</sup></li> <li>• Yellow fever, see page 79</li> <li>• Leishmaniasis beware of sand flies (dogs)</li> </ul>

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

- i Higher intestinal susceptibility due to HIV-associated GALT destruction, low CD4 count. More severe malaria with CD4 count < 350 cells/μL
- ii According to malaria risk at travel destination and national guidelines adherence counselling is particularly important in persons visiting friends and relatives. See [Drug-drug Interactions between Antimalarial Drugs and ARVs](#)

# Drug-drug Interactions between Antimalarial Drugs and ARVs

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

## Colour legend

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

## Legend

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

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

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

## Interactions with ZDV

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

## Comments

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

## Further Information

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

# Vaccination

<ul style="list-style-type: none"> <li>• Vaccinate according to national guidelines for healthy population, preferably after having achieved suppressed viraemia and immune reconstitution (CD4 count &gt; 200 cells/μL)</li> <li>• Consider repeating vaccinations performed at CD4 count &lt; 200 cells/μL (&lt; 14%) or unsuppressed viraemia once adequate immune reconstitution is achieved (HIV-VL undetectable and CD4 count &gt; 200 cells/μL)</li> <li>• As vaccine responses may be significantly lower in PLWH (i.e. lower seroconversion rates, faster titer decline), do not use rapid schedules and consider antibody titers to assess their effectiveness if vaccinated at CD4 count &lt; 200 cells/μL or unsuppressed viraemia (e.g. rabies, tick-borne encephalitis, HAV, meningococci)</li> <li>• Avoid polysaccharide vaccination</li> <li>• For background data, see <a href="http://www.bhiva.org/vaccination-guidelines.aspx">http://www.bhiva.org/vaccination-guidelines.aspx</a></li> </ul>	<ul style="list-style-type: none"> <li>• For attenuated live vaccines<sup>(i)</sup> (in addition to restrictions for general population):             <ul style="list-style-type: none"> <li>• <b>*Varicella, measles, mumps, rubella, yellow fever</b> Contraindicated if CD4 count &lt; 200 cells/μL (14%) and/or AIDS. Impaired protection after vaccination with unsuppressed viraemia</li> <li>• <b>Oral live typhoid</b> Contraindicated if CD4 count &lt; 200 cells/μL (14%); give inactivated parenteral polysaccharide vaccine. Preferred if CD4 count &gt; 200 cells/μL (&gt; 14%)</li> </ul> </li> </ul>
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Infection	Vaccination rationale in PLWH	Comment
Influenza Virus	Higher rate of pneumonia. Explicitly recommended in all PLWH	Yearly
Human Papilloma Virus (HPV)	Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer	Vaccinate all PLWH with 3 doses between ages 9 and 40 (health insurance coverage differs by country according to age, sex, sexual orientation). Use 9-valent vaccine if available. Persons treated for high grade cervical dysplasia could benefit from a full course vaccination for secondary prevention
Hepatitis B Virus (HBV)	Shared risk with HIV of contracting infection. HIV accelerates liver disease progression	Vaccinate if seronegative. Repeat doses until anti-HBs antibodies ≥ 10 IU/L / ≥ 100 IU/L according to national guidelines. In order to reach ≥ 100 IU/L in non-responders repeat 3 doses if anti-HBs < 10 IU/L, 1 dose if anti-HBs < 100 IU <sup>(ii)</sup> ; consider double dose (40 μg) in particular with low CD4 count and high HIV-VL. See page 95
Hepatitis A Virus (HAV)	According to risk profile (travel, close contact with children, MSM, IVU, active hepatitis B or C infection, chronic liver disease)	Vaccinate if seronegative. Consider checking antibody titres in PLWH with high risk. Weaker immune response expected with HAV/HBV co-vaccine. See page 95
<i>Neisseria meningitidis</i>	According to risk profile (travel, close contact with children, MSM)	Use conjugated <sup>(iii)</sup> 4-valent vaccine (2 doses 1-2 months apart) if available. Booster every five years if exposure continues. Polysaccharide vaccine not recommended anymore
<i>Streptococcus pneumoniae</i>	Higher rate and severity of invasive disease. Vaccine explicitly recommended for all PLWH	One dose of conjugated <sup>(iii)</sup> 13-valent vaccine (CPV-13) for all PLWH, also if pre-vaccinated with PPV-23 polysaccharide vaccine. No general recommendation for any booster dose. Some national guidelines consider one dose of PPV-23 at least 2 months after CPV-13 for all PLWH
Varicella Zoster Virus (VZV)	Higher rate and severity of both chickenpox and zoster	Perform serology if exposure history negative. Vaccinate if seronegative. For contraindications, see*. To prevent shingles consider adjuvant sub-unit vaccine rather than live-attenuated vaccine according to national guidelines
Yellow Fever Virus	Mandatory for travel to selected countries (provide exemption letter if no true risk of exposure)	Contraindicated if past or current haematological neoplasia or thymus affection (thymoma, resection/radiation) For other contraindications, see*. Booster q 10 years
Rabies		For PLWH with CD4 count < 200 cells/μL or unsuppressed viraemia consider pre-exposure vaccination with 3 doses (0, 7, 28 days) and titer control 14 days later as well as post-exposure immunoglobulins for all non-vaccinated

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

# Sexual and Reproductive Health of Women and Men Living with HIV

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

Effective Measures to Reduce Sexual transmission of HIV	
Measure	Comment
<b>Male condom or female condom use</b>	<ul style="list-style-type: none"> <li>Effective in treated and untreated PLWH</li> </ul>
<b>Post-exposure prophylaxis (PEP)</b>	<ul style="list-style-type: none"> <li>Consider after situations of unprotected anal or vaginal intercourse, if one partner has detectable HIV-VL and the other partner is seronegative</li> <li>Start as soon as possible and within 48/72 hours post sexual exposure</li> <li>See <a href="#">Post-exposure prophylaxis (PEP)</a></li> </ul>
<b>Pre-exposure prophylaxis (PrEP)</b>	<ul style="list-style-type: none"> <li>Effective in HIV-negative persons with high risk sexual situations, see <a href="#">Pre-exposure prophylaxis (PrEP)</a></li> </ul>
<b>ART for HIV-positive partner</b>	<ul style="list-style-type: none"> <li>Considered effective from 6 months of fully suppressive ART if no active STIs</li> <li>Consider in e.g. sero-different couples<sup>(i)</sup></li> </ul>

Undetectable = untransmittable U=U [19], [20]. The evidence is now clear that people living with HIV with an undetectable VL do not transmit HIV sexually. Large studies of sexual HIV transmission among thousands of sero-different couples, one partner of which was living with HIV and the other was not, were undertaken in recent years. In those studies, there was not a single case of linked sexual transmission of HIV from a virally suppressed PLWH to their HIV-negative partner. However, a person can only know whether he or she is virally suppressed by taking a VL test

<sup>i</sup> see page 11

## Reproductive health

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

### Conception:

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

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

Start ART in partner living with HIV if naïve. Screening for STIs (and treatment, if required) of both partners is mandatory.

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

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

- Unprotected intercourse during times of maximum fertility (determined by ovulation monitoring), if the partner living with HIV has undetectable HIV-VL
- Vaginal syringe injection of seminal fluid during times of maximum fertility if the male partner is HIV-negative

Sperm washing, with or without intra-cytoplasmic sperm injection, is no longer necessary because of effectiveness of ART in avoiding HIV transmission at conception in male PLWH with undetectable HIV-VL

## Contraception

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

## Post-reproductive sexual health

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

## Sexual dysfunction

Guidelines for treatment of sexual dysfunction in the general population are available for men but not women. Refer to specialist where appropriate, see [Sexual Dysfunction](#) and [Treatment of Sexual Dysfunction in Men Living with HIV](#)

## STI screening and treatment

STI screening should be offered to all sexually active PLWH at the time of HIV diagnosis, annually thereafter or at any time STI symptoms are reported and during pregnancy. Diagnosis procedures should follow local or national guidelines. More comprehensive advice can be found at <http://www.iusti.org/regions/Europe/euroguidelines.htm>

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

	Therapy	Comment
<b>Chlamydia infection</b>	Consider doxycycline (100 mg bid po 7-10 days, contraindicated in pregnancy) for urethritis and cervicitis <sup>(i)</sup> For <i>Lymphogranuloma venereum (LGV)</i> doxycycline (100 mg po bid for 21 days) <b>Alternatives:</b> erythromycin (500 mg/6 h po <sup>(ii)</sup> ) or levofloxacin (500 mg/day) for 7 days (or 21 days in case of LGV)	<ul style="list-style-type: none"> <li>• May cause therapy-resistant proctitis in HIV-positive MSM</li> <li>• Consider co-infections with <i>Neisseria gonorrhoeae</i></li> </ul>
<b>Gonorrhoea</b>	Ceftriaxone (500 mg im as a single dose) <sup>(i)</sup>	<ul style="list-style-type: none"> <li>• Can cause proctitis, prostatitis and epididymitis</li> <li>• In women often asymptomatic</li> <li>• Fluoroquinolone resistance is highly prevalent in all regions</li> </ul>
<b>HBV infection HCV infection</b>	See detailed information on HIV/HCV or HIV/HBV co-infections, pages 96-97	<ul style="list-style-type: none"> <li>• Interruption of TDF, 3TC or FTC can lead to HBV reactivation</li> <li>• Clusters of acute HCV infection in HIV-positive MSM across Europe</li> </ul>
<b>HPV infection</b>	There are several treatment modalities for the management of genital warts with no evidence to suggest one approach is better than another approach. Consider operative removal by laser surgery, infrared coagulation, cryotherapy, etc. Management of both pre-invasive cervical lesions as well as peri- and intra-anal lesions should follow local or national guidelines	<ul style="list-style-type: none"> <li>• Infection is mostly asymptomatic; relapse of genital warts is frequent</li> <li>• Cervical PAP smear test recommended in all HIV-positive women</li> <li>• Anal HPV screening and cytology should be considered in all PLWH practicing anal sex</li> <li>• Consider high resolution anoscopy in case of suspicious cytological findings (rectal palpation or external inspection is not sufficient)</li> </ul>
<b>HSV infection</b>	<b>Primary infection:</b> aciclovir (400-800 mg po tid), famciclovir (250-500 mg tid) or valaciclovir (1000 mg po bid) for 7-10 days <b>Recurrent episodes:</b> aciclovir (400 mg po tid) or valaciclovir (500 mg po bid) for 5-10 days <b>Suppressive management:</b> Chronic suppressive therapy is usually offered to persons who experience six or more clinical episodes per year or who experience significant anxiety or distress related to their clinical recurrences. Chronic suppression: aciclovir (400 – 800 mg bid or tid) or famciclovir 500 mg bid or valaciclovir 500 mg po bid	<ul style="list-style-type: none"> <li>• Treatment of HSV2 alone does not prevent HIV-transmission and only modestly prevents HIV disease progression</li> </ul>
<b>Syphilis</b>	Penicillin is the gold standard for the treatment of syphilis in both pregnant and non-pregnant individuals. <b>Primary/secondary syphilis:</b> benzathine penicillin G (2.4 million IU im as single dose). In early syphilis adjunctive treatment with prednisolone (20–60 mg daily for 3 days) prevents optic neuritis, uveitis and Jarisch–Herxheimer reaction Alternative regimen include doxycycline 100 mg po bid for 14 days <b>Late latent syphilis and syphilis of unknown duration:</b> 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 <b>Neurosyphilis:</b> penicillin G (6 x 3 - 4 million IU iv for at least 2 weeks) There is no evidence to give a general recommendation on prednisolone use in this condition Alternative regimen: ceftriaxone (2 g iv daily for 10 to 14 days) if the person can be safely treated with other beta-lactam drugs. Doxycycline (200 mg orally twice daily) for 21 days is also an alternative approach, but should be reserved for exceptional circumstances. This regimen has very limited supporting data <sup>(i)</sup>	<ul style="list-style-type: none"> <li>• Expect atypical serology and clinical courses</li> <li>• Consider cerebrospinal fluid (CSF) testing in persons with neurological symptoms (evidence for intrathecally-produced specific antibodies, pleocytosis, etc.)</li> <li>• Successful therapy clears clinical symptoms and decreases VDRL test four-fold within 6-12 months</li> </ul>

