EACS
European
AIDS
Clinical
Society

# GUIDELINES

## Version 9.0
## October 2017

*English*

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

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# Introduction to the EACS Guidelines 2017

Welcome to the EACS Guidelines!

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

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

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

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

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

A list of the main references used to produce the Guidelines is provided as a separate section. Please reference the EACS Guidelines as follows: EACS Guidelines version 9.0, October 2017. 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 co-morbidities continue to require a multidisciplinary effort for which we hope the 2017 version of the EACS Guidelines will provide you with an easily accessible and updated overview.

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

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

Enjoy!

Manuel Battegay and Lene Ryom

October 2017

# Summary of Changes from v8.2 to v9.0

## ART section

- **What to start with:** Older ARVs (LPV/r) have been removed. The order of the listed regimens was changed to reflect the preference of use based on the data available. The structure of the table was changed to facilitate the reading of essential information. Footnotes were added: a note on when to prefer TAF over TDF; a note on the potential CVD toxicity of DRV; a note on ATV and renal toxicity, page 11
- **Primary HIV infection:** Recommendation that all HIV-positive women of reproductive age should have a pregnancy test was added, page 12
- **Switch strategies:** Indications for switch were added (HCV treatment, renal/bone toxicity). DTG+RPV regimen was added as switch option. DTG monotherapy was added in the strategies not recommended. The wording and structure of "Class-sparing strategies" was changed to improve clarity, page 13
- **Virological failure:** Changes in the definition were made to differentiate "incomplete suppression" from "virological rebound". A note on the importance of taking into consideration all the available resistance tests when choosing a new regimen in patient with virological failure was added, page 14
- **ARV in pregnancy:** A recommendation on use of INSTI in pregnant women who start ARVs in the late second or third trimester was added. A warning note on EFV in pregnancy was removed. EFV, RAL, RPV or DRV/r can be continued during pregnancy. Women on EVG/c need to be informed that more monitoring of HIV-VL and drug levels may be necessary during pregnancy. A recommendation against the initial use of TAF and cobicistat was added. A recommendation against breastfeeding was added, page 15
- **Post-Exposure Prophylaxis (PEP):** A note on providing emergency contraception counselling for sexual exposure was added, page 17

## Co-morbidities and related sections

- Four entirely new sections were introduced on:
  - Non-Alcoholic Fatty Liver Disease (NAFLD), page 57
  - Chronic lung disease, page 73
  - Prescribing in elderly, page 76
  - Solid Organ Transplantation (SOT), page 77
- New drug-drug interaction tables were included on bronchodilators, pulmonary antihypertensives and immunosuppressants, pages 26, 30 and 31
- The drug-drug interaction table on antimalarial drugs was changed to a format, similar to all remaining drug-drug interaction tables, page 29
- ATV/c data were added to all drug-drug interaction tables
- Ischaemic heart disease was added as a potential adverse effect of DRV/r, page 19
- Recommendations for screening for anal cancer were extended to also include all persons with HPV-associated dysplasia; screening for cervical cancer now includes all HIV-positive women > 21 years of age or within one year after sexual debut, pages 7 and 38
- Blood pressure targets were lowered for high risk individuals and where resources allow to SBT < 130 and DBT < 80 mmHg, pages 40-41
- Diabetes management was revised and sulfonylureas are now only recommended in combination with metformin. Limited data remain for any oral antidiabetic agents in terms of CVD prevention in the HIV-positive population, page 45
- A new lipid lowering drug class of PCSK9-inhibitors was added and is to be considered in high risk individuals inadequately controlled on top statin dose or when statin intolerant, page 46
- Recommendations on clinical situations where TAF may be preferred over TDF were added to the bone and kidney section, pages 47 and 50
- More dynamic measures of kidney function declines were added, page 50
- HPV vaccination is now recommended for all HIV-positive persons up to 26 years of age and up to 40 years if MSM, page 6 and page 64
- A recommendation to screen for STIs not only for those at risk, but also during pregnancy was added, page 65
- As part of an interim update in Jan 2017, we have further included video links to EACS online courses on HIV management, page 101
- In the Introduction to the Guidelines we have further emphasised that the EACS Guidelines aim to cover wide ranges of recommendations as opposed to the often more uniform national guidelines as the Guidelines geographically cover a relatively large and diverse area with different national levels of access to care, page 2

## Co-infections section

- HCV core-antigen testing has been added, page 79
- HCC screening recommendations have been updated, pages 56 and 79
- HBV treatment figure has been removed. Footnotes have been converted into full text with new recommendations for individuals with HBV who face immunosuppression
- Evaluation of concurrent causes of liver disease has been added to the diagnostic procedures table, page 81
- Text on HCV treatment has been shortened with emphasis on DAA table
- Recommendations for individuals with failure on DAA treatment have been updated, page 82
- Recommendations for individuals with acute HCV have been updated, page 82
- HCV management figure was removed
- DDI table has been updated and now includes GLE/PIB and SOF/VEL/VOX, boceprevir and telaprevir have been deleted, page 84
- Figure on management of acute HCV has been amended, page 85
- All tables and figures dealing with IFN-containing HCV therapy have been removed. We refer to an older online version of the Guidelines for details on IFN-treatment, page 82

## Opportunistic infections section

- A comment for TMP-SMX as preferred therapy for cerebral toxoplasmosis when the oral route is not available was added, page 88
- The preliminary results of the REALITY trial in the cryptococcal disease section were added, page 89. An enhanced infection prophylaxis in severely immunosuppressed individuals (< 50 CD4 cells/µL) including INH 12 weeks, fluconazole 100 mg/day 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
- A comment on the possibility to add fluconazole to liposomal amphotericin B during the induction phase for cryptococcal meningitis treatment in countries where flucytosine is not available was added, page 89
- Intermittent TB regimens (2 or 3 times per week) are contraindicated in HIV-positive persons, page 95
- A comment on the possibility to add steroid therapy to avoid IRIS in individuals with TB was added, page 95
- The preliminary results of the Nix-TB trial in the section of treatment for resistant TB (MDR- and XDR-TB) were added, page 96
- A duration of 9-months for latent TB treatment, particularly in countries with high TB prevalence, was emphasised, page 97
- A comment explaining that other preventive regimens are needed for treating latent infection with MDR-/XDR-TB in countries with high resistant TB rates was added, page 97

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


Imprint

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# Abbreviations

## Antiretroviral drug (ARV) abbreviations

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

## Other abbreviations

| | |
|---|---|
| **ACE** | angiotensin converting enzyme |
| **ALP** | alkaline phosphatase |
| **ALT** | alanine aminotransferase |
| **aMDRD** | abbreviated modification of diet in renal disease formula |
| **ART** | antiretroviral therapy |
| **AST** | aspartate aminotransferase |
| **bid** | twice daily |
| **BMD** | bone mineral density |
| **BMI** | body mass index |
| **BP** | blood pressure |
| **cART** | combination antiretroviral treatment |
| **CKD** | chronic kidney disease |
| **CKD-EPI** | CKD epidemiology collaboration formula |
| **CMV** | cytomegalovirus |
| **CNS** | central nervous system |
| **COPD** | chronic obstructive pulmonary disease |
| **CSF** | cerebrospinal fluid |
| **CVD** | cardiovascular disease |
| **CXR** | chest X-ray |
| **DAA** | direct acting antiviral drug |
| **DXA** | dual energy X-ray absorptiometry |
| **ECG** | electrocardiogram |
| **eGFR** | estimated glomerular filtration rate |
| **FBC** | full blood count |
| **FRAX** | fracture risk assessment tool |
| **GT** | genotype |
| **HAV** | hepatitis A virus |
| **HBV** | hepatitis B virus |
| **HCV** | hepatitis C virus |
| **HDL-c** | HDL-cholesterol |
| **HIVAN** | HIV-associated nephropathy |
| **HPV** | human papillomavirus |
| **HSR** | hypersensitivity reaction |
| **IGRA** | interferon-gamma release assay |
| **ICS** | inhaled corticosteroids |
| **IHD** | ischaemic heart disease |
| **im** | intramuscular |
| **IRIS** | immune reconstitution inflammatory syndrome |
| **iv** | intravenous |
| **IVDU** | intravenous drug use |
| **LABA** | long-acting β2-agonist |
| **LAMA** | long-acting muscarinic antagonist |
| **LDL-c** | LDL-cholesterol |
| **LGV** | lymphogranuloma venereum |
| **Mg** | magnesium |
| **MSM** | men who have sex with men |
| **NAFLD** | non-alcoholic fatty liver disease |
| **NASH** | non-alcoholic steatohepatitis |
| **PAP** | papanicolaou test |
| **PEG-IFN** | pegylated-interferon |
| **PHI** | primary HIV infection |
| **po** | per oral |
| **PPD** | purified protein derivative |
| **PPI** | proton pump inhibitor |
| **PRT** | proximal renal tubulopathy |
| **PSA** | prostate specific antigen |
| **PTH** | parathyroid hormone |
| **qd** | once daily |
| **RAS** | resistance-associated substitutions |
| **RBV** | ribavirin |
| **SABA** | short-acting β2-agonist |
| **SAMA** | short-acting muscarinic antagonist |
| **sc** | subcutaneous |
| **SOT** | solid organ transplant |
| **STI** | sexually transmitted infection |
| **SVR** | sustained virological response |
| **TC** | total cholesterol |
| **TDM** | therapeutic drug monitoring |
| **TG** | triglycerides |
| **tid** | three times daily |
| **TMP-SMX** | trimethoprim-sulfamethoxazole |
| **UA/C** | urine albumin/creatinine ratio |
| **UP/C** | urine protein/creatinine ratio |
| **VL** | viral load (HIV-RNA) |
| **WB** | western blot |
| **Zn** | zinc |

# Part I Assessment of HIV-positive Persons at Initial & Subsequent Visits

| | Assessment | At HIV diagnosis | Prior to starting ART | Follow-up frequency | Comment | See page |
|---|---|---|---|---|---|---|
| **HISTORY** | | | | | | |
| **Medical** | Complete medical history including: | + | + | First visit | On transfer of care repeat assessment | |
| | • Family history (e.g. premature CVD, diabetes, hypertension, CKD) | + | | First visit | Premature CVD: cardiovascular events in a first degree relative (male < 55, female < 65 years) | 40-42, 44, 50 |
| | • Concomitant medicines[(i)] | + | + | Every visit | | |
| | • Past and current co-morbidities | + | + | Every visit | | |
| | • Vaccination history | + | | Annual | Measure antibody titres and offer vaccinations where indicated, see Vaccination | |
| **Psychosocial** | Current lifestyle (alcohol use, smoking, diet, exercise, drug use) | + | + | 6-12 months | Adverse lifestyle habits should be addressed more frequently | 39 |
| | Employment | + | + | Every visit | Provide advice and support if needed | |
| | Social and welfare | + | + | | Provide counselling if needed | |
| | Psychological morbidity | + | + | | | |
| | Partner and children | + | | | Test partner and children if at risk | |
| **Sexual and Reproductive Health** | Sexual history | + | | 6-12 months | Address issues concerning sexual dysfunction | 65-67 |
| | 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 | 66 |
| **HIV DISEASE** | | | | | | |
| **Virology** | Confirmation of HIV Ab pos | + | | 3-6 months | More frequent monitoring of HIV-VL at start of ART | 10-14 |
| | Plasma HIV-VL | + | + | | Perform genotypic resistance test before starting ART if not previously tested or if at risk of super-infection | |
| | Genotypic resistance test and sub-type | + | +/- | At virological failure | | |
| | R5 tropism (if available) | | +/- | | Screen if considering R5 antagonist in regimen | |
| **Immunology** | CD4 absolute count and %, CD4/CD8 ratio (optional: CD8 and %) | + | + | 3-6 months | Annual CD4 count if stable on ART and CD4 count > 350 cells/µL[(ii)] CD4/CD8 ratio is a stronger predictor of serious outcomes | 10-14 |
| | HLA-B*5701 (if available) | + | +/- | | Screen before starting ABC containing ART, if not previously tested | |
| **CO-INFECTIONS** | | | | | | |
| **STIs** | Syphilis serology | + | | Annual/ as indicated | Consider more frequent screening if at risk | 65 |
| | STI screen | + | | Annual/ as indicated | Screen if at risk and during pregnancy | |
| **Viral Hepatitis** | HAV serology | + | | Annual/ as indicated | Screen at risk (e.g. MSM); vaccinate if non-immune | 64, 79 |
| | HCV screen | + | | | Annual screen if ongoing risk (e.g. MSM, IVDU) Measure HCV-RNA if HCV Ab pos or if acute infection suspected | |
| | HBV screen | + | + | | Annual screen in susceptible persons; vaccinate if non-immune. Use ART containing TDF or TAF in vaccine non-responders | |
| **Tuberculosis** | CXR | + | | Re-screen if exposure | Consider routine CXR in persons from high TB prevalence populations. Use of PPD/IGRA depending on availability and local standard of care. IGRA should, however, be tested before PPD if both are to be used, given the potential for a false positive IGRA after PPD See Diagnosis and Treatment of TB in HIV-positive Persons | 95-97, 16 |
| | PPD if CD4 count > 400 cells/µL | + | | | | |
| | IGRA in selected high-risk populations (if available) | + | | | | |
| **Others** | Varicella zoster virus serology | + | | | Offer vaccination where indicated | 64 |
| | Measles/Rubella serology | + | | | Offer vaccination where indicated | |
| | Toxoplasmosis serology | + | | | | |
| | CMV serology | + | | | | |
| | Cryptococcus antigen | +/- | | | Consider screening for cryptococcus antigen in serum in persons with CD4 count < 100 cells/µL | 89 |
| | Leishmania serology | +/- | | | Screen according to travel history/origin | |
| | Tropical screen (e.g. Schistosoma serology) | +/- | | | Screen according to travel history/origin | |
| | Influenza virus | + | | Annual | In all HIV-positive persons, see Vaccination | 64 |
| | *Streptococcus pneumoniae* | + | | | No recommendations available regarding the need for a booster dose, see Vaccination | 64 |
| | Human papilloma virus | + | | As indicated | Vaccinate all HIV-positive persons up to age 26 / age 40 if MSM. If HPV infection is established, efficacy of vaccine is questionable, see Vaccination | 64 |

| | Assessment | At HIV diagnosis | Prior to starting ART | Follow-up frequency | Comment | See page |
|---|---|---|---|---|---|---|
| **CO-MORBIDITIES** | | | | | | |
| **Haematology** | FBC | + | + | 3-12 months | | |
| | Haemoglobinopathies | + | | | Screen at risk persons | |
| | G6PD | + | | | Screen at risk persons | |
| **Body Composition** | Body-mass index | + | + | Annual | | 39 |
| **Cardiovascular Disease** | Risk assessment (Framingham score[iii]) | + | + | 2 years | Should be performed in all men > 40 years and women > 50 years without CVD | 40 |
| | ECG | + | +/- | As indicated | Consider baseline ECG prior to starting ARVs associated with potential conduction problems | |
| **Hypertension** | Blood pressure | + | + | Annual | | 41-43 |
| **Lipids** | TC, HDL-c, LDL-c, TG[iv] | + | + | Annual | Repeat in fasting state if used for medical intervention (i.e. ≥ 8h without caloric intake) | 46 |
| **Glucose** | Serum glucose | + | + | Annual | Consider oral glucose tolerance test / HbA1c if fasting glucose levels of 5.7-6.9 mmol/L (100-125 mg/dL) | 44-45 |
| **Pulmonary Disease** | Respiratory symptoms and risk factors[xii] | + | + | Annual | If severe shortness of breath is reported with preserved spirometry, echocardiography may be performed to rule out heart failure and/or pulmonary hypertension | 73 |
| | Spirometry | | | As indicated | Spirometry should be performed in all symptomatic persons[xii] | |
| **Liver Disease** | Risk assessment[v] | + | + | Annual | | 54-59 |
| | 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) | 55-56, 82 |
| | Hepatic ultrasound | | | 6 months | Persons with liver cirrhosis and persons with HBV co-infection at high risk of HCC[xiii] | 56, 79, 82 |
| **Renal Disease** | Risk assessment[vi] | + | + | Annual | More frequent monitoring if eGFR < 90mL/min, CKD risk factors present[vi] and/or prior to starting and on treatment with nephrotoxic drugs[ix] | 50-53 |
| | eGFR (CKD-EPI)[vii] | + | + | 3-12 months | | |
| | Urine dipstick analysis[viii] | + | + | Annual | Every 6 months if eGFR < 60 mL/min or rapid decline in eGFR [xiv], if proteinuria ≥ 1+ and/or eGFR < 60 mL/min perform UP/C or UA/C[viii] | |
| **Bone Disease** | Bone profile: calcium, $PO_4$, ALP | + | + | 6-12 months | | 47, 49 |
| | Risk assessment[x] (FRAX®[xi] in persons > 40 years) | + | + | 2 years | Consider DXA in specific persons (see page 47 for details) | |
| **Vitamin D** | 25(OH) vitamin D | + | | As indicated | Screen at risk persons | 48 |
| **Neurocognitive Impairment** | Screening questionnaire | + | + | As indicated | Screen all persons without highly confounding conditions. If abnormal or symptomatic, see algorithm page 72 for further assessment. | 72 |
| **Depression** | Questionnaire | + | + | As indicated | Screen at risk persons | 68-70 |
| **Cancer** | Mammography | | | 1-3 years | Women 50-70 years | 38, 56 |
| | Cervical PAP | | | 1-3 years | HIV-positive women > 21 years or within 1 year after sexual debut | |
| | Rectal exam and anoscopy | | | 1-3 years | MSM and persons with HPV-associated dysplasia. Evidence of benefit not known | |
| | Ultrasound and alpha-foetoprotein | | | 6 months | Controversial; persons with cirrhosis and persons with HBV co-infection at high risk of HCC[xiii] | |
| | Others | | | | Controversial | |

i Review all concomitant medicines which may potentially interact with ARVs or increase co-morbidities, see
Drug-drug Interactions between Antidepressants and ARVs
Drug-drug Interactions between Antihypertensives and ARVs
Drug-drug Interactions between Analgesics and ARVs
Drug-drug Interactions between Anticoagulants/Antiplatelet Agents and ARVs
Drug-drug Interactions between Antimalarial Drugs and ARVs
Drug-drug Interactions between Bronchodilators (for COPD) and ARVs
Drug-drug Intercations between Immunosuppressants (for SOT) and ARVs
Drug-drug Interactions between Pulmonary Antihypertensives and ARVs
Drug-drug Interactions between Corticosteroids and ARVs
Drug-drug Interactions between Contraceptives and ARVs
Drug-drug Interactions between DAAs and ARVs
and http://www.hiv-druginteractions.org

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

iii A risk equation developed from HIV populations is available, see http://www.chip.dk/Tools Of note, if an individual receives medicines to control dyslipidaemia and/or hypertension, the estimation should be interpreted with caution.

iv A calculator for LDL-cholesterol in cases where TG is not high can be found at http://www.hivpv.org.

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

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

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

viii Some experts recommend UA/C (urinary albumin creatinine ratio) or UP/C (urinary protein creatinine ratio) as a screening test for proteinuria in all persons. UA/C predominantly detects glomerular disease. Use in persons with diabetes. UP/C detects total protein secondary to glomerular and tubular disease.

ix Different models have been developed for calculating a 5-year CKD risk score while using different nephrotoxic ARVs, integrating HIV independent and HIV-related risk factors [6], [7].

x Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m$^2$), vitamin D deficiency, smoking, physical inactivity, history of low impact fracture, alcohol excess (> 3 units/day), steroid exposure (minimum 5 mg for > 3 months).

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

xii Respiratory symptoms: shortness of breath, chronic cough and sputum. Risk factors: tobacco, occupation, in- and outdoor pollution and host factors including previous PCP or TB, recurrent pneumonia and Alpha-1 antitrypsin deficiency. A diagnosis of COPD should be considered in persons over the age of 35 years who have a risk factor (current or ex-smoker) and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheeze.

xiii HCC screening is indicated in all cirrhotic individuals regardless of the underlying reason. In HBV infected non-cirrhotics, HCC screening should be performed in those who ever had chronic hepatitis (elevated transaminases) or with risk factors for HCC (including family history of HCC, Asians, Africans, see http://www.easl.eu/research/our-contributions/clinical-practice-guidelines). On a case-by-case basis, omitting HCC screening can be discussed in those without risk factors and normal transaminases before starting HBV-active treatment.

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

# Part II ART of HIV-positive Persons

This section provides an overview of the important aspects of the management of HIV-positive individuals 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 move to 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. We highlight two important areas of ART: pregnancy and TB. Details on the use of PrEP, which is being rolled out across Europe, are also included. Finally, with the increasing complexity of co-morbidities and concomitant treatments, a large part of the section is devoted to adverse effects, drug interactions and dose adjustments in renal and hepatic disease.

## Assessing HIV-positive Persons' Readiness to Start and Maintain ART(x)

| **Goal: to help persons start and/or maintain ART** | |
|---|---|
| The equipoise when to start ART has changed in light of the START trial [1]. Evidence is accumulating that starting ART on the same day after establishing a diagnosis of HIV infection is feasible and acceptable to HIV-positive persons. Nevertheless, assessment of the readiness to start ART is essential to enable the HIV-positive person to express their preference and not feel pressured to start ART immediately, unless clinically indicated.<br><br>Successful ART requires a person's readiness to start and adhere to the regimen over time. The trajectory from problem awareness to maintenance on ART can be divided into five stages. Knowing a person's stage, health care providers use appropriate techniques to assist them to start and maintain ART. | Identify the person's stage of readiness using WEMS(i) techniques, and start discussion with an open question/invitation:<br>"I would like to talk about HIV medicines." <wait> "What do you think about them?"<br>Based on the person's response, identify his/her stage of readiness and intervene accordingly(ii)<br><br>Immediate (same day) start of ART should be considered, especially in the following situations:<br><br>- 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.<br>- The wish of an HIV-positive person to start ART immediately.<br>- In a setting where loss-to-follow-up is more likely if ART is not started the same day. |

| **Stages of readiness to start ART** | |
|---|---|
| **Precontemplation:**<br>*"I don't need it, I feel good."*<br>*"I don't want to think about it."* | Support: Show respect for the person's attitude. / Try to understand the person's health and therapy beliefs. / Establish trust. / Provide concise, individualised information. / Schedule next appointment. |
| **Contemplation:**<br>*"I am weighing things up and feel torn about what to do about it."* | Support: Allow ambivalence. / Support the person in weighing pros and cons. / Assess the person's information needs and support his/her information seeking. / Schedule the next appointment. |
| **Preparation:**<br>*"I want to start, I think the drugs will allow me to live a normal life."* | Support: Reinforce the person's decision. / Decide with the person which is the most convenient regimen. / Educate the person on adherence, resistance and side effects. / Discuss integration into daily life. / Assess self-efficacy.<br>Ask: How confident are you that you can take your medicines as we discussed (specify) once you have started? Use VAS 0-10(iii)<br>Consider skills training:<br>• Medicines-taking training, possibly Medication Event Monitoring System, e.g. electronic pill boxes<br>• Directly observed therapy with educational support<br>• Use aids: mobile phone alarm, pillboxes<br>• Involve supportive tools/persons where appropriate |
| START ART | |
| **Action:**<br>***"I will start now."*** | **'Final check': With a treatment plan established, is the person capable of taking ART and is ART available?** |
| **Maintenance**:<br>*"I will continue." or "I have difficulties continuing over the long run."*<br><br>Caveat: A person can relapse to an earlier stage, even from "maintenance" to "precontemplation" | Assess: Adherence every 3-6 months(iv)<br>Evaluate adherence: For persons with good adherence: show respect for their success.<br>Assess: The person's own perception of ability to adhere to and continue treatment.<br>Ask: In the next 3-6 months, how confident are you that you can take your medicines? Use VAS 0-10(iii)<br>For a person without sufficient adherence: use mirroring techniques(v) on problems, ask open questions to identify dysfunctional beliefs.<br>Assess: Stage of readiness and provide stage-based support<br>Assess: Barriers and facilitators(vi)<br>Schedule next appointment and repeat support |

**Several barriers are known to influence ART decision making and adherence to ART**

Screen for and talk about problems and facilitators

| Consider systematic assessment of: | Consider talking about: |
|---|---|
| • Depression[vii], see page 68-69<br>• Cognitive problems[viii], see page 72<br>• Harmful alcohol[ix] or recreational drug use, see page 37, 39 | • Social support and disclosure<br>• Health insurance and continuity of drug supply<br>• Therapy-related factors |

Recognise, discuss and reduce problems wherever possible in a multidisciplinary team approach.

i WEMS: Waiting (> 3 sec), Echoing, Mirroring, Summarising [2]

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

iii VAS (= Visual Analogue Scale; range from 0 to 10, i.e. 0= I will not manage, 10= I am sure I will manage).

iv Suggested adherence questions: “In the past 4 weeks how often have you missed a dose of your HIV medicines: every day, more than once a week, once a week, once every 2 weeks, once a month, never?” / “Have you missed more than one dose in a row?” [3].

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

vi Adherence to long-term therapies [4].

vii PHQ-2 or PHQ-9 [5]. 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 [6]

viii Ask: “Do you feel having problems to concentrate in your daily life?” / “Do you feel slowed in your thinking?” / “Do you feel having problems with your memory?” / “Did relatives or friends express that they feel you have problems with your memory or difficulty concentrating?” [7].

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

x Algorithm adapted from [9].

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

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

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

i ART should always be recommended irrespective of the CD4 count, but the lower the CD4 count, the greater the urgency to start ART immediately. Use of ART should also be recommended at any CD4 count in order to reduce sexual transmission and mother-to-child transmission of HIV (before third trimester of pregnancy).

- For best timing for starting ART in persons with tuberculosis and cryptococcal meningitis, see page 16 and page 89.
- A possible exception could be 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, dampen inflammation and lower the risk of emerging infection with higher HIV-VL.
- Genotypic resistance testing is recommended prior to initiation of ART, ideally at the time of HIV diagnosis; otherwise before initiation of ART.
- If ART needs to be initiated before genotypic testing results are available, it is recommended to include a drug with a high genetic barrier to resistance in the first-line regimen (e.g. a PI/r, PI/c or DTG). Ideally, before starting treatment, the HIV-VL level and CD4 count should be repeated to more reliably assess the infection status and subsequent response to ART.

