SAHCS
GUIDELINES

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY GUIDELINES FOR ANTIRETROVIRAL THERAPY IN ADULTS: **2023 UPDATE**

A publication of the Southern African HIV Clinicians Society

SOUTHERN AFRICAN HIV CLINICIANS SOCIETY GUIDELINES FOR ANTIRETROVIRAL THERAPY IN ADULTS: **2023 UPDATE**

Authors: Jeremy Nel, Graeme Meintjes, Regina Osih (Chairpersons), Larisse Badenhorst, John Black, Rosie Burton, Nomathemba Chandiwana, Francesca Conradie, Natasha Davies, Mariam Edoo, Ute Feucht, Cloete Jansen Van Vuuren, John Joska, Richard Lessells, Gary Maartens, Pheto Mangena, Thandekile Manzini, Yunus Moosa, Ndiviwe Mphothulo, Jennifer Nash, Dulcy Rakumakoe, Evan Shoul, Phumla Sinxadi, David Spencer, Helen van der Plas, Camilla Wattrus, Jeannette Wessels, Joana Woods, Jarrod Zamparini (Authors in alphabetical order by surname)

Corresponding author: Jeremy Nel, Jeremy.nel@wits.ac.za

Disclaimer: Specific recommendations provided here are intended only as a guide to clinical management, based on expert consensus and best current evidence. Treatment decisions for patients should be made by their responsible clinicians, with due consideration for individual circumstances. The most current version of this document should always be consulted.

TABLE OF CONTENTS

Abbreviations		4
1.	What's new in the 2023 guidelines update?	5
2.	Nucleoside/nucleotide reverse transcriptase inhibitor class of antiretroviral drugs	6
3.	Integrase strand transfer inhibitor class of antiretroviral drugs	9
4.	Non-nucleoside reverse transcriptase inhibitor class of antiretroviral drugs	13
5.	Protease inhibitor class of antiretroviral drugs	16
6.	Initiation and timing of antiretroviral therapy	18
7.	Baseline investigations	22
8.	Viral load	23
9.	CD4+ cell count	25
10.	Resistance and genotyping	27
11.	Initial antiretroviral therapy regimens for the previously untreated patient	31
12.	Management of patients currently receiving first-line therapy	33
13.	Management of patients starting or currently receiving second-line therapy	36
14.	Third-line antiretroviral therapy	39
15.	Laboratory monitoring of the efficacy and safety of antiretroviral therapy	43
16.	Patients who return after stopping antiretroviral therapy	44
17.	Drug-drug interactions	45
18.	Tuberculosis	47
19.	Pregnancy and breastfeeding	50
20.	Liver disease	53
21.	Renal disease	56
22.	Mental Health	58
23.	Malaria	59
24.	Antiretroviral drug-induced liver injury	60
25.	Dyslipidaemia	62
26.	Immune reconstitution inflammatory syndrome (IRIS)	63
27.	Prophylaxis for TB and cryptococcal meningitis	65
28.	Adherence	68