<sup>i</sup> Refer to local guidelines

<sup>ii</sup> Rarely used

# Sexual Dysfunction

<b>When sexual complaints exist:</b>	What is the exact nature of the problem? In which phase(s) of the sexual response cycle does the problem occur?	<b>1. Desire</b> (lack of sexual desire or libido; desire discrepancy with partner; aversion to sexual activity) <b>2. Arousal</b> (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) <b>3. Orgasm</b> (difficulties experiencing orgasm) <b>4. Pain</b> (pain with sexual activity; difficulties with vaginal/anal penetration—anxiety, muscle tension; lack of sexual satisfaction and pleasure)	
	Self-assessment of sexual function (questionnaires):	<b>Men</b> International Index of Erectile Function, see <a href="http://files.sld.cu/urologia/files/2011/08/iief.pdf">http://files.sld.cu/urologia/files/2011/08/iief.pdf</a> <b>Women</b> Female Sexual Function Index (FSFI), see <a href="http://www.fsfiquestionnaire.com">http://www.fsfiquestionnaire.com</a>	
<b>Check for endocrine causes:</b>	Signs of hypogonadism	<b>Men</b> - Look for signs of testosterone insufficiency (main: decreased or absent nocturnal erections, decrease in testes size, decreased volume of ejaculate, hot flushes, sweats, reduction of body hair and beard; others: reduced sexual arousal and libido, decreased frequency of sexual thoughts and fantasies, decreased genital sensitivity, erectile dysfunction, loss of vitality; fatigue; loss of muscle mass and muscle strength) - If signs or symptoms of hypogonadism are present ask for hormonal assessment: luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone; sex hormone-binding globulin evaluation to calculate free testosterone, see <a href="http://www.issam.ch/freetesto.htm">http://www.issam.ch/freetesto.htm</a>	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
		<b>Women</b> - 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
<b>Check for other causes:</b>	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	<b>Men</b> - 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
		<b>Women</b> - Urogenital infections	Refer to gynaecologist
Relevant medicines, drugs, lifestyle factors	Drugs associated with sexual dysfunction: 1) Psychotropics – Men and Women (antidepressants, antiepileptics, antipsychotics, benzodiazepines), 2) Lipid-lowering drugs - Men (statins, fibrates), 3) Antihypertensives - Men (ACE-inhibitors, betablockers, alfablockers), 4) Others - Men and Women (omeprazole, spironolactone, metoclopramide, finasteride, cimetidine); 5) Men and Women - contribution from ART is controversial and benefit from switching studies is not proven		Consider therapy changes



## Treatment of Sexual Dysfunction in Men Living with HIV

Treatment of erectile dysfunction	Treatment of premature ejaculation
<p>Primarily oral PDE5-inhibitors (sildenafil, tadalafil, vardenafil).</p> <ul style="list-style-type: none"><li>• All at least 30 minutes before initiation of sexual activity</li><li>• Use lower dose if on PI/r</li></ul> <p>- sildenafil (25 mg every 48 hours) - tadalafil 5 mg initial dose with maximum dose 10 mg in 72 hours - vardenafil 2.5 mg maximum dose in 72 hours</p> <p><b>Cave:</b> Poppers have a synergistic effect with PD5-blockers which can lead to profound hypotension thus concurrent use is not recommended</p> <ul style="list-style-type: none"><li>• Tadalafil also licensed for use as an everyday ongoing therapy</li></ul>	<p>Consider behavioural interventions and/or psychosexual counselling, SSRIs, tricyclic antidepressants, clomipramine and topical anaesthetics</p> <ul style="list-style-type: none"><li>• Use lower dose of clomipramine and other tricyclic antidepressants if on PI/r</li><li>• Dapoxetine, a short-acting SSRI, is the only drug approved for on-demand treatment of premature ejaculation in Europe</li><li>• Treatment must be maintained as recurrence is highly likely following withdrawal of medicine</li></ul>

# Depression: Screening and Diagnosis

## Significance

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

## Screening and diagnosis of depression

Who?	How to screen?	How to diagnose?
<p><b>Screening of all PLWH recommended in view of the high prevalence of depression</b></p> <p><b>Populations at particularly high risk</b></p> <ul style="list-style-type: none"> <li>• Positive history of depression in family</li> <li>• Depressive episode in personal history</li> <li>• Older age</li> <li>• Adolescence</li> <li>• Persons with history of drug addiction, psychiatric, neurologic or severe somatic co-morbidity</li> <li>• Use of EFV</li> <li>• Use of neurotropic and recreational drugs</li> <li>• As part of investigation of neurocognitive impairment, see page 88</li> </ul>	<ul style="list-style-type: none"> <li>• Screen every 1–2 years</li> <li>• Two main questions:               <ol style="list-style-type: none"> <li>1. Have you often felt depressed, sad or without hope in the last few months?</li> <li>2. Have you lost interest in activities that you usually enjoy?</li> </ol> </li> <li>• Specific symptoms in men:               <ul style="list-style-type: none"> <li>– Stressed, burn out, angry outbursts, coping through work or alcohol</li> </ul> </li> <li>• Rule out organic cause (such as hypothyroidism, hypogonadism, Addison's disease, non-HIV drugs, vitamin B12 deficiency)</li> </ul>	<p><b>Symptoms – evaluate regularly</b></p> <p><b>A.</b> At least 2 weeks of depressed mood OR</p> <p><b>B.</b> Loss of interest OR</p> <p><b>C.</b> Diminished sense of pleasure</p> <p><b>PLUS 4 out of 7 of the following:</b></p> <ol style="list-style-type: none"> <li>1. Weight change of <math>\geq 5\%</math> in one month or a persistent change of appetite</li> <li>2. Insomnia or hypersomnia on most days</li> <li>3. Changes in speed of thought and movement</li> <li>4. Fatigue</li> <li>5. Feelings of guilt and worthlessness</li> <li>6. Diminished concentration and decisiveness</li> <li>7. Suicidal ideation or a suicide attempt<sup>(i)</sup></li> </ol>

<sup>i</sup> EFV has been associated with a higher risk of suicidal ideation

## Depression: Management

Degree of depression	Number of symptoms (see page 84: A, B or C + 4/7)	Treatment	Consultation with expert
No	< 4	No	
Mild	4	<ul style="list-style-type: none"> <li>• Problem-focused consultation</li> <li>• Consider antidepressant treatment<sup>(i)</sup></li> <li>• Recommend physical activity</li> </ul>	<ul style="list-style-type: none"> <li>• Always if treating doctor is unfamiliar with use of antidepressants</li> <li>• If depression not responding to treatment</li> <li>• If person has suicidal ideation</li> <li>• In case of complex situations such as drug addiction, anxiety disorders, personality disorders, dementia, acute severe life events</li> </ul>
Intermediate	5-6	Start antidepressant treatment <sup>(i)</sup>	
Severe	> 6	Refer to expert (essential)	

<sup>i</sup> See [Drug-drug Interactions between Antidepressants and ARVs](#)

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

## Classification, Doses, Safety and Adverse Effects of Antidepressants

Mechanisms & classification	Start dose	Standard dose	Lethality in overdose	Insomnia and agitation <sup>(ii)</sup>	Sedation	Nausea or GI effects	Sexual dysfunction	Weight gain
	mg/day							
<b>Selective serotonin-reuptake inhibitors (SSRIs)<sup>(i)</sup></b>								
paroxetine	10-20	20-40	Low	+	- / +	+	++	++
sertraline	25-50	50-150	Low	+	- / +	+	+	+
citalopram	10-20	20-40	Low	+	- / +	+	+	+
escitalopram	5-10	10-20	Low	+	- / +	+	+	+
<b>Mixed or dual-action reuptake inhibitors</b>								
venlafaxine	37.5-75	75-225	Moderate	++	- / +	+	+	- / +
<b>Mixed-action newer agents</b>								
mirtazapine	30	30-60	Low	- / +	++	- / +	- / +	++

- none  
 + moderate  
 ++ severe

- i For many PLWH, SSRI induction may be associated with adverse effects (GI tract, dizziness, anxiety, panic attacks). Commencing at lower doses (i.e. 10, 25 & 10 mg for paroxetine, sertraline and citalopram, respectively) and increasing to the above starting doses after 4 to 7 days if tolerated may reduce such effects
- ii Insomnia is associated with DTG and other INSTI containing ART regimens and with the use of some antidepressants. Clinicians should be aware when prescribing DTG and INSTI and antidepressants together

# Drug-drug Interactions between Antidepressants and ARVs

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

## Colour legend

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

## Legend

- ↑ Potential elevated exposure of the antidepressant
- ↓ Potential decreased exposure of the antidepressant
- ↔ No significant effect
- D Potential decreased exposure of ARV drug
- E Potential elevated exposure of ARV drug
- ATV/c ATV co-formulated with COBI (300/150 mg qd)
- DRV/c DRV co-formulated with COBI (800/150 mg qd)

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and antidepressants

## Comments

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

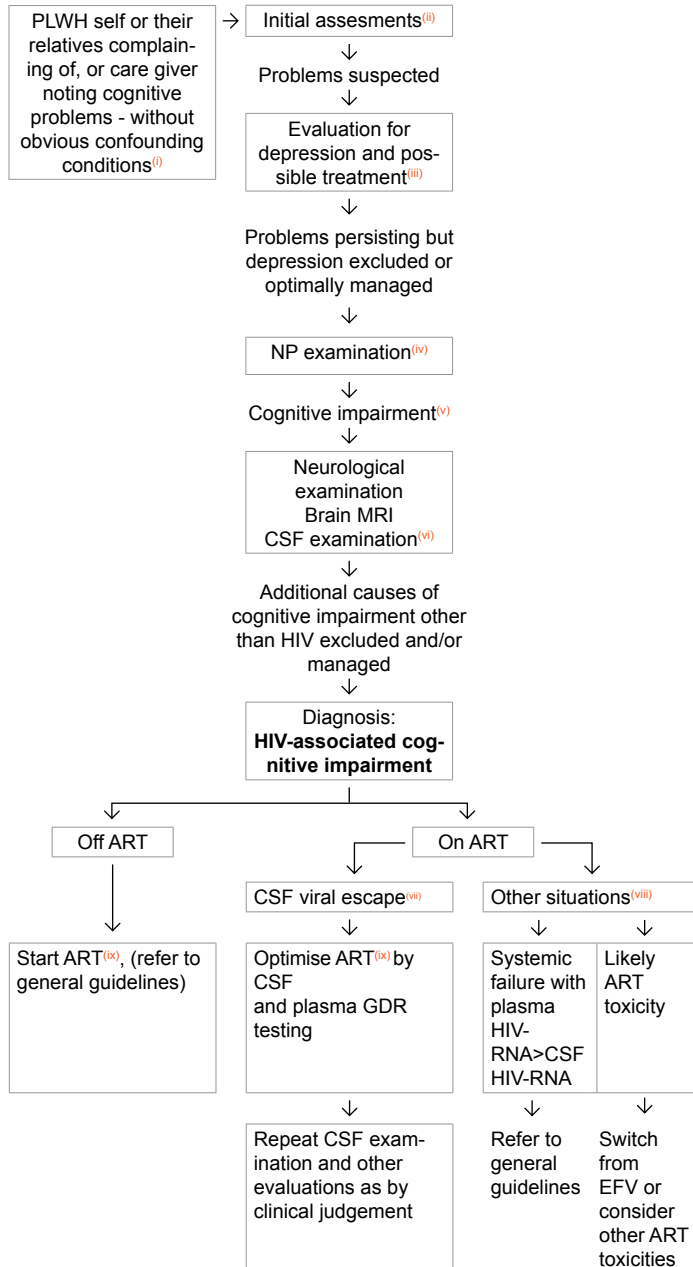
## Further Information

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

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

## Abbreviations

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



### i Obvious confounding conditions:

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

### ii The following questions may be used to guide doctor assessment

1. Do you experience frequent memory loss (e.g. do you forget the occurrence of special events even the more recent ones, appointments, etc.)?
2. Do you feel that you are slower when reasoning, planning activities, or solving problems?
3. Do you have major difficulties paying attention (e.g. to a conversation, book or film)?