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

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

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

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

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

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

** Generic HIV drugs are becoming more available and can be used as long as they replace the same drug and do not break recommended fixed dose combinations.

i ABC contraindicated if HLA-B*5701 positive. Even if HLA-B*5701 negative, counselling on HSR risk still mandatory. ABC should be used with caution in persons with a high CVD risk (> 20%).

ii Use this combination only if HBsAg-negative.

iii In certain countries TDF is labelled as 245 mg rather than 300 mg to reflect the concentration of the active metabolite (tenofovir disoproxil). When available, combinations containing TDF can be replaced by the same combinations containing TAF, TAF is used at 10 mg when co-administered with drugs that inhibit P-gp, and at 25 mg when co-administered with drugs that do not inhibit P-gp. 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.
TAF*** should be considered as a first choice**** over TDF in individuals with:
- established or high risk of CKD, see page 50;
- co-medication with nephrotoxic drugs or prior TDF toxicity, see page 51;
- osteoporosis / progressive osteopenia or risk factors, see page 47;
- history of fragility fracture, see page 49.
*** There are limited data on use of TAF with eGFR < 30 mL/min; **** Expert opinion pending clinical data.

iv TDF/FTC/EVG/c use only if eGFR ≥ 70 mL/min. It is recommended that TDF/FTC/EVG/c is not initiated in persons with eGFR < 90 mL/min unless this is the preferred treatment.

v A single study has shown increase in CVD risk with cumulative use of DRV [13].

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

vii Co-administration of PPI is contraindicated. If PPI co-administration is judged unavoidable, consider an alternative regimen; if given, dose increase of ATV to 400 mg qd may be considered, close clinical monitoring is recommended and doses of PPI comparable to omeprazole 20 mg should not be exceeded and must be taken approximately 12 hours prior to the ATV/r. H2 antagonists to be taken 12 hours before or 4 hours after ATV.

viii Potential renal toxicity with ATV/r and ATV/c.

# Primary HIV Infection (PHI)

## Definition of PHI[i-iv]

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

## Classification of PHI[i-iv]

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

## Starting treatment[v-vi]

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

**Circumstances where immediate treatment initiation should be advised**

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

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

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

## Treatment selection

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

## Other considerations

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

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

ii Where available, Western Blot (WB) or Immunoblot patterns of reactivity can be used to stage the infection as follows [12];
- Stage I: HIV-RNA positive only (average duration 5 days). HIV-VL levels are median 2,000 copies/mL (IQR 300-20,000 copies/ml), and are < 100 copies/mL in approximately 10% of HIV-positive persons. Low HIV-VL levels should be interpreted with caution due to the risk of false positivity (e.g., due to contamination)
- Stage II: HIV-RNA and p24 Ag positive only (average duration 5.3 days). NB: HIV-VL levels are usually > 10,000 copies/mL
- Stage III: HIV-RNA, p24 Ag and anti-HIV antibody positive by immuneassay, no specific WB bands (average duration 3.2 days)
- Stage IV: as Stage III but indeterminate WB pattern (5.6 days)
- Stage V: as Stage III, but reactive WB pattern lacking p31 reactivity (average duration 69.5 days)
- Stage VI: as stage III but full WB reactivity including a p31 band (indefinite)

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

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

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

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

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 defined suppression as an HIV-VL < 50 copies/mL for at least 6 months.

## Indications

1. **Documented toxicity** caused by one or more of the antiretrovirals included in the regimen. Examples of these reactive switches: lipoatrophy (d4T, AZT), central nervous system adverse events (EFV), diarrhoea (PI/r) and jaundice (ATV), 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 lipoatrophy in persons receiving d4T or AZT and prevention of proximal renal tubulopathy with TDF, see Adverse Effects of ARVs and Drug Classes.
3. **Avoid serious drug-drug interactions**
4. **Planned pregnancy**
5. **Ageing and/or co-morbidity** with a possible negative impact of drug(s) in current regimen, e.g. on CVD risk, metabolic parameters.
6. **Simplification:** to reduce pill burden, adjust food restrictions and improve adherence.
7. **Starting of HCV treatment in case of drug-drug interaction,** see Drug-drug Interactions between DAAs and ARVs.

## Principles

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

1. The objectives of treatment modification should be to eliminate or improve adverse events, facilitate adequate treatment of co-morbid conditions, and improve quality of life.
2. 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.
3. A complete ARV history with HIV-VL, tolerability issues and cumulative genotypic resistance history should be analysed prior to any drug switch.
4. A PI/r or PI/c may be switched to unboosted ATV, an NNRTI, or an INSTI only if full activity of the 2 NRTIs remaining in the regimen can be guaranteed. Switches have to be planned especially carefully when they result in a decrease in the genetic barrier of the regimen in case of prior virologic failures. Clinicians should review the complete ARV history and available resistance test and HIV-VL results before switching, and ensure no drug-drug interactions may lead to suboptimal drug levels (e.g. unboosted ATV and TDF).
5. Before switching, remaining treatment options in case of potential virological failure of the new regimen should be taken into consideration. For example, the development of the M184V RT mutation in HIV-positive persons who fail a 3TC-containing regimen might preclude the future use of all currently available single-tablet regimens.
6. Switches of single drugs with the same genetic barrier (for example EFV to RAL) is usually virologically safe in the absence of resistance to the new compound.
7. Clinicians should carefully review the possibility of drug-drug interactions with the new regimen.
8. If the switch implies discontinuing TDF and not starting TAF, clinicians should check the HBV status (avoid discontinuation of TDF in persons with chronic HBV and assess HBV vaccination status).
9. HIV-positive persons should be seen soon (e.g. 4 weeks) after treatment switches to check for maintenance of suppression and possible toxicity of the new regimen.
10. If a HIV-positive person receives and tolerates a regimen that is no longer a preferred option, there is no need to change. Example: persons tolerating EFV-containing regimens.
11. See online video lecture How to Change ART from the EACS online course Clinical Management of HIV.

## Class-sparing strategies

**Dual therapy:**
DTG + RPV
3TC + (DRV/r or DRV/c) or
3TC + (ATV/r or ATV/c)
In clinical trials these strategies have not been associated with more virological rebounds than triple therapy.

**Monotherapy with DRV/r:**
In clinical trials this strategy has been associated with more virological rebounds than triple therapy. DRV/r monotherapy is an option only for exceptional persons who are not candidates for dual therapies.

Dual therapy with 3TC + PI/r or monotherapy with DRV/r may only be given to persons with a) no resistance to the PI, b) suppression of HIV-VL to < 50 copies/mL for at least the past 6 months and c) absence of chronic HBV co-infection.

## Strategies not recommended

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

# Virological Failure

| | |
|---|---|
| **Definition** | **INCOMPLETE SUPPRESSION**: HIV-VL > 200 copies/mL at 6 months[i] after starting therapy in persons not previously on ART.<br>**REBOUND**: confirmed HIV-VL > 50 copies/mL in persons with previously undetectable HIV-VL. |
| **General measures** | Review expected potency of the regimen |
| | Evaluate adherence, compliance, tolerability, drug-drug interactions, drug-food interactions, psychosocial issues |
| | Perform resistance testing on failing therapy (usually routinely available for HIV-VL levels > 350-500 copies/mL and in specialised laboratories for lower levels of viraemia) and obtain historical resistance testing for archived mutations |
| | Tropism testing |
| | Consider TDM |
| | Review ART history |
| | Identify treatment options, active and potentially active drugs/combinations |
| **Management of virological failure (VF)** | **If HIV-VL > 50 and < 500 copies/mL:** |
| | Check for adherence |
| | Check HIV-VL 1 to 2 months later |
| | If genotype not possible, consider changing regimen based on past treatment and resistance history |
| | **If HIV-VL confirmed > 500 copies/mL:** |
| | Change regimen as soon as possible. What to change will depend on the resistance testing results: |
| | If no resistance mutations found: re-check for adherence, perform TDM |
| | If resistance mutations found: switch to a suppressive regimen based on drug history; multidisciplinary expert discussion advised |
| | Goal of new regimen: HIV-VL < 50 copies/mL within 6 months |

| | |
|---|---|
| **In case of demonstrated resistance mutations** | **General recommendations:** |
| | Use at least 2 and preferably 3 active drugs in the new regimen (including active drugs from previously used classes) based on resistance mutations present in current and earlier genotypic analyses |
| | Any regimen should use at least 1 fully active PI/r (e.g. DRV/r) plus 1 drug from a class not used previously e.g. fusion, integrase or CCR5 antagonist (if tropism test shows R5 virus only), or 1 NNRTI (e.g. ETV), assessed by genotypic testing |
| | Defer change if < 2 active drugs available, based on resistance data, except in persons with low CD4 count (< 100 cells/μL) or with high risk of clinical deterioration for whom the goal is the preservation of immune function through partial reduction of HIV-VL (> 1*$\log_{10}$ reduction) by recycling |
| | If limited options, consider experimental and new drugs, favouring clinical trials (but avoid functional monotherapy) |
| | Treatment interruption is not recommended |
| | Consider continuation of 3TC or FTC in particular situations even if documented resistance mutation (M184V/I) |
| | If many options are available, criteria of preferred choice include: simplicity of the regimen, toxicity risks evaluation, drug-drug interactions, and future salvage therapy |

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

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

# Treatment of HIV-positive Pregnant Women

Pregnant women should be monitored every month and as close as possible to the predicted delivery date

| Criteria for starting ART in pregnant women (see different scenarios) | Same as for non-pregnant |
|---|---|
| Objective of treatment in pregnant women | Full plasma HIV-VL suppression at least by third trimester and specifically at time of delivery. In such instance, risk of transmission is 0 to < 0.5% |
| Resistance testing | Same as for non-pregnant women, i.e. before starting ART and in case of virological failure |
| **SCENARIO** | |
| 1. Women planning to be pregnant while already on ART | 1. Maintain ART, unless taking some contraindicated regimen during pregnancy (ddI + d4T, triple NRTI combinations) |
| 2. Women becoming pregnant while already on ART | 2. Maintain ART, unless taking some contraindicated regimen during pregnancy (ddI + d4T, triple NRTI combinations) |
| 3. Women becoming pregnant while treatment-naïve | 3. Starting ART as soon as possible is highly recommended |
| 4. Women whose follow-up starts late in the second or in the third trimester | 4. Start ART immediately and consider INSTI as the preferred choice to obtain rapid HIV-VL decline and to ensure the HIV-VL is undetectable by the time of delivery |
| 5. Women whose HIV-VL is not undetectable at third trimester | 5. Perform resistance testing and consider changing to or adding INSTI if not on this class to obtain rapid HIV-VL decline |
| Antiretroviral regimen in pregnancy | Same as non-pregnant |
| | If on RAL, DTG, RPV or DRV/r: could be continued. Women on EVG/c need to be informed that more monitoring of HIV-VL and drug levels may be necessary during pregnancy |
| | Among PI/r, prefer ATV/r |
| | EFV is a suitable alternative for pregnant persons needing to start treatment. It can be continued if already started before pregnancy |
| | NVP not to be initiated, but continuation is possible if started before pregnancy |
| | Limited experience with TAF and COBI in pregnancy: not recommended in initial regimen |
| Drugs contraindicated during pregnancy | ddI + d4T, triple NRTI combinations |
| iv ZDV during labour | Only if HIV-VL > 50 copies/mL at week 34-36 |
| Single dose NVP during labour | Not recommended |
| Caesarean section | Only if HIV-VL > 50 copies/mL at week 34-36 |
| Breastfeeding | We advise against breastfeeding. In case a woman insists on breastfeeding, we recommend follow-up with increased clinical and virological monitoring of both the mother and the infant |

# ART in TB/HIV Co-infection

## Principles

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

All persons with TB/HIV co-infection should start ART irrespective of CD4 count. Treatment supervision and adherence evaluation are very important.

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

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

≥ 50 cells/μL: Can be deferred until between 8 and 12 weeks of TB treatment, especially when there are difficulties with drug-drug interactions, adherence and toxicities

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

* Be aware of IRIS reaction in persons starting ART at low CD4 count levels and with early initiation of ART. Corticosteroids should be considered for treatment of symptomatic IRIS, with dosages and duration tailored according to response.
See online video lectures HIV and IRIS-Part 1 and HIV and IRIS-Part 2 from the EACS online course Clinical Management of HIV.

** Although the data suggest a cut-off of 50 cells/μL, because of the daily variability in CD4 count, a cut-off of 100 cells/μL may be more appropriate.

## Recommended 1st line ARV combination with anti-TB medicines

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

## Alternatives

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

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

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

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

*** Only pharmacokinetic and not clinical data are available, use with caution.

**Important drug-drug interactions between ART and rifampicin / rifabutin**

| ARV drug class | Specific ARVs | Drug-drug interactions and recommended adjustment of dose of either or both drugs |
|---|---|---|
| **NRTIs**[i] | | rifampicin: standard dose of all drugs |
| | | rifabutin: standard dose of all drugs |
| **PI/r and PI/c** | | rifampicin: not recommended |
| **PI/r** | Monitor liver enzymes and, whenever possible, perform TDM for PI | rifabutin: dose as 150 mg qd[ii]. PI/r at standard dose |
| **PI/c** | | rifabutin: not recommended. If needed recommended dose of rifabutin: 150 mg qd[iii] |
| **NNRTIs** | EFV | rifampicin: No dose change required. EFV: standard dose ARV TDM recommended after 2 weeks |
| | | rifabutin: 450 mg qd. EFV: standard dose |
| | NVP | neither rifampicin nor rifabutin recommended |
| | RPV | rifampicin: not recommended |
| | | rifabutin: standard dose. RPV dose should be increased (use with caution) |
| | ETV | rifampicin: not recommended |
| | | rifabutin: standard dose of both drugs (few data – use with caution) |
| **INSTI** | EVG/c | rifampicin: not recommended |
| | | rifabutin: 150 mg qd. EVG: standard dose. Use with caution. |
| | RAL | rifampicin: standard dose. RAL 400 or 800 mg bid and perform TDM for RAL |
| | | rifabutin: standard dose of both drugs |
| | DTG | rifampicin: standard dose. DTG 50 mg bid (use only in absence of INSTI resistance) |
| | | rifabutin: standard dose of both drugs |
| **Other ART** | MVC | rifampicin: MVC 600 mg bid |
| | | rifabutin: standard dose of MVC (300 mg bid in absence of a PI, 150 mg bid in presence of a PI) |

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

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

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

# Post-exposure Prophylaxis (PEP)

**PEP recommended in case of:**

| Risk | Nature of exposure | Status of source person |
|---|---|---|
| **Blood** | Subcutaneous or intramuscular penetration with iv or im needle, or intravascular device | HIV-positive or recent serostatus unknown, but presence of HIV risk factors |
| | Percutaneous injury with sharp instrument (lancet), im or sc needle, suture needle<br>Contact > 15 min of mucous membrane or non-intact skin | HIV-positive |
| **Genital secretions** | Anal or vaginal sex | Viraemic HIV-positive or serostatus unknown but presence of HIV risk factors. If source person is on ART, PEP should be started, HIV-VL should be repeated, and, if undetectable, PEP can be stopped |
| | Receptive oral sex with ejaculation | Viraemic HIV-positive |
| **Intravenous drug use** | Exchange of syringe, needle, preparation material or any other material | HIV-positive |

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

- Full sexual health screen in case of sexual exposure.

- 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)

# 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 chemsex may be markers of increased risk for HIV acquisition.
- May be considered in HIV-negative heterosexual women and men who are inconsistent in their use of condoms and have multiple sexual partners where some of whom are likely to have HIV infection and not being on treatment.

2. PrEP is a medical intervention that provides a high level of protection against HIV acquisition but does not protect against other 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 prior to starting PrEP. During PrEP, this test should be repeated every 3 months, and PrEP should be stopped immediately in case of early clinical signs of HIV seroconversion or a positive HIV diagnostic test and the person referred for evaluation to an HIV unit.
- Before PrEP is initiated, HBV serology status should be documented. If HBsAg positive, see Clinical Management and Treatment of HBV and HCV Co-infection in HIV-positive Persons.
- Counsel that PrEP does not prevent other types of STIs; screen for STI (including HCV) when starting PrEP and regularly during use of PrEP.
- Counsel that PrEP may impact renal and bone health, see page 51 and 47. 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. For MSM with high-risk sexual behavior PrEP may be dosed ‘on demand’ (double dose of TDF/FTC 2-24 hours before each sexual intercourse, followed by two single doses of TDF/FTC, 24 and 48 hours after the first drug intake). If dosed ‘on demand’, the total dose per week should not exceed 7 tablets.
- Use of generic formulations of TDF/FTC, if and where available, may help to improve the cost-effectiveness of PrEP, which is essential for its use as public health approach.
- There are not currently clinical data on the use of 3TC or TAF for PrEP.

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

# Adverse Effects of ARVs and Drug Classes

**Bold: Frequent effects**
Red: Severe effects
Black: Neither Frequent nor Severe[i]

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

| | Skin | Digestive | Liver | CV | Musculo-skeletal | Genito-urinary | Nervous | Body fat | Metabolic | Other |
|---|---|---|---|---|---|---|---|---|---|---|
| **FI** | | | | | | | | | | |
| ENF | Injection nodules | | | | | | | | | Hypersensitivity |
| **INSTI** | | | | | | | | | | |
| RAL | | Nausea | | | Myopathy, Rhabdomy-olysis | | Sleep disturbances, Headache | | | Systemic hypersensitivity syndrome[viii] |
| DTG | Rash | Nausea | | | | ↓ eGFR[iv] | **Sleep disturbances, Headache** | | | Systemic hypersensitivity syndrome (< 1%) |
| EVG/c | | **Nausea,** Diarrhoea | | | | ↓ **eGFR**[iv] | Sleep disturbances, Headache | | | |
| **CCR5 inhibitor** | | | | | | | | | | |
| MVC | | | Hepatitis | | | | | | | |

i **"Frequent effects" (events expected in at least 10% of treated HIV-positive persons), in bold.**
"Severe effects" (events that can put a person's life at risk and represent a medical emergency), in red.
"Neither frequent nor severe effects", in black.

ii Still available, but generally not recommended due to toxicity.

iii TDF has been the classical prodrug of tenofovir. TAF has lower tenofovir-related kidney and bone adverse effects, but long-term experience is lacking, see pages 50-51 and page 47.

iv Due to inhibition of renal tubular creatinine secretion without affecting glomerular filtration itself.

v ATV can be used unboosted, or boosted with low-dose RTV or COBI. ATV-related adverse effects are more common with boosting. DRV can be used boosted with low-dose RTV or COBI. Both low-dose RTV and COBI as boosters may cause similar minor digestive problems.

vi Still available but seldom used. Requires RTV-boosting.

vii Frequency and severity differs between individual ARVs.

viii DRESS syndrome reported, but currently in only 6 cases.

* Refers to effects seen in relation to hypersensitivity reactions.

Note: the adverse effects included in the table above are not exhaustive, but represent the most important effects with a likely causal relation. Nausea, diarrhoea and rash are frequently observed in persons on ART, and these symptoms are indicated in the table for drugs where clinical experience suggests a possible causal link.

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

# Drug-drug Interactions between ARVs and Non-ARVs[i]

| | Non-ARV drugs | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cardiovascular drugs | atorvastatin | ↑822% | ↑ | ↑290% | ↑ | ↑490% | ↓43% | ↓37% | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | fluvastatin | ↑ | ↑ | ↑ | ↔ | ↔ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | pravastatin | ↑ | ↑ | ↑ | ↑81% | ↔ | ↓44% | ↓ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | rosuvastatin | ↑242% | ↑213% | ↑93% | ↑48% | ↑107% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑38% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | simvastatin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓68% | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | amlodipine | ↑[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | diltiazem | ↑[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↓69% | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | metoprolol | ↑[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | verapamil | ↑[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↓ | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | E | E | ↔ |
| | warfarin | ↑ | ↑ or ↓ | ↑ | ↓ | ↓ | ↑ or ↓ | ↑ | ↑ or ↓ | ↔ | ↔ | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| CNS drugs | diazepam | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↑ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | midazolam (oral) | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | triazolam | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | citalopram | ↑[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↓ | ↓ | ↓ | ↔[iv] | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | mirtazapine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | paroxetine | ↑↓? | ↑↓? | ↑↓? | ↓39% | ↑↓? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑↓? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sertraline | ↑ | ↓ | ↑ | ↓49% | ↓ | ↓39% | ↓ | ↓ | ↔ | ↔ | ↔ | ↓7% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | bupropion | ↔ | ↓ | ↔ | ↓ | ↓57% | ↓55% | ↔ | ↓ | ↔ | ↔ | ↔ | ↑? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | pimozide | ↑[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↑ | ↓ | ↓ | ↔[iv] | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | carbamazepine | ↑D | ↑D | ↑D | ↑ | ↑D | ↓27%D36% | D | ↓D | D | D | D | D | D | ↑ | ↔ | ↔ | D | ↔ | ↑[ix] |
| | lamotrigine | ↔ | ↓32%[ii] | ↔ | ↓[ii] | ↓50% | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | phenytoin | D | ↓D | D | ↓D | ↓D | ↓D | D | ↓D | D | D | D | D | D | D | ↔ | ↔ | D | ↔ | ↓ |
| Anti-infectives | clarithromycin | ↑E[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↓ | ↓E | ↓ | E | E | ↔ | ↑E | ↔ | ↔ | ↔ | ↔ | E | E | D |
| | fluconazole | ↑? | ↔ | ↑? | ↔ | ↔ | ↔ | E86% | E100% | E | ↔ | ↔ | ↑? | ↔ | ↔ | ↔ | ↔ | E? | ↔ | E74% |
| | itraconazole | ↑E | ↑E | ↑E | ↑E | ↑E | ↓ | ↓E | ↓61% | E | E | ↔ | ↑E | ↔ | ↔ | ↔ | ↔ | E | E | ↔ |
| | rifabutin | ↑D | ↑ | ↑D | ↑E50% | ↑ | ↓38% | D37% | ↑17% | D | * | ↔ | ↑D | ↔ | ↔ | ↔ | ↔ | D | ↔ | ↔ |
| | rifampicin | D | D72% | D | D | D | D26% | D | D58% | D80% | D | D54%[x] | D | D40% | D | ↔ | ↔ | D | ↔ | D47% |
| | voriconazole | ↑E | ↓ | ↑E | ↓ | ↓ | ↓E | ↑E | ↓E | E | E | ↔ | ↑E | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Miscellaneous | antacids | D | D | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | D | ↔ | D | D | D | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | PPIs | D | D | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | D | ↔ | ↔ | ↔ | E | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | H2 blockers | D | D | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | D | ↔ | ↔ | ↔ | E | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | alfuzosin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | beclometasone inhal. | ↑[v] | ↑[v] | ↑?[v] | ↓11% | ↑[v] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑[v] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | buprenorphine | ↑ | ↑67% | ↑ | ↑[vi] | ↔ | ↓50% | ↓25% | ↔ | ↔ | ↔ | ↔ | ↑35% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | budesonide inhal. | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | ergot derivatives | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | E | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | ethinylestradiol | ↔ | ↓19%[vii] | ↑30% | ↓44% | ↓ 2% | ↔[viii] | ↑22% | ↓20% | ↑14% | ↔ | ↑3% | ↓25% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | fluticasone inhal. | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | methadone | ↑?[iii] | ↓[ii, iii] | ↑? | ↓16% | ↓53%[iii] | ↓52% | ↑6% | ↓≈50% | ↓16% | ↔ | ↔ | ↑7% | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | E29-43% |
| | salmeterol inhal. | ↑[iii] | ↑[iii] | ↑ | ↑ | ↑[iii] | ↓ | ↓ | ↓ | ↔[iv] | ↔ | ↔ | ↑[iii] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sildenafil (erec. dys.) | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓37% | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | St John's wort | D | D | D | D | D | D | D | D | D | D | D | D | D? | ↔ | ↔ | ↔ | D | ↔ | ↔ |
| | varenicline | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Comments**

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

**Legend**

↑ potential elevated exposure of non-ARV drug

↓ potential decreased exposure of non-ARV drug

↔ no significant effect

E potential elevated exposure of ARV

D potential decreased exposure of ARV

Numbers refer to decreased/increased AUC of non-ARV/ARV drugs as observed in drug interactions studies.

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

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

ii no PK changes with unboosted PI

iii ECG monitoring is recommended

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

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

vi concentration of parent drug unchanged but concentration of metabolite increased

vii increase in ethinylestradiol with unboosted ATV

viii no effect on ethinylestradiol but ↓ progestin

ix potential haematological toxicity

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

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

**Colour legend**

no clinically significant interaction expected

these drugs should not be co-administered

potential 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).

# Drug-drug Interactions between Antidepressants and ARVs

| Antidepressants | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SSRI** | citalopram | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | escitalopram | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | fluvoxamine | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | E | ↔ | ↔ | ↔ | ↑ | ↔ |
| | fluoxetine | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | paroxetine | ↑↓? | ↑↓? | ↑↓? | ↓39% | ↑↓? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑↓? | ↔ |
| | sertraline | ↑ | ↓ | ↑ | ↓49% | ↓ | ↓39% | ↓ | ↓ | ↔ | ↔ | ↔ | ↓7% | ↔ |
| **SNRI** | duloxetine | ↑ | ↑↓ | ↑ | ↑↓ | ↑↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | venlafaxine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | D | ↔ | ↑ | ↔ |
| **TCA** | amitriptyline | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↔ | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | clomipramine | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑[a] | ↔ |
| | desipramine | ↑[a] | ↑[a] | ↑ | ↑ | ↑5%[a] | ↔ | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | doxepin | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | imipramine | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑[a] | ↔ |
| | nortriptyline | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↔ | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | trimipramine | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| **TeCA** | maprotiline | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | mianserine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | mirtazapine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ |
| **Oth-ers** | bupropion | ↔ | ↓ | ↔ | ↓ | ↓57% | ↓55% | ↔ | ↓ | ↔ | ↔ | ↔ | ↑? | ↔ |
| | lamotrigine | ↔ | ↓32% | ↔ | ↓ | ↓50% | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nefazodone | ↑ | ↑ | ↑ | ↑ | ↑ | ↓E | ↓E | ↓E | E | E | ↔ | ↑ | ↔ |
| | St John's wort | D | D | D | D | D | D | D | D | D | D | D[c] | D | D? |
| | trazodone | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑ | ↔ |

**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)
a ECG monitoring is recommended
b caution as both drugs can induce QT interval prolongation
c the US Prescribing Information recommends that co-administration should be avoided as there are insufficient data to make dosing recommendations

Numbers refer to decreased AUC of the antidepressant as observed in drug-drug interactions studies.

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

**Colour legend**

- no clinically significant interaction expected
- these drugs should not be co-administered
- potential 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).