ABBREVIATIONS

/r	ritonavir-boosted
3TC	lamivudine
ABC	abacavir
ADR	adverse drug reaction
AKI	acute kidney injury
ALT	alanine transaminase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate transaminase
ATV	atazanavir
ATV/r	atazanavir/ritonavir
AZT	zidovudine
bd	twice daily
CD4+	cluster of differentiation 4
CM	cryptococcal meningitis
CrAg	cryptococcal antigen
CrCl	creatinine clearance
CSF	cerebrospinal fluid
CTX	cotrimoxazole
CVS	cardiovascular
d4T	stavudine
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DOR	doravirine
DRV	darunavir
DRV/r	darunavir/ritonavir
DTG	dolutegravir
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
ETR	etravirine
FBC	full blood count
FDC	fixed dose combination
FTC	emtricitabine
GI	gastrointestinal
Hb	haemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HIV	human immunodeficiency virus
ICU	intensive care unit
InSTI	integrase strand transfer inhibitor
IPT	isoniazid preventive therapy
LAM	lipoarabinomannan
LDL-C	low-density lipoprotein cholesterol
LP	lumbar puncture
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MDRD	modification of diet in renal disease
MTCT	mother-to-child transmission of HIV
MVC	maraviroc
NGT	nasogastric tube
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside reverse transcriptase inhibitor
NTDs	neural tube defects
NtRTI	nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OI	opportunistic infection
PCR	polymerase chain reaction
PI	protease inhibitor
PI/r	ritonavir-boosted protease inhibitor
PMTCT	prevention of mother-to-child transmission of HIV
PPIs	proton pump inhibitors
PrEP	pre-exposure prophylaxis
PWH	people with HIV
RAL	raltegravir
RCTs	Randomised controlled trials
RIF	rifampicin
RFB	rifabutin
RNA	ribonucleic acid
RPV	rilpivirine
RTV or /r	ritonavir
sCr	serum creatinine
sCrAg	serum cryptococcal antigen
TAF	tenofovir alafenamide
TAM	thymidine analogue mutation
TB	tuberculosis
TB-IRIS	tuberculosis immune reconstitution inflammatory syndrome
TBM	tuberculosis meningitis
TC	total cholesterol
TDF	tenofovir disoproxil fumarate
TG	triglycerides
TST	tuberculin skin test
ULN	upper limit of normal
VL	viral load
VTP	vertical transmission prevention of HIV
WHO	World Health Organization

MODULE 1

WHAT'S NEW IN THE 2023 GUIDELINES UPDATE?

This 2023 update to the Southern African HIV Clinicians Society guidelines for Antiretroviral Therapy in Adults reflects the changing treatment paradigms of the current era, specifically the consolidation towards dolutegravir- and darunavir-based treatment regimens, rather than efavirenz- or lopinavir-ritonavir-based ones.

Numerous other changes have also been incorporated to ensure that these guidelines remain up to date and helpful to the healthcare workers who use them. These include, but are not limited to:

Key updates

- Recommendation to shift most patients to a dolutegravir-based regimen if possible (see **modules 12-14**).
- For patients requiring a protease inhibitor (PI), recommendation for darunavir as the PI of choice, and for lopinavir/ritonavir to only be considered where a PI is required to be coadministered with rifampicin-based tuberculosis treatment (see **modules 5 and 13**).
- New recommendations on the move away from routine use of zidovudine (AZT) in second-line therapy in favour of recycling tenofovir or, in patients with renal dysfunction, abacavir (see **module 13**).
- Advice on how to assess the increase in serum creatinine seen with dolutegravir/tenofovir fixed dose therapy (see **module 3**).
- Guidance on the role of tenofovir alafenamide; TAF (see **modules 2 and 11**).
- Inclusion of enhanced baseline screening for tuberculosis and sexually transmitted infections (see **module 7**).
- Expansion of the module on HIV and mental health (see **module 22**).

While many antiretroviral therapy (ART) guidelines are available internationally, the current guidelines have been written to address issues relevant to Southern Africa. Only treatment and diagnostic options available in Southern Africa are included. These guidelines also consider affordability, since countries in the region vary between low- and middle-income settings. We recognise the need to bridge the gap in treatment recommendations between public and private sector programmes, considering that many patients transition between the two sectors for treatment, and have borne this in mind when providing our own guidance.