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

### iii See [Depression: Screening and Diagnosis](#)

**iv NP examination** should include tests exploring the following cognitive domains: fluency, executive functions, speed of information processing, attention/working memory, verbal and visual learning, verbal and visual memory, motor skills plus assessment of daily functioning

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

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

### vii CSF escape definition:

Either CSF HIV-RNA above LOQ and plasma HIV-RNA below LOQ; or HIV-RNA above LOQ in both CSF and plasma, with CSF HIV-RNA greater than plasma HIV-RNA.

In CSF escape:

- Avoid dual ART therapies
- Avoid ATV (boosted or unboosted) due to association with CSF escape in retrospective cohorts
- Avoid RAL 1200 mg qd and COBI as boosting due to lack of evidence in CSF escape

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

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

See online video lectures [CNS and HIV-Part 1](#) and [CNS and HIV-Part 2](#) from the EACS online course Clinical Management of HIV

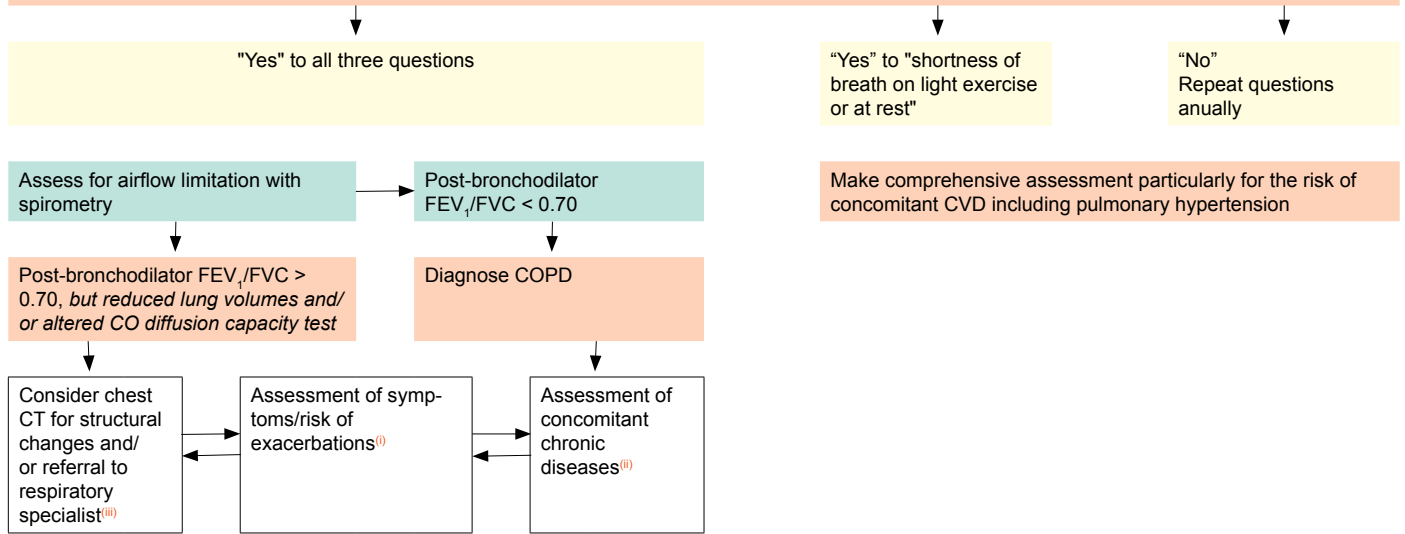
# Chronic Lung Disease in PLWH

## Screen for chronic lung disease:

1. Are you 40 years or older?
2. Have you smoked more than 10 pack years in your entire lifetime?

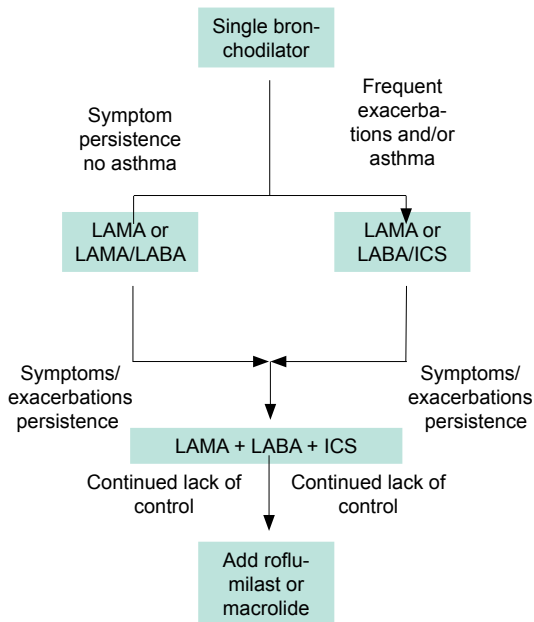
## Then check for respiratory symptoms:

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



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

## Treatment of COPD<sup>(iv)</sup>



- LABA:** long-acting  $\beta$ 2-agonist  
**LAMA:** long-acting muscarinic antagonist  
**ICS:** inhaled corticosteroid

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

## There are 3 life saving interventions:

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

i Assessment of either dyspnoea using mMRC, see <https://www.verywell.com/guidelines-for-the-mmrc-dyspnea-scale-914740> or symptoms using CAT™, see <http://www.catestonline.org/> and history of exacerbations (including prior hospitalisations)

ii COPD itself has significant extra-pulmonary (systemic) effects including weight loss, nutritional abnormalities and skeletal muscle dysfunction

iii Based on expert opinion

iv Each pharmacological treatment should be individualised and guided by the severity of symptoms, risk of exacerbations, adverse effects, co-morbidities, drug availability and cost, and the individual's response, preference and ability to use various drug delivery devices. Inhaler technique needs to be assessed regularly. Long-term use of oral glucocorticoids has no evidence of benefits in COPD and increase the risk of pneumonia. The addition of ICS to LAMA or LABA/LAMA is recommended in individuals with history of frequent exacerbations and/or asthma and/or eosinophilia (> 3%), or anyway in individuals not adequately controlled by LAMA/LABA combination. ICS should be avoided in subjects with eosinopenia (< 1%)

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

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

Bronchodilators		ATV/c	ATV/r	DRV/c	DRV/r	LPV/r	DOR	EFV	ETV	NVP	RPV	MVC	BIC	DTG	EVG/c	RAL	ABC	FTC	3TC	TAF	TDF
LAMA	acclidinium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	glycopyrronium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	tiotropium bromide	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	umeclidinium bromide	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SAMA	ipratropium	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
LABA	formoterol	↔ <sup>a</sup>	↔ <sup>a</sup>	↔	↔	↔ <sup>a</sup>	↔	↔	↔	↔	↔ <sup>a</sup>	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	indacaterol	↑ <sup>b</sup>	↑ <sup>b</sup>	↑ <sup>b</sup>	↑ <sup>b</sup>	↑ <sup>b</sup>	↔	↓	↓	↓	↔	↔	↔	↔	↑ <sup>b</sup>	↔	↔	↔	↔	↔	↔
	olodaterol	↑	↑	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
	salmeterol	↑ <sup>c</sup>	↑ <sup>c</sup>	↑ <sup>c</sup>	↑ <sup>c</sup>	↑ <sup>c</sup>	↔	↓	↓	↓	↔ <sup>a</sup>	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	vilanterol	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
SABA	salbutamol (albuterol)	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
MX	aminophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	theophylline	↔	↓	↔	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
PD4	roflumilast	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↑	↔	↔	↔	↔	↔	↔
ICS	beclomethasone	↑ <sup>d</sup>	↑ <sup>d</sup>	↑ <sup>d</sup>	↓11%	↑ <sup>d</sup>	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	budesonide	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
	fluticasone	↑	↑	↑	↑	↑	↔	↓	↓	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

## Colour legend

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

## Legend

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

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

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and bronchodilators

## Comments

- a** Caution as both drugs can induce QT interval prolongation
- b** Exposure can be increased up to 2-fold however this increase does not raise any concerns based on indacaterol's safety data
- c** ECG monitoring is recommended
- d** Increase in concentration of active metabolite observed with RTV 100 mg bid alone but without significant effect on adrenal function. Caution is still warranted, use the lowest possible corticosteroid dose and monitor for corticosteroid side effects

## Further Information

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



# Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

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

## Colour legend

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

## Legend

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

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and pulmonary antihypertensives

## Comments

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

## Further Information

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

## Frailty in the Context of Ageing

Frailty defines age-related exhaustion of homeostatic reserves. An individual with frailty is exposed to enhanced vulnerability to stressors, and associated risk of negative health-related outcomes. This geriatric syndrome, comprising biological, psychological and social issues is more prevalent than expected in PLWH compared to HIV-negative matched controls [21]. The most common instruments to measure frailty include the Frailty Phenotype [22] and Frailty Index [23]

Feature	Frailty Phenotype	Frailty Index
<b>Clinical definition</b>	Based on presence of signs, symptoms (pre-disability syndrome)	Based on presence of diseases, disabilities (accumulation of deficits)
<b>How to assess</b>	Assessed by five specific features [22]: 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 [23]  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
<b>How to interpret</b>	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
<b>How to address frailty [24]</b>	Promote Comprehensive Geriatric Assessment (CGA), aimed at personalising interventions according to benefits/priorities for a given person through a multidisciplinary diagnostic and treatment process, that identifies medical, psychosocial, and functional limitations aimed at maximising overall health with ageing and the improvement of quality of life	
<b>Recommendations [25], [26]</b>	In PLWH who are frail: 1. Sustain and recover physical function impairment and sarcopenia prescribing physical activity with a resistance training component 2. Address polypharmacy by reducing or deprescribing any inappropriate/superfluous medications, see <a href="#">Prescribing in Elderly PLWH</a> 3. Screen for, and address modifiable causes of fatigue 4. For PLWH exhibiting unintentional weight loss, screen for reversible causes and consider food fortification and protein/caloric supplementation 5. Prescribe vitamin D for individuals deficient in vitamin D, see page 62	