# Drug-drug Interactions between Antihypertensives and ARVs

| Antihypertensives | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACE inhibitors | 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 | ↔[d] | ↔[d] | ↔ | ↔ | ↔[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | bisoprolol | ↑[d] | ↑[d] | ↑ | ↑ | ↑[d] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | carvedilol | ↑[d] | ↑↓[d] | ↑ | ↑↓ | ↑↓[d] | ↑↓ | ↑↓ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | metoprolol | ↑[d] | ↑[d] | ↑ | ↑ | ↑[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | propranolol | ↑[d] | ↑[d] | ↑ | ↑ | ↑[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Calcium channel blockers | amlodipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | diltiazem | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓69% | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | felodipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | lacidipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | lercanidipine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nicardipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nifedipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nisoldipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | verapamil | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | E | E | ↔ |
| Diuretics | amiloride | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | bendroflumethiazide | ? | ? | ? | ? | ? | ? | ? | ? | ↔ | ↔ | ↔ | ? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | chlortalidone | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | furosemide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | E | ↔ |
| | indapamide | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | hydrochlorothiazide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | torasemide | ↔ | ↓ | ↔ | ↓ | ↓ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Others | doxazosin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sacubitril | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | E | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | spironolactone | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Legend**

| | |
|---|---|
| ↑ | potential elevated exposure of the antihypertensive |
| ↓ | potential decreased exposure of the antihypertensive |
| ↔ | no significant effect |
| D | potential decreased exposure of ARV drug |
| E | potential elevated exposure of ARV drug |
| ATV/c | ATV co-formulated with COBI (300/150 mg qd); |
| DRV/c | DRV co-formulated with COBI (800/150 mg qd) |
| a | [parent drug] decreased but [active metabolite] increased |
| b | [parent drug] increased but [active metabolite] decreased |
| c | ECG monitoring recommended |
| d | risk of PR interval prolongation |
| e | use with caution as both LPV and calcium channel blockers prolong the PR interval. Clinical monitoring is recommended. |

Numbers refer to decreased AUC of the antihypertensive as observed in drug-drug interactions studies.

**Colour legend**

- no clinically significant interaction expected
- these drugs should not be co-administered
- potential 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
- there are no clear data, actual or theoretical, to indicate whether an interaction will occur

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

**Comment**

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 Analgesics and ARVs

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

**Legend**

↑ potential elevated exposure of the analgesic
↓ potential decreased exposure of the analgesic
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
ATV/c ATV co-formulated with COBI (300/150 mg qd);
DRV/c DRV co-formulated with COBI (800/150 mg qd)
a clinical significance unknown. Use the lowest recommended dose particularly in individuals with risk factors for CVD, those indviduals at risk of developing gastrointestinal complications, persons with hepatic or renal impairment, and in elderly persons
b potential additive haematological toxicity
c [parent drug] unchanged but [metabolite] increased
d both drugs can potentially prolong the QT interval, ECG monitoring recommended
e potential decrease of the analgesic effect due to the reduced conversion to the active metabolite
f [parent drug] decreased and increased [neurotoxic metabolite]
g [parent drug] decreased but no change in [more active metabolite]
h potential risk of nephrotoxicity which is increased if NSAID is used for a long duration, if the 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
i inhibition of P-gp by RTV and COBI could potentiate the effect of opiate in the CNS

Numbers refer to increased or decreased AUC of the analgesic as observed in drug-drug interactions studies

**Colour legend**

no clinically significant interaction expected
these drugs should not be co-administered
potential 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).

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

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

**Legend**

↑ potential elevated exposure of the anticoagulant/antiplatelet agent
↓ potential decreased exposure of the anticoagulant/antiplatelet agent
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
ATV/c ATV co-formulated with COBI (300/150 mg qd);
DRV/c DRV co-formulated with COBI (800/150 mg qd)
a unboosted ATV predicted to increase the anticoagulant, monitor INR and adjust the anticoagulant dosage accordingly
b potential risk of nephrotoxicity, monitor renal function
c decreased conversion to active metabolite leading to non-responsiveness to clopidogrel. An alternative to clopidogrel should be considered
d increase in amount of active metabolite via induction of CYP3A4 and CYP2B6
e unboosted ATV predicted to increase dipyridamole exposure due to UGT1A1 inhibition
f reduced active metabolite, but without a significant reduction in prasugrel activity

**Colour legend**

no clinically significant interaction expected
these drugs should not be co-administered
potential 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).

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

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

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

**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

**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).

# Drug-drug Interactions between Contraceptives/Hormone Replacement Therapy and ARVs

| | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Es | ethinylestradiol (COC, TS, VR) | ↔ | ↓19%[a] | ↓30% | ↓44%[b] | ↓42%[b] | ↔[c] | ↑22% | ↓20% | ↑14% | ↔ | ↑3% | ↓25%[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Progestins | desogestrel (COC) | ↑ | ↑[e,a] | ↑ | ↑[f] | ↑[f] | ↓[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑[d,e] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | desogestrel (POP) | ↑ | ↑ | ↑ | ↑ | ↑ | ↓[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | drospirenone (COC) | ↑ | ↑[e,a] | ↑[f] | ↑[f] | ↑[f] | ↓[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑[d,e] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | etonogestrel (IP) | ↑ | ↑ | ↑ | ↑ | ↑52% | ↓63%[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | etonogestrel (VR) | ↑ | ↑[h] | ↑ | ↑[h] | ↑[h] | ↓[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑[h] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | gestodene (COC) | ↑ | ↑[e,a] | ↑ | ↑[f] | ↑[f] | ↓[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑[d,e] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | levonorgestrel (COC) | ↑ | ↑[e,a] | ↑ | ↑[f] | ↑[f] | ↓[g] | ↓ | ↑ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | levonorgestrel (IP) | ↑ | ↑ | ↑ | ↑ | ↑ | ↓47%[g] | ↓ | ↑14% | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | levonorgestrel (POP) | ↑ | ↑ | ↑ | ↑ | ↑ | ↓[g] | ↓ | ↑ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | levonorgestrel (IUD) | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | medroxyprogesterone (POI) | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | norelgestromin (TS) | ↑ | ↑[e,a] | ↑ | ↑[f] | ↑83%[f] | ↓[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑[d,e] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | norethisterone (COC) | ↑ | ↑[e,a,i] | ↑ | ↓14%[f] | ↓17%[f] | ↓[g] | ↓5% | ↓19% | ↓11% | ↔ | ↔ | ↑[d,e] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | norethisterone (POI) | ↔ | ↔ | ↔ | ↔ | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | norethisterone (POP) | ↑ | ↑50% | ↑ | ↑50% | ↑50% | ↓[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | norgestimate (COC) | ↑ | ↑85%[e,a] | ↑ | ↑[f] | ↑[f] | ↓64%[g] | ↓ | ↓ | ↔ | ↔ | ↔ | ↑126%[d,e] | ↑14% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | norgestrel (COC) | ↑ | ↑[e,a] | ↑ | ↑[f] | ↑[f] | ↓[g] | ↓ | ↑ | ↔ | ↔ | ↔ | ↑[d,e] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Other | levonorgestrel (EC) | ↑[j] | ↑[j] | ↑[j] | ↑[j] | ↑[j] | ↓58%[k] | ↔ | ↔ | ↔ | ↔ | ↔ | ↑[j] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | mifepristone | ↑[j] | ↑[j] | ↑[j] | ↑[j] | ↑[j] | ↓ | ↓ | ↓ | E[j] | E[j] | ↔ | ↑[j] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | ulipristal | ↑[j] | ↑[j] | ↑[j] | ↑[j] | ↑[j] | ↓[l] | ↓[l] | ↓[l] | ↔ | ↔ | ↔ | ↑[j] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**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)

a unboosted ATV increased ethinylestradiol AUC by 48%. Use no more than 30 µg of ethinylestradiol if co-administered with unboosted ATV and at least 35 µg of ethinylestradiol if co-administered with ATV/r
b alternative or additional contraceptive measures are recommended or, if used for hormone replacement therapy, monitor for signs of oestrogen deficiency
c no effect on ethinylestradiol exposure, however levels of co-administered progestin are markedly decreased. Use with EFV is not recommended as it may impair contraceptive efficacy
d European SPC states a hormonal contraceptive should contain at least 30 ug 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/d) 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 norethisterone AUC by 110%
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

Es = estrogens
Contraceptive options: **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

**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 or unlikely to impair contraceptive efficacy. 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).

# Drug-drug Interactions between Corticosteroids and ARVs

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

**Legend**

↑ potential increased exposure of the corticosteroid
↓ potential decreased exposure of the corticosteroid
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
ATV/c ATV co-formulated with COBI (300/150 mg qd);
DRV/c DRV co-formulated with COBI (800/150 mg qd)

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

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

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

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

**Colour legend**

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

**Comment**

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 | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First line and second line drugs | amodiaquine | ↔ | ↑ | ↔ | ↑ | ↑ | ↑[c] | ↓? | ↓29%[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[e] |
| | artemisinin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ ≈50% | ↓D | ↓D | D | D | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | atovaquone | ↔ | ↓46%[a] | ↔ | ↓[a] | ↓74%[a] | ↓75%[a] | ↓E55%[a] | ↓[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[e] |
| | chloroquine | ↔[b] | ↔[b] | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↔ | ↔[f] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | clindamycin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | doxycycline | ↔ | ↔ | ↔ | ↔ | ↔ | ↓? | ↓? | ↓? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | lumefantrine | ↑[b] | ↑[b] | ↑ | ↑ | ↑[b] | ↓ ≈40% | ↓ | ↓D46% | ↔[f] | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | mefloquine | ↑[b] | ↑[b] | ↑ | ↑ | ↑[b] | ↓ | ↓ | ↓ | ↔[f] | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | primaquine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[d] | ↔[d] | ↔[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[e] |
| | proguanil | ↔ | ↓41%[a] | ↔ | ↓[a] | ↓38%[a] | ↓44%[a] | ↓E55%[a] | ↓[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | pyrimethamine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↑ | ↔ | ↔ | ↔[e] |
| | quinine | ↑[b] | ↑[b] | ↑ | ↑ | ↑[b] | ↓ | ↓ | ↓ | ↔[f] | ↑ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sulfadoxine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↑ | ↔ | ↔ | ↔[e] |

**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)
a take with high fat meal, consider dose increase
b ECG monitoring is recommended
c liver toxicity
d increase of haemotoxic metabolites
e additive haematotoxicity
f both drugs can induce QT interval prolongation (only at supratherapeutic dose for RPV)

**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).

# Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

| Pulmonary antihypertensives | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ERA | ambrisentan | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | bosentan | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓ | ↓ | ↓[b] | D | D | D | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | macitentan | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| PDE5 | sildenafil | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | tadalafil | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| sGC | riociguat | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| PA | epoprostenol | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | iloprost | ↔ | ↔ ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | treprostinil | ↔ | ↑ | ↔ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| IPr | selexipag | ↔[c] | ↔[c] | ↔[c] | ↔[c] | ↔[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**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)
a 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

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

**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).

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

| Immunosuppressants | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CS | prednisone | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| AM | azathioprine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | mycophenolate | ↔ | ↓ | ↔ | ↓ | ↓ | ↓ | ↔ | ↓E13% | ↔ | ↔ | ↔ | ↓ | ↔ | ↓? | ↔ | ↔ | ↔ | E[b] | ↓? |
| CNI | cyclosporine | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | E | E | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | E | E[b] | ↔ |
| | tacrolimus* | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | ↔ | ↔ | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[b] | ↔ |
| mTOR | everolimus | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | ↔ | ↔ | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sirolimus | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | ↔ | ↔ | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[b] | ↔ |
| Other | anti-thymocyte globulin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | basiliximab | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | belatacept | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Legend**

↑ potential increased exposure of the immunosuppressant
↓ potential decreased exposure of the immunosuppresant
↔ 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 decreased/increased AUC of the immunosuppressant as observed in drug-drug interaction studies
a TDM of immunosuppressant is recommended
b monitor renal function
c potential additive haematotoxicity

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

**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).

# Dose Adjustment of ARVs for Impaired Hepatic Function

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

| PIs | |
|---|---|
| **ATV** | Child-Pugh Class B: 300 mg qd |
| | Child-Pugh Class C: not recommended |
| | RTV boosting is not recommended in persons with hepatic impairment (Child-Pugh Class B or C) |
| **DRV** | Child-Pugh Class A or B: no dosage adjustment |
| | Child-Pugh Class C: not recommended |
| **DRV/c** | Child-Pugh Class A or B: no dosage adjustment |
| | Child-Pugh Class C: not recommended |
| **FPV** | **PI-naïve persons:** |
| | Child-Pugh Class A or B: 700 mg bid |
| | Child-Pugh Class C: 350 mg bid |
| | **PI-experienced persons:** |
| | Child-Pugh Class A: 700 mg bid + RTV 100 mg qd |
| | Child-Pugh Class B: 450 mg bid + RTV 100 mg qd |
| | Child-Pugh Class C: 300 mg bid + RTV 100 mg qd |
| **IDV** | Child-Pugh Class A or B: 600 mg q8h |
| | Child-Pugh Class C: no data |
| **LPV/r** | No dosage recommendation; use with caution in persons with hepatic impairment |
| **RTV** | Refer to recommendations for the primary PI |
| **SQV** | Child-Pugh Class A or B: use with caution |
| | Child-Pugh Class C: contraindicated |
| **TPV** | Child-Pugh Class A: use with caution |
| | Child-Pugh Class B or C: contraindicated |
| **FI** | |
| **ENF** | No dosage adjustment |
| **CCR5 Inhibitor** | |
| **MVC** | No dosage recommendations. Concentrations will likely be increased in persons with hepatic impairment |
| **INSTI** | |
| **RAL** | No dosage adjustment |
| **EVG** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **DTG** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **TAF/FTC/EVG/c** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **TDF/FTC/EVG/c** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **ABC/3TC/DTG** | Use separate compounds and refer to those adjustments |

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

# Dose Adjustment of ARVs for Impaired Renal Function

| | | eGFR[i] (mL/min) | | | | Haemodialysis |
|---|---|---|---|---|---|---|
| | | ≥ 50 | 30-49 | 10-29 | < 10 | |
| **NRTIs** | | | | | | |
| **ABC** | | 300 mg q12h | No dose adjustment required | | | |
| **ddI**[ii] | ≥ 60 kg | 400 mg q24h | 200 mg q24h | 150 mg q24h | 100 mg q24h | 100 mg q24h[iv] |
| | < 60 kg | 250 mg q24h | 125 mg q24h | 100 mg q24h | 75 mg q24h | 75 mg q24h[iv] |
| **d4T** | ≥ 60 kg | 40 mg q12h | 20 mg q12h | 20 mg q24h | 20 mg q24h | 20 mg q24h[iv] |
| | < 60 kg | 30 mg q12h | 15 mg q12h | 15 mg q24h | 15 mg q24h | 15 mg q24h[iv] |
| **FTC** | | 200 mg q24h | 200 mg q48h | 200 mg q72h | 200 mg q96h | 200 mg q96h[iv] |
| **3TC** | | 300 mg q24h | 150 mg q24h | 100 mg q24h[iii] | 50-25 mg q24h[iii] | 50-25 mg q24h[iii], [iv] |
| **TAF/FTC** | | 25[ix]/200 mg q24h | | Not recommended | | |
| **TDF**[v] | | 300[viii] mg q24h | 300[viii] mg q48h | Not recommended (300[viii] mg q72-96h, if no alternative) | Not recommended (300[viii] mg q7d, if no alternative) | 300[viii] mg q7d[iv] |
| **ZDV** | | 300 mg q12h | No dose adjustment required | | 100 mg q8h | 100 mg q8h[iv] |
| **ABC/3TC** | | 600/300 mg q24h | Use individual drugs | | | |
| **ZDV/3TC** | | 300/150 mg q12h | | | | |
| **ABC/3TC/ZDV** | | 300/150/300 mg q12h | | | | |
| **TDF/FTC** | | 300[viii]/200 mg q24h | 300[viii]/200 mg q48h | Use individual drugs | | |
| **NNRTIs** | | | | | | |
| **EFV** | | 600 mg q24h | No dose adjustment required | | | |
| **ETV** | | 200 mg q12h | No dose adjustment required | | | |
| **NVP** | | 200 mg q12h | No dose adjustment required | | | |
| **TDF/FTC/EVG/c** | | Do not initiate if eGFR < 70 mL/min | Do not use | | | |
| **TAF/FTC/EVG/c** | | 10/200/150/150 mg q24h | | Not recommended | | |
| **TAF/FTC/RPV** | | 25/200/25 mg q24h | | Not recommended | | |
| **TDF/FTC/RPV** | | 300[viii]/200/25 mg q24h | Do not use | | | |

| | eGFR[i] (mL/min) | | | | Haemodialysis |
|---|---|---|---|---|---|
| | ≥ 50 | 30-49 | 10-29 | < 10 | |
| **PIs**[v] | | | | | |
| **ATV/r** | 300/100 mg q24h | No dose adjustment required[vi] | | | |
| **DRV/r** | 800/100 mg q24h<br>600/100 mg q12h | No dose adjustment required[vi] | | | |
| **DRV/c** | 800/150 mg q24h | No dose adjustment required[vi] | | | |
| **FPV/r** | 700/100 mg q12h | No dose adjustment required[vi] | | | |
| **LPV/r** | 400/100 mg q12h | No dose adjustment required[vi] | | | |
| **SQV/r** | 1000/100 mg q12h | No dose adjustment required[vi] | | | |
| **TPV/r** | 500/200 mg q12h | No dose adjustment required[vi] | | | |
| **Other ART** | | | | | |
| **RAL** | 400 mg q12h | No dose adjustment required[vi] | | | |
| **DTG** | 50 mg q24h | No dose adjustment required[vi] | | | No clinical data; PK data suggest safety |
| **ABC/3TC/DTG** | 600/300/50 mg q24h | Use individual drugs | | | |
| **MVC: co-administered without CYP3A4 inhibitors**[vii] | 300 mg q12h | No dose adjustment required[vi] | | | |
| **MVC: co-administered with CYP3A4 inhibitors**[vii] | If eGFR < 80 mL/min 150 mg q24h[vii] except: 150 mg q12h if co-administered with FPV/r | | | | |

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

ii Dose reduction if combined with TDF

iii 150 mg loading dose

iv After dialysis

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

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

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

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

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

# Administration of ARVs in Persons with Swallowing Difficulties

| Drug | Formulation | Crush tablets | Open capsules | Comment |
|---|---|---|---|---|
| **NRTIs** | | | | |
| ABC | tablet (300 mg)<br>solution (20 mg/mL) | yes | | Bitter taste. Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately |
| d4T | capsule (20, 30, 40 mg)<br>oral solution (1 mg/mL) | no | yes | Take on empty stomach |
| FTC | capsule (200 mg)<br>solution (10 mg/mL) | no | yes | Dissolve in ≥ 30 mL of water, contains Na 460 µmol/mL<br>Bioequivalence: 240 mg solution = 200 mg capsule; adjust dosage accordingly |
| 3TC | tablet (150, 300 mg)<br>solution (10 mg/mL)[vii] | yes | | Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately |
| TDF | tablet (300[i] mg) | yes | | Better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste) |
| ZDV | capsule (250 mg) | no | no | Sticky, bitter taste |
| | syrup (10 mg/mL) | | | Better: use syrup or iv 6 mg/kg per day in glucose 5% |
| TAF/FTC | tablet (25/200 mg and 10/200 mg)[v] | no | | Tablets should be swallowed whole and should not be chewed, broken, cut or crushed |
| TDF/FTC | tablet (300[i]/200 mg) | yes | | Better: dissolve in ≥ 1 dL of water/orange or grape juice (bitter taste) |
| ABC/3TC | tablet (600/300 mg) | no | | Use solution of individual compounds |
| ZDV/3TC | tablet (300/150 mg) | yes | | Disperse in ≥ 15 mL water, alternative: use solution of individual compounds |
| ABC/3TC/ZDV | tablet (300/150/300 mg) | no | | Use solution of individual compounds |
| **NNRTIs** | | | | |
| EFV | tablet (600 mg) | yes | | Difficult to dissolve; solution has lower bioavailability; if > 40 kg use 720 mg |
| | capsule (50, 100, 200 mg) | no | yes | |
| | solution (30 mg/mL) | | | |
| ETV | tablet (200 mg) | no | | Disperse in ≥ 5 mL water. The glass should be rinsed with water several times and each rinse completely swallowed to ensure the entire dose is consumed. |
| NVP | tablet (200, 400 mg)[ii]<br>suspension (10 mg/mL) | yes[ii] | | Dissolve in water |
| RPV | tablet (25 mg) | no | | Crushing of tablets and dispersion into a liquid is not recommended. RPV is insoluble in water over a wide pH range |
| TDF/FTC/EFV | tablet (300[i]/200/600 mg) | no | | |
| TAF/FTC/RPV | tablet (25/200/25 mg) | no | | Tablets should be swallowed whole and should not be chewed, crushed or split |
| TDF/FTC/RPV | tablet (300[i]/200/25 mg) | no | | Crushing of tablets and dispersion into a liquid is not recommended. RPV is insoluble in water over a wide pH range. |
| **PIs** | | | | |
| ATV | capsule (150, 200, 300 mg) | no | yes | Difficult to open; take with food |
| ATV/c | tablet (300/150 mg) | no | | Tablets should be swallowed whole and should not be chewed, broken, cut or crushed |
| DRV | tablet (75,150, 400, 600, 800 mg)<br>solution (100 mg/mL) | yes | | Take with food. Crushed tablets can be added to small amount of semi-solid food or liquid, all of which should be consumed immediately |
| DRV/c | tablet (800/150 mg) | no | | |
| FPV | tablet (700 mg)<br>suspension (50 mg/mL) | | | Bitter taste; adults take suspension on empty stomach |
| LPV/r | tablet (200/50 mg)<br>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)<br>solution (80 mg/mL) | no | | 43% alcohol, do not dilute solution (risk of precipitation), rinse with milk (no water); bitter taste; take with food |
| SQV | tablet (500 mg) | no | | |
| **Others** | | | | |
| DTG | tablet (50 mg) | yes | | Tablets may be split or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately |
| MVC | tablet (150, 300 mg) | yes | | While the company does not have any specific kinetic information, crushing the tablet is not expected to negatively affect the bioavailability |
| RAL[iii] | tablet (400 mg)<br>chewable tablets (25, 100 mg) | yes | | The bioavailability of the chewable tablet is higher: 300 mg chewable tablet (= 400 mg film-coated tablet) |
| TAF/FTC/EVG/c | tablet (10/200/150/150 mg) | no | | Tablets should be swallowed whole and should not be chewed, broken, cut or crushed |
| TDF/FTC/EVG/c | tablet (300[i]/200/150/150 mg) | yes | | Crushing of tablets does not significantly modify the pharmacokinetic profiles[iv] |
| ABC/3TC/DTG[vi] | tablet (600/300/50 mg) | yes | | Tablets may be split or crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately |

| Drug | Formulation | Crush tablets | Open capsules | Comment |
|---|---|---|---|---|
| **Prophylaxis/treatment of opportunistic infections** | | | | |
| azithromycin | tablet (250, 500 mg)<br>suspension (40 mg/mL) | no | | |
| cotrimoxazole | tablet (400/80 mg, forte 800/160 mg)<br>solution (40/8 mg/mL) | yes; forte difficult | | Dilute solution 3-5 times with water (high osmolality) |
| fluconazole | capsule (50, 200 mg)<br>suspension (40 mg/mL) | no | yes | |
| pyrimethamine | tablet (25 mg) | yes | | Take with food |
| valganciclovir | tablet (450 mg)<br>solution (50 mg/mL) | no | no | Difficult to dissolve |
| rifampicin | tablet (450, 600 mg) | yes | | Take on empty stomach |
| | capsule (150, 300 mg) | no | yes | |
| | suspension (20 mg/mL) | | | |
| rifabutin | capsule (150 mg) | no | yes | Mix with apple sauce, syrup (insoluble in water) |
| isoniazid | tablet (100, 150 mg) | yes | | Take on empty stomach |
| pyrazinamide | tablet (500 mg) | yes | | |
| ethambutol | tablet (100, 400 mg) | yes | | Difficult to dissolve<br>Better: use iv solution |
| rifampicin/isoniazid | tablet (150/100, 150/75 mg) | yes | | Take on empty stomach |
| Rifater (rifampicin, isoniazid, pyrazinamide) | tablet (120/50/300 mg) | yes | | Take on empty stomach |
| Rimstar (rifampicin, isoniazid, pyrazinamide, ethambutol) | tablet (150/75/400/275 mg) | yes | | Take on empty stomach |
| ribavirin | capsule (200 mg) | no | yes | Disperse in orange juice, take with food |

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

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

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

iii Crushing tablets is not recommended in the product information, however absorption of RAL was not compromised when the drug was crushed, dissolved in 60 mL warm water and administered by gastrostomy tube [10]. In addition, RAL drug absorption has been shown to be higher in HIV-positive persons taking RAL 400 mg bid by chewing the tablets as compared to swallowing the intact tablets [11].

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

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

vi The pharmacokinetic profiles of DTG/ABC/3TC were not modified to a clinically significant extent when the fixed-dose combination tablet (Triumeq) was crushed and administered suspended in water or in enteral nutrition [14].

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) [15].

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

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

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

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

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.

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

Depending on future clinical research findings, these recommendations will be regularly updated as required. The online version at http://www.eacsociety.org and the EACS Guidelines App contain more detailed information and links to other relevant websites; these will be regularly updated.
The current recommendations highlight co-morbidities that are seen frequently in the routine care of HIV-positive persons and those for which specific issues should be considered.

# Drug Dependency and Drug Addiction

**Characteristics of drugs used as opioid substitution therapy (OST)**[i]

| Feature | Methadone | Buprenorphine |
|---|---|---|
| **Dose required to prevent withdrawal symptoms according to degree of opioid dependency** | Linear relationship (from 10-300 mg per day) | Linear relationship for persons with less opioid dependency only – ceiling effect (max daily dose 24 mg) |
| **Interaction with ARVs** | Methadone plasma concentrations are reduced if used together with NNRTIs or PIs:<br>• NVP & EFV: ↓ 50%<br>• ETV: ↓ < 10%[ii]<br>• LPV/r: ↓ 50%<br>• SQV/r, DRV/r, FPV/r: ↓ 15-25%<br>• ATV, IDV: ↓ < 10% | Buprenorphine (B) and active metabolite norbuprenorphine (N) plasma concentrations are reduced if combined with NNRTIs and increased if combined with some PIs or INSTIs<br>• EFV: ↓ up to 50% (B) and 70% (N)<br>• ETV: ↓ 25% (B)<br>• ATV/r, IDV, SQV/r: ↑ 50-100% (B&N)<br>• DRV/r: ↑ 50% (N)<br>• **CAVE:** B reduces ATV; do not use without RTV or COBI boosting<br>• EVG/c, ↑ 35-42% (B&N)<br>(DTG, RAL, RPV & LPV/r do not affect B & N metabolism) |
| | **CAVE:** withdrawal symptoms if combined with ARV that decreases plasma concentration and risk of drug toxicity if such ARVs are interrupted – reverse if ARVs increase plasma concentration | |
| **Risk of overdose** | Yes | No, if used as a co-formulation with naloxone |
| **Causing QT prolongation on ECG** | Yes (dose-response relationship)[iii] | No |
| **Risk of obstipation** | High | High |
| **Type of administration** | Tablet or liquid | Tablet applied sublingual |
| **Risk of further impairment in persons with existing liver impairment** | Yes | Yes |

i See Drug-drug Interactions between Analgesics and ARVs

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

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

# Cancer: Screening Methods[i]

| Problem | Persons | Procedure | Evidence of benefit | Screening interval | Additional comments |
|---|---|---|---|---|---|
| **Anal cancer** | MSM and persons with HPV-associated dysplasia[ii] | Digital rectal exam ± anal cytology | Unknown; advocated by some experts | 1-3 years | If anal cytology abnormal, anoscopy |
| **Breast cancer** | Women 50-70 years | Mammography | ↓ Breast cancer mortality | 1-3 years | |
| **Cervical cancer** | HIV-positive women > 21 years or within 1 year after sexual debut | Liquid based cervical cytology test | ↓ Cervical cancer mortality | 1-3 years | HPV testing may aid screening |
| **Colorectal cancer** | Persons 50-80 years with a life expectancy > 10 years | Faecal occult blood test annually or sigmoidoscopy every 5 years or colonoscopy every 10 years | ↓ Colorectal cancer mortality | 1-3 years | |
| **HepatoCellular Carcinoma (HCC)** | Persons with cirrhosis, persons with HBV co-infection at high risk of HCC or those who ever had chronic hepatitis[iii] | Ultrasound (and alpha-foetoprotein) | Earlier diagnosis allowing for improved ability for surgical eradication | Every 6 months | See pages 56 and 79 |
| **Prostate cancer** | Men > 50 years with a life expectancy >10 years | PSA[iv] | Use of PSA is controversial | 2-4 years | Pros: ↑ early diagnosis and modest ↓ prostate cancer specific mortality. Cons: overtreatment, adverse effects of treatment on quality of life |

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

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

iii HCC screening is indicated in all cirrhotic individuals regardless of the underlying reason. In HBV co-infected non-cirrhotics, HCC screening should be performed in those who ever had chronic hepatitis (elevated transaminases) or with risk factors for HCC (including family history of HCC, Asians, Africans, see http://www.easl.eu/research/our-contributions/clinical-practice-guidelines. On a case-by-case basis, omitting HCC screening can be discussed in those without risk factors and normal transaminases before starting HBV-active treatment.

iv Whilst prostate cancer screening with PSA can reduce prostate cancer specific mortality, the absolute risk reduction is very small. Given limitations in the design and reporting of the randomized trials, there remain important concerns that the benefits of screening are outweighed by the potential harms to quality of life, including the substantial risks for over-diagnosis and treatment complications.