MODULE 2

NUCLEOSIDE/NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITOR CLASS OF ANTIRETROVIRAL DRUGS

Key points

- The recommended nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) drugs for first-line therapy are tenofovir disoproxil fumarate (TDF) and either lamivudine (3TC) or emtricitabine (FTC).
- Patients with an estimated glomerular filtration rate (eGFR) < 50 mL/min/1.73m^2 or osteoporosis should generally be started on abacavir (ABC) instead of TDF for first-line therapy, provided they do not have chronic hepatitis B infection.
- Tenofovir alafenamide (TAF) is recommended instead of TDF or ABC for patients with hepatitis B and an eGFR 30-50 mL/min/1.73m^2, or osteoporosis. It can be considered as an alternative to ABC for patients without hepatitis B but with an eGFR 30-50 mL/min/1.73m^2 or osteoporosis.
- Zidovudine (AZT) should only be used in special circumstances.
- Tenofovir can cause renal failure or a renal-tubular wasting syndrome. Serum creatinine monitoring at regular intervals is recommended.
- ABC can cause a fatal hypersensitivity reaction in patients with HLA-B*5701. If feasible, this allele should be excluded prior to starting ABC, although it is very rare in people of African descent. Routine testing for HLA-B*5701 is not currently part of the standard of care in the public sector.

Available nucleoside/nucleotide reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs) work by acting as nucleotide base analogues. Following incorporation into the DNA chain by HIV's reverse transcriptase enzyme, they block further chain elongation. A summary of NRTIs is provided in **Table 1**, and the appropriate baseline investigations and required monitoring in **Table 2**. NRTIs may be available as single tablets or in fixed dose combinations (FDC). The latter is recommended where possible to decrease overall pill burden. Many NRTIs require dose adjustment in renal failure (see **module 21**).

Lamivudine and emtricitabine

Lamivudine (3TC) and emtricitabine (FTC) are well-tolerated drugs recommended as part of a first-line regimen. Although there are minor differences between them, 3TC and FTC are considered functionally interchangeable. Their use may be continued in the presence of 'high-level resistance' caused by the M184V mutation, since this mutation impairs HIV's replication ability, causing a ~0.5 log decrease in viral load (VL). Therefore, these drugs are often also recycled in second- and third-line therapy (see the management of patients on second-line ART in **module 13**). 3TC and FTC are active against hepatitis B, but when used in the absence of a second drug active against hepatitis B, such as TDF, then resistance rates of approximately 50% at 1 year, and 90% at 5 years, are seen.[1] See **module 20**.

Pure red cell aplasia (PRCA), which presents with severe anaemia and a low reticulocyte production index, has rarely been associated with 3TC and FTC.[2,3] A bone marrow examination should be performed to confirm the condition. Parvovirus B19 infection should be excluded with a polymerase chain reaction (PCR) test. If 3TC and FTC are contraindicated due to PCRA, then we suggest contacting an expert for advice about alternative regimens (see **module 11** for some 3TC/FTC-sparing regimen options.)

Tenofovir

Tenofovir is available in two oral prodrug forms: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). Both are converted to the pharmacologically active form, tenofovir diphosphate, intracellularly. Similar to 3TC/FTC, when tenofovir has been part of an initial ART regimen, it may be continued in subsequent regimens even in the face of high-level resistance, as sufficient antiviral activity is maintained if combined with drugs with a high genetic barrier to resistance.[4]

Both forms of tenofovir offer durable therapy against hepatitis B virus (HBV) as HBV resistance against tenofovir is exceedingly rare. In a minority of patients, tenofovir may cause a tubular wasting syndrome (including wasting of phosphate and potassium).[5] If patients receiving tenofovir develop muscle weakness or other muscle symptoms, then potassium and phosphate levels must be assessed. Tenofovir can also cause acute and chronic renal failure, but this is uncommon.[6] Long-term use of TDF together with other nephrotoxic agents (e.g. aminoglycosides or non-steroidal anti-inflammatory agents) should nonetheless be avoided.

TDF also causes a decrease in bone mineral density, but this is generally mild, and most studies have not found an increase in fracture risk.

Of the two forms of tenofovir, we recommend TDF as the drug for use with 3TC or FTC in most instances, as it aligns with public sector programmes, is more widely available as a FDC, and is generally well-tolerated. TDF should not be used if the estimated glomerular filtration rate (eGFR) is < 50 mL/min/1.73m^2.