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

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

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

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

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

# Solid Organ Transplantation (SOT) in PLWH

## General features

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

## Organ criteria for SOT

- PLWH should be considered for organ transplantation using the same indications as used in HIV-negative persons. PLWH with HCC can be evaluated for liver transplantation if they fulfill the Milan criteria<sup>(i)</sup>
- Organ donation
- PLWH can receive organs from living (renal) and deceased (all types of SOT) HIV-negative donors
  - In some European countries the use of organs from HIV-positive donors is allowed but the efficacy and safety of this approach is currently being evaluated in the context of research studies

## HIV-infection criteria for SOT

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

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

## Preparing PLWH for transplantation

### Antiretroviral therapy

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

### Viral hepatitis co-infection

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

### Prevention of infections

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

## Follow-up after transplantation

### Antiretroviral therapy

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

### Primary and secondary disease-specific chemoprophylaxis

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

### Viral hepatitis co-infection

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

### Immunosuppressive regimens

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

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

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

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

## Colour legend

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

## Legend

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

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

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

\* available as prolonged release formulation

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

- AM** antimetabolite
- CNI** calcineurin inhibitors
- CS** corticosteroids
- mTOR** mTOR inhibitors

## Interactions with ZDV

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

## Comments

- a** TDM of immunosuppressant is recommended
- b** Monitor renal function

## Further Information

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

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

Every person with HCV/HIV co-infection should receive DAA therapy to eradicate HCV, regardless of liver fibrosis stage in the context of faster liver fibrosis progression in co-infected persons and the availability of DAAs with excellent tolerability and efficacy. DAAs achieve similar cure rates and tolerability in HCV/HIV co-infected compared to HCV mono-infected persons. Therefore, treatment indication and regimens are the same as in HCV mono-infected persons. All persons with HBV/HIV co-infection should receive ART including TDF or TAF, unless history of tenofovir intolerance. All HBsAg-positive persons should be screened for Hepatitis Delta (HDV)

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

### Screening at baseline

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

### Screening for complications

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

### End Stage Liver Disease (ESLD)

8. PLWH with liver cirrhosis require the same measures for the treatment of oesophageal varices, hepatorenal syndrome, hepatic encephalopathy or ascites as HIV-negative persons, see page 70-71 and [Diagnosis and Management of Hepatorenal Syndrome \(HRS\)](#)
9. Persons with viral hepatitis/HIV co-infection suffering from ESLD warrant particular attention in the management of liver insufficiency, see [Dose Adjustment of ARVs for Impaired Hepatic Function](#). ART in cirrhotic PLWH improves overall survival
10. PLWH with HCC or a MELD-score > 15<sup>(4)</sup>, CD4 count > 100 cells/ $\mu$ L and options for efficacious and durable ART should be evaluated for liver transplantation (OLT), see [Solid Organ Transplantation \(SOT\) in PLWH](#)
11. Renal complications are frequent, see page 64 and [Diagnosis and Management of Hepatorenal Syndrome \(HRS\)](#)

### Vaccination, see page 79

12. PLWH lacking anti-HAV IgG antibodies or anti-HBs antibodies should be offered vaccination for the respective virus to prevent infection regardless of their CD4 count. The response to the HBV vaccine is influenced by the CD4 count and level of HIV-VL. In PLWH with low CD4 count (< 200 cells/ $\mu$ L) and ongoing HIV replication, ART should be initiated first, prior to respective vaccination. Because of the lack of data on the impact of immunisation in isolated anti-HBc IgG positive persons (HBsAg negative, anti-HBc positive and anti-HBs negative profile), vaccination is not recommended in this population. However, if anti-HBc results are not available, HBV vaccination is recommended in all HBs-Ag negative persons
13. In PLWH vaccinated for HBV with insufficient response (anti-HBs < 10 IU/L), re-vaccination should be considered. Double-dose (40  $\mu$ g) at 3-4 time points (months 0, 1, 6 and 12) may help to improve response rates to the HBV vaccine. Persons who fail to seroconvert after HBV vaccination and remain at risk for HBV should have annual serological tests for evidence of HBV infection. TDF based cART has been associated with prevention of HBV infection in these persons and ART including TDF or TAF is recommended

### Prevention/Support

14. Psychiatric, psychological, social and medical support should be made available to persons with alcohol intake to stop drinking
15. Substitution therapy (opioid replacement therapy) in persons with active drug use as a step towards cessation of active drug use should be encouraged. Help provided (e.g. through needle and syringe exchange programs) reduces the risk of re-infection including parenteral viral transmission (harm reduction strategy), see [Drug Dependency and Drug Addiction](#)
16. Since HBV and HIV, and occasionally HCV, are transmitted sexually, adequate counselling including the use of condoms is advisable. Information on the risk of HCV transmission due to mucosal traumatic sexual practices associated with a high likelihood of blood contact or ongoing IDU, "chemsex" (sex under the influence of recreational drugs taken predominantly intravenously immediately before and/or during sexual contacts), should be provided and risk reduction should be discussed
17. In women of childbearing age, HCV treatment should be initiated prior to conception because of limited safety data in pregnancy, and to reduce the risk of MTCT of HCV
  - i Screening intervals to detect recently acquired HCV infection should be adapted to individual risk assessments and local epidemiology as described in the European AIDS Treatment Network (NEAT) consensus conference statement, [www.neat-id.org](http://www.neat-id.org)
  - ii Anti HCV-Antibodies: turn positive 1-6 months after infection; late seroconversions have been described; may rarely be lost due to immunosuppression
  - iii There is no standard conversion formula for converting the amount of HCV-RNA reported in copies/mL to the amount reported in IU/mL. The conversion factor ranges from about one to five HCV-RNA copies per IU/mL
  - iv Risk for percutaneous HCV transmission by sharing equipment for injection drug use; risk for mucosal HCV transmission including fisting, receptive condomless anal intercourse, sharing equipment during nasally administered drug use, sharing sex toys, sharing anal douching equipment, and engaging in sexual intercourse causing rectal trauma with bleeding; the presence of ulcerative sexually transmitted infections (STIs) increases the risk of HCV transmission
  - v Serum fibrosis markers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices. The combination of blood biomarkers, of liver stiffness measurement and blood tests or repeated assessments may improve accuracy (<https://easl.eu/publication/easl-recommendations-treatment-of-hepatitis-c/>) and page 102. For HCC, see [General Recommendation for Persons with Viral Hepatitis/HIV Co-infection, Cancer: Screening Methods and Liver Cirrhosis: Management](#)
  - vi MELD calculation, see page 71

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

## Treatment indication

1. All PLWH with HBV/HIV co-infection should receive ART that includes TDF or TAF unless history of tenofovir intolerance
2. Stopping anti-HBV active ART should be avoided in persons with HIV/HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis

## Treatment selection

3. If TDF or TAF is strictly contraindicated, entecavir may be prescribed in PLWH with no prior 3TC exposure and together with fully active ART
4. PLWH with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes (for management of cirrhotic PLWH, see pages 70-74). Please note that diagnosis of cirrhosis may be difficult in persons already on HBV treatment
5. Caution is warranted to switch from a TDF/TAF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pre-treated cirrhotic PLWH as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir
6. Prior to ART simplification with a regimen without TDF/TAF, HBV status should be re-checked
7. For HBV/HIV co-infected persons with BMD changes or CKD, see recommendations for [Dose Adjustment of ARVs for Impaired Renal Function](#) and pages 61-66

## Treatment goal

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

## Treatment monitoring

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

## HBV reactivation

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



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

## Treatment indication

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

## Treatment selection

3. IFN- and preferably also RBV-free DAA combinations are now standard of care for chronic HCV see Tables [HCV Treatment Options in HCV/HIV Co-infected Persons](#). IFN-containing HCV regimens are no longer recommended. For diagnostics and management of IFN-containing HCV regimens please refer to previous versions of these Guidelines, available online at [http://www.eacsociety.org/files/guidelines\\_8.2-english.pdf](http://www.eacsociety.org/files/guidelines_8.2-english.pdf)
4. Selection of DAA combinations is based upon HCV GT<sup>1</sup>, stage of liver fibrosis, pre-treatment history and resistance-associated substitutions (RAS) if tested
5. Use of older, first generation HCV PIs (boceprevir and telaprevir) are no longer recommended because of increased toxicities
6. Due to drug-drug interactions in particular with HIV and HCV PIs, careful checking for interactions is urgently recommended prior to starting HCV therapy, see [Drug-drug Interactions between DAAs and ARVs](#) or <http://www.hep-druginteractions.org>
7. Resistance testing, if available, should be performed before re-treatment of persons who failed after a PI-and/or NS5A inhibitor-containing agent. The triple combination of SOF/VEL/VOX for 12 weeks is the treatment of choice for re-treatment, especially if resistance testing is not available. In persons with complex mutations patterns SOF+GLE/PIB + RBV for 12-16 weeks can also be considered. In case of unavailability of SOF/VEL/VOX or SOF + GLE/PIB other regimens with at least two active DAAs could be combined with the preferential use of one drug with high genetic barrier to resistance and with extended treatment durations and potentially addition of RBV. In patients with decompensated cirrhosis SOF/VEL + RBV for 24 weeks is the only available option for re-treatment in case of contraindication to liver transplantation

## Treatment goal

8. The primary aim of HCV treatment is SVR<sub>12</sub> 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<sub>12</sub> corresponds to a definitive cure of HCV infection in the vast majority of cases
- i If the PLWH is a candidate for pangenotypic drugs, HCV GT determination is not mandatory before starting anti-HCV treatment. Re-testing for GT and sub-type should be performed in persons with tests carried out before second-generation tests were available (second-generation line-probe assay or real-time PCR assay) or in persons at risk of 'super-infection' for whom the GT/sub-type should be performed on most recent available specimen

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

## Treatment monitoring

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

## Post-Treatment monitoring

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

## Treatment of recently acquired HCV infection

16. IFN-containing HCV regimens are no longer recommended. For diagnostics and management of IFN-containing HCV regimens please see online EACS Guidelines v8.2 at [http://www.eacsociety.org/files/guidelines\\_8.2-english.pdf](http://www.eacsociety.org/files/guidelines_8.2-english.pdf)
17. After diagnosis of recently acquired HCV infection, HCV-RNA should be re-measured 4 weeks later. Treatment recommended in PLWH without a decrease of 2\*log of HCV-RNA at 4 weeks compared with initial HCV-RNA, due to the very low probability of spontaneous clearance, and in persons with persistent serum HCV-RNA 12 weeks after diagnosis of recently acquired HCV, see [Algorithm for Management of Recently acquired HCV in Persons with HIV Co-infection](#). HCV treatment immediately after diagnosis is recommended in PLWH with ongoing risk behavior to reduce onward transmission. IFN-free treatment with DAAs is recommended as in naïve non-cirrhotic (except for those with pre-existing cirrhosis), see pages 98-99
18. For more detailed information on the management of recently acquired HCV infection we refer to the European AIDS Treatment Network (NEAT) consensus conference guideline, [www.neat-id.org](http://www.neat-id.org)