See online video lectures Epidemiology of cancers and HIV-Part 1, Epidemiology of cancers and HIV-Part 2, Clinical Management of cancers and HIV-Part 1 and Clinical Management of cancers and HIV-Part 2 from the EACS online course Clinical Management of HIV.

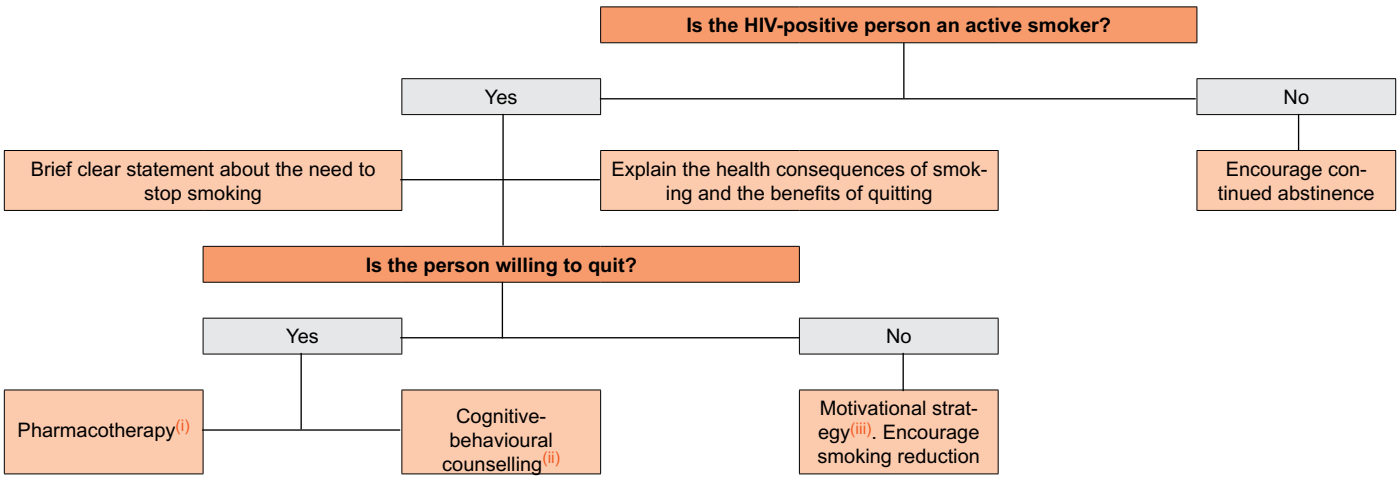
# Lifestyle Interventions[i]

| | |
|---|---|
| **Dietary counselling** | • Dietary intervention should not interfere with the dietary requirements necessary for appropriate absorption of ART drugs<br>• Keep caloric intake balanced with energy expenditure<br>• Limit intake of saturated fat, cholesterol and refined carbohydrates<br>• Reduce total fat intake to < 30% and dietary cholesterol to < 300 mg/day<br>• Emphasise intake of vegetables, fruit and grain products with fibre<br>• Cut back on beverages and foods with added sugar<br>• Choose and prepare foods with little or no salt. Aim to eat less than 1,500 mg of sodium per day<br>• Emphasise consumption of fish, poultry (without skin) and lean meat<br>• Consider referral to dietician, one-week food and drink diary to discover 'hidden' calories<br>• Avoid binge eating ('yo-yo dieting')<br>• In persons with HIV-related wasting and dyslipidaemia, address wasting first and consider referral to dietician<br>• Persons who are obviously overweight should be motivated to lose weight. Starvation diets are not recommended (immune defence mechanisms potentially decreased). Malnutrition has to be addressed where observed. Normal BMI range: 18.5-24.9; Overweight: 25.0-29.9, Obesity: > 30.0 kg/m$^2$ |
| | • The following questions are helpful to determine average alcohol intake<br>**1.** How often do you drink alcohol: never, ≤ 1/month, 2-4x/month, 2-3x/week, > 4x/week<br>**2.** If you drink alcohol, how much typically at a time: 1-2, 3-4, 5-6, 7-9, > 10 drinks<br>**3.** How many times do you have 6 or more alcoholic drinks at one occasion: never, < 1/month, 1x/month, 1x/week, more or less daily.<br>• Intake of alcohol should be restricted to no more than one drink per day for women and two drinks per day for men (< 20-40 g/day).<br>• In particular, persons with hepatic disease, see NAFLD, adherence problems, inadequate CD4 count increase, tumours, past tuberculosis, diarrhoea and other conditions associated with high alcohol intake should be motivated to decrease or stop alcohol intake. |
| **Exercise promotion** | • Promote active lifestyle to prevent and treat obesity, hypertension and diabetes<br>• Encourage self-directed moderate level physical activity (take the stairs, cycle or walk to work, cycling, swimming, hiking, etc.)<br>• Emphasise regular moderate-intensity exercise rather than vigorous exercise<br>• Achieve cardiovascular fitness (e.g. 30 minutes brisk walking > 5 days a week)<br>• Maintain muscular strength and joint flexibility |

i Based on recommendations by the US Preventive Services Task Force

## Smoking cessation

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




Adapted from [1] and [2]

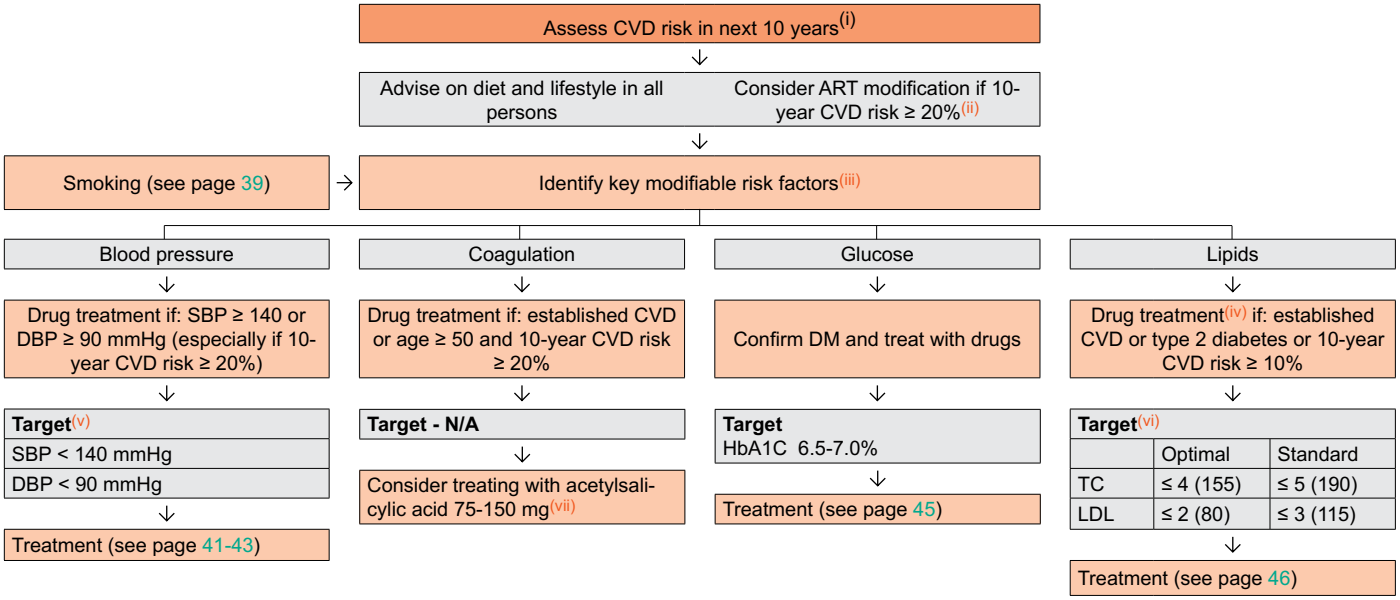
i Pharmacotherapy: Nicotine replacement therapy: nicotine substitution (patch, chewing gum, spray), varenicline and bupropion are approved by the EMA. Bupropion is contraindicated with epilepsy and varenicline may induce depression. Bupropion may interact with PIs and NNRTIs, see Drug-drug Interactions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

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

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

# Prevention of CVD

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




i Use the Framingham equation or whatever system local National Guidance recommends; a risk equation developed from HIV populations is available: see http://www.chip.dk/Tools. This assessment and the associated considerations outlined in this figure should be repeated annually in all persons under care, see pages 6-7, 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 pages 19-20
(2) Consider replacing ZDV or ABC with TDF or use an NRTI-sparing regimen

iii Of the modifiable risk factors outlined, drug treatment is reserved for certain subgroups where benefits are considered to outweigh potential harm. Of note, there is a combined benefit of various interventions in target groups identified. Per 10 mmHg reduction in systolic blood pressure, per 1 mmol/L (39 mg/dL) reduction in TC and with use of acetylsalicylic acid, each reduces risk of IHD by 20-25%; the effect is additive. Observational studies suggest that smoking cessation results in about 50% less risk of IHD – and this is additive to other interventions.

iv See discussion on drug treatment of persons with lower CVD risk at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3_rpt.htm

v For higher risk individuals (e.g. diabetes) where resources allow target SBP < 130 and DBP < 80 mmHg.

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 calculated because of high triglyceride levels, the non-HDL-c (TC minus HDL-c) target should be used which is 0.8 mmol/L (30 mg/dL) higher than the corresponding LDL-c target. Target levels for TG are not listed because an independent contribution from TG to CVD risk is uncertain, and hence whether this condition should be treated, see page 46.

vii Evidence for benefit when used in persons without a history of CVD (including diabetics) is less compelling. BP should be reasonably controlled before aspirin use in such a setting.

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 |
| **No other risk factors** | • No BP intervention | • Lifestyle changes(i) for several months<br>• Then add BP drugs targeting < 140/90 | • Lifestyle changes(i) for several weeks<br>• Then add BP drugs targeting < 140/90 | • Lifestyle changes(i)<br>• Immediate BP drugs targeting < 140/90 |
| **1-2 risk factors** | • Lifestyle changes(i)<br>• No BP Intervention | • Lifestyle changes(i) for several weeks<br>• Then add BP drugs targeting < 140/90 | • Lifestyle changes(i) for several weeks<br>• Then add BP drugs targeting < 140/90 | • Lifestyle changes(i)<br>• Immediate BP drugs targeting < 140/90 |
| **≥ 3 risk factors** | • Lifestyle changes(i)<br>• No BP intervention | • Lifestyle changes(i) for several weeks<br>• Then add BP drugs targeting < 140/90 | • Lifestyle changes(i)<br>• BP drugs targeting < 140/90 | • Lifestyle changes(i)<br>• Immediate BP drugs targeting < 140/90 |
| **Organ damage, CKD stage 3 or diabetes** | • Lifestyle changes(i)<br>• Consider blood pressure drugs targeting < 130/80 | • Lifestyle changes(i)<br>• BP drugs targeting < 140/90(ii) | • Lifestyle changes(i)<br>• BP drugs targeting < 140/90(ii) | • Lifestyle changes(i)<br>• Immediate BP drugs targeting < 140/90(ii) |
| **Symptomatic CVD, CKD stage ≥ 4 or diabetes with organ damage/risk factors** | • Lifestyle changes(i)<br>• Consider blood pressure drugs targeting < 130/80 | • Lifestyle changes(i)<br>• BP drugs targeting < 140/90(ii) | • Lifestyle changes(i)<br>• BP drugs targeting < 140/90(ii) | • Lifestyle changes(i)<br>• Immediate BP drugs targeting < 140/90(ii) |

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

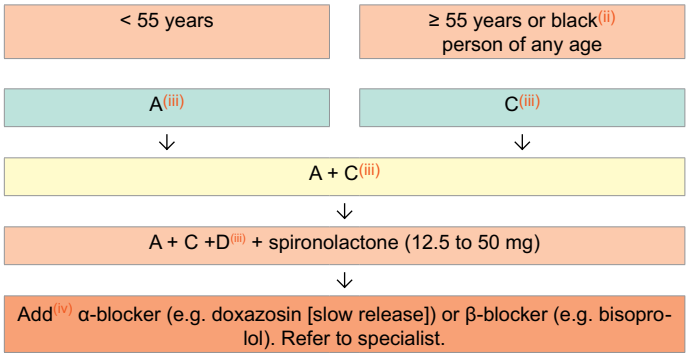
Repeated blood pressure measurements should be used for stratification

i Recommended lifestyle interventions, see page 39
ii Consider targeting < 130/80 when resources allow

Table adapted from [3].

# Hypertension: Drug Sequencing Management

**Choosing drugs[i] for persons newly diagnosed with hypertension**




**Abbreviations + details**

A ACE inhibitor (e.g. perindopril, lisinopril or ramipril) or low cost angiotensin receptor blockers (ARB) (e.g. losartan, candesartan)

C Dihydropyridine calcium-channel blocker (e.g. amlodipine). If not tolerated or if deemed at high risk of heart failure, 'D' drugs can be used instead. Where a C drug is preferred but not tolerated, verapamil or diltiazem may be used (note: dose with caution with PIs as these may increase plasma concentrations of these calcium-channel blockers, potentially leading to toxic reactions)

D Thiazide-type diuretic* e.g. indapamide or chlorthalidone

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

ii Black persons are those of African or Caribbean descent, and not mixed race, Asian or Chinese persons

iii Wait 4-6 weeks to assess whether target, see page 40, is achieved; if not, go to next step

iv Requirement of 4-5 drugs to manage hypertension needs specialist training

* This excludes thiazides (e.g. hydrochlorothiazide (HCTZ), bendroflumethiazide etc.)

# Drug-drug Interactions between Antihypertensives and ARVs

| Antihypertensives | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ACE inhibitors | 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 | ↔[d] | ↔[d] | ↔ | ↔ | ↔[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | bisoprolol | ↑[d] | ↑[d] | ↑ | ↑ | ↑[d] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | carvedilol | ↑[d] | ↑↓[d] | ↑ | ↑↓ | ↑↓[d] | ↑↓ | ↑↓ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | metoprolol | ↑[d] | ↑[d] | ↑ | ↑ | ↑[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | propranolol | ↑[d] | ↑[d] | ↑ | ↑ | ↑[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Calcium channel blockers | amlodipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | diltiazem | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓69% | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | felodipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | lacidipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | lercanidipine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nicardipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nifedipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nisoldipine | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | verapamil | ↑[c] | ↑[c] | ↑ | ↑ | ↑[e] | ↓ | ↓E | ↓ | E | E | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | E | E | ↔ |
| Diuretics | amiloride | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | bendroflumethiazide | ? | ? | ? | ? | ? | ? | ? | ? | ↔ | ↔ | ↔ | ? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | chlortalidone | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | furosemide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | E | ↔ |
| | indapamide | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | hydrochlorothiazide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | torasemide | ↔ | ↓ | ↔ | ↓ | ↓ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Others | doxazosin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sacubitril | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | E | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | spironolactone | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Legend**

↑ potential elevated exposure of the antihypertensive
↓ potential decreased exposure of the antihypertensive
↔ no significant effect
D potential decreased exposure of ARV drug
E potential elevated exposure of ARV drug
ATV/c ATV co-formulated with COBI (300/150 mg qd);
DRV/c DRV co-formulated with COBI (800/150 mg qd)
a [parent drug] decreased but [active metabolite] increased
b [parent drug] increased but [active metabolite] decreased
c ECG monitoring recommended
d risk of PR interval prolongation
e use with caution as both LPV and calcium channel blockers prolong the PR interval. Clinical monitoring is recommended.

Numbers refer to decreased AUC of the antihypertensive as observed in drug-drug interactions studies.

**Colour legend**

- no clinically significant interaction expected
- these drugs should not be co-administered
- potential 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
- there are no clear data, actual or theoretical, to indicate whether an interaction will occur

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

**Comment**

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

# Type 2 Diabetes: Diagnosis

**Diagnostic criteria**[i]

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

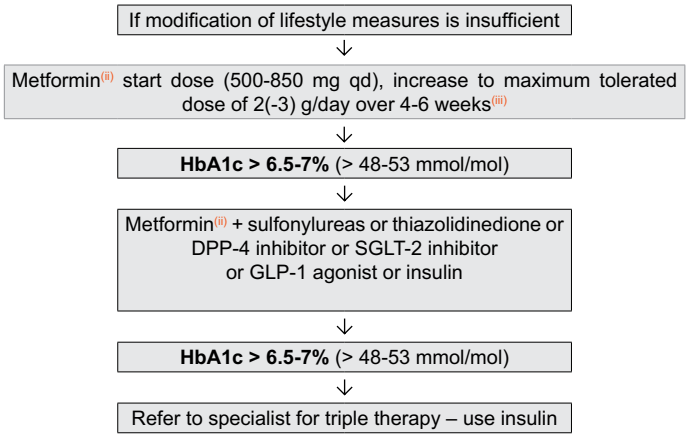
i As defined by WHO, [4] and [5]

ii An abnormal finding should be repeated before confirming the diagnosis

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

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

# Type 2 Diabetes[i]: Management




**Treatment goals:**

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

- Normal blood lipids, see page 40, and blood pressure < 130/80 mmHg, see page 41.
- Acetylsalicylic acid (75-150 mg qd) considered in diabetics with elevated underlying CVD risk, see page 40.
- Nephropathy, polyneuropathy and retinopathy screening should be performed as in diabetic persons without HIV
- Consultation with a specialist in diabetology is recommended

i Type 1 diabetes should be treated according to national guidelines.

ii Metformin may worsen lipoatrophy.
No data for any oral antidiabetic agents in terms of CVD prevention in HIV-positive persons. Incretins (DDP-4 inhibitors [e.g. linagliptin, saxagliptin (reduce dose when given with a booster), sitagliptin and vildagliptin], GLP-1 agonists [liraglutide, exenatide], and SGLT-2 inhibitors [e.g. dapagliflozin, canagliflozin, empagliflozin] have not been evaluated in HIV-positive persons, but some (e.g empagliflozin, 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 persons with long-standing type 2 diabetes and evidence of CVD.

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

# Dyslipidaemia

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

Less calories, more exercise, reducing bodyweight, and stopping smoking tend to improve HDL. Eating fish, reducing calories, saturated fat and alcohol intake reduce triglyceride levels. Reducing dietary saturated fat intake improves LDL-levels; if not effective, consider change of ART, then consider lipid-lowering medicine, see page 40. Statins should be used by all those with established vascular disease and among those with type 2 diabetes or at high risk of CVD, irrespective of lipid levels.

**Drugs used to lower LDL-c**

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

i A statin is preferred first-line therapy; different statins have variable intrinsic LDL-c lowering ability

ii, iii, iv Target levels for LDL-c, see page 40. In persons where LDL-c targets are difficult to achieve, consult/refer to specialist
Expected range of reductions of LDL-c: ii 1.5-2.5 mmol/L (60-100 mg/dL), iii 0.8-1.5 mmol/L (35-60 mg/dL), iv 0.2-0.5 mmol/L (10-20 mg/dL)

v, vi The ARV may v inhibit (statin toxicity, ↓ dose) or vi induce (=less effect of statin, ↑ dose gradually to achieve expected benefit ii, iii) the excretion of the statin

vii **Exception:** If used with DRV/r, start with lower dose of pravastatin

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

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

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 |
|---|---|---|---|
| **Osteoporosis**<br>• Postmenopausal women and men aged ≥ 50 years with BMD T-score ≤ -2.5<br>• Premenopausal women and men aged < 50 years with BMD Z-score ≤ -2 and fragility fracture | • Reduced bone mass<br>• Increased incidence of fractures in HIV-positive persons<br>• Asymptomatic until fractures occur<br><br>Common in HIV<br>• Up to 10-15% prevalence of osteoporosis<br>• Aetiology multifactorial<br>• Loss of BMD observed with ART initiation<br>• Greater loss of BMD with initiation of certain ARVs[i] | Consider classic risk factors[ii] and estimate fracture risk using FRAX.<br><br>Consider DXA in any person with ≥ 1 risk of:[iii]<br>1. Postmenopausal women<br>2. Men ≥ 50 years<br>3. Those between 40-50 years with high fracture risk (> 20% 10-year fracture risk based on FRAX assessment without DXA)<br>4. History of low impact fracture<br>5. High risk for falls[iv]<br>6. Clinical hypogonadism (symptomatic, see Sexual Dysfunction)<br>7. Oral glucocorticoid use (minimum 5 mg/qd prednisone equivalent for > 3 months)<br>Preferably perform DXA in those with above risk factors prior to ART initiation. Assess effect of risk factors on fracture risk by including DXA results in the FRAX® score (http://www.shef.ac.uk/FRAX)<br>• Only use if > 40 years<br>• May underestimate risk in HIV-positive persons<br>• Consider using HIV as a cause of secondary osteoporosis[v] | **DXA scan**<br><br>**Rule out causes of secondary osteoporosis if BMD low**[vi]<br><br>**Lateral spine X-rays** (lumbar and thoracic) if low spine BMD, osteoporosis on DXA, or significant height loss or kyphosis develops. (DXA-based vertebral fracture assessment can be used as an alternative to lateral spine X-ray). |
| **Osteomalacia** | • Defective bone mineralisation<br>• Increased risk of fractures and bone pain<br>• Vitamin D deficiency may cause proximal muscle weakness<br>• High prevalence (> 80%) of vitamin D insufficiency in some HIV cohorts and in the general population | • Dark skin<br>• Dietary deficiency<br>• Avoidance of sun exposure<br>• Malabsorption<br>• Obesity<br>• Renal phosphate wasting[vii] | Measure 25(OH) vitamin D in all persons at presentation<br><br>ng/mL / nmol/L<br>Deficiency: < 10 / < 25<br>Insufficiency: < 20 / < 50<br><br>If deficient or insufficient, check PTH levels<br>Consider vitamin D replacement if clinically indicated, see page 48 |
| **Osteonecrosis** | • Infarct of epiphyseal plate of long bones resulting in acute bone pain<br>• Rare but increased prevalence in HIV | **Risk factors:**<br>• Low CD4 count<br>• Glucocorticoid exposure<br>• IVDU | **MRI** |

i Greater loss of BMD observed with initiation of regimens containing TDF and some PIs. Additional loss and gains in BMD observed with switch to and away from TDF-containing ARV regimens, respectively. Clinical relevance to fracture risk not determined. TAF has not shown the same bone effects as TDF.
Consider replacing TDF* by non-tenofovir drug or TAF** if:
- Osteoporosis / progressive osteopenia
- History of fragility fracture
- FRAX score for major osteoporotic fracture > 10%
- Use of a PI/r as third agent

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

ii Classic risk factors: older age, female gender, hypogonadism, family history of hip fracture, low BMI (≤ 19 kg/m$^2$), vitamin D deficiency, smoking, physical inactivity, history of low trauma fracture, alcohol excess (> 3 units/day), steroid exposure (minimum prednisone 5 mg/qd or equivalent for > 3 months)

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

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

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

vi Causes of secondary osteoporosis include hyperparathyroidism, hyperthyroidism, malabsorption, hypogonadism/amenorrhoea, diabetes mellitus, and chronic liver disease.

vii For diagnosis and management of renal phosphate wasting, see Indications and Tests for Proximal Renal Tubulopathy (PRT).

# Vitamin D Deficiency: Diagnosis and Management

| Vitamin D | Test | Therapy[i] |
|---|---|---|
| **Deficiency:**<br>< 10 ng/mL (< 25 nmol/L)[ii]<br>**Insufficiency:**<br>< 20 ng/mL (< 50 nmol/L) | Serum 25-hydroxy vitamin D (25(OH) vitamin D)<br>If deficient, consider checking parathyroid hormone (PTH), calcium, phosphate[iii], alkaline phosphatase | If vitamin D deficient, replacement recommended. Various regimens suggested[iv]<br>Consider re-checking 25(OH) vitamin D levels 3 months after replacement.<br>After replacement, maintenance with 800-2,000 IU vitamin D daily. |
| **Vitamin D deficiency prevalent in both HIV-positive and HIV-negative populations – may not be directly associated with HIV.**<br><br>**Factors associated with lower vitamin D:**<br>• Dark skin<br>• Dietary deficiency<br>• Avoidance of sun exposure<br>• Malabsorption<br>• Obesity<br>• Chronic kidney disease<br>• Some ARVs[v] | Check vitamin D status in persons with history of:<br>• low bone mineral density and/or fracture<br>• high risk for fracture<br><br>Consider assessment of vitamin D status in persons with other factors associated with lower vitamin D levels (see left column) | Replacement and/or supplementation of vitamin D is recommended for persons with both vitamin D insufficiency[vi] and one of the following:<br>• osteoporosis<br>• osteomalacia<br>• increased PTH (once the cause has been identified)<br><br>Consider re-testing after 6 months of vitamin D intake |

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

ii Some experts consider a value of ≤ 30 ng/mL as vitamin D deficiency. Low vitamin D has a prevalence of up to 80% in HIV cohorts and was associated with increased risk for osteoporosis, type 2 diabetes, mortality and AIDS events. Consider seasonal differences (in winter approximately 20% lower than in summer).

iii Consider that hypophosphataemia can be associated with TDF therapy. This phosphate loss through proximal renal tubulopathy may be independent of low vitamin D, see page 52. A combination of low calcium + low phosphate +/- high alkaline phosphatase may indicate osteomalacia and vitamin D deficiency.