TAF has fewer renal and bone side-effects than TDF, although the extent of this has been questioned.[7,8] When coformulated with 3TC/FTC, TAF can be given down to a minimum eGFR of 30 mL/min/1.73m^2. However, if given as a separate tablet, TAF can be given down to an eGFR of 15 mL/min/1.73m^2, as well as to patients on chronic haemodialysis. Compared to TDF, TAF is associated with greater weight gain, an adverse lipid profile, and several important drug-drug interactions (see **module 17** for more details).[9-11] The TAF 25mg dose currently available in South Africa should not be used with ritonavir-containing PI regimens. Although rifampicin reduces serum TAF levels, intracellular concentrations of the active tenofovir metabolite are in fact higher than achieved with TDF, and thus rifampicin-based TB treatment is safe to co-administer.[12] TAF/FTC combinations can be considered as an alternative to TDF in patients with eGFR 30-50 mL/min/1.73m^2 or with osteoporosis, although abacavir (ABC) is also available in these instances as an alternative. TAF is recommended in patients who have one or more of these conditions and hepatitis B.

Tenofovir (either TDF or TAF) should be switched to ABC or an alternative NRTI immediately in patients with acute kidney injury, as it may exacerbate injury even if it is not the primary cause. Consider recommencing tenofovir (either TDF or TAF) with careful monitoring when the eGFR returns to baseline and if an alternative cause of renal failure is established. In patients in whom tenofovir is avoided because of a low eGFR at baseline, it may be possible to switch to tenofovir at a later point if renal function improves. This is often the case where patients had diarrhoea or other opportunistic infections (OIs) at the time of ART initiation.

For monitoring while on TDF see **Table 2**.

Common pitfall: Permanently discontinuing TDF in patients with a transiently decreased eGFR. Most cases of acute kidney injury (AKI) are not due to TDF, and if another cause of AKI is identified (e.g. severe diarrhoea or pneumonia), then TDF can be re-introduced with monitoring once renal function improves.

Abacavir

Abacavir (ABC) does not require dose adjustment in renal failure and is especially useful in patients with chronic renal failure, in whom tenofovir is nephrotoxic and zidovudine (AZT) could aggravate the anaemia of renal failure. A meta-analysis showed that virological suppression is equivalent with ABC- and TDF-containing first-line regimens regardless of baseline VL.[13]

Common pitfall: Avoiding ABC in patients with a high VL. This is a common misconception and is unnecessary, as viral suppression rates are equivalent in meta-analyses.

ABC has been associated with an increased risk of myocardial infarction in some but not other cohort studies, but the association was not confirmed in a meta-analysis of randomised controlled trials (RCTs).[13-15]

ABC hypersensitivity is a systemic reaction occurring within the first 8 weeks of therapy in ~6% of people of European ancestry.[16] Fatalities may occur on rechallenge. **ABC must be discontinued and never reintroduced if hypersensitivity is suspected.** The manifestations of hypersensitivity include fever, rash,

fatigue and abdominal or respiratory symptoms. If there is any doubt concerning the diagnosis (e.g. if the patient has a cough with fever), then the patient should be admitted for observation of the next dose: if symptoms progress, hypersensitivity is present. The hypersensitivity reaction has been shown to occur on a genetic basis, with a very strong association with the HLA-B*5701 allele. This allele is very uncommon in people of African descent thus ABC hypersensitivity is less frequent. If testing is affordable and available, then the presence of HLA-B*5701 should be excluded prior to prescribing ABC, especially in patients who are not of African descent.

Zidovudine

We recommend reserving zidovudine (AZT) for use only in special circumstances where both tenofovir and ABC are unavailable or contraindicated. In these instances, AZT can be used, provided that the haemoglobin (Hb) is > 8 g/dL. AZT can cause neutropenia and anaemia; platelet counts generally rise with the use of the drug. Monitoring is necessary with AZT (see **Table 2**). It is unusual, however, to see haematological toxicity develop after 6 months. Macrocytosis is usual with AZT therapy and is of no consequence. Routine measurement of vitamin B12 and folate concentrations is not needed.