## HCV Treatment Options in HCV/HIV Co-infected Persons

Preferred DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors)				
HCV GT	Treatment regimen	Treatment duration & RBV usage		
		Non-cirrhotic	Compensated cirrhotic	Decompensated cirrhotics CTP class B/C
1 & 4	EBR/GZR	12 weeks <sup>(i)</sup>		Not recommended
	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV
	SOF/LDV +/- RBV	8-12 weeks without RBV <sup>(ii)</sup>	12 weeks with RBV <sup>(iii)</sup>	
2	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/VEL	12 weeks		12 weeks with RBV
3	GLE/PIB	8 weeks <sup>(iv)</sup>	12 weeks <sup>(iv)</sup>	Not recommended
	SOF/VEL +/- RBV	12 weeks <sup>(v)</sup>	12 weeks with RBV <sup>(vi)</sup> or 24 weeks without RBV	
	SOF/VEL/VOX	-	12 weeks	Not recommended
5 & 6	GLE/PIB	8 weeks	12 weeks	Not recommended
	SOF/LDV +/- RBV	12 weeks +/- RBV <sup>(vii)</sup>	12 weeks with RBV <sup>(iii)</sup>	
	SOF/VEL	12 weeks		12 weeks with RBV

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

- i** Extension of treatment to 16 weeks and addition of RBV in PLWH with GT1a with baseline HCV-RNA > 800.000 IU/mL and/or NS5A RASs causing at least 5-fold reduction in activity of EBR to minimise the risk of treatment failure and in HCV GT4 experienced PLWH with HCV-RNA > 800.000 IU/mL. 8 weeks can be considered in GT 1b treatment-naïve with F0-F2
- ii** 8 weeks treatment without RBV only in treatment-naïve PLWH with F < 3 and baseline HCV-RNA < 6 million IU/mL
- iii** In persons intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS
- iv** Treatment duration in HCV GT3 who failed previous treatment with IFN and RBV +/- SOF or SOF and RBV should be 16 weeks
- v** Addition of RBV in treatment experienced PLWH with baseline NS5A RASs, if RAS testing available; if these persons are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV
- vi** If RAS testing is available and demonstrates absence of NS5A RAS Y93H, RBV can be omitted in treatment naïve PLWH with compensated cirrhosis
- vii** In treatment experienced (exposure to IFN/RBV/SOF) PLWH RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV



DAA HCV treatment options (except for persons pre-treated with Protease or NS5A inhibitors) to be used if preferred option is not available

HCV GT	Treatment regimen	Treatment duration & RBV usage		
		Non-cirrhotic	Compensated cirrhotic	Decompensated cirrhotics CTP class B/C
1 & 4	OBV/PTV/r + DSV	8 <sup>(i)</sup> -12 weeks in GT 1b	12 weeks in GT 1b	Not recommended
	OBV/PTV/r + DSV + RBV	12 weeks in GT 1a	24 weeks in GT 1a	Not recommended
	OBV/PTV/r + RBV	12 weeks in GT 4		Not recommended
	SOF + DCV +/- RBV	12 weeks +/- RBV <sup>(ii)</sup>	12 weeks with RBV <sup>(iii)</sup>	
	SOF/VEL/VOX	8 weeks <sup>(iv)</sup>	12 weeks	Not recommended
2	SOF + DCV	12 weeks		12 weeks with RBV
	SOF/VEL/VOX	8 weeks <sup>(iv)</sup>	12 weeks	Not recommended
3	SOF + DCV +/- RBV	12 weeks +/- RBV <sup>(v)</sup> or 24 weeks without RBV	24 weeks with RBV	
	SOF/VEL/VOX	8 weeks <sup>(iv)</sup>	12 weeks	Not recommended
5 & 6	SOF + DCV +/- RBV	12 weeks +/- RBV or 24 weeks without RBV <sup>(vi)</sup>	12 weeks with RBV <sup>(iii)</sup>	
	SOF/VEL/VOX	8 weeks <sup>(iv)</sup>	12 weeks	Not recommended

DCV = daclatasvir

DSV = dasabuvir

OBV = ombitasvir

PTV/r = paritaprevir/RTV

RBV = ribavirin

SOF = sofosbuvir

VEL = velpatasvir

VOX = voxilaprevir

RAS = resistance associated substitutions

i 8 weeks treatment without RBV only in PLWH without cirrhosis

ii Addition of RBV in GT1a treatment experienced PLWH, but not in PLWH without NS5A RASs, if RASs testing is available

iii In PLWH intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced PLWH with compensated cirrhosis without baseline NS5A RAS

iv Extension of treatment to 12 weeks in DAA treatment experienced PLWH

v Addition of RBV only in treatment experienced persons with baseline NS5A RASs, if RAS testing available; if these PLWH are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV

vi In treatment experienced (exposure to IFN/RBV/SOF) PLWH RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV

# Drug-drug Interactions between DAAs and ARVs

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

## Colour legend

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

## Legend

- ↑ Potential elevated exposure of DAA
- ↓ Potential decreased exposure of DAA
- ↔ No significant effect
- D Potential decreased exposure of ARV drug
- E Potential elevated exposure of ARV drug

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

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

## Interactions with ZDV

No clinically relevant interactions expected with ZDV and DAAs

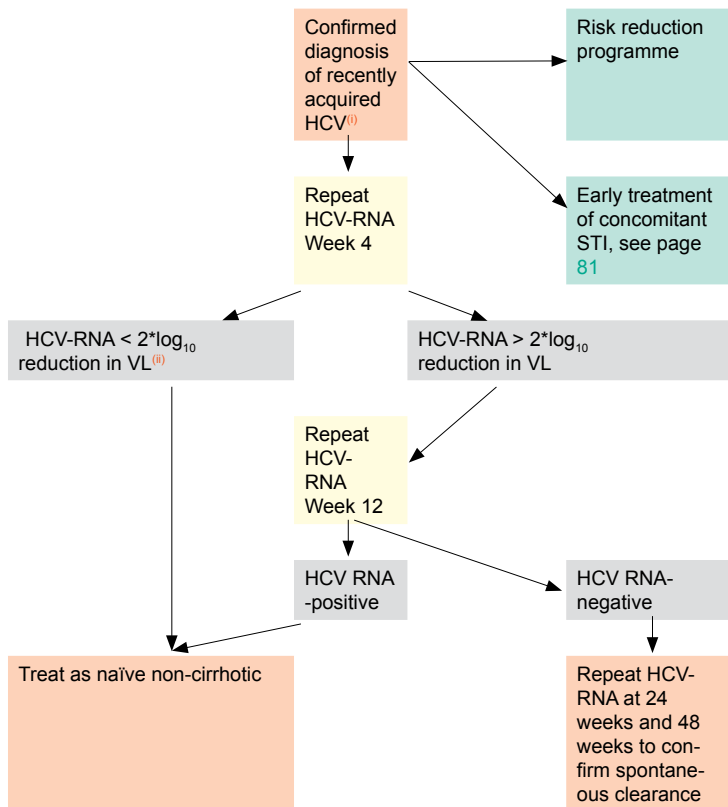
## Comments

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

## Further Information

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

# Algorithm for Management of Recently Acquired HCV Infection in PLWH



- i Where available initiate DAA-based treatment immediately in persons with risk of onward transmission
- ii HCV-RNA < 2\*log<sub>10</sub> reduction at week 4 is considered as chronic HCV infection

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

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

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

These cut-offs were derived from different studies and the optimal values might vary between populations and must be interpreted together with the individual clinical assessment

\*The distinction between F3 and F4 is often imprecise and must be interpreted in the individual clinical context

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

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

# Hepatitis D and E in PLWH

## Hepatitis Delta Virus (HDV)

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

## Hepatitis E Virus (HEV)

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

## Part VI Opportunistic Infections

This section provides:

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

For more detailed discussion, we refer to national guidelines

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

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

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

### Immune Reconstitution Inflammatory Syndrome (IRIS)

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

## Primary Prophylaxis of OIs According to Stage of Immunodeficiency

CD4 count threshold/indication			
<b>CD4 count &lt; 200 cells/μL, CD4 percentage &lt; 14%, recurrent oral thrush, or relevant concomitant immunosuppression*</b>			
<b>Prophylaxis against <i>Pneumocystis jirovecii</i> Pneumonia (PcP) &amp; <i>Toxoplasma gondii</i> infection</b>			
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	<b>trimethoprim-sulfamethoxazole (TMP-SMX)</b>	800/160 mg x 3/week po or 400/80 mg qd po or 800/160 mg qd po	
Negative serology for toxoplasmosis	<b>pentamidine</b>	300 mg in 6 mL sterile water x 1 inhalation/month	Does not prevent the rare extrapulmonary manifestations of <i>P. jirovecii</i>
Negative serology for toxoplasmosis	<b>dapsone</b>	100 mg qd po	Check for G6PD-deficiency
Negative serology for toxoplasmosis	<b>atovaquone suspension</b>	1500 mg qd (with food)	
Positive serology for toxoplasmosis	<b>dapsone</b> <b>+ pyrimethamine</b> <b>+ folinic acid</b>	200/mg week po 75/mg week po 25-30/mg week po	Check for G6PD-deficiency
Positive serology for toxoplasmosis	<b>atovaquone suspension</b> <b>+/- pyrimethamine</b> <b>+ folinic acid</b>	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	
CD4 count < 50 cells/μL			
<b>Prophylaxis against Non-Tuberculous Mycobacteria (NTM) (<i>M. avium</i> complex, <i>M. genavense</i>, <i>M. kansasii</i>)</b>			
Prophylaxis is not recommended if ART is started			
Prophylaxis may be considered for persons with CD4 counts < 50 cells/μL who remain viraemic on ART (drug resistant HIV with no option to achieve virologic control); exclude disseminated MAC disease before starting			
Regimens listed are alternatives	<b>azithromycin</b>	1200-1250 mg/week po	Check for interactions with ARVs, see <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a>
	or <b>clarithromycin</b>	500 mg bid po	
	or <b>rifabutin</b>	300 mg qd po	Check for interactions with ARVs, see <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a>