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

v The role of HIV-therapy or specific drugs remains unclear. Some studies suggest an association of EFV with reductions in 25(OH)D but not 1.25(OH)D. PIs may also affect vitamin D status by inhibiting conversion of 25(OH)D to 1.25(OH)D.

vi The implications of vitamin D levels that are below the physiological reference range but not markedly reduced and the value of supplementation are not completely understood.

# Approach to Fracture Reduction in HIV-positive Persons

| | |
|---|---|
| **Reducing risk of fractures** | • Aim to decrease falls by addressing fall risks(i)<br>• Ensure sufficient dietary calcium (1-1.2 g daily) and vitamin D (800-2,000 IU daily) intake(ii)<br>• Where appropriate, screen for osteoporosis(iii) and refer to national/regional guidelines on treatment of osteoporosis<br>– If no guidelines available, consider bisphosphonate(iv) treatment in all osteoporotic postmenopausal women and men > 50 years old (BMD T-score ≤ -2.5) and those with a history of fragility fracture. Consider treatment based on BMD alongside consideration of other risk factors for fracture, especially age.<br>– Use bisphosphonate and ensure adequate calcium and vitamin D intake<br>– No significant interactions between bisphosphonates and antiretrovirals<br>– If antiretroviral-naïve, consider options for ART that preserve BMD(v)<br>– If diagnosed with osteoporosis and requiring therapy, consider optimising ART to preserve or improve BMD<br>• In complicated cases (e.g. young men, premenopausal women, recurrent fracture despite bone protective therapy), refer to osteoporosis specialist<br>• If on bisphosphonate treatment, repeat DXA after 2 years and reassess need for continued treatment after 3-5 years |

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

ii See page 48 for diagnosis and management of vitamin D deficiency.

iii See page 47 for screening and diagnosis of bone disease in HIV.

iv Bisphosphonate treatment with either of: alendronate 70 mg once weekly po; risedronate 35 mg once weekly po; ibandronate 150 mg po once a month or 3 mg iv every 3 months; zoledronic acid 5 mg iv once yearly.

v BMD loss is greatest in the first year after ART initiation, with more BMD loss with ART regimens containing TDF and some PIs. Consider relative risk/benefit of using these agents in persons with high fracture risk. Reduced BMD loss is seen in those with optimised vitamin D status.

# Kidney Disease: Definition, Diagnosis and Management

**Diagnosis of kidney disease**

| | | eGFR[i] | | | |
|---|---|---|---|---|---|
| | | **> 60 mL/min** | **> 60 mL/min, but accelerated decline of eGFR*** | **> 30 - ≤ 60 mL/ min** | **≤ 30 mL/min** |
| **Proteinuria[ii]** | UP/C[iii] < 50 | Regular follow-up | | | • Check risk factors for CKD and nephrotoxic medicines including ART[iv]<br>• Discontinue or adjust drug dosages where appropriate[v]<br>• Perform renal ultrasound<br>• Urgent referral to nephrologist |
| | UP/C[iii] 50-100 | • Check risk factors for CKD[x] and nephrotoxic medicines including ART[iv, x]<br>• Discontinue or adjust drug dosages where appropriate[v]<br>• Perform renal ultrasound<br>• If haematuria present with any level of proteinuria refer to nephrologist<br>• Refer to nephrologist if new CKD or progressive decline in eGFR | | | |
| | UP/C[iii] > 100 | | | | |

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

**Management of HIV-associated kidney disease[vi]**

| Prevention of progressive renal disease | Comment |
|---|---|
| **1. ART** | Start ART immediately where HIV-associated nephropathy (HIVAN)[vii] or HIV immune complex disease strongly suspected. Immunosuppressive therapy may have a role in immune complex diseases. Renal biopsy to confirm histological diagnosis recommended<br>**Consider replacing TDF** by non-tenofovir drug or TAF*** if:**<br>• UP/C 20-50 mg/mmol<br>• eGFR > 60 mL/min, but decrease in eGFR by 5 mL/min per year for at least 3 consecutive years or confirmed 25% eGFR decline from baseline<br>• co-morbidities with a high risk of CKD (i.e. diabetes and hypertension)<br>• body weight < 60 kg<br>• use of a PI/r as a third agent<br>**Replace TDF** by non-tenofovir drug or TAF*** if:**<br>• eGFR ≤ 60 mL/min<br>• UP/C > 50 mg/mmol<br>• nephrotoxic comedication<br>• previous TDF toxicity (proximal renal tubulopathy)<br>** Expert opinion pending clinical data<br>***There are limited data on use of TAF with eGFR ≤ 30 mL/min, and longer term outcomes are unknown. |
| **2. Start ACE inhibitors or angiotensin-II receptor antagonists if:**<br>a. Hypertension and/or<br>b. Proteinuria | **Monitor eGFR and $K^+$ level closely on starting treatment or increasing dose**<br>a. Blood pressure target: < 130/80 mmHg |
| **3. General measures:**<br>a. Avoid nephrotoxic drugs<br>b. Lifestyle measures (smoking, weight, diet)<br>c. Treat dyslipidaemia[viii] and diabetes[ix]<br>d. Adjust drug dosages where necessary[v] | CKD and proteinuria are independent risk factors for CVD |

i For eGFR: Use CKD-EPI formula based on serum creatinine, gender, age and ethnicity because eGFR quantification is validated > 60 mL/min. The abbreviated modification of diet in renal disease (aMDRD) or the Cockcroft-Gault (CG) equation may be used as an alternative; see http://www.chip.dk/Tools.
Definition CKD: eGFR ≤ 60 mL/min for ≥ 3 months (see http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf). If not previously known to have CKD, confirm pathological eGFR within 2 weeks. Use of DTG, COBI and RTV boosted PIs is associated with an increase in serum creatinine/reduction of eGFR due to inhibition of proximal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1-2 months

ii Urinalysis: use urine dipstick to screen for haematuria. To screen for proteinuria, use urine dipstick and if ≥ 1+ check urine protein/creatinine (UP/C), or screen with UP/C. Proteinuria defined as persistent if confirmed on ≥ 2 occasions > 2-3 weeks apart. If UP/C not available, use urine albumin/creatinine (UA/C), see[iii]

iii UP/C in spot urine is preferred to UA/C as detects total urinary protein secondary to glomerular and tubular disease. UA/C largely detects glomerular disease and can be used for screening for HIV-associated renal disease where UP/C is not available, but is not appropriate for screening for tubular proteinuria secondary to drug nephrotoxicity (e.g. TDF). If both UP/C and UA/C are measured, UP/C > UA/C suggests tubular proteinuria. Screening values for UA/C are: < 30, 30-70 and > 70. UA/C should be monitored in persons with diabetes. UPC ratio is calculated as urine protein (mg/L) / urine creatinine (mmol/L); may also be expressed as mg/mg. Conversion factor for mg to mmol creatinine is x 0.000884

iv Repeat eGFR and urinalysis as per screening table, see page 7

v See Dose Adjustment of ARVs for Impaired Renal Function

vi Joint management with a nephrologist

vii HIVAN suspected if black ethnicity & UP/C > 100 mg/mmol & no haematuria

viii See page 46

ix See page 44-46

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 [6], [7]

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

# ARV-associated Nephrotoxicity

| Renal abnormality* | ARV | Management |
|---|---|---|
| **Proximal tubulopathy with any combination of:**<br>1. Proteinuria: urine dipstick ≥ 1, or confirmed increase in UP/C > 30 mg/mmol(i)<br>2. Progressive decline in eGFR and eGFR ≤ 90 mL/min(ii)<br>3. Phosphaturia(iii): confirmed hypophosphataemia secondary to increased urine phosphate leak<br>4. Glucosuria in non-diabetics | **TDF**** | **Assessment:**<br>• Tests for proximal renal tubulopathy/renal Fanconi syndrome(iii)<br>• Consider renal bone disease if hypophosphataemia of renal origin: measure 25(OH) vitamin D, PTH, DXA<br><br>**Replace TDF by non-tenofovir drug or TAF*** if:**<br>• Documented tubular proteinuria and/or glucosuria<br>• Progressive decline in eGFR and no other cause<br>• Confirmed hypophosphataemia of renal origin and no other cause<br>• Osteopenia/osteoporosis in the presence of increased urine phosphate leak |
| **Nephrolithiasis:**<br>1. Crystalluria<br>2. Haematuria(iv)<br>3. Leukocyturia<br>4. Loin pain<br>5. Acute renal insufficiency | **IDV**<br>**ATV**<br>**(DRV)** | **Assessment:**<br>• Urinalysis for crystalluria/stone analysis<br>• Exclude other cause for nephrolithiasis<br>• Renal tract imaging including CT scan<br><br>**Consider stopping IDV/ATV if:**<br>• Confirmed renal stones<br>• Recurrent loin pain +/- haematuria |
| **Interstitial nephritis:**<br>1. Progressive decline in eGFR(ii)<br>2. Tubular proteinuria(iii)/ haematuria<br>3. Eosinophiluria (if acute)<br>4. Leukocyte casts | **IDV**<br>**ATV** | **Assessment:**<br>• Renal ultrasound<br>• Refer to nephrologist<br><br>**Consider stopping IDV/ATV if:**<br>• Progressive decline in eGFR and no other cause |
| **Progressive decline in eGFR, but none of the above(v)** | **TDF****<br>**PI/r** | **Complete assessment:**<br>• Risk factors for CKD(v) (see Kidney Disease: Definition, Diagnosis and Management)<br>• PRT, UA/C, UP/C (see Kidney Disease: Definition, Diagnosis and Mangement and Indications and Tests for Proximal Renal Tubulopathy (PRT)<br>• Renal tract ultrasound<br><br>**Consider stopping ARVs with potential nephrotoxicity if:**<br>• Progressive decline in eGFR and no other cause(v) |

* Use of COBI, DTG, RPV, but also PI/r is associated with an increase in serum creatinine/reduction of eGFR due to inhibition of proximal tubular creatinine transporters without impairing actual glomerular filtration: consider new set point after 1-2 months

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

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

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

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

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

iv Microscopic haematuria is usually present.

v Different models have been developed for calculating a 5-years CKD risk score while using different nephrotoxic ARVs integrating HIV-independent and HIV-related risk factors [6], [7].

# Indications and Tests for Proximal Renal Tubulopathy (PRT)

| Indications for proximal renal tubulopathy tests | Proximal renal tubulopathy tests[iv], including | Replace TDF by non-tenofovir drug or TAF* alternative drug if: |
|---|---|---|
| • Progressive decline in eGFR[i] & eGFR ≤ 90 mL/min & no other cause and/or<br>• Confirmed hypophosphataemia[ii] and/or<br>• Confirmed increase in UP/C[iii]<br>• Renal insufficiency even if stable (eGFR ≤ 60 mL/min)<br>• Tubular proteinuria[v] | • Blood phosphate and urinary phosphate excretion[vi]<br>• Blood glucose and glucosuria<br>• Serum bicarbonate and urinary pH[vii]<br>• Blood uric acid level and urinary uric acid excretion[viii]<br>• Serum potassium and urinary potassium excretion | • Confirmed proximal renal tubulopathy with no other cause |

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

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

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

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

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

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

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

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

* 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[i] (mL/min) | | | | Haemodialysis |
|---|---|---|---|---|---|---|
| | | ≥ 50 | 30-49 | 10-29 | < 10 | |
| **NRTIs** | | | | | | |
| **ABC** | | 300 mg q12h | No dose adjustment required | | | |
| **ddI**[ii] | ≥ 60 kg | 400 mg q24h | 200 mg q24h | 150 mg q24h | 100 mg q24h | 100 mg q24h[iv] |
| | < 60 kg | 250 mg q24h | 125 mg q24h | 100 mg q24h | 75 mg q24h | 75 mg q24h[iv] |
| **d4T** | ≥ 60 kg | 40 mg q12h | 20 mg q12h | 20 mg q24h | 20 mg q24h | 20 mg q24h[iv] |
| | < 60 kg | 30 mg q12h | 15 mg q12h | 15 mg q24h | 15 mg q24h | 15 mg q24h[iv] |
| **FTC** | | 200 mg q24h | 200 mg q48h | 200 mg q72h | 200 mg q96h | 200 mg q96h[iv] |
| **3TC** | | 300 mg q24h | 150 mg q24h | 100 mg q24h[iii] | 50-25 mg q24h[iii] | 50-25 mg q24h[iii], [iv] |
| **TAF/FTC** | | 25[ix]/200 mg q24h | | Not recommended | | |
| **TDF**[v] | | 300[viii] mg q24h | 300[viii] mg q48h | Not recommended (300[viii] mg q72-96h, if no alternative) | Not recommended (300[viii] mg q7d, if no alternative) | 300[viii] mg q7d[iv] |
| **ZDV** | | 300 mg q12h | No dose adjustment required | | 100 mg q8h | 100 mg q8h[iv] |
| **ABC/3TC** | | 600/300 mg q24h | Use individual drugs | | | |
| **ZDV/3TC** | | 300/150 mg q12h | | | | |
| **ABC/3TC/ZDV** | | 300/150/300 mg q12h | | | | |
| **TDF/FTC** | | 300[viii]/200 mg q24h | 300[viii]/200 mg q48h | Use individual drugs | | |
| **NNRTIs** | | | | | | |
| **EFV** | | 600 mg q24h | No dose adjustment required | | | |
| **ETV** | | 200 mg q12h | No dose adjustment required | | | |
| **NVP** | | 200 mg q12h | No dose adjustment required | | | |
| **TDF/FTC/EVG/c** | | Do not initiate if eGFR < 70 mL/min | Do not use | | | |
| **TAF/FTC/EVG/c** | | 10/200/150/150 mg q24h | | Not recommended | | |
| **TAF/FTC/RPV** | | 25/200/25 mg q24h | | Not recommended | | |
| **TDF/FTC/RPV** | | 300[viii]/200/25 mg q24h | Do not use | | | |

| | eGFR[i] (mL/min) | | | | Haemodialysis |
|---|---|---|---|---|---|
| | ≥ 50 | 30-49 | 10-29 | < 10 | |
| **PIs**[v] | | | | | |
| **ATV/r** | 300/100 mg q24h | No dose adjustment required[vi] | | | |
| **DRV/r** | 800/100 mg q24h<br>600/100 mg q12h | No dose adjustment required[vi] | | | |
| **DRV/c** | 800/150 mg q24h | No dose adjustment required[vi] | | | |
| **FPV/r** | 700/100 mg q12h | No dose adjustment required[vi] | | | |
| **LPV/r** | 400/100 mg q12h | No dose adjustment required[vi] | | | |
| **SQV/r** | 1000/100 mg q12h | No dose adjustment required[vi] | | | |
| **TPV/r** | 500/200 mg q12h | No dose adjustment required[vi] | | | |
| **Other ART** | | | | | |
| **RAL** | 400 mg q12h | No dose adjustment required[vi] | | | |
| **DTG** | 50 mg q24h | No dose adjustment required[vi] | | | No clinical data; PK data suggest safety |
| **ABC/3TC/DTG** | 600/300/50 mg q24h | Use individual drugs | | | |
| **MVC: co-administered without CYP3A4 inhibitors**[vii] | 300 mg q12h | No dose adjustment required[vi] | | | |
| **MVC: co-administered with CYP3A4 inhibitors**[vii] | If eGFR < 80 mL/min 150 mg q24h[vii] except: 150 mg q12h if co-administered with FPV/r | | | | |

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

ii Dose reduction if combined with TDF

iii 150 mg loading dose

iv After dialysis

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

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

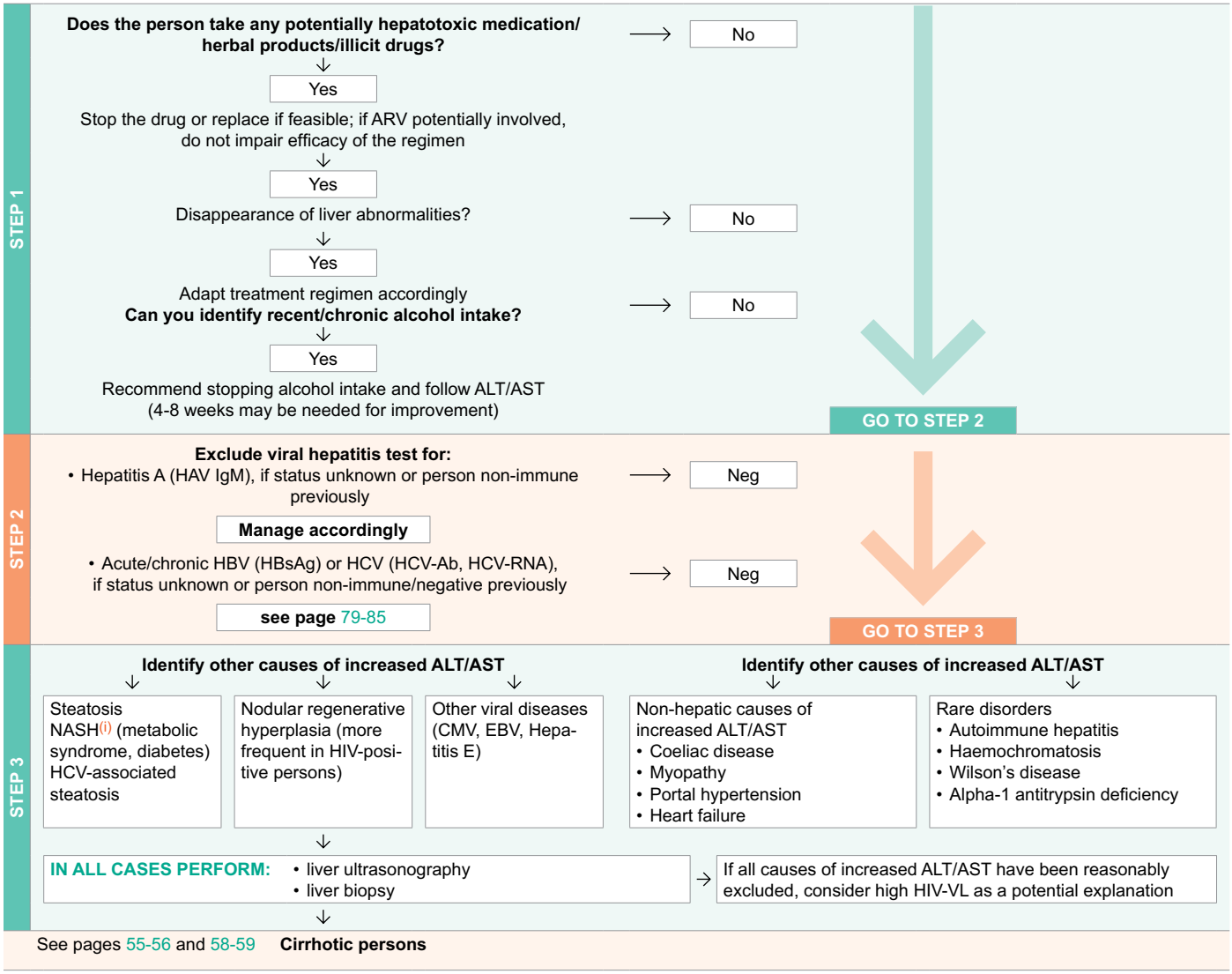
vii See summary of product characteristics for specific recommendations; use with caution if eGFR ≤ 30 mL/min

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

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

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

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




i Non-Alcoholic SteatoHepatitis, see NAFLD

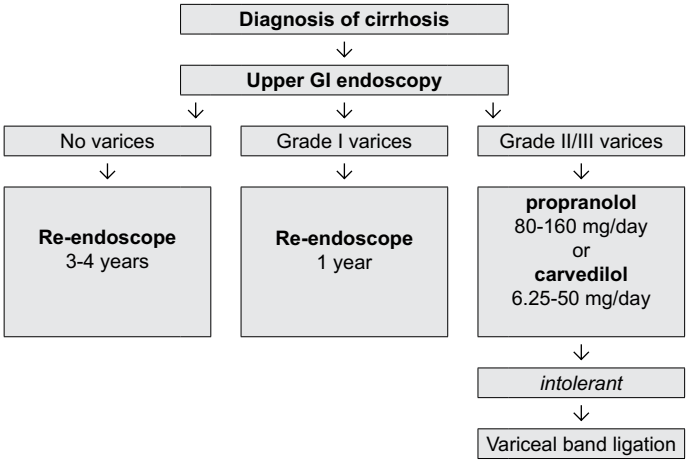
# Liver Cirrhosis: Classification and Surveillance

**Child-Pugh classification of the severity of cirrhosis**

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

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

**Algorithm for surveillance for varices and primary prophylaxis**



# Liver Cirrhosis: Management

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

| Management of hypervolaemic hyponatraemia | Management strategy of hepatic encephalopathy (HE) |
|---|---|
| 1. Fluid restriction: 1000-1500 mL/day (consumption of bouillon allowed ad libitum)<br>2. If fluid restriction is ineffective, consider use of oral tolvaptan<br>a. To be started in hospital at 15 mg/day for 3-5 days, then titrated to 30-60 mg/day until normal s-Na; duration of treatment unknown (efficacy/safety only established in short-term studies (1 month))<br>b. S-Na should be monitored closely, particularly after initiation, dose modification or if clinical status changes<br>c. Rapid increases in s-Na concentration (> 8 mmol/day) should be avoided to prevent osmotic demyelination syndrome<br>d. Persons may be discharged after s-Na levels are stable and without need to further adjust dose | **General management**<br>1. Identify and treat precipitating factor (GI haemorrhage, infection, pre-renal azotaemia, constipation, sedatives)<br>2. Short-term (< 72 hours) protein restriction may be considered if HE is severe<br><br>**Specific therapy**<br>Lactulose 30 cm³ po every 1-2h until bowel evacuation, then adjust to a dosage resulting in 2-3 formed bowel movements per day (usually 15-30 cm³ po bid)<br><br>Lactulose enemas (300 cm³ in 1L of water) in persons who are unable to take it po. Lactulose can be discontinued once the precipitating factor has resolved |

| Management strategy in uncomplicated ascites | |
|---|---|
| **General management** | • Treat ascites once other complications have been treated<br>• Avoid NSAIDs<br>• Norfloxacin prophylaxis (400 mg po, qd) in persons with **1)** an ascites protein level of < 1.5 mg/dL, **2)** impaired renal function (serum creatinine level > 1.2 mg/dL, BUN > 25 mg/dL), **3)** s-Na level < 130mE g/L), or **4)** severe liver failure (Child-Pugh score > 9 points with s-bilirubin level > 3 mg/dL) |
| **Specific management** | • Salt restriction: 1-2 g/day. Liberalise if restriction results in poor food intake<br>• Large volume paracentesis as initial therapy only in persons with tense ascites<br>• Administer iv albumin (= 6-8 g/L ascites removed) |
| **Follow-up and goals** | • Adjust diuretic dosage every 4-7 days<br>• Weigh the person at least weekly and BUN, s-creatinine, and electrolytes measured every 1-2 weeks while adjusting dosage<br>• Double dosage of diuretics if: weight loss < 2 kg a week and BUN, creatinine and electrolytes are stable<br>• Halve the dosage of diuretics or discontinue if: weight loss ≥ 0.5 kg/day or if there are abnormalities in BUN, creatinine or electrolytes<br>• Maximum diuretic dosage: spironolactone (400 mg qd) and furosemide (160 mg qd) |

| Nutrition of cirrhotic persons | |
|---|---|
| **Caloric requirements**<br>• 25-30 Kcal/kg/day of normal body weight<br>**Protein requirements**<br>• Protein restriction is not recommended (see above for exception if HE) | • Type: rich in branched chain (non-aromatic) amino acids<br>• Some studies support that parenteral proteins carry less risk of encephalopathy since not converted by colonic bacteria into $NH_3$<br>**Micronutrients**<br>• Mg and Zn |

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

**Screening for HepatoCellular Carcinoma (HCC)**

- Indicated for all individuals with documented liver cirrhosis, either by: 1) liver biopsy 2) biomarker score or 3) transient elastography (Fibroscan®) supported by findings in conventional ultrasound.
- In HBV co-infected non-cirrhotics, HCC screening should be performed in those who ever had chronic hepatitis (elevated transaminases) or with risk factors for HCC (including family history of HCC, Asians, Africans, http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/management-of-hepatocellular-carcinoma-easl-eortc-clinical-practice-guidelines). On a case-by-case basis, omitting HCC screening can be discussed in those without risk factors and normal transaminases before starting HBV-active treatment.
- Ultrasound (US) every 6 months.
  Alpha-foetoprotein is a suboptimal surveillance tool because of low sensitivity and specificity
- In case of suspicious lesions on US, perform CT scan (+arterial phase) or dynamic contrast-enhanced MRI.
- Confirm diagnosis by fine needle aspiration or biopsy should CT scan or MRI be inconclusive.

**When to refer for liver transplantation**
**Best to refer early as disease progresses rapidly**

= MELD(i) score 10-12 (listing at 15)
Decompensated cirrhosis (at least one of the following complications)

- Ascites
- Hepatic encephalopathy
- Variceal bleeding
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome
- Hepatopulmonary syndrome
- HCC

See Solid Organ Transplantation (SOT) in HIV-positive Persons

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/

# Non-Alcoholic Fatty Liver Disease (NAFLD)

The prevalence of NAFLD is higher in individuals with HIV infection (30- 40% in the US) than in the general population [9]. Nearly half of the HIV-positive persons that undergo evaluation for unexplained liver test abnormalities are found to have NAFLD. The diagnosis of NAFLD requires the exclusion of both secondary causes and of a daily alcohol consumption ≥ 30 g for men and ≥ 20 g for women.