TABLE 1: Dosage and common adverse drug reactions of nucleoside/nucleotide reverse transcriptase inhibitors available in southern Africa (adult dosing).

Generic name	Drug class	Recommended dosage	Common or severe ADR‡
Tenofovir disoproxil fumarate (TDF)	NtRTI	300 mg daily	**Renal failure**, tubular wasting syndrome, reduced bone mineral density, nausea
Tenofovir alafenamide (TAF)	NtRTI	25 mg daily	Less **renal failure** and bone mineral reduction than TDF, but more weight gain and worse lipid profile
Lamivudine (3TC)	NRTI	150 mg 12-hourly or 300 mg daily	**Anaemia (pure red cell aplasia)** (rare)
Emtricitabine (FTC)†	NRTI	200 mg daily	**Anaemia (pure red cell aplasia)** (rare), palmar hyperpigmentation
Abacavir (ABC)	NRTI	300 mg 12-hourly or 600 mg daily	**Hypersensitivity reaction**
Zidovudine (AZT)	NRTI	300 mg 12-hourly	**Anaemia, neutropenia,** gastrointestinal upset, headache, myopathy, hyperlactataemia/ steatohepatitis (medium potential), lipoatrophy

ARV, antiretroviral; ADR, adverse drug reaction; NtRTI, nucleotide reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor. †, FTC is not available as a single drug in South Africa, only co-formulated. ‡, Life-threatening reactions are indicated in **bold.**

TABLE 2: Baseline investigations and monitoring required for nucleoside/nucleotide reverse transcriptase inhibitors.

Generic name	Monitoring required	Comment
Tenofovir disoproxil fumarate (TDF)	eGFR before initiation, then at 3 months, 6 months, and then 6-12 monthly thereafter	Avoid if eGFR < 50 mL/min/1.73m^2 In high-risk patients (particularly those with co-existent hypertension or diabetes), eGFR should also be checked at 1 and 2 months
Tenofovir alafenamide (TAF)	eGFR before initiation, then at 3 months, 6 months, and then 6 monthly thereafter	When coformulated with 3TC/FTC, avoid if eGFR < 30 mL/min/1.73m^2 (if using single drug, avoid if eGFR <15 mL/min/1.73m^2 and not on haemodialysis). In high-risk patients (particularly those with eGFR 15-30 mL/min/1.73m^2), eGFR should also be checked at 1 and 2 months
Lamivudine (3TC)	None routinely required	-
Emtricitabine (FTC)	None routinely required	-
Abacavir (ABC)	HLA-B*5701 before initiation, if testing is affordable and available	Allele very rare in people of African descent
Zidovudine (AZT)	Hb and neutrophil count before initiation, then at months 1, 2, 3 and 6	Avoid if Hb < 8 g/dL. If neutrophil count is 1–1.5 x 10^9/L, then repeat in 4 weeks. If neutrophil count is 0.75–0.99 x 10^9/L, then repeat in 2 weeks or consider switching from AZT. If neutrophils < 0.75 x 10^9/L, then switch from AZT.

eGFR, estimated glomerular filtration rate; Hb, haemoglobin.

MODULE 3

INTEGRASE STRAND TRANSFER INHIBITOR CLASS OF ANTIRETROVIRAL DRUGS

Key points

- DTG is the preferred integrase strand transfer inhibitor (InSTI) because it has a high barrier to resistance, is well tolerated, is available in a FDC formulation, and can be taken once daily.
- DTG causes a small increase in serum creatinine (usually <30 µmol/L) due to interference with tubular creatinine secretion; however, this does not represent a decline in renal function.
- Contrary to initial concerns, DTG does not cause neural tube defects, and should be freely offered to women of reproductive age, throughout pregnancy and breastfeeding.
- Although DTG is associated with more weight gain compared to other regimens, it appears to unmask it rather than cause it. There is no role for switching ART regimens in patients who experience significant weight gain on DTG.