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

## *Pneumocystis jirovecii* Pneumonia (PcP)

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



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

## Toxoplasma gondii Encephalitis

Primary prophylaxis			
<b>Start:</b> if CD4 count < 200 cells/ $\mu$ L, or CD4 percentage < 14%, oral thrush, or relevant concomitant immunosuppression (see above)			
<b>Stop:</b> if CD4 count > 100 cells/ $\mu$ L and HIV-VL undetectable over 3 months			
	Drug	Dose	Comments
Preferred prophylaxis	<b>TMP-SMX</b>	800/160 mg x 3/week po or 400/80 mg qd po or 800/160 mg qd po	All regimens are also effective against PcP
Alternative prophylaxis	<b>atovaquone suspension</b>	1500 mg qd po (with food)	
	<b>dapsone</b> <b>+ pyrimethamine</b> <b>+ folinic acid</b>	200 mg/week po 75 mg/week po 25-30 mg/week po	Check for G6PD-deficiency
	<b>atovaquone suspension</b> <b>+ pyrimethamine</b> <b>+ folinic acid</b>	1500 mg qd po (with food) 75 mg/week po 25-30 mg/week po	
Treatment			
<b>Treat 6 weeks, then secondary prophylaxis until CD4 count &gt; 200 cells/<math>\mu</math>L and HIV-VL undetectable over 6 months</b>			
<b>Diagnosis:</b>			
<b>Definitive diagnosis:</b> clinical symptoms, typical neuroradiology AND cytological / histological detection of organism in tissue			
<b>Presumptive diagnosis:</b> clinical symptoms, typical neuroradiology AND response to empirical treatment. It is the standard in most clinical settings			
	Drug	Dose	Comments
Preferred therapy	<b>pyrimethamine</b>	Day 1: 200 mg qd po, <b>then</b> • If $\geq$ 60 kg: 75 mg qd po • If < 60 kg: 50 mg qd po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia
	<b>+ sulfadiazine</b>	• If $\geq$ 60 kg: 3000 mg bid po/iv • If < 60 kg: 2000 mg bid po/iv	Sulfadiazine is associated with crystalluria and may lead to renal failure and urolithiasis. Good hydration is essential. Check renal function and urine sediment for microhematuria and crystalluria
	<b>+ folinic acid</b>	10-15 mg qd po	
Alternative therapy	<b>pyrimethamine</b>	Day 1: 200 mg qd po, <b>then</b> • If $\geq$ 60 kg: 75 mg qd po • If < 60 kg: 50 mg qd po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia
	<b>+ clindamycin</b> <b>+ folinic acid</b>	600-900 mg qid po/iv 10-15 mg qd po	Additional PcP prophylaxis is necessary, where required
	or <b>TMP-SMX</b>	5 mg TMP/kg bid iv/po 25 mg SMX/kg bid iv/po	Preferred intravenous regimen if oral route not possible
	or <b>pyrimethamine</b>	Day 1: 200 mg qd po, <b>then</b> If $\geq$ 60 kg: 75 mg qd po If < 60 kg: 50 mg qd po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia
	<b>+ atovaquone</b> <b>+ folinic acid</b>	1500 mg bid po (with food) 10-15 mg qd po	
	or <b>sulfadiazine</b>	• If $\geq$ 60 kg: 3000 mg bid po/iv • If < 60 kg: 2000 mg bid po/iv	Sulfadiazine is associated with crystalluria and may lead to renal failure and urolithiasis. Good hydration is essential. Check renal function and urine sediment for microhematuria and crystalluria
<b>+ atovaquone</b>	1500 mg bid po (with food)		
or <b>pyrimethamine</b>	Day 1: 200 mg qd po, <b>then</b> • If $\geq$ 60 kg: 75 mg qd po • If < 60 kg: 50 mg qd po	Monitor for myelotoxicity of pyrimethamine, mostly neutropenia	
<b>+ azithromycin</b> <b>+ folinic acid</b>	900-1200 mg qd po 10-15 mg qd po		

## Secondary prophylaxis / Maintenance therapy

**Stop:** if CD4 count > 200 cells/ $\mu$ L and HIV-VL undetectable over 6 months

	Drug	Dosage	Comments
Regimens listed are alternatives	<b>sulfadiazine + pyrimethamine + folinic acid</b>	2000-3000 mg bid - qid po 25-50 mg qd po 10-15 mg qd po	
	or <b>clindamycin + pyrimethamine + folinic acid</b>	600 mg tid po 25-50 mg qd po 10-15 mg qd po	Additional PcP prophylaxis is necessary
	or <b>atovaquone suspension + pyrimethamine + folinic acid</b>	750-1500 mg bid po (with food) 25-50 mg qd po 10-15 mg qd po	
	or <b>atovaquone suspension</b>	750-1500 mg bid po (with food)	
	or <b>TMP-SMX</b>	800/160 mg bid po	

## Cryptococcosis – disease caused by *Cryptococcus neoformans*

### Treatment

Cryptococcal meningitis is the most frequent manifestation of cryptococcosis. Cryptococcal infection can also cause a pneumonitis which may be difficult to distinguish from Pneumocystis pneumonia. Infection may also involve other organs or may be disseminated

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

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

### Treatment (Cryptococcal meningitis and disseminated cryptococcosis)

14 days induction therapy, then 8 weeks consolidation therapy, then secondary prophylaxis for at least 12 months. Stop, if CD4 count > 100 cells/ $\mu$ L and HIV-VL undetectable over 3 months

	Drug	Dose	Comments
<b>Pre-emptive therapy</b>	<b>fluconazole</b>	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/ $\mu$ L - cryptococcal meningitis, pulmonary or other site infection ruled out
<b>Induction therapy</b>	<b>liposomal amphotericin B + flucytosine</b>	3 mg/kg qd iv 25 mg/kg qid po	<b>14 days</b> - Perform repeated lumbar puncture (LP), until opening pressure is < 20 cm H <sub>2</sub> O: - if CSF culture is sterile, switch to oral regimen - Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure which is associated with better survival - Corticosteroids have no effect in reducing increased intracranial pressure, could be detrimental and are contraindicated - Flucytosine dosage must be adapted to renal function - Defer start of cART for at least 4 weeks, since early initiation of cART is associated with decreased survival - Due to substantial nephrotoxicity amphotericin B deoxycholate should only be used, if liposomal amphotericin B is not available. - Flucytosine may not be available in all European countries. Consider replacing it by fluconazole 800 mg qd during the induction phase - In resource-limited settings, a large RCT suggested that one week of amphotericin B + flucytosine or two weeks of fluconazole 1200 mg qd plus flucytosine may be acceptable induction regimens [6]
	or <b>amphotericin B deoxycholate + flucytosine</b>	0.7 mg/kg qd iv 25 mg/kg qid po	
<b>Consolidation therapy</b>	<b>fluconazole</b>	400 mg qd po (single loading dose of 800 mg on 1 <sup>st</sup> day)	8 weeks. See <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a>

## Secondary prophylaxis / Maintenance therapy

At least 12 months

Consider to stop: if CD4 count >100 cells/ $\mu$ L and HIV-VL undetectable over 3 months

	Drug	Dose	Comments
	fluconazole	200 mg qd po	See <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a>

## Candidiasis

### Oropharyngeal Candidiasis

**Diagnosis:** typical clinical appearance, see [Drug-drug Interactions Between ARVs and Non-ARVs](#), for all azole therapies

	Drug	Dose	Comments
Preferred alternatives	fluconazole	150-200 mg qd po	Once or until improvement (5-7 days)
	nystatin	3-6 lozenges at 400000 units (aprox. 4-6 mL of oral suspension)/day	7-14 days
	or amphotericin B	oral suspension 1-2 g bid - qid	

### Oesophagitis

**Definitive diagnosis:** macroscopic inspection at endoscopy, OR histology of biopsy, OR cytology of specimen from the mucosal surface

**Presumptive diagnosis:** if recent onset of dysphagia AND oropharyngeal candidiasis

	Drug	Dose	Comments
Preferred alternatives	fluconazole	400 mg qd or 400 mg loading dose, then 200 mg qd po	3 days  10-14 days
	consider posaconazole or voriconazole or caspofungin and other echinocandins	400 mg bid po  200 mg bid po  70 mg iv qd day 1, then 50 mg qd	In cases of refractory disease, treat according to resistance testing. Adapt posaconazole and voriconazole dose according to MIC's of candida and drug trough levels

## Histoplasmosis (*Histoplasma capsulatum*)

### Treatment

In high endemic regions (French Guiana), histoplasmosis is the most prevalent OI.

**Diagnosis:** antigen detection in blood, urine or broncho-alveolar fluid, OR positive microscopy, OR mycological culture of blood, urine, broncho-alveolar fluid, CSF or tissue biopsy, OR PCR in blood or other clinical samples. Commercial antigen assays are not available in all European countries and PCR techniques are being developed but are not routinely available. *Aspergillus* galactomanan assays may be helpful to diagnose disseminated infections as cross reactivity occurs.

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

Fluconazole should not be used for treatment of histoplasmosis. Little clinical evidence is available for the use of voriconazole or posaconazole. **Be aware of interactions of azoles with ARVs**, see [Drug-drug Interactions Between ARVs and Non-ARVs](#). Measurement of plasma concentration of itraconazole is advised to guide optimal treatment, and itraconazole oral suspension should be preferred due to better bioavailability. Serum itraconazole concentration should be at least 1 mcg/mL if measured by high-performance liquid chromatography (HPLC).

	Drug	Dose	Comments
Severe disseminated histoplasmosis	<b>Induction therapy:</b> liposomal amphotericin B	3 mg/kg qd iv	For 2 weeks or until clinical improvement
	<b>Consolidation therapy:</b> itraconazole	200 mg tid po for 3 days, then 200 mg bid po	For at least 12 months
Moderate disseminated histoplasmosis	itraconazole	200 mg tid po for 3 days, then 200 mg bid po	For at least 12 months
Histoplasma meningitis	<b>Induction therapy:</b> liposomal amphotericin B	5 mg/kg qd iv	For 4-6 weeks
	<b>Consolidation therapy:</b> itraconazole	200 mg bid - tid po	For at least 12 months and until resolution of abnormal CSF findings. Measure plasma concentration of itraconazole

### Secondary prophylaxis / Maintenance therapy

**Stop:** if CD4 count > 150 cells/ $\mu$ L and HIV-VL undetectable over 6 months, negative fungal blood cultures, histoplasma serum antigen < 2  $\mu$ g/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

	Drug	Dose	Comments
	itraconazole	200 mg qd po	

## Talaromycosis (*Talaromyces* (former *Penicillium marneffe*))

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

## Herpes simplex virus (HSV) infections

Treatment			
<b>Diagnosis:</b> antigen testing / PCR / culture of swab / CSF / biopsy. Clinical appearance of skin lesions not reliable			
<b>During treatment:</b> monitor renal function, adjust drug dose in renal impairment			
	Drug	Dose	Comments
Initial and recurrent genital / mucocutaneous HSV			See <a href="#">Sexual and Reproductive Health of Women and Men Living with HIV</a> section, page 80
Severe mucocutaneous lesions	<b>aciclovir</b>	5 mg/kg tid iv	After lesions begin to regress, switch to oral treatment until lesions have healed
Encephalitis	<b>aciclovir</b>	10 mg/kg tid iv	14-21 days
Aciclovir resistant mucocutaneous HSV infection	<b>foscarnet</b>	90 mg/kg bid iv	Until clinical response

## Varicella zoster virus (VZV) infections

Treatment			
<b>Diagnosis:</b> typical clinical appearance with/without antibody testing, OR antigen testing / PCR / culture of swab / CSF / biopsy			
<b>During treatment:</b> monitor renal function, adjust drug dose in renal impairment			
	Drug	Dose	Comments
Primary Varicella infection (Chickenpox)	<b>valaciclovir</b>	1000 mg tid po	5-7 days
Herpes Zoster (Shingles): Not disseminated	<b>valaciclovir</b>	1000 mg tid po	7-10 days
	or <b>famciclovir</b>	500 mg tid po	7-10 days
	or <b>aciclovir</b>	800 mg x 5/day po	
Herpes Zoster: Disseminated	<b>aciclovir</b>	10 mg/kg tid iv	10-14 days
Encephalitis (including vasculitis)	<b>aciclovir</b>	10-15 mg/kg tid iv	14-21 days