## Spectrum of NAFLD

Often associated with components of the metabolic syndrome:

**Non-Alcoholic Fatty Liver (NAFL)**
- Pure steatosis

**NAFLD**
- Steatosis and mild lobular inflammation

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

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

## Consideration on ARV drugs

- d-drugs (ddi, d4T) are contraindicated in individuals at risk of or with NAFLD
- Consider use of lipid neutral regimens in individuals at risk of or with NAFLD

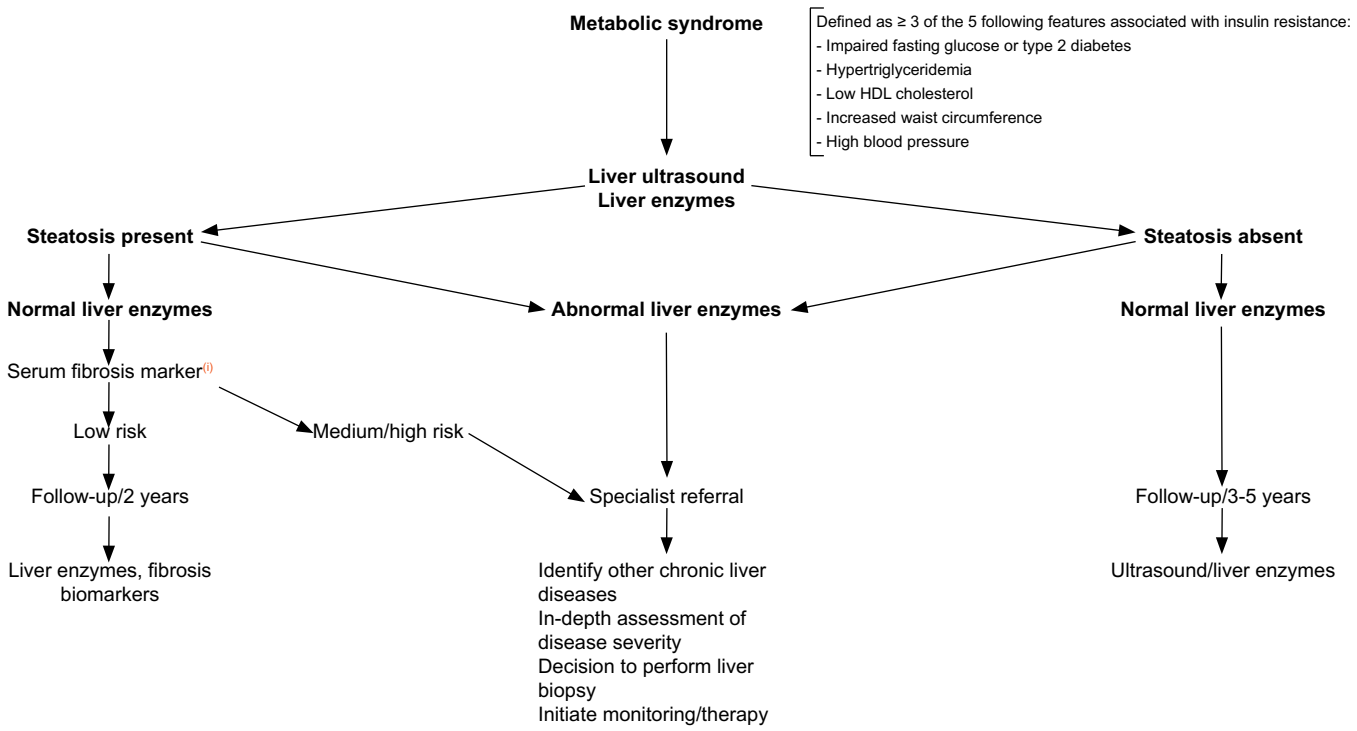
## Diagnosis

- 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. Fibroscan is not validated for this purpose.
- A quantitative estimation of liver fat can only be obtained by 1H-MRS. 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
- Pharmacotherapy should be reserved for individuals with NASH, particularly for those with significant fibrosis ≥ F2 and individuals with less severe disease, but at high risk of faster disease progression (i.e. with diabetes, metabolic syndrome, persistently increased ALT, high necroinflammation).
- Management and treatment of NASH should be discussed with hepatologists. Options with proven efficacy include pioglitazone, vitamin E and bariatric surgery.
- 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




i Serum fibrosis markers: NAFLD-Fibrosis Score, FIB-4, Commercial tests (FibroTest, FibroMeter, ELF)

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 (EASO) [8].

# Diagnosis and Management of Hepatorenal Syndrome (HRS)

| | | | |
|---|---|---|---|
| **Diagnosis** | Consider HRS in a person with cirrhosis and ascites and a creatinine level of > 1.5 mg/dL. It is a diagnosis of exclusion. Before making the diagnosis, the following need to be ruled out and treated:<br>• Sepsis (person needs to be pancultured)<br>• Volume depletion (haemorrhage, diarrhoea, overdiuresis)<br>• Vasodilatators<br>• Organic renal failure (urine sediment; kidney ultrasound)<br>Diuretics should be discontinued and intravascular volume expanded with iv albumin.<br>If renal dysfunction persists despite above, diagnose HRS. | | |
| **Recommended therapy** | Liver transplant (priority dependent on MELD score, see page 56). If person is on transplant list, MELD score should be updated daily and communicated to transplant centre, see Solid Organ Transplantation (SOT) in HIV-positive Persons. | | |
| **Alternative (bridging therapy)** | Vasoconstrictors | octreotide | 100-200 µg sc tid<br>→ 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<br>(both for at least 7 days) | | 50-100 g iv qd |

# Dose Adjustment of ARVs for Impaired Hepatic Function

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

| PIs | |
|---|---|
| **ATV** | Child-Pugh Class B: 300 mg qd |
| | Child-Pugh Class C: not recommended |
| | RTV boosting is not recommended in persons with hepatic impairment (Child-Pugh Class B or C) |
| **DRV** | Child-Pugh Class A or B: no dosage adjustment |
| | Child-Pugh Class C: not recommended |
| **DRV/c** | Child-Pugh Class A or B: no dosage adjustment |
| | Child-Pugh Class C: not recommended |
| **FPV** | **PI-naïve persons:** |
| | Child-Pugh Class A or B: 700 mg bid |
| | Child-Pugh Class C: 350 mg bid |
| | **PI-experienced persons:** |
| | Child-Pugh Class A: 700 mg bid + RTV 100 mg qd |
| | Child-Pugh Class B: 450 mg bid + RTV 100 mg qd |
| | Child-Pugh Class C: 300 mg bid + RTV 100 mg qd |
| **IDV** | Child-Pugh Class A or B: 600 mg q8h |
| | Child-Pugh Class C: no data |
| **LPV/r** | No dosage recommendation; use with caution in persons with hepatic impairment |
| **RTV** | Refer to recommendations for the primary PI |
| **SQV** | Child-Pugh Class A or B: use with caution |
| | Child-Pugh Class C: contraindicated |
| **TPV** | Child-Pugh Class A: use with caution |
| | Child-Pugh Class B or C: contraindicated |
| **FI** | |
| **ENF** | No dosage adjustment |
| **CCR5 Inhibitor** | |
| **MVC** | No dosage recommendations. Concentrations will likely be increased in persons with hepatic impairment |
| **INSTI** | |
| **RAL** | No dosage adjustment |
| **EVG** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **DTG** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **TAF/FTC/EVG/c** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **TDF/FTC/EVG/c** | Child-Pugh Class A or B: no dosage adjustment<br>Child-Pugh Class C: no data |
| **ABC/3TC/DTG** | Use separate compounds and refer to those adjustments |

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

# Lipodystrophy: Prevention and Management

| Lipoatrophy | Lipohypertrophy[i] |
|---|---|
| **Prevention**<br>• Avoid d4T and ZDV or pre-emptively switch away from them. No evidence of benefit by switching other antiretrovirals.<br>• Avoid excessive weight loss due to diet and exercise.<br>• In ART-naïve persons, limb fat usually increases with initiation of ART not containing d4T or ZDV, reflecting "return-to-health" type of response. | **Prevention**<br>• No proven strategy<br>• No current antiretroviral drug has been specifically associated with increased visceral adiposity<br>• An excess of visceral fat has been reported in HIV vs. non-HIV non-obese persons for the same body mass index<br>• Weight reduction or avoidance of weight gain may decrease visceral fat<br>• Avoid corticosteroids with RTV or COBI-boosted drugs as it may cause Cushing syndrome or adrenal insufficiency (see Drug-Drug Interactions between Corticosteroids and ARVs) |
| **Management**<br>• Modification of ART: Switch away from d4T or ZDV<br>— Increase in total limb fat ~400-500 g/year (in the first two years)<br>— Risk of toxicity from new drug, see Adverse Effects of ARVs & Drug Classes<br>• Surgical intervention<br>— Offered for cosmetic relief of (facial) lipoatrophy only | **Management**<br>• Diet and exercise may reduce visceral adiposity;<br>— Limited data, but not consistently associated with improvement in insulin sensitivity and blood lipids<br>— No prospective trials in HIV-positive persons to definitely indicate degree of diet and/or exercise needed to maintain reduction in visceral fat<br>• Pharmacological interventions to treat lipohypertrophy have not been proven to provide long-term effects and may introduce new complications;<br>• Growth hormone (not approved for this indication in Europe)<br>— Decreases visceral adipose tissue<br>— May worsen insulin resistance<br>• Tesamorelin (not approved in Europe; approved for this indication by FDA)[ii]<br>• Metformin (not approved for this indication in Europe)<br>— Decreases visceral adipose tissue in insulin resistant persons<br>— May worsen subcutaneous lipoatrophy<br>• Surgical therapy can be considered for localised lipomas/buffalo humps<br>— Duration of effect variable |

i Lipohypertrophy may occur as localised lipomas in the subcutaneous region or as increased visceral adiposity, both intraabdominally and/or in the epicardium.

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

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

# Hyperlactataemia and Lactic Acidosis: Diagnosis, Prevention and Management

| Risk factors | Prevention/Diagnosis | Symptoms |
|---|---|---|
| • Use of ddI > d4T > ZDV<br>• HCV/HBV co-infection<br>• Use of ribavirin<br>• Liver disease<br>• Low CD4 count<br>• Pregnancy<br>• Female sex<br>• Obesity | • Avoid d4T + ddI combination<br>• Routine monitoring of serum lactate levels not recommended - does not predict risk of lactic acidosis<br>• Measurement of serum lactate, bicarbonate & arterial blood gases + pH indicated in case of symptoms suggestive of hyperlactataemia<br>• Close monitoring for symptoms if > 1 risk factor | • Hyperlactataemia: unexplained nausea, abdominal pain, hepatomegaly, elevated ALT and/or AST, weight loss<br>• Acidaemia: asthenia, dyspnoea, arrhythmias<br>• Guillain-Barré-like syndrome |

**Management**

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

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

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

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

# Travel

| | |
|---|---|
| **General precautions** | • Delay travel until clinically stable and treatment established<br>• Provide drug prescription and referral letter for emergencies<br>• Provide medical certificate for import of personal medicines/syringes<br>• Carry antiretrovirals split between suitcase and hand luggage<br>• Beware of fake drugs |
| **ART** | • Maintain hours of medicines (e.g. 23.00 local time) when switching time zones, shortening the interval to the next dose when flying east |
| **Acknowledge increased susceptibility[i] of HIV-positive** | **1. Observe food hygiene**<br>• Bacterial enterocolitis<br>e.g. diarrhoeagenic *E. coli, Salmonella, Shigella, Campylobacter*<br>• Opportunistic intestinal parasitosis<br>Cryptosporidium, Cyclospora, Cystoisospora, Microsporidia<br><br>**2. Prevent insect bites**<br>• Repellents (DEET ≥ 30%), spray clothing with insecticide (permethrin)<br>• Sleep under bednet<br>• Malaria chemoprophylaxis/emergency standby treatment[ii]<br>• Yellow fever, see page 64<br>• Leishmaniasis<br>beware of sand flies (dogs) |

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

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

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

# Drug-drug Interactions between Antimalarial Drugs and ARVs

| Antimalarial drugs | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| First line and second line drugs | amodiaquine | ↔ | ↑ | ↔ | ↑ | ↑ | ↑[c] | ↓? | ↓29%[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[e] |
| | artemisinin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ ≈50% | ↓D | ↓D | D | D | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | atovaquone | ↔ | ↓46%[a] | ↔ | ↓[a] | ↓74%[a] | ↓75%[a] | ↓E55%[a] | ↓[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[e] |
| | chloroquine | ↔[b] | ↔[b] | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↔ | ↔[f] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | clindamycin | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | doxycycline | ↔ | ↔ | ↔ | ↔ | ↔ | ↓? | ↓? | ↓? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | lumefantrine | ↑[b] | ↑[b] | ↑ | ↑ | ↑[b] | ↓ ≈40% | ↓ | ↓D46% | ↔[f] | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | mefloquine | ↑[b] | ↑[b] | ↑ | ↑ | ↑[b] | ↓ | ↓ | ↓ | ↔[f] | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | primaquine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[d] | ↔[d] | ↔[d] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[e] |
| | proguanil | ↔ | ↓41%[a] | ↔ | ↓[a] | ↓38%[a] | ↓44%[a] | ↓E55%[a] | ↓[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | pyrimethamine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↑ | ↔ | ↔ | ↔[e] |
| | quinine | ↑[b] | ↑[b] | ↑ | ↑ | ↑[b] | ↓ | ↓ | ↓ | ↔[f] | ↑ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sulfadoxine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↑ | ↔ | ↔ | ↔[e] |

**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)
a take with high fat meal, consider dose increase
b ECG monitoring is recommended
c liver toxicity
d increase of haemotoxic metabolites
e additive haematotoxicity
f both drugs can induce QT interval prolongation (only at supratherapeutic dose for rilpivirine)

**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).

# Vaccination

- Vaccinate according to national guidelines for healthy population, preferably after having achieved suppressed viraemia and immune reconstitution (CD4 count > 200 cells/μL)
- Consider repeating vaccinations performed at CD4 count < 200 cells/μL (< 14%) or unsuppressed viraemia once adequate immune reconstitution is achieved (HIV-VL undetectable and CD4 count > 200 cells/μL)
- As vaccine responses may be significantly lower in HIV-positive persons (i.e. lower seroconversion rates, faster titer decline), consider antibody titers to assess their effectiveness
- Avoid polysaccharide vaccination
- For background data, see http://www.bhiva.org/vaccination-guidelines.aspx.

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

| Infection | Vaccination rationale in HIV-positive persons | Comment |
|---|---|---|
| Influenza Virus | Higher rate of pneumonia. Explicitly recommended in all HIV-positive persons | Yearly |
| Human Papilloma Virus (HPV) | Shared risk with HIV of contracting infection. Higher rate of cervical and anal cancer | Vaccinate with 3 doses for all HIV-positive persons up to age 26 / age 40 if MSM (health insurance coverage differs by country according to age, sex, sexual orientation). Use 9-valent vaccine if available.<br>If HPV infection is established, efficacy of vaccine is questionable |
| Hepatitis B Virus (HBV) | Shared risk with HIV of contracting infection. HIV accelerates liver disease progression | Vaccinate if seronegative. Repeat doses until anti-HBs antibodies ≥ 10 IU/L / ≥ 100 IU/L according to national guidelines. In order to reach ≥ 100 IU/L in non-responders repeat 3 doses if anti-HBs < 10 IU/L, 1 dose if anti-HBs < 100 IU[ii]; consider double dose (40 μg) in particular with low CD4 count and high HIV-VL. See page 79 |
| Hepatitis A Virus (HAV) | According to risk profile (travel, MSM, IVDU, active hepatitis B or C infection) | Vaccinate if seronegative. Consider checking antibody titres in individuals with high risk. Weaker immune response expected with HAV/HBV co-vaccine. See page 79 |
| *Neisseria meningitidis* | As general population | Use conjugated[iii] vaccine (2 doses 1-2 months apart) if available. Booster every five years if exposure continues. Polysaccharide vaccine not recommended anymore. |
| *Streptococcus pneumoniae* | Higher rate and severity of invasive disease. Vaccine explicitly recommended for all HIV-positive persons | One dose of conjugated[iii] 13-valent vaccine (CPV-13) for all individuals, 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 individuals. |
| Varicella Zoster Virus (VZV) | Higher rate and severity of both chickenpox and zoster | Perform serology if exposure history negative. Vaccinate if seronegative.<br>For contraindications, see* |
| 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)<br>For other contraindications, see*. Booster q 10 years. |

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 HIV-positive Women and Men

Screening questions about sexual and reproductive health and sexual functioning should be routinely asked in every HIV consultation.

## Sexual transmission of HIV

Effective measures to reduce sexual transmission of HIV include:

| Measure | Comment |
|---|---|
| **Male condom or female condom use** | • Effective in treated and untreated HIV-positive persons |
| **Post-exposure prophylaxis (PEP)** | • Consider after situations of unprotected anal or vaginal intercourse, if one partner has detectable HIV-VL and the other partner is seronegative<br>• Start as soon as possible and within 48/72 hours post sexual exposure<br>See Post-exposure prophylaxis (PEP) |
| **Pre-exposure prophylaxis (PrEP)** | • Effective in HIV-negative persons with high risk sexual situations, see Pre-exposure prophylaxis (PrEP) |
| **ART for HIV-positive partner** | • Considered effective from 6 months of fully suppressive ART if no active STIs<br>• Consider in e.g. serodifferent couples(i) |

i See page 10

## STI screening and treatment

STI screening should be offered to all sexually active HIV-positive persons at the time of HIV diagnosis, annually thereafter or at any time STI symptoms are reported 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 HIV-positive persons and their sexual partner(s):

| | Therapy | Comment |
|---|---|---|
| **Chlamydia infection** | Consider doxycycline (100 mg bid po 7-10 days, contraindicated in pregnancy) or azithromycin (1 g po as a single dose) for urethritis and cervicitis.<br>For *Lymphogranuloma venereum (LGV)* doxycycline (100 mg po bid for 21 days) or azithromycin (1 g po every week for 3 weeks).<br>**Alternatives:**<br>erythromycin (500 mg/6 h po(i)) or levofloxacin (500 mg/day) for 7 days (or 21 days in case of LGV) | • May cause therapy-resistant proctitis in HIV-positive MSM<br>• Consider co-infections with *Neisseria gonorrhoeae* |
| **Gonorrhoea** | Ceftriaxone (500 mg im as a single dose) together with azithromycin (1 g po as a single dose). | • Can cause proctitis, prostatitis and epididymitis<br>• In women often asymptomatic<br>• Fluoroquinolone resistance is highly prevalent in all regions |
| **HBV infection**<br>**HCV infection** | See table on HIV/HCV or HIV/HBV co-infections, pages 80-85 | • Interruption of TDF, 3TC or FTC can lead to HBV reactivation<br>• Clusters of acute HCV infection in HIV-positive MSM across Europe |
| **HPV infection** | There are several treatment modalities for the management of genital warts with no evidence to suggest one approach is better than another approach. Consider operative removal by laser surgery, infrared coagulation, cryotherapy, etc.<br>Management of both pre-invasive cervical lesions as well as peri- and intra-anal lesions should follow local or national guidelines | • Infection is mostly asymptomatic; relapse of genital warts is frequent<br>• Cervical PAP smear test recommended in all HIV-positive women<br>• Anal HPV screening and cytology should be considered in all HIV-positive persons practising anal sex<br>• Consider high resolution anoscopy in case of suspicious cytological findings (rectal palpation or external inspection is not sufficient) |
| **HSV2 infection** | Primary infection: aciclovir (400–800 mg po tid) or valaciclovir (500 mg po bid) for 5 days, see page 91 | • Treatment of HSV2 alone does not prevent HIV-transmission and only modestly prevents HIV disease progression |
| **Syphilis** | Penicillin is the gold standard for the treatment of syphilis in both pregnant and non-pregnant individuals.<br>**Primary/secondary syphilis:** 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.<br>**Late latent syphilis and syphilis of unknown duration:** benzathine penicillin (2.4 million IU im weekly on days 1, 8 and 15); the alternative doxycycline (100 mg po bid for 2 weeks) is considered less effective.<br>**Neurosyphilis:** penicillin G (6 x 3 - 4 million IU iv for at least 2 weeks).<br>There is no evidence to give a general recommendation on prednisolone use in this condition. | • Expect atypical serology and clinical courses<br>• Consider cerebrospinal fluid (CSF) testing in persons with neurological symptoms (evidence for intrathecally-produced specific antibodies, pleocytosis, etc.)<br>• Successful therapy clears clinical symptoms and decreases VDRL test four-fold within 6-12 months |

i Rarely used

## Reproductive health

Reproductive health issues should be preferentially discussed with both partners, particularly in serodifferent couples. See Drug-drug Interactions between Contraceptives/Hormone Therapy Replacement Treatment and ARVs

**Approaches for serodifferent couples who want to have children**

Screening for STIs (and treatment, if required) of both partners is mandatory.

For HIV-positive women wishing to conceive:

(1) avoid using ddI, d4T or triple NRTIs, among PI/r, prefer ATV/r, already started NVP, EFV, DTG, RAL or DRV/r can be continued. Women on EVG/c need to be informed that monitoring of HIV-VL and drug levels may be necessary during pregnancy, see page 15;

(2) consider treating the HIV-positive partner to reduce risk of HIV transmission to the HIV-negative partner.

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

- Unprotected intercourse during times of maximum fertility (determined by ovulation monitoring), if the HIV-positive partner has undetectable HIV-VL.
- Vaginal syringe injection of seminal fluid during times of maximum fertility, if the male partner is HIV-negative.
- Sperm washing, with or without intra-cytoplasmic sperm injection, is no longer necessary because of effectiveness of ART in avoiding HIV transmission at conception in HIV-positive male persons with undetectable HIV-VL.

## Sexual dysfunction

Guidelines for treatment of sexual dysfunction in the general population are available for men but not women. Refer to specialist where appropriate. See Sexual Dysfunction and Treatment of Sexual Dysfunction in HIV-positive Men

# Sexual Dysfunction

| | | | |
|---|---|---|---|
| **When sexual complaints exist:** | What is the exact nature of the problem? In which phase(s) of the sexual response cycle does the problem occur? | **1. Desire** (lack of sexual desire or libido; desire discrepancy with partner; aversion to sexual activity)<br>**2. Arousal** (difficulties with physical and/or subjective sexual arousal; difficulties or inability to achieve or sustain an erection of sufficient rigidity for sexual intercourse MEN; i.e. erectile dysfunction; lack or impaired nocturnal erections MEN; difficulties lubricating WOMEN; difficulties sustaining arousal)<br>**3. Orgasm** (difficulties experiencing orgasm)<br>**4. Pain** (pain with sexual activity; difficulties with vaginal/anal penetration–anxiety, muscle tension; lack of sexual satisfaction and pleasure) | |
| | Self-assessment of sexual function (questionnaires): | **MEN**<br>International Index of Erectile Function (IIEF) -5, see https://www.hiv.va.gov/provider/manual-primary care/urology-tool2.asp) or IIEF-15, see http://files.sld.cu/urologia/files/2011/08/iief.pdf<br>**WOMEN**<br>Female Sexual Function Index (FSFI), see http://www.fsfiquestionnaire.com | |
| **Check for endocrine causes:** | Signs of hypogonadism | **MEN**<br>- 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)<br>- If signs or symptoms of hypogonadism are present ask for hormonal assessment: lutropin hormone (LH), follicle stimulating hormone (FSH), total testosterone; sex hormone-binding globulin evaluation to calculate free testosterone, see http://www.issam.ch/freetesto.htm | If hypogonadism is present (total testosterone < 300 ng/dl or calculated free testosterone below normal): refer to endocrinologist or andrologist<br><br>If hypogonadism is not present: check for other causes |
| | | **WOMEN**<br>- 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)<br>- If symptoms of menopause are present ask for hormonal assessment: LH, FSH, estradiol | If symptoms of menopause are present: refer to endocrinologist or gynaecologist<br><br>If hypogonadism is not present: check for other causes |
| **Check for other causes:** | Psychological or sociological problems | Stigma, body image alteration, depression, fear of infecting an HIV-negative partner, anxiety, awareness of a chronic disease, condom use | Refer to clinical psychologist |
| | Infections | **MEN**<br>- Urogenital infections (note: if complete sexual response possible, e.g. with another partner, with masturbation or nocturnal erections-then no major somatic factors are involved) | Refer to urologist, andrologist, cardiologist |
| | | **WOMEN**<br>- 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 ARVs is controversial and benefit from switching studies is not proven | Consider therapy changes |

# Treatment of Sexual Dysfunction in HIV-positive Men

| Treatment of erectile dysfunction | Treatment of premature ejaculation |
|---|---|
| Primarily oral PDE5-inhibitors (sildenafil, tadalafil, vardenafil).<br>• All at least 30 minutes before initiation of sexual activity<br>• Use lower dose if on PI/r<br>— sildenafil (25 mg every 48 hours)<br>— tadalafil 5 mg initial dose with maximum dose 10 mg in 72 hours<br>— vardenafil 2.5 mg maximum dose in 72 hours<br>• Tadalafil also licensed for use as an everyday ongoing therapy | Consider behavioural interventions and/or psychosexual counselling, SSRIs, tricylclic antidepressants, clomipramine and topical anaesthetics.<br>• Use lower dose of clomipramine and other tricyclic antidepressants if on PI/r<br>• Dapoxetine, a short-acting SSRI, is the only drug approved for on-demand treatment of premature ejaculation in Europe.<br>• Treatment must be maintained as recurrence is highly likely following withdrawal of medicine |

# Depression: Screening and Diagnosis

**Significance**

- Higher prevalence of depression reported in HIV-positive persons (20-40% versus 7% in general population)
- Significant disability and poorer HIV treatment outcomes associated with depression

| Screening and diagnosis | | |
|---|---|---|
| **Who?** | **How to screen?** | **How to diagnose?** |
| **Screening of all HIV-positive persons recommended in view of the high prevalence of depression**<br><br>**Populations at particularly high risk**<br>• Positive history of depression in family<br>• Depressive episode in personal history<br>• Older age<br>• Adolescence<br>• Persons with history of drug addiction, psychiatric, neurologic or severe somatic co-morbidity<br>• Use of EFV<br>• Use of neurotropic and recreational drugs<br>• As part of investigation of neurocognitive impairment, see page 72 | • Screen every 1-2 years<br>• Two main questions:<br>1. Have you often felt depressed, sad or without hope in the last few months?<br>2. Have you lost interest in activities that you usually enjoy?<br>• Specific symptoms in men:<br>– Stressed, burn out, angry outbursts, coping through work or alcohol<br>• Rule out organic cause (such as hypothyroidism, hypogonadism, Addison's disease, non-HIV drugs, vitamin B12 deficiency) | **Symptoms – evaluate regularly**<br>**A.** At least 2 weeks of depressed mood<br>OR<br>**B.** Loss of interest<br>OR<br>**C.** Diminished sense of pleasure<br>**PLUS 4 out of 7 of the following:**<br>1. Weight change of ≥ 5% in one month or a persistent change of appetite<br>2. Insomnia or hypersomnia on most days<br>3. Changes in speed of thought and movement<br>4. Fatigue<br>5. Feelings of guilt and worthlessness<br>6. Diminished concentration and decisiveness<br>7. Suicidal ideation or a suicide attempt(i) |

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

# Depression: Management

| Degree of depression | Number of symptoms (see page 68: A, B or C + 4/7) | Treatment | Consultation with expert |
|---|---|---|---|
| No | < 4 | No | |
| Mild | 4 | • Problem-focused consultation<br>• Consider antidepressant treatment(i)<br>• Recommend physical activity | • Always if treating doctor is unfamiliar with use of antidepressants<br>• If depression not responding to treatment<br>• If person has suicidal ideation<br>• In case of complex situations such as drug addiction, anxiety disorders, personality disorders, dementia, acute severe life events |
| Intermediate | 5-6 | Start antidepressant treatment(i) | |
| Severe | > 6 | Refer to expert (essential) | |

i See Drug-drug Interactions between Antidepressants and ARVs

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

# Classification, Doses, Safety and Adverse Effects of Antidepressants

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

- none
\+ moderate
++ severe

i For many persons, SSRI induction may be associated with adverse effects (GI tract, dizziness, anxiety, panic attacks). Commencing at lower doses (i.e. 10, 25 & 10 mg for paroxetine, sertraline and citalopram, respectively) and increasing to the above starting doses after 4 to 7 days if tolerated may reduce such effects.