Overview of integrase strand transfer inhibitors

Integrase strand transfer inhibitors (InSTIs) – often simply termed 'integrase inhibitors' – work by preventing the transfer of proviral DNA strands into the host chromosomal DNA. Currently, two InSTIs are available in Southern Africa: dolutegravir (DTG) and raltegravir (RAL). DTG is preferred due to its higher barrier to resistance, its availability in fixed-dose combination (FDC) formulation, and the ability to take the drug once daily.[17,18]

DTG use has been shown to be virologically superior to EFV-based ART in the SINGLE trial.[19] This difference was largely driven by the superior tolerability of the DTG arm: 2% vs. 10% in the EFV arm had an adverse event leading to discontinuation of the study drug. DTG showed superior rates of viral suppression (71% vs. 63% respectively at 144 weeks).

DTG-based regimens have also been shown to be superior to PI-based regimens when used as initial therapy. As first-line therapy, DTG was superior to DRV/r with respect to both viral suppression rates and side-effect profile in the FLAMINGO trial.[20] The ARIA trial of ART-naïve women demonstrated a superior viral suppression rate compared to ATV/r, and with fewer side-effects.[21] When compared to PIs in second line therapy, DTG is non-inferior to DRV/r but superior to LPV/r.[4,22]

A key advantage of DTG when used as initial therapy is its extremely high barrier to resistance, with treatment-emergent resistance being exceptionally rare.[23] This is less true of DTG when used in subsequent regimens following virological failure, where approximately 1-3% of patients can be expected to develop DTG resistance within 1-3 years.[4,22,24,25] Prior InSTI exposure with RAL also puts a patient at an increased risk of DTG resistance.

Common side-effects

DTG and RAL are generally well tolerated, with most side-effects being mild and very rarely leading to discontinuation. DTG may cause a mild increase in serum creatinine due to interference with tubular secretion. This does not represent renal damage and is not an indication for switching to another drug. The rise in creatinine occurs within the first few weeks and then plateaus, and will persist for as long as the patient remains on DTG. Since DTG and TDF are commonly commenced together, it can be difficult to evaluate an early rise in serum creatinine. One suggested approach is outlined in **Figure 1**.