## Cytomegalovirus (CMV) infections

Treatment			
<p><b>Diagnosis of retinitis:</b> clinical appearance of typical retinal lesions AND response to therapy. PCR of aqueous and vitreous humor optional</p> <p><b>Diagnosis of esophagitis/colitis:</b> endoscopic presence of ulcerations AND typical histopathological picture (cellular / nuclear inclusion bodies)</p> <p><b>Diagnosis of encephalitis/myelitis:</b> clinical appearance AND positive PCR in CSF AND other pathology excluded. Antibody testing and PCR in blood not useful for diagnosis of end-organ disease</p> <p><b>During treatment:</b> monitor renal function, adjust drug dose in renal impairment</p>			
	Drug	Dose	Comments
Retinitis, immediate sight-threatening lesions	<b>ganciclovir</b>	5 mg/kg bid iv	3 weeks, then secondary prophylaxis
	or <b>foscarnet</b>	90 mg/kg bid iv	Foscarnet used as alternative therapy if toxicity or resistance to ganciclovir. Some experts would add intravitreal injections of ganciclovir (2 mg) or foscarnet (2.4 mg) for 1-4 doses over 7-10 days in combination with systemic CMV treatment
Retinitis, small peripheral retinal lesions	<b>valganciclovir</b>	900 mg bid po (with food)	2-3 weeks, then secondary prophylaxis
	or <b>foscarnet</b>	90 mg/kg bid iv	
Oesophagitis/Colitis	<b>ganciclovir</b>	5 mg/kg bid iv	3-6 weeks, until symptoms resolved, then secondary prophylaxis
	or <b>foscarnet</b>	90 mg/kg bid iv	
	or <b>valganciclovir</b>	900 mg bid po (with food)	In milder disease if oral treatment tolerated
Encephalitis/Myelitis	<b>ganciclovir</b>	5 mg/kg bid iv	Treat until symptoms resolved and CMV replication in CSF has cleared (negative PCR DNA-CMV in CSF) Treatment is individualised according to clinical symptoms and response to treatment. Some guidelines recommend ganciclovir combined with foscarnet
	<b>foscarnet</b>	90 mg/kg bid iv	

### Secondary Prophylaxis/ Maintenance therapy: Cytomegalovirus (CMV) Retinitis

**Stop:** if CD4 count > 100 cells/ $\mu$ L and HIV-VL undetectable over 3 months

Regimens listed are alternatives	<b>valganciclovir</b>	900 mg qd po (with food)	
	or <b>ganciclovir</b>	5 mg/kg qd (x 5 days/ week) iv	
	or <b>foscarnet</b>	90-120 mg/kg qd (x 5 days/ week) iv	
	or <b>cidofovir + probenecid + NaCL 0.9% hydration</b>	1 x 5 mg/kg every 2 weeks iv	

## Progressive Multifocal Leukoencephalopathy (PML)

Treatment	
<p><b>Definitive diagnosis (laboratory):</b> evidence of JCV-DNA in CSF AND presence of compatible clinical-radiological picture</p> <p><b>Definitive diagnosis (histology):</b> typical histological findings with in situ evidence of JCV-DNA antigen or JCV-DNA AND presence of compatible clinical-radiological picture</p> <p><b>Presumptive diagnosis:</b> compatible clinical-radiological picture if JCV-DNA in CSF negative or not performed. JCV-DNA in plasma may complement PML diagnosis, particularly if CSF not available. May also be a marker of disease progression [8].</p>	
<b>Person off-ART</b>	Initiate cART immediately (following general guidelines for treatment, see <a href="#">Initial Combination Regimen for ART-naïve Adult PLWH</a> , INSTI may reasonably be preferred, given the importance of rapid immune reconstitution in PML. Attention should be made to development of IRIS, see <a href="#">IRIS section</a> )
<b>Person on-ART, HIV-VL failure</b>	Optimise cART (following general guidelines for treatment, see <a href="#">Virological Failure</a> ), INSTI may reasonably be preferred, given the importance of rapid immune reconstitution in PML. Attention should be made to development of IRIS, see <a href="#">IRIS section</a> )
<b>Person on-ART, treated for weeks-months or on effective cART</b>	Continue current cART
	<p><b>Note:</b> There is no specific treatment for JCV infection that proved to be effective in PML outside of anecdotal case reports, therefore there is no recommendation to use the following drugs which previously or occasionally were used in PML: Alpha-IFN, cidofovir, corticosteroids (except for treatment of IRIS-PML, see <a href="#">IRIS section</a>), cytarabine, iv immunoglobulins, mefloquine, mirtazapine. Newer immune-based approaches have shown some efficacy, including Interleukin-7, infusion of polyomavirus-specific HLA-matched T-cells, anti-PD1 inhibitors, but no conclusive data are currently supporting their recommendation for clinical use</p>

## Bacillary Angiomatosis (*Bartonella henselae*, *Bartonella quintana*)

Treatment			
<b>Diagnosis:</b> typical histology			
	Drug	Dose	Comments
	<b>doxycycline</b>	100 mg bid po	Until improvement (until 2 months) Possible interactions with ARVs, see <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a>
	or <b>clarithromycin</b>	500 mg bid po	

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

Primary prophylaxis				
<b>Primary prophylaxis</b>				
Prophylaxis is not recommended if ART is started				
Prophylaxis may be considered for persons with CD4 counts < 50 cells/μL who remain viraemic on cART (drug resistant HIV with no option to achieve virologic control); exclude disseminated MAC disease before starting				
	Drug	Dose	Comments	
Regimens listed are alternatives	azithromycin	1200-1250 mg/week po	Check for interactions with ARVs, see <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a>	
	or clarithromycin	500 mg bid po		
Treatment				
<b>Diagnosis:</b> clinical appearance and cultures of blood, lymph nodes, bone marrow or other usually sterile specimen. For any treatment regimen, check interactions with ARVs, see <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a>				
<i>Mycobacterium avium-intracellulare</i> complex (MAC)				
Preferred therapy	clarithromycin + ethambutol +/- rifabutin	500 mg bid po 15-20 mg/kg qd po 300 mg qd po (or 150 mg qd if PI/b)	12 months, then secondary prophylaxis	
	rifabutin can be replaced by: + levofloxacin or + amikacin	500 mg qd po 10-15 mg/kg qd iv	rifabutin especially indicated in case of severe disease, if resistance to macrolides or ethambutol is suspected or severe immunodeficiency (CD4 count < 50 cells/μL), high bacterial load (> 2*log of CFU/mL of blood), no cART  levofloxacin or amikacin can be considered as a 4th drug for disseminated or severe/refractory disease (no data on additional clinical benefit)	
	azithromycin + ethambutol	500 mg qd po 15-20 mg/kg qd po	Consider additional drugs as above	
<i>Mycobacterium kansasii</i>				
	rifampicin + isoniazid + ethambutol	600 mg qd po (or rifabutin 300 mg qd po) 300 mg qd po 15-20 mg/kg qd po	12 months after negative culture	
	or rifampicin + clarithromycin + ethambutol	600 mg qd po (or rifabutin 300 mg qd po) 500 mg bid po 15 -20 mg qd po	12 months after negative culture	
Secondary prophylaxis/Maintenance therapy for MAC				
<b>Stop:</b> if CD4 count > 100 cells/μL and HIV-VL undetectable over 6 months and MAC treatment for at least 12 months				
<i>Mycobacterium avium</i> (MAC) infection	Regimens listed are alternatives	Drug	Dose	Comments
	clarithromycin + ethambutol	500 mg bid po 15-20 mg/kg qd po		
	or azithromycin + ethambutol	500 mg qd po 15-20 mg/kg qd po		

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

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

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

Treatment			
<b>Diagnosis</b> of cystoisosporiasis is made in persons with chronic, mostly watery diarrhoea by UV fluorescence or microscopy of stools, duodenal aspirates or intestinal tissue biopsy. If the diarrhea lasts > 4 weeks, the diagnosis of cystoisosporiasis is an AIDS defining illness Besides antiprotozoal treatment, additional measures are symptomatic treatment, rehydration and electrolyte management			
	Drug	Dose	Comments
Preferred therapy	<b>TMP-SMX</b>	1600/320 mg bid po or 800/160 mg bid po	Treat minimally 10 days, increase duration to 3-4 weeks if symptoms worsen or persist  Treat minimally 10 days, increase dose to 2 x 2 tablet/day, if symptoms worsen or persist
Alternative therapy, if TMP-SMX is not tolerated	<b>pyrimethamine + folinic acid</b> or <b>ciprofloxacin</b>	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			
<b>Stop:</b> if CD4 count > 200 cells/ $\mu$ L and HIV-VL undetectable over 6 months and no signs of persistent cystoisosporiasis			
	Drug	Dose	Comments
Preferred therapy	<b>TMP-SMX</b>	800/160 mg three times weekly po or 800/160 mg qd po or 1600/320 mg three times weekly po	
Alternative therapy, if TMP-SMX is not tolerated	<b>pyrimethamine + folinic acid</b>	25 mg qd po 10-15 mg qd po	Monitor for myelotoxicity, mostly neutropenia, for pyrimethamine

## Leishmaniasis

Treatment			
<b>Diagnosis:</b> microscopy or PCR in smears, body fluids or tissue			
	Drug	Dose	Comments
Preferred treatment	<b>liposomal amphotericin B</b>	2-4 mg/kg qd iv for 10 consecutive days	Then secondary prophylaxis
	or <b>liposomal amphotericin B</b>	4 mg/kg qd iv on day 1-5, 10, 17, 24, 31 and 38	
Alternative therapy	<b>lipidcomplex amphotericin B</b>	3 mg/kg qd iv	10 days
	or <b>amphotericin B deoxycholate</b>	0.5-1 mg/kg qd iv (total dose 1.5-2 g)	
	or <b>pentavalent antimonium salt (Glucantime®)</b>	20 mg/kg qd iv or im	4 weeks
	or <b>miltefosine</b>	100 mg/kg qd po	4 weeks
Secondary prophylaxis / Maintenance therapy			
<b>Consider stopping:</b> if CD4 count > 200-350 cells/ $\mu$ L and HIV-VL undetectable over 3 months, no relapse for at least 6 months and negative PCR in blood or negative urinary antigen			
	Drug	Dose	Comments
Preferred treatment	<b>liposomal amphotericin B</b>	4 mg/kg every 2-4 weeks iv	
	or <b>lipidcomplex amphotericin B</b>	3 mg/kg every 3 weeks iv	
Alternative therapy	<b>pentavalent antimonium salts (Glucantime®)</b>	20 mg/kg every 4 weeks iv/im	
	or <b>miltefosine</b>	100 mg qd po	
	or <b>pentamidine</b>	300 mg every 3 to 4 weeks iv	