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

# Drug-drug Interactions between Antidepressants and ARVs

| Antidepressants | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **SSRI** | citalopram | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | escitalopram | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | fluvoxamine | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | E | ↔ | ↔ | ↔ | ↑ | ↔ |
| | fluoxetine | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | paroxetine | ↑↓? | ↑↓? | ↑↓? | ↓39% | ↑↓? | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑↓? | ↔ |
| | sertraline | ↑ | ↓ | ↑ | ↓49% | ↓ | ↓39% | ↓ | ↓ | ↔ | ↔ | ↔ | ↓7% | ↔ |
| **SNRI** | duloxetine | ↑ | ↑↓ | ↑ | ↑↓ | ↑↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | venlafaxine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | D | ↔ | ↑ | ↔ |
| **TCA** | amitriptyline | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↔ | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | clomipramine | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑[a] | ↔ |
| | desipramine | ↑[a] | ↑[a] | ↑ | ↑ | ↑5%[a] | ↔ | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | doxepin | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | imipramine | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑[a] | ↔ |
| | nortriptyline | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↔ | ↔ | ↔ | ↔[b] | ↔ | ↔ | ↑ | ↔ |
| | trimipramine | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| **TeCA** | maprotiline | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | mianserine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ |
| | mirtazapine | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ |
| **Oth-ers** | bupropion | ↔ | ↓ | ↔ | ↓ | ↓57% | ↓55% | ↔ | ↓ | ↔ | ↔ | ↔ | ↑? | ↔ |
| | lamotrigine | ↔ | ↓32% | ↔ | ↓ | ↓50% | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | nefazodone | ↑ | ↑ | ↑ | ↑ | ↑ | ↓E | ↓E | ↓E | E | E | ↔ | ↑ | ↔ |
| | St John's wort | D | D | D | D | D | D | D | D | D | D | D[c] | D | D? |
| | trazodone | ↑[a] | ↑[a] | ↑ | ↑ | ↑[a] | ↓ | ↓ | ↓ | ↔[b] | ↔ | ↔ | ↑ | ↔ |

**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)
a ECG monitoring is recommended
b caution as both drugs can induce QT interval prolongation
c the US Prescribing Information recommends that co-administration should be avoided as there are insufficient data to make dosing recommendations

Numbers refer to decreased AUC of the antidepressant as observed in drug-drug interactions studies.

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

**Colour legend**

no clinically significant interaction expected
these drugs should not be co-administered
potential 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

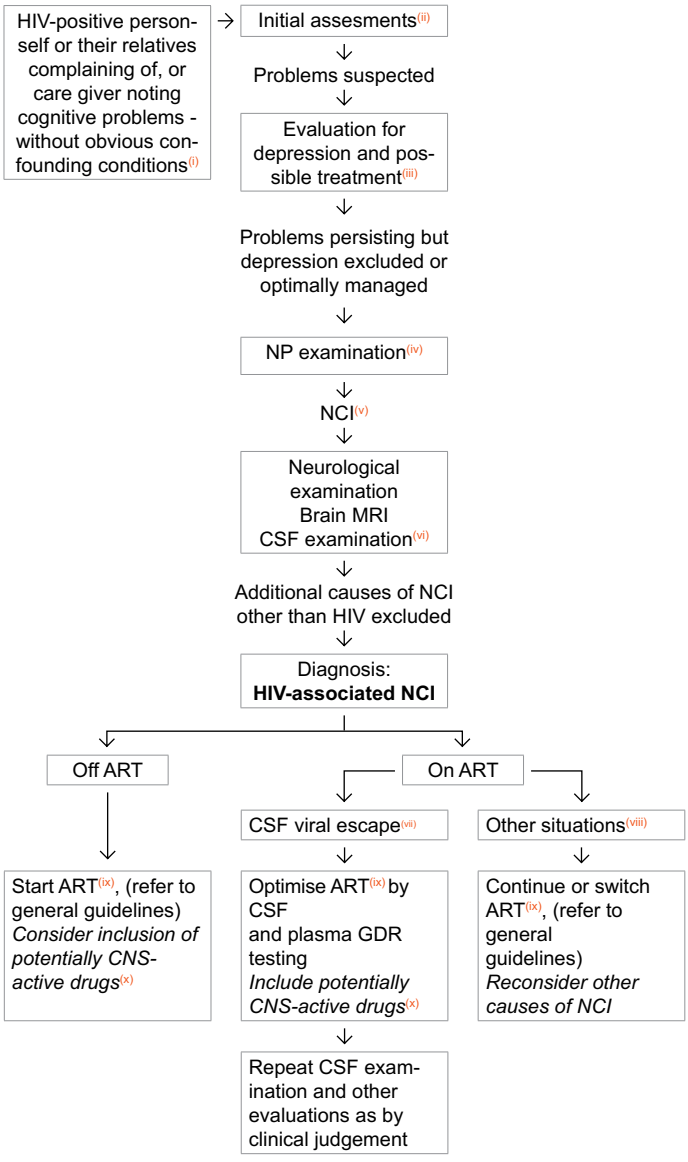
**Comment**

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).

# Algorithm for Diagnosis and Management of HIV-Associated Neurocognitive Impairment (NCI) in Persons without Obvious Confounding Conditions

**Abbreviations**

| | |
|---|---|
| **CSF** | cerebrospinal fluid |
| **GDR** | genotypic drug resistance test |
| **HAD** | HIV-associated dementia |
| **MND** | mild neurocognitive disorder |
| **MRI** | brain magnetic resonance imaging |
| **NP** | neuropsychological |
| **OIs** | opportunistic infections |




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

ii **The following 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 difficulties paying attention (e.g. to a conversation, book or movie)?

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** will have to include tests exploring the following cognitive domains: fluency, executive functions, speed of information processing, attention/working memory, verbal and visual learning, verbal and visual memory, motor skills plus assessment of daily functioning.

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

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

vii **CSF escape definition:**
either CSF HIV-VL detectable and plasma HIV-VL undetectable; or both CSF HIV-VL and plasma HIV-VL detectable, with CSF HIV-VL higher than plasma HIV-VL.

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

ix **Triple ART regimen**

x **ART drugs with potential beneficial or detrimental effects on the CNS**

**Definition of potentially CNS-active drug**

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

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

* When administered bid. Once-daily administration of these drugs, although common in clinical practice, has not been studied extensively with regard to CNS effects/CSF penetration and may have different CNS activity. RTV is preferred as PI booster

** Avoid EFV because of its detrimental effects on neurocognitive 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 HIV

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

**Then check for respiratory symptoms:**
- Do you have ANY of the following on a regular basis: 1) shortness of breath when walking up a slight hill or hurrying on flat ground; 2) cough and/or sputum; 3) wheezing

"Yes" to all three questions

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

"No"
Repeat questions anually

Assess for airflow limitation with spirometry

Post-bronchodilator $FEV_1/FVC < 0.70$

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

Diagnose COPD

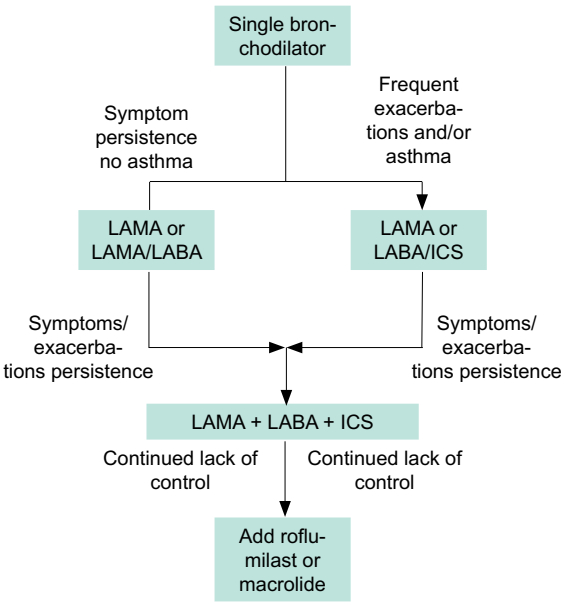
Consider chest CT for structural changes and/ or referral to respiratory specialist[iii]

Assessment of symptoms/risk of exacerbations[i]

Assessment of concomitant chronic diseases[ii]

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

**Treatment of COPD**[iv]




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

**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 acute hypercapnic respiratory failure

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. Because of the risk of pneumonia and because of proven superiority of LABA/LAMA over LABA/ICS, the addition of ICS to LABA is recommended only in individuals with history of frequent exacerbations and/or asthma or in individuals not adequately controlled by LAMA/LABA combination. Do not use inhaled glucocorticoids with boosted ART regimens, see Drug-drug Interactions between Corticosteroids and ARVs.
Influenza and pneumococcal vaccination decreases 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 | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| LAMA | aclidinium bromide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | glycopyrronium bromide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | tiotropium bromide | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | umeclidinium bromide | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| SAMA | ipratropium | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| LABA | formoterol | ↔[a] | ↔[a] | ↔ | ↔ | ↔[a] | ↔ | ↔ | ↔ | ↔[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | indacaterol | ↑[d] | ↑[d] | ↑[d] | ↑[d] | ↑[d] | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | olodaterol | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | salmeterol | ↑[b] | ↑[b] | ↑[b] | ↑[b] | ↑[b] | ↓ | ↓ | ↓ | ↔[a] | ↔ | ↔ | ↑[b] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | vilanterol | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| SABA | salbutamol (albuterol) | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| MX | aminophylline | ↔ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | theophylline | ↔ | ↓ | ↔ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| PDE4 | roflumilast | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| ICS | beclometasone | ↑[c] | ↑[c] | ↑?[c] | ↓11% | ↑[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↑[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | budesonide | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | fluticasone | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

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

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

**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).

# Drug-drug Interactions between Pulmonary Antihypertensives and ARVs

| Pulmonary antihypertensives | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ERA | ambrisentan | ↑ | ↑ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | bosentan | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓ | ↓ | ↓[b] | D | D | D | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | macitentan | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| PDE5 | sildenafil | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | tadalafil | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| sGC | riociguat | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| PA | epoprostenol | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | iloprost | ↔ | ↔ ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | treprostinil | ↔ | ↑ | ↔ | ↑ | ↑ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| IPr | selexipag | ↔[c] | ↔[c] | ↔[c] | ↔[c] | ↔[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**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)
a 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

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

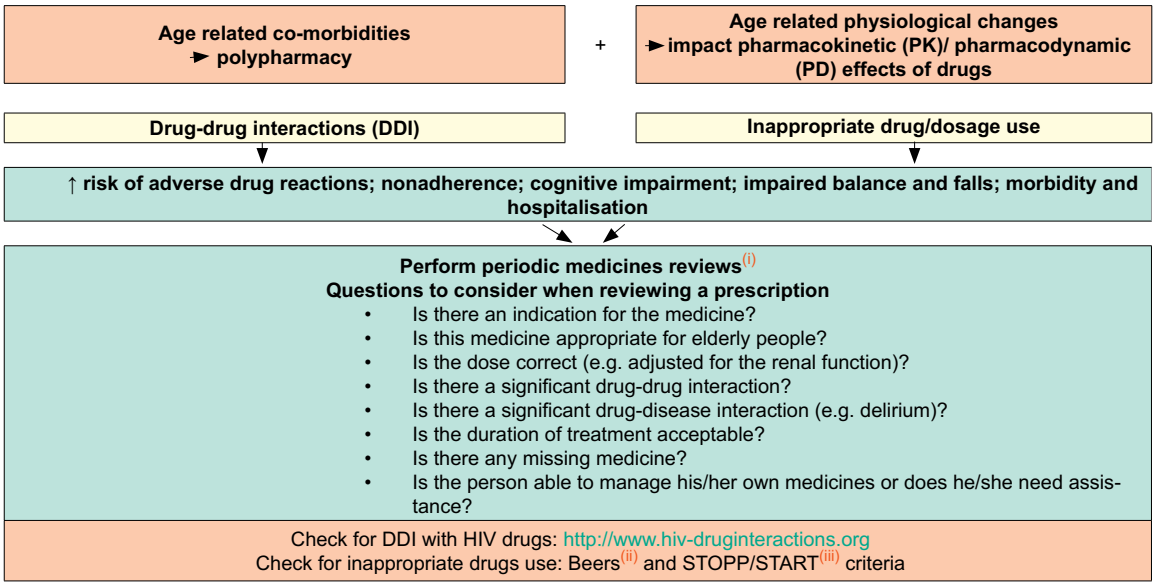
**Colour legend**

- 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).

# Prescribing in the Elderly




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.

# Solid Organ Transplantation (SOT) in HIV-Positive Persons

## 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

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

## HIV-infection criteria for SOT

According to most international guidelines, HIV-positive individuals 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 HIV-positive persons 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, see pages 80 and 82-84. 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 HIV-positive persons, see page 97, 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.
- Before starting or restarting abacavir containing ART the HLA-B*5701 status of the donor should be assessed.

Primary and secondary disease-specific chemoprophylaxis

- HIV-positive transplant recipients 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 97.

Viral hepatitis co-infection

- The efficacy and safety of DAAs in liver transplant HIV-positive recipients 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.

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

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

| Immunosuppressants | | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| CS | prednisone | ↑ | ↑ | ↑ | ↑ | ↑ | ↓ | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| AM | azathioprine | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | mycophenolate | ↔ | ↓ | ↔ | ↓ | ↓ | ↓ | ↔ | ↓E13% | ↔ | ↔ | ↔ | ↓ | ↔ | ↓? | ↔ | ↔ | ↔ | E[b] | ↓? |
| CNI | cyclosporine | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | E | E | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | E | E[b] | ↔ |
| | tacrolimus* | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | ↔ | ↔ | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[b] | ↔ |
| mTOR | everolimus | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | ↔ | ↔ | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | sirolimus | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↑[a] | ↓[a] | ↓[a] | ↓[a] | ↔ | ↔ | ↔ | ↑[a] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[b] | ↔ |
| Other | anti-thymocyte globulin | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔[c] | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | basiliximab | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| | belatacept | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Legend**

↑ potential increased exposure of the immunosuppressant
↓ potential decreased exposure of the immunosuppresant
↔ 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 decreased/increased AUC of the immunosuppressant as observed in drug-drug interaction studies
a TDM of immunosuppressant is recommended
b monitor renal function
c potential additive haematotoxicity

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

**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).

# Part IV Clinical Management and Treatment of HBV and HCV Co-infection in HIV-positive Persons

Every person with HCV/HIV co-infection should receive IFN-free 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. Life-long therapy is recommended if anti-HBV nucleos(t)ides are given as part of ART. In HBsAg-positive persons without HBV active ART (including 3TC), TDF/TAF should be added as prophylaxis regardless of baseline HBV-DNA levels in case of chemotherapy or other immunosuppression (e.g. rituximab treatment) [1].

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

### Screening

1. All HIV-positive persons should be screened for HCV at time of HIV diagnosis and annually thereafter. Screening should use an anti-HCV antibody test. A positive result should be followed by HCV-RNA and genotype determination. Alternatively, HCV core-antigen testing can be performed to establish chronic HCV infection. Persons with risk factors like ongoing IDU, “chem sex” (sex under the influence of recreational drugs taken predominantly intravenously immediately before and/or during sexual contacts), mucosal traumatic sex, ongoing unprotected anal intercourse, recent sexually transmitted infection) with unexplained increase in hepatic transaminases and a negative anti-HCV antibody test should be tested for HCV-RNA for early detection of a recent infection. HCV-RNA testing is also recommended in persons with high risk factors for HCV re-infection after successful treatment or spontaneous clearance.
2. HIV-positive persons should be screened for HAV and HBV. Persons who are anti-HBc positive and HBsAg negative, in particular those with elevated liver transaminases, should be screened for HBV-DNA in addition to HBsAg to rule out occult HBV infection.
3. Hepatitis Delta antibodies should be screened for in all HBsAg positive persons.
4. HCC screening is indicated in all cirrhotic HBV or HCV co-infected persons. In HBV-infected non-cirrhotics, HCC screening should be performed in those who ever had chronic hepatitis (elevated transaminases) or with risk factors for HCC (including family history of HCC, Asians, Africans, see http://www.easl.eu/research/our-contributions/clinical-practice-guidelines/detail/management-of-hepatocellular-carcinoma-easl-eortc-clinical-practice-guidelines. On a case-by-case basis, omitting HCC screening can be discussed in those without risk factors and normal transaminases before starting HBV-active treatment, see page 38 and 56. Routine screening is also advised for oesophageal varices in co-infected persons with liver cirrhosis, see page 55.

### Vaccination, see page 64

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

### ART

7. ART initiation is recommended in all HIV-positive persons with HBV and/or HCV co-infection irrespective of CD4 count. ART should contain TDF or TAF in HBV co-infected persons. Stopping ART has been associated with higher risk for AIDS and non-AIDS related events; indeed, the risk for non-AIDS events was particularly increased for persons with hepatitis co-infection. Stopping anti-HBV containing ART should be avoided in persons with HIV/HBV co-infection because of the high risk of severe hepatitis flares and decompensation following HBV reactivation hepatitis.

### End Stage Liver Disease (ESLD)

8. HIV-positive persons 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 55-56 and Diagnosis and Management of Hepatorenal Syndrome (HRS).
9. Persons with viral hepatitis/HIV co-infection suffering from ESLD warrant particular attention in the management of liver insufficiency; see Dose Adjustment of ARVs for Impaired Hepatic Function. Nevertheless, it is important to highlight that ART initiation in cirrhotic persons generally improves overall survival and is therefore strongly recommended in these persons.
10. Persons with HCC or a MELD-score > 15[i], CD4 count > 100 cells/µL and options for efficacious and durable ART should be evaluated for liver transplantation (OLTX). OLTX outcomes in persons with HIV/HBV co-infection are particularly promising. Post-transplant survival in persons with HIV/HCV co-infection has been historically somewhat lower than in persons with HCV mono-infection mainly due to the complicated course of HCV re-infection after transplantation but improvements in survival in HIV/HCV co-infected persons have been seen due to the possibility to eradicate HCV pre- or post-transplant with direct acting antiviral drug (DAA)-based therapy, see Solid Organ Tranplantation (SOT) in HIV-positive Persons.
11. Renal complications are frequent, see page 56 and Diagnosis and Management of Hepatorenal Syndrome (HRS).

i MELD calculation, see page 56.

### Prevention/Support

12. Psychiatric, psychological, social and medical support should be made available to persons with alcohol intake to stop drinking.
13. Substitution therapy (opioid replacement therapy) in persons with active drug use as a step towards cessation of active drug use should be encouraged. Help provided (e.g. through needle and syringe exchange programme) reduces the risk of re-infection including parenteral viral transmission (harm reduction strategy), see Drug Dependency and Drug Addiction.
14. Since HBV and HIV, and occasionally HCV, are transmitted sexually, adequate counselling including the use of condoms is advisable. Information on the risk of HCV transmission due to mucosal traumatic sexual practices associated with a high likelihood of blood contact or ongoing IDU, “chem sex” (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.

### Delta Virus

15. In persons with Delta virus co-infection and significant liver fibrosis (≥ F2), long-term (> 18 months) treatment with PEG-IFN might be considered in association with TDF-based ART. Because of its anti-HBV activity, TDF/TAF should be added to PEG-IFN in order to reduce HBV-DNA load. Treatment efficacy should be monitored with HBV-DNA and HDV-RNA measurements, when available, and with follow-up of biochemical and liver fibrosis estimates. Persons with anti-HCV antibodies and detectable HCV-RNA should be offered anti-HCV treatment in order to eradicate HCV co-infection. Persistent off-treatment HDV-RNA negativity and anti-HBs seroconversion are the ideal goals of antiviral treatment for hepatitis Delta even if they can only be obtained in a minority of persons. Histological remission of liver disease is a less ambitious but more likely achievable goal. In persons with Delta virus and ESLD or HCC, liver transplantation from HBsAg negative donor should be strongly considered especially in the absence of active HCV co-infection. Transplant with anti-HBV prophylaxis post-OLTX cures HBV and Delta virus infection.

# Treatment of HBV/HIV Co-infection

1. All persons with HBV/HIV co-infection should receive ART that includes TDF or TAF unless history of tenofovir intolerance.
2. For HBV/HIV co-infected persons with bone mineral density changes or CKD, see recommendations for Dose Adjustment of ARVs for Impaired Renal Function and page 51.
3. If TDF or TAF is strictly contraindicated, entecavir may be prescribed in persons with no prior 3TC exposure and together with fully active ART.
4. Persons with liver cirrhosis and low CD4 count require careful surveillance in the first months after starting ART in order not to overlook immune reconstitution syndrome and subsequent liver decompensation due to flares of liver enzymes (for management of cirrhotic persons, see pages 55-59). Please note that diagnosis of cirrhosis may be difficult in persons already on HBV treatment.
5. NRTI substitution should only be performed if feasible and appropriate from the perspective of maintaining HIV suppression.
   Caution is warranted to switch from a TDF/TAF-based regimen to drugs with a lower genetic barrier, e.g. FTC or 3TC, in particular in 3TC-pretreated cirrhotic persons as viral breakthrough due to archived YMDD mutations is likely to happen. This has also been described in individuals with previous 3TC HBV-resistance who have been switched from TDF to entecavir.
6. The optimal treatment duration for nucleos(t)ide analogues with anti-HBV activity has not yet been determined and experts recommend life-long therapy if anti-HBV nucleos(t)ides are given as part of ART. In those on ART where the nucleoside backbone needs changing, anti-HBV therapy may be stopped cautiously in HBeAg-positive persons who have achieved HBe-seroconversion for at least one year or after confirmed HBs-seroconversion in those who are HBeAg-negative. In persons with liver cirrhosis, stopping of effective anti-HBV treatment is not recommended in order to avoid liver decompensation due to flares of liver enzymes.
7. In case of chemotherapy or other immunosuppression (e.g. rituximab-treatment) TDF/TAF should be added as prophylaxis in HBsAg-positive persons without HBV active ART (including 3TC) regardless of baseline HBV-DNA levels, see Solid Organ Tranplantation (SOT) in HIV-positive Persons.
8. Anti-HBc positive persons 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.
9. In anti-HBc positive persons treated with other immunosuppressive therapy (e.g. TNF alpha inhibitor, rituximab) careful monitoring with HBV-DNA and HBsAg is required for HBV re-activation. If this is not possible, addition of TDF/TAF is recommended.
10. In case of non-response to HBV vaccinations, ART should contain TDF or TAF.

# Diagnostic Procedures for HCV in Persons with HCV/HIV Co-infection

| |
|---|
| **Diagnosis of HCV** |
| HCV-Ab (turn positive 1-6 months after infection as late seroconversions have been described, may rarely be lost due to immunosuppression) |
| HCV-RNA levels[i] |
| **Evaluation of concurrent causes of liver disease and/or extra-hepatic HCV disease** |
| Alcohol consumption, cardiac disease, renal impairment, autoimmunity, genetic or metabolic liver diseases (e.g. genetic haemochromatosis, diabetes mellitus or obesity) and drug-induced hepatotoxicity |
| **Status of liver damage** |
| Staging of fibrosis (e.g. FibroScan, liver biopsy, serum fibrosis markers[ii]) |
| Complete blood count, ALT, AST, GGT, ALP, hepatic synthetic function (e.g. coagulation, albumin, cholinesterase) |
| Ultrasound every 6 months if cirrhosis (gastroscopy upon diagnosis of cirrhosis and every 3-4 years thereafter according to presence of ongoing liver disease if negative for oesophageal varices), see page 55 |
| **Before IFN-free HCV treatment** |
| HCV genotype (GT)[iii], HCV-RNA, renal and liver function tests |
| **Monitoring of IFN-free HCV treatment** |
| Differential blood count, creatinine, liver enzymes at week 2. In persons with significant fibrosis (≥ F2) differential blood count, creatinine, liver enzymes, bilirubin, albumin and INR every 2-4 weeks. |
| HCV-RNA at 2-4 weeks and whenever needed in order to assess compliance and/or breakthrough in persons experienced to oral DAAs at end-of-treatment and at week 12 after treatment cessation (to assess SVR). In persons receiving all oral DAA therapy no association between viral load at any given time-point during therapy and SVR has yet been found. |
| CD4 count and HIV-VL every 12 weeks |

i There is no standard conversion formula for converting the amount of HCV-RNA reported in copies/mL to the amount reported in IU/mL. The conversion factor ranges from about one to five HCV-RNA copies per IU/mL.

ii Serum fibrosis markers include APRI, FIB-4, Hyaluronic acid, Fibrometer, Fibrotest, Forns, Hepascore and other indices; recently more complex tests such as Fibrometer, Fibrotest and Hepascore have shown to more accurately predict liver fibrosis than simple biochemical tests such as APRI, FIB-4 or Forns.

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

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 of HCV in Persons with HCV/HIV Co-infection

## Treatment indication

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

## Treatment selection

4. IFN-free DAA combinations are now standard of care for chronic HCV see 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.
5. Selection of DAA combinations is based upon HCV GT, stage of liver fibrosis, pre-treatment history and resistance-associated substitutions (RAS) if tested.
6. Use of older, first generation HCV PIs (boceprevir and telaprevir; only indicated in GT1) are no longer recommended because of increased toxicities. The second generation PI simeprevir can cause hyperbilirubinaemia and skin reactions/photosensibility.
7. Due to drug-drug interactions in particular HIV and HCV PIs careful checking for interactions is urgently recommended prior to starting HCV therapy, see Drug-drug Interactions between DAAs and ARVs or http://www.hep-druginteractions.org.
8. In persons failing a first course with DAAs, current re-treatment strategies should include at least 2 active drug classes according to resistance testing results with a preferential use of one drug with high genetic barrier to resistance and with extended treatment durations and addition of RBV. Otherwise, new treatment options should be awaited if deferred treatment can be justified and in presence of relevant RASs at failure. In persons with decompensated cirrhosis, usage of SOF/VEL without protease inhibitors in combination with RBV for 24 weeks could be considered. In order to facilitate the best choice of HCV therapy before starting re-treatment, HCV resistance testing should be repeated (only in the gene with previous RASs) and should be based on population sequencing with a 15% detection cut-off. Shorter treatment duration (8 weeks in non-cirrhotics and 12 weeks in compensated cirrhotics) without RBV can be used in persons never treated with NS5A inhibitors and not infected with HCV GT 3; all other persons should be treated for at least 16 weeks; addition of SOF to GLE/PIB could be considered in those already treated with NS3 and NS5A inhibitors according to resistance testing. If available, SOF/VEL/VOX should be used for 12 weeks without RBV in all persons without decompensated cirrhosis.

## Treatment goal

9. The primary aim of HCV treatment is $SVR_{12}$ defined as undetectable HCV-RNA 12 weeks after the end of therapy (evaluated using sensitive molecular tests) or HCV core antigen levels where HCV- RNA assays are not available or not affordable.

## Treatment of acute HCV

10. 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.

    After diagnosis of acute HCV, HCV-RNA should be measured 4 weeks later. Treatment can be discussed in persons without a decrease of 2*log of HCV-RNA at 4 weeks compared with initial HCV-RNA and in persons with persistent serum HCV-RNA 12 weeks after diagnosis of acute HCV, see Algorithm for Management of Acute HCV in Persons with HCV/HIV Co-infection. Immediate treatment of persons with high risk of transmission could be considered at diagnosis. IFN-free treatment with DAAs is recommended as in non-cirrhotic chronic HCV/HIV co-infection, see pages 82-83. Shorter treatment duration is possible in persons with low baseline HCV-RNA (< 6*log IU/mL). Enrolment of persons with acute HCV co-infection in ongoing trials using IFN-free DAA combination therapy is strongly encouraged.

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

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

**DCV =** daclatasvir
**DSV =** dasabuvir
**EBR =** elbasvir
**GLE =** glecaprevir
**GZR =** grazoprevir
**LDV =** ledipasvir
**OBV =** ombitasvir
**PIB =** pibrentasvir
**PTV/r =** paritaprevir/RTV
**RBV =** ribavirin
**SMP =** simeprevir
**SOF =** sofosbuvir
**VEL =** velpatasvir
**VOX =** voxilaprevir
**RAS =** resistance associated substitutions

i In treatment experienced persons RBV treatment for 12 weeks or prolong treatment to 24 weeks without RBV.
ii 8 weeks treatment without RBV only in treatment-naïve persons with F < 3 and baseline HCV-RNA < 6 million IU/mL.
iii Addition of RBV in GT1a treatment experienced persons, but not in persons without NS5A RASs, if RASs testing is available.
iv In persons intolerant to RBV, treatment may be prolonged to 24 weeks. RBV can be omitted in treatment-naïve or -experienced persons with compensated cirrhosis without baseline NS5A RAS.
v 8 weeks treatment without RBV only in persons without cirrhosis.
vi Extension of treatment to 16 weeks and addition of RBV in persons with GT1a with baseline HCV-RNA > 800.000 IU/mL and NS5A RASs and in HCV GT4 experienced persons with HCV-RNA > 800.000 IU/mL.
vii Addition of RBV only in treatment experienced persons with baseline NS5A RASs, if RAS testing available; if these persons are intolerant to RBV, treatment may be prolonged to 24 weeks without RBV.
viii Extension of treatment to 12 weeks in DAA treatment experienced persons.
ix Treatment duration in HCV GT3 who failed previous treatment with IFN and RBV +/- SOF or SOF and RBV should be 16 weeks.

# Drug-drug Interactions between DAAs and ARVs

| | HCV drugs | ATV/c | ATV/r | DRV/c | DRV/r | LPV/r | EFV | ETV | NVP | RPV | MVC | DTG | EVG/c | RAL | ABC | FTC | 3TC | TAF | TDF | ZDV |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| DAAs | daclatasvir | ↑[i] | ↑110%[i] | ↑ | ↑41% | ↑15% | ↓32%[ii] | ↓ | ↓ | ↔ | ↔ | E33% | ↑[i] | ↔ | ↔ | ↔ | ↔ | ↔ | ↑10% E10% | ↔ |
| | elbasvir/ grazoprevir | ↑ | ↑ | ↑ | ↑ | ↑ | ↓54/83% | ↓ | ↓ | ↔ | ↔ | ↔ | ↑ | E43% | ↔ | ↔ | ↔ | ↔ | ↓7/14% E34% | ↔ |
| | glecaprevir/ pibrentasvir | ↑ | ↑553/64% | ↑ | ↑397%/- | ↑338/146% | ↓ | ↓ | ↓ | E84% | E | ↔ | ↑205/57% E47% | E47% | ↔ | ↔ | ↔ | ↔ | E29% | ↔ |
| | parita-previr/r/ ombitasvir/ dasabuvir | ↑ | ↑94%[iii] | ↑ | D[iv] | ↑ | [vi] | ↓E | ↓E | E[vii] | E | ↔ | ↑ | E134% | ↔ | ↔ | ↔ | E | ↔ | ↔ |
| | paritaprev-ir/r/ombi-tasvir | ↑ | ↑[iii] | ↑ | ↑[v] | ↑ | [vi] | ↓E | ↓E | E[vii] | E | ↔ | ↑ | E20% | ↔ | ↔ | ↔ | E | ↔ | ↔ |
| | simeprevir | ↑ | ↑ | ↑ | ↑ | ↑ | ↓71% | ↓ | ↓ | ↑6% E12% | ↔ | ↔ | ↑ | ↓11% E8% | ↔ | ↔ | ↔ | ↔ | ↓14% E18% | ↔ |
| | sofosbuvir/ ledipasvir | ↑[viii] | ↑8/113%[viii] | ↑[viii] | ↑34/ 39%[viii] | ↔[viii] | ↓-/34% | ↔ | ↔ | ↔[viii] | E | ↔ | ↑36/ 78%E[viii] | D≈20% | ↔ | ↔ | ↔ | E32% | E[viii] | ↔ |
| | sofosbuvir/ velpatasvir | ↔[viii] | ↑-/142%[viii] | ↔[viii] | ↓28%/-[viii] | ↓29%/-[viii] | ↓-/53% | ↓ | ↓ | ↔ | E | ↔ | ↑[viii] | ↔ | ↔ | ↔ | ↔ | ↔ | E[viii] | ↔ |
| | sofosbuvir/ velpatasvir/ voxilaprevir | ↑ | ↑40/93/331% | ↑[viii] | ↑-/- /143%[viii] | ↑ | ↓ | ↓ | ↓ | ↔ | E | ↔ | ↑-/-/171%[viii] | ↔ | ↔ | ↔ | ↔ | ↔ | E[viii] | ↔ |
| | sofosbuvir | ↔ | ↔ | ↑ | ↑34% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↓5%D27% | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |

**Legend**

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

Numbers refer to decreased/increased AUC of DAAs and ARVs as observed in drug interactions studies. 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

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

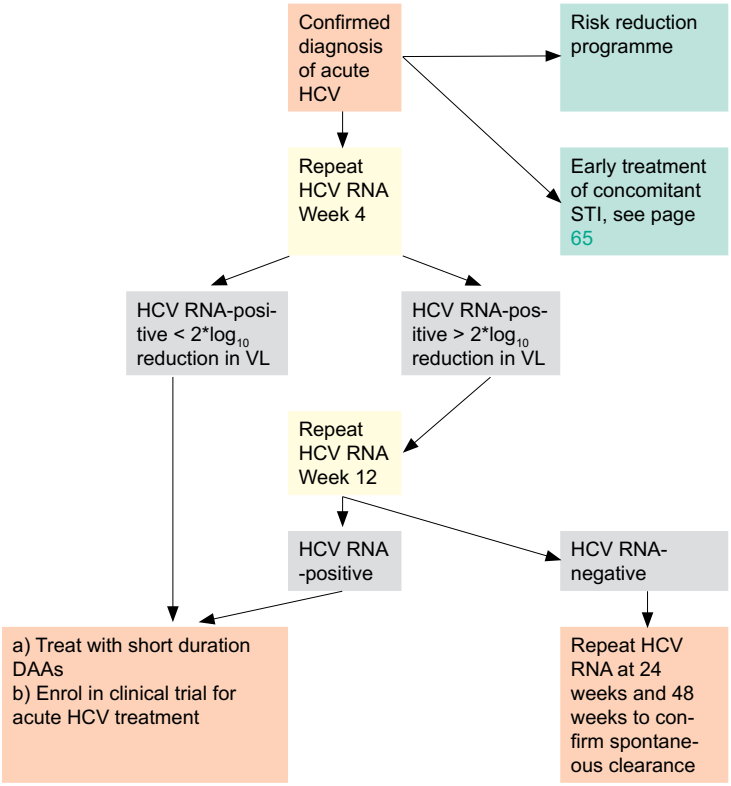
i DCV should be reduced to 30 mg once daily with ATV/r or EVG/c. No dose reduction with unboosted ATV
ii DCV should be increased to 90 mg once daily
iii use only with unboosted ATV (ATV increased PTV exposure due to CYP3A4 and OATP1B1/3 inhibition, not recommended without DSV)
iv co-administration decreased DRV trough concentration by approximately 50%. Although co-administration of DRV with OBV/PTV/r + DSV is not recommended in the US Prescribing Information, the European SPC advises that DRV (dosed at 800 mg qd and administered at the same time as OBV/PTV/r + DSV) can be used in the absence of extensive HIV PI resistance and should be taken without additional RTV
v 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
vi severe tolerability issues
vii 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
viii monitoring of kidney function recommended due to increase of tenofovir concentration if the regimen contains TDF

**Colour legend**

- no clinically significant interaction expected
- these drugs should not be co-administered
- potential interaction which may require a dosage adjustment or close monitoring
- potential interaction likely to be of weak intensity. Additional action/ monitoring or dosage adjustment is unlikely to be required

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

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



# Part V Opportunistic Infections

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

This chapter provides an overview of the most important aspects in management of the most frequent OIs occurring in HIV-positive persons in Europe. For more detailed discussion, we refer to national guidelines [1-7].
See online video lectures HIV and Pulmonary Infections-Part 1, HIV and Pulmonary Infections-Part 2 and HIV and Pulmonary Infections-Part 3 and CNS and HIV-related opportunistic infections-Part 1 and CNS and HIV-related opportunistic infections-Part 2 from the EACS online course Clinical Management of HIV.

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

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

**Pneumocystis jirovecii Pneumonia (PcP)**

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

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

**Toxoplasma gondii**
**Encephalitis**

| Primary prophylaxis | | | |
|---|---|---|---|
| **Start:** if CD4 count < 200 cells/µL, or CD4 percentage < 14%, oral thrush, or relevant concomitant immunosuppression (see above)<br>**Stop:** if CD4 count > 200 cells/µL over 3 months or CD4 count 100-200 cells/µL and HIV-VL undetectable over 3 months | | | |
| | **Drug** | **Dose** | **Comments** |
| Preferred prophylaxis | **TMP-SMX** | 1 double-strength tablet (ds) (800/160 mg) 3 x/week po or 1 single-strength tablet (ss) (400/80 mg) 1 x/day po or 1 ds tablet 1 x/day po | All regimens are also effective against PcP |
| Alternative prophylaxis | **atovaquone suspension** | 1 x 1500 mg/day po (with food) | |
| | **dapsone**<br>**+ pyrimethamine**<br>**+ folinic acid** | 200 mg 1 x/week po<br>75 mg 1 x/week po<br>25-30 mg 1 x/week po | Check for G6PD-deficiency |
| | **atovaquone suspension**<br>**+ pyrimethamine**<br>**+ folinic acid** | 1 x 1500 mg/day po (with food)<br>75 mg 1 x/week po<br>25-30 mg 1 x/week po | |
| **Treatment** | | | |
| **Treat 6 weeks**, then secondary prophylaxis until CD4 count > 200 cells/µL over 6 months<br>**Diagnosis:**<br>- **Definitive diagnosis:** clinical symptoms, typical radiology of the cerebrum AND cytological / histological detection of organism<br>- **Presumptive diagnosis:** clinical symptoms, typical radiology AND response to empirical treatment. It is the standard in most clinical settings. | | | |
| | **Drug** | **Dose** | **Comments** |
| Preferred therapy | **pyrimethamine**<br><br>**+ sulfadiazine**<br><br><br><br>**+ folinic acid** | Day 1: 200 mg po, **then**<br>• If ≥ 60 kg; 1 x 75 mg/day po<br>• If < 60 kg: 1 x 50 mg/day po<br>• If ≥ 60 kg: 2 x 3000 mg/day po/iv<br>• If < 60 kg: 2 x 2000 mg/day po/iv<br>1 x 10-15 mg/day po | Monitor for myelotoxicity of pyrimethamine, mostly neutropenia<br><br>Sulfadiazine is associated with crystalluria and may lead to renal failure and urolithiasis. Good hydration is essential. Check renal function and urine sediment for microhematuria and crystalluria |
| Alternative therapy | **pyrimethamine**<br><br>**+ clindamycin**<br>**+ folinic acid** | Day 1: 200 mg/day po, **then**<br>• If ≥ 60 kg: 1 x 75 mg/day po<br>• If < 60 kg: 1 x 50 mg/day po<br>4 x 600-900 mg/day po/iv<br>1 x 10-15 mg/day po | Monitor for myelotoxicity of pyrimethamine, mostly neutropenia<br><br>Additional PcP prophylaxis is necessary |
| | or<br>**TMP-SMX** | 2 x 5 mg TMP/kg/day iv/po<br>2 x 25 mg SMX/kg/day iv/po | Preferred regimen if oral route not possible |
| | or<br>**pyrimethamine**<br><br>**+ atovaquone**<br>**+ folinic acid** | Day 1: 200 mg po, **then**<br>If ≥ 60 kg; 1 x 75 mg/day po<br>If < 60 kg: 1 x 50 mg/day po<br>2 x 1500 mg/day po (with food)<br>1 x 10-15 mg/day po | Monitor for myelotoxicity of pyrimethamine, mostly neutropenia |
| | or<br>**sulfadiazine**<br><br><br>**+ atovaquone** | • If ≥ 60 kg: 2 x 3000 mg/day po/iv<br>• If < 60 kg: 2 x 2000 mg/day po/iv<br>2 x 1500 mg/day po (with food) | Sulfadiazine is associated with crystalluria and may lead to renal failure and urolithiasis. Good hydration is essential. Check renal function and urine sediment for microhematuria and crystalluria |
| | or<br>**pyrimethamine**<br><br>**+ azithromycin**<br>**+ folinic acid** | Day 1: 200 mg po, then<br>• If ≥ 60 kg; 1 x 75 mg/day po<br>• If < 60 kg: 1 x 50 mg/day po<br>1 x 900-1200 mg/day po<br>1 x 10-15 mg/day po | Monitor for myelotoxicity of pyrimethamine, mostly neutropenia |

| Secondary prophylaxis / Maintenance therapy | | | |
|---|---|---|---|
| **Stop:** if CD4 count > 200 cells/µL and HIV-VL undetectable over 6 months | | | |
| Regimens listed are alternatives | **sulfadiazine**<br>**+ pyrimethamine**<br>**+ folinic acid** | 2-3 g/day po (in 2-4 doses)<br>1 x 25-50 mg/day po<br>1 x 10-15 mg/day po | |
| | or<br>**clindamycin**<br>**+ pyrimethamine**<br>**+ folinic acid** | 3 x 600 mg/day po<br>1 x 25-50 mg/day po<br>1 x 10-15 mg/day po | Additional PCP prophylaxis is necessary |
| | or<br>**atovaquone suspension**<br>**+ pyrimethamine**<br>**+ folinic acid** | 2 x 750-1500 mg/day po (with food)<br>1 x 25-50 mg/day po<br>1 x 10-15 mg/day po | |
| | or<br>**atovaquone suspension** | 2 x 750-1500 mg/day po (with food) | |
| | or<br>**TMP-SMX** | 1 ds tablet (800/160 mg) 2 x/day po | |

**Cryptococcal meningitis**

| Treatment | | | |
|---|---|---|---|
| **14 days induction therapy, then 8 weeks consolidation therapy, then secondary prophylaxis for at least 12 months. Stop, if CD4 count > 100 cells/µL and HIV-VL undetectable over 3 months**<br><br>**Diagnosis:** positive microscopy, OR detection of antigen, OR culture from CSF<br><br>**Other organ manifestations:** Cryptococcal infection can also cause a pneumonitis which may be difficult to distinguish from Pneumocystis pneumonia. Infection may also involve other organs or may be disseminated.<br><br>**Primary prophylaxis:** One large RCT in Africa (the REALITY trial [9]) suggests that an enhanced infection prophylaxis in severely immunosuppressed persons (< 50 CD4 cells/µL) 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.<br><br>**Pre-emptive therapy:** Early stages of disseminated cryptocccal infections may be oligosymptomatic. Newer data from mainly resource limited settings support determination of serum cryptococcal antigen in all newly diagnosed HIV-positive persons with CD4 counts < 100 cells/µL. If cryptococcal antigen is detected, CSF should be examined to rule out cryptococcal meningitis. If meningitis is ruled out, pre-emptive therapy with fluconazole 800 mg/day po for two weeks is recommended before starting cART to reduce the risk of unmasking IRIS. | | | |
| | **Drug** | **Dose** | **Comments** |
| **Pre-emptive therapy** | **fluconazole** | 1 x 800 mg/day po for 2 weeks followed by<br>1 x 400 mg/day po for 8 weeks | In case of:<br>- positive cryptococcal serum antigen<br>- asymptomatic individual<br>- cryptococcal meningitis ruled out by CSF examination |
| **Induction therapy** | **liposomal amphotericin B**<br>**+ flucytosine** | 3 mg/kg/day iv<br>4 x 25 mg/kg/day po | **14 days**<br>- Then perform lumbar puncture (LP): if CSF culture is sterile, switch to oral regimen<br>- Opening pressure should always be measured, when LP is performed<br>- Repeated LPs or CSF shunting are essential to effectively manage increased intracranial pressure which is associated with better survival<br>- Corticosteroids have no effect in reducing increased intracranial pressure, could be detrimental and are contraindicated<br>- Flucytosine dosage must be adapted to renal function<br>- Defer start of cART for at least 4 weeks<br>- Amphotericin B deoxycholate may not be available in all European countries<br>- Flucytosine may not be available in all European countries. Consider replacing it by fluconazole 2 x 400 mg/day during the induction phase |
| | **or**<br>**amphotericin B deoxycholate**<br>**+ flucytosine** | 0.7 mg/kg/day iv<br>4 x 25 mg/kg/day po | |
| **Consolidation therapy** | **fluconazole** | 1 x 400 mg/day po<br>(loading dose 1 x 800 mg 1st day) | 8 weeks. Repeated LP until opening pressure < 20 cm $H_20$<br>See Drug-drug Interactions between ARVs and Non-ARVs |
| **Secondary prophylaxis / Maintenance therapy** | | | |
| **At least 12 months**<br>**Consider to stop:** if CD4 count >100 cells/µL and HIV-VL undetectable over 3 months | | | |
| | **Drug** | **Dose** | **Comments** |
| | **fluconazole** | 1 x 200 mg/day po | See Drug-drug Interactions between ARVs and Non-ARVs |

**Candidiasis**

| Oropharyngeal Candidiasis | | | |
|---|---|---|---|
| **Diagnosis:** typical clinical appearance, see Drug-drug Interactions Between ARVs and Non-ARVs, for all azole therapies | | | |
| | **Drug** | **Dose** | **Comments** |
| **Preferred alternatives** | **fluconazole** | 1 x 150-200 mg/day po | Once or until improvement (5-7 days) |
| | **itraconazole** | 1-2 x 100-200 mg/day po (oral solution fasting) | 7-14 days. Be aware of interactions with ARVs, see Drug-drug Interactions Between ARVs and Non-ARVs |
| | **nystatin** | 3-6 lozenges at 400000 units (aprox. 4-6 mL)/day | 7-14 days |
| | **or amphotericin B** | 3-6 lozenges at 10 mg/day or oral suspension 1-2 g/day (in 2-4 doses) | |
| **Oesophagitis** | | | |
| **Definitive diagnosis:** macroscopic inspection at endoscopy, OR histology of biopsy, OR cytology of specimen from the mucosal surface<br>**Presumptive diagnosis:** if 1. Recent onset of dysphagia AND 2. Oropharyngeal candidiasis | | | |
| | **Drug** | **Dose** | **Comments** |
| **Preferred alternatives** | **fluconazole** | 1 x 400 mg/day<br>or<br>400 mg loading dose, then 200 mg/day po | 3 days<br><br>10-14 days |
| | consider<br>**itraconazole**<br>**or**<br>**posaconazole**<br>**or**<br>**voriconazole**<br>**or**<br>**caspofungin** | <br>1-2 x 100-200 mg/day po (oral solution fasting)<br>2 x 400 mg/day po<br><br>2 x 200 mg/day po<br><br>1 x 70 mg iv/day, then 1 x 50 mg/day iv | 10-14 days. Be aware of interactions with ARVs, see Drug-drug Interactions Between ARVs and Non-ARVs<br>In cases of refractory disease, treat according to resistance testing.<br>Adapt posaconazole and voriconazole dose according to MIC's of candida and drug trough levels. |

**Histoplasmosis (Histoplasma capsulatum)**

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

**Herpes simplex virus (HSV) infections**

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

**Varicella zoster virus (VZV) infections**

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

**Cytomegalovirus (CMV) infections**

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

**Progressive Multifocal Leukoencephalopathy (PML)**

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

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

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

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

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

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

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

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

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

**Leishmaniasis**

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

# Diagnosis and Treatment of TB in HIV-positive Persons

| Treatment of TB in HIV-positive persons |
|---|
| For standard treatment of TB in HIV-positive persons, including appropriate choice of ARVs, see table and ART in TB/HIV Co-infection<br>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 | Comments* |
|---|---|---|---|
| Susceptible *Mycobacterium tuberculosis* | | | |
| Initial phase | **rifampicin**<br>**+ isoniazid**<br>**+ pyrazinamide**<br>**+ ethambutol** | Weight based | **Initial phase** for 2 months, then **Continuation phase** (rifampicin+isoniazid) according to TB type (see below)<br>Possibility to omit ethambutol, if *M. tuberculosis* is known to be fully drug sensitive<br><br>Preventive steroid therapy may be considered to avoid IRIS. |
| Alternative | **rifabutin**<br>**+ isoniazid**<br>**+ pyrazinamide**<br>**+ ethambutol** | Weight based | **Initial phase** for 2 months, then **Continuation phase** according to TB type (see below)<br>Possibility to omit ethambutol, if *M. tuberculosis* is known to be fully drug sensitive |
| Continuation phase | **rifampicin/rifabutin**<br>**+ isoniazid**<br>according to TB type | | Total duration of therapy:<br>1. Pulmonary, drug susceptible TB: 6 months<br>2. Pulmonary TB & positive culture at 8 weeks of TB treatment: 9 months<br>3. Extrapulmonary TB with CNS involvement or disseminated TB: 9-12 months<br>4. Extrapulmonary TB with bone/joint involvement: 9 months<br>5. Extrapulmonary TB in other sites: 6-9 months |

* Intermittent regimens (2 or 3 times per week) are contraindicated in HIV-positive persons. Missed doses can lead to treatment failure, relapse or acquired drug resistance.

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

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

- Previous TB treatment
- Contact with MDR/XDR-TB index case
- Birth, travel or work in an area endemic for MDR-TB
- History of poor adherence
- No clinical improvement on standard therapy and/or sputum smear positive after 2 months of TB therapy or culture positive at 3 months
- Homelessness/hostel living and in some countries recent/current incarceration
- In areas with very high MDR-TB/XDR-TB prevalence

MDR-TB: Resistance to isoniazid and rifampicin
XDR-TB: Resistance to isoniazid and rifampicin and quinolones and at least one at the following injectable drugs: kanamycin, capreomycin or amikacin

## Rapid detection

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

## Treatment of resistant TB [8]

INH-resistant TB

- RIF or RFB + Z+ E for 2 months and RIF or RFB + E for 10 months

Some experts recommend to add a FQ in the intensive phase and replace E by the FQ in the maintenance phase.

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

- In persons with rifampicin-resistant or MDR-TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C.
- If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.
- In persons with rifampicin-resistant or MDR-TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol.
- Preliminary results of a recent RCT (Nix-TB trial) suggest that a 3-drug combination of pretomanid 200 mg/day, bedaquiline 200 mg tiw after a 3-week load, and linezolid 1200 mg/day during 6 months (3 additional months if culture positive at 4$^{th}$ month) may be at least as effective as the 5-drug regimens suggested above. Majority of cases included were pulmonary TB.

## Drug choices

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

| | |
|---|---|
| **Group A: Fluoroquinolones** | • levofloxacin (LFX)<br>• moxifloxacin (MFX)<br>• gatifloxacin (G) |
| **Group B: Injectable agents** | • amikacin (Am)<br>• capreomycin (Cm)<br>• kanamycin (Km)<br>• streptomycin (S): use only if susceptibility is proven and the above medications are unavailable |
| **Group C: Other core second-line agents** | • ethionamide (ETO) or prothionamide (PTO)<br>• cycloserine (CS) or terizidone (TRD)<br>• linezolid (LZD)<br>• clofazimine (CFZ) |
| **Group D1: Add on agents** | • pyrazinamide (Z)<br>• ethambutol (E)<br>• high-dose isoniazid (high-dose INH) |
| **Group D2:** | • bedaquiline (BED)<br>• delamanid (DLM) |
| **Group D3:** | • p-aminosalicylic acid (PAS)<br>• imipenem-cilastatin (IPM/CLN)<br>• meropenem (MPM)<br>• amoxicillin clavulanate (Amx/CLV)<br>• thioacetazone (THZ) |

## Duration of MDR/XDR treatment

8 months of intensive phase using 5 or more drugs, followed by 12 months of 3 drugs depending on response.
E.g. 8 months of Z, MFX, Km, OFX, PTO and CS, followed by 12 months of MFX, PTO and CS.
In persons with rifampicin-resistant or MDR-TB who have not been previously 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.

## Drug interactions with ART and MDR/XDR regimens

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

| Latent tuberculosis | |
|---|---|
| Indication: TST > 5 mm or positive IGRA or close contacts to persons with sputum smear positive tuberculosis<br>Some national guidelines consider the ethnicity, CD4 count and ART usage to define indication for latent tuberculosis treatment. | |
| **Regimen*** | **Comments** |
| **isoniazid** 5 mg/kg/day (max 300 mg) po<br>+<br>**pyridoxine** (Vit B6) 25 mg/day po | 6-9 months<br><br>Consider 9-month duration in high-prevalent TB countries. |
| **rifampicin** 600 mg/day po<br>or **rifabutin** po (dose according to current cART) | 4 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs |
| **rifampicin** 600 mg/day po<br>or **rifabutin** po (dose according to current cART)<br>+<br>**isoniazid** 5 mg/kg/day (max 300 mg) po<br>+<br>**pyridoxine** (Vit B6) 25 mg/day po | 3 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs |
| **rifampicin** 600 mg 2 x/week po<br>+<br>**isoniazid** 900 mg 2 x/week po<br>+<br>**pyridoxine** (Vit B6) 300 mg 1 x/ week po | 3 months, check interactions with ARVs, see Drug-drug Interactions between ARVs and Non-ARVs |
| **rifapentine** 900 mg 1 x/week po<br>+<br>**isoniazid** 900 mg 1 x/week po | 3 months, check interactions with ARVs, see Drug-drug interactions between ARVs and non-ARVs<br>Rifapentine is not yet available in Europe. |

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

# References

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

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Please see references for Part III

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## Part V Opportunistic Infections

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3. France: http://www.sante.gouv.fr/IMG/pdf/Rapport_Morlat_2013_Mise_en_ligne.pdf
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# Video links

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