## Diagnosis and Treatment of TB in PLWH

### Treatment of TB in PLWH

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

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

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

<sup>i</sup> For dose details, please see separate table TB drug doses, page 117



<b>Diagnosis of Multi-Drug Resistant TB (MDR-TB) / Extensively-Drug Resistant TB (XDR-TB)</b>
MDR-TB/XDR-TB should be suspected in case of: <ul style="list-style-type: none"> <li>• Previous TB treatment</li> <li>• Contact with MDR/XDR-TB index case</li> <li>• Birth, travel or work in an area endemic for MDR-TB</li> <li>• History of poor adherence</li> <li>• No clinical improvement on standard therapy and/or sputum smear positive after 2 months of TB therapy or culture positive at 3 months</li> <li>• Homelessness/hostel living and, in some countries, recent/current incarceration</li> <li>• In areas with very high MDR-TB/XDR-TB prevalence</li> </ul>
MDR-TB: Resistance to isoniazid and rifampicin XDR-TB: Resistance to isoniazid and rifampicin and quinolones and at least one of the following injectable drugs: kanamycin, capreomycin or amikacin
<b>Rapid detection</b>
Gene Xpert or similar technology has the advantage of rapid detection of rifampicin resistance. Drug susceptibility testing is important for optimising treatment. Some countries/regions have neither of the above and have to use an empirical approach.
<b>Treatment of resistant TB</b>
<b>INH-resistant TB [11]</b> <ul style="list-style-type: none"> <li>• RIF or RFB + Z + E for 2 months and RIF or RFB + E for 10 months</li> <li>• RIF + E + Z + a FQ for 6 months</li> </ul> Some experts recommend to add a FQ in the intensive phase and replace E by the FQ in the maintenance phase
<b>Rifampicin-resistant TB and MDR-/XDR-TB</b> Treatment of MDR-/XDR-TB is a specialist area. WHO has recently published new guidelines [12]. Other specialists have different views and practice may vary Initial therapy should include 4 likely effective TB drugs, and treatment should include at least 3 active drugs after bedaquiline is stopped. Treatment compliance is crucial. If needed, each dose of MDR/XDR-TB regimen should be given as DOT throughout the whole treatment period Surgery Surgical resection may be part of the management for selected persons with focal pulmonary MDR-/XDR-TB

<b>Drug choices</b>	
Each empiric regimen should be reassessed and modified if needed once drug sensitivity results become available.	
<b>Group A: Include all three medicines</b>	<ul style="list-style-type: none"> <li>• levofloxacin (LFX) or moxifloxacin (MXF)</li> <li>• bedaquiline (BED)</li> <li>• linezolid (LZD)</li> </ul>
<b>Group B: Add one or both medicines</b>	<ul style="list-style-type: none"> <li>• clofazimine (CFX)</li> <li>• cycloserine (CS) or terizidone (TRD)</li> </ul>
<b>Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used</b>	<ul style="list-style-type: none"> <li>• ethambutol (E)</li> <li>• delamanide (DLM)</li> <li>• pyrazinamide (Z)</li> <li>• amikacin (AMK) (or streptomycin (S) – only if susceptible)</li> <li>• imipenem–cilastatin (IPM-CLN) or meropenem (MPM) with amoxicillin/clavulanic acid (AMX)</li> <li>• ethionamide (ETO) or prothionamide (PTO)</li> <li>• p-aminosalicylic acid (PAS)</li> </ul>
<b>Duration of MDR/XDR treatment</b>	
6 months of intensive phase using 4 or more drugs, followed by 12-14 months of 3 drugs depending on response In persons with rifampicin-resistant or MDR-TB who have not previously been treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9-12 months may be used instead of a conventional regimen [13,14] For XDR-TB, a 3-drug combination of pretomanid, bedaquiline, and linezolid during 6 months (3 additional months if culture positive at 4 <sup>th</sup> month) show promising results [15]	
<b>Drug interactions with ART and MDR/XDR regimens</b>	
When treating MDR-TB or XDR-TB, careful review of DDIs and potential toxicities is mandatory before initiating ART	

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

\* Other preventive regimens may be considered if high risk of latent infection with MDR/XDR-TB

\*\* Rifabutin is not a WHO recommended regimen

\*\*\* Rifapentine is not approved by EMA

## TB Drug Doses [12,17]

Drug name	Dose	Comments
<b>First line drugs</b>		
<b>Isoniazid</b>	5 mg/kg qd (usual dose 300 mg)	Max 375 mg qd Caution: neurotoxicity, add pyridoxine 20 mg qd
<b>Rifampin</b>	10 mg/kg qd (usual dose 600 mg)	Rifampin is not recommended in persons receiving PIs, ETR, RPV, EVG/c or TAF, see <a href="#">Drug-drug Interactions between ARVs and Non-ARVs</a> and table on Drug-drug interactions relevant for ART co-administered with rifampicin and rifabutin, page 20
<b>Rifabutin</b> 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	
<b>Pyrazinamide</b> 40-55 kg 56-75 kg 76-90 kg > 90 kg	1000 mg qd 1500 mg qd 2000 mg qd 2000 mg qd	
<b>Ethambutol</b> 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
<b>Other drugs</b>		
<b>Levofloxacin</b> 30-46 kg > 46 kg	750 mg qd 1000 mg qd	Max 1500 mg qd
<b>Moxifloxacin</b>	400 mg qd	Max 800 mg qd (used in the standardized shorter MDR-TB regimen) Monitor ECG in respect of QT prolongation
<b>Bedaquiline</b>	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
<b>Linezolid</b>	600 mg qd	Max 1200 mg qd Caution: hematological side effects and neurotoxicity, including optic neuropathy
<b>Clofazimine</b>	100 mg qd	Alternative: 200 mg for 2 months then 100 mg qd Caution: skin toxicity Monitor ECG in respect of QT prolongation
<b>Cycloserine or terizidone</b> 30-46 kg > 46 kg	500 mg qd 750 mg qd	Max 1000 mg qd Caution: neurotoxicity; add pyridoxine, up to 50 mg/250 mg cycloserine
<b>Delamanid</b>	100 mg bid for 24 weeks	Monitor ECG in respect of QT prolongation
<b>Imipenem/cilastatin</b>	1000/1000 mg bid iv	
<b>Meropenem</b>	1000 mg tid iv	
<b>Amoxicillin/clavulanic acid</b>	500/125 mg tid	Only to be used with carbapenems (imipenem/meropenem)
<b>Amikacin</b> 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
<b>Streptomycin</b>	12-18 mg/kg qd iv	Max 1000 mg qd iv
<b>Ethionamide or prothionamide</b> 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
<b>Para-aminosalicylic acid</b>	4000 mg bid	In weight > 70 kg can be increased to 4000-6000 mg bid Caution: gastrointestinal toxicity

## Video links

EACS Guidelines	Video lectures	Link to video lecture
Primary HIV Infection	When to Start ART Part 1	<a href="https://vimeo.com/197164442/93941a8e75">https://vimeo.com/197164442/93941a8e75</a>
	When to Start ART Part 2	<a href="https://vimeo.com/197167665/3f00ac2634">https://vimeo.com/197167665/3f00ac2634</a>
	What ART to Start Part 1	<a href="https://vimeo.com/197374541/32232bd037">https://vimeo.com/197374541/32232bd037</a>
	What ART to Start Part 2	<a href="https://vimeo.com/197378793/215317ddab">https://vimeo.com/197378793/215317ddab</a>
Switch Strategies for Virologically Suppressed Persons	How to Change ART	<a href="https://vimeo.com/197161843/ae0c46e0be">https://vimeo.com/197161843/ae0c46e0be</a>
Virological Failure	Adherence and Prevention of HIV Drug Resistance	<a href="https://vimeo.com/197381327/d7e972c0d5">https://vimeo.com/197381327/d7e972c0d5</a>
Pre-exposure Prophylaxis	PrEP Part 1	<a href="https://vimeo.com/196714648/6a196a71a4">https://vimeo.com/196714648/6a196a71a4</a>
	PrEP Part 2	<a href="https://vimeo.com/196716750/a12a32989b">https://vimeo.com/196716750/a12a32989b</a>
Adverse Effects of ARVs and Drug Classes	Adverse Effects and Monitoring	<a href="https://vimeo.com/197275138/3df1c99e55">https://vimeo.com/197275138/3df1c99e55</a>
Cancer: Screening Methods	Clinical Management of Cancers and HIV Part 1	<a href="https://vimeo.com/197398883/6cbeebb66e">https://vimeo.com/197398883/6cbeebb66e</a>
	Clinical Management of Cancers and HIV Part 2	<a href="https://vimeo.com/197748761/68cc01229a">https://vimeo.com/197748761/68cc01229a</a>
	Epidemiology of Cancers Part 1	<a href="https://vimeo.com/197749519/afea560124">https://vimeo.com/197749519/afea560124</a>
	Epidemiology of Cancers Part 2	<a href="https://vimeo.com/197749948/e7e5062f2d">https://vimeo.com/197749948/e7e5062f2d</a>
Prevention of CVD	HIV and CVD, CKD, Endocrinology	<a href="https://vimeo.com/197488153/396253a733">https://vimeo.com/197488153/396253a733</a>
Kidney Disease: Definition, Diagnosis and Management	HIV and CVD, CKD, Endocrinology	<a href="https://vimeo.com/197488153/396253a733">https://vimeo.com/197488153/396253a733</a>
Lipodystrophy: Prevention and Management	HIV and CVD, CKD, Endocrinology	<a href="https://vimeo.com/197488153/396253a733">https://vimeo.com/197488153/396253a733</a>
Algorithm for Diagnosis and Management of HIV-Associated Neurocognitive Impairment (NCI) in Persons without Obvious Confounding Conditions	CNS and HIV Part 1	<a href="https://vimeo.com/197280954/e995f1c097">https://vimeo.com/197280954/e995f1c097</a>
	CNS and HIV Part 2	<a href="https://vimeo.com/197370416/ee3655aa09">https://vimeo.com/197370416/ee3655aa09</a>
Diagnostic Procedures for HCV in Persons with HCV/HIV Co-infection	Hepatitis C and HIV Co-infection Part 1	<a href="https://vimeo.com/197259934/bc5cac91d1">https://vimeo.com/197259934/bc5cac91d1</a>
	Hepatitis C and HIV Co-infection Part 2	<a href="https://vimeo.com/197261826/0462d2df0e">https://vimeo.com/197261826/0462d2df0e</a>
	Hepatitis C and HIV Co-infection Part 3	<a href="https://vimeo.com/197262690/a323b6cd72">https://vimeo.com/197262690/a323b6cd72</a>
Introduction to OIs	HIV and the Management of IRIS Part 1	<a href="https://vimeo.com/197762901/a147257ffc">https://vimeo.com/197762901/a147257ffc</a>
	HIV and the Management of IRIS Part 2	<a href="https://vimeo.com/197765956/9b61e5d15d">https://vimeo.com/197765956/9b61e5d15d</a>
	Pulmonary Infections Part 1	<a href="https://vimeo.com/197388161/dc24235ab6">https://vimeo.com/197388161/dc24235ab6</a>
	Pulmonary Infections Part 2	<a href="https://vimeo.com/197389876/7c26fb8551">https://vimeo.com/197389876/7c26fb8551</a>
	Pulmonary Infections Part 3	<a href="https://vimeo.com/197392161/f90020ae21">https://vimeo.com/197392161/f90020ae21</a>
	CNS and HIV-related Opportunistic Infections Part 1	<a href="https://vimeo.com/197752868/34462456dd">https://vimeo.com/197752868/34462456dd</a>
	CNS and HIV-related Opportunistic Infections Part 2	<a href="https://vimeo.com/197758431/6b2939c62a">https://vimeo.com/197758431/6b2939c62a</a>
Diagnosis and Treatment of TB in PLWH	Tuberculosis and HIV Co-infection Part 1	<a href="https://vimeo.com/196723861/7a067d0254">https://vimeo.com/196723861/7a067d0254</a>
	Tuberculosis and HIV Co-infection Part 2	<a href="https://vimeo.com/197161188/4e881b687c">https://vimeo.com/197161188/4e881b687c</a>

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Green colour refers to specific references used in each section

Black colour refers to general references used in each section

## Part I Assessment of PLWH at Initial & Subsequent Visits

Please see references for Part IV

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