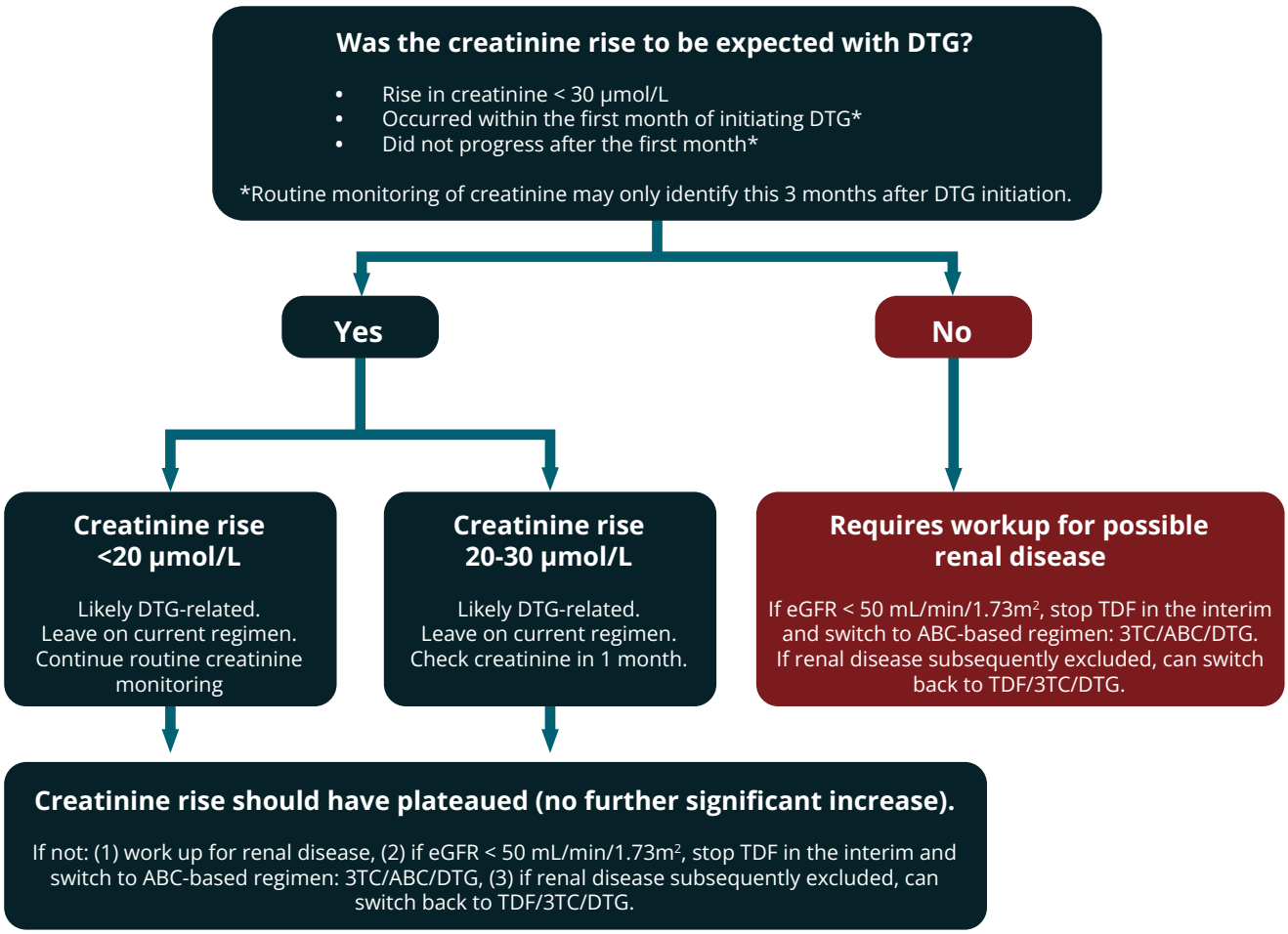


FIGURE 1: Assessment and management of rise in creatinine in patients on dolutegravir (DTG).

(DTG, dolutegravir; TDF, tenofovir; 3TC, lamivudine; ABC, abacavir; eGFR, estimated glomerular filtration rate)

Common pitfall: Assuming that the rise in creatinine seen in patients on DTG necessarily represents renal failure. In reality, the effect of DTG on creatinine secretion is of no consequence and does not represent a decline in renal function.

RAL and DTG can cause headaches when started, but this usually resolves. These drugs may also cause insomnia and neuropsychiatric side-effects. RAL and DTG can occasionally cause hypersensitivity rashes, including life-threatening rashes.

Although early results from the Tsepamo surveillance study in Botswana initially flagged a higher rate of neural tube defects (NTDs) among infants of women who were taking DTG at the time of conception compared to other ART, this has not been borne out by subsequent data from Tsepamo study, nor has it been seen in other similar cohorts from other countries.[26-29] In addition, women on DTG-based regimens in pregnancy demonstrate faster time to viral suppression and better viral suppression rates at delivery, which may translate to better outcomes for both mother and child.[30-33] Therefore, as for all adults, DTG is recommended as first-line treatment for pregnant and breastfeeding women, and for women of reproductive age.

Contrary to initial speculation that the integrase inhibitor class may cause weight gain, the association now appears not to be causal. Instead, the association may be the result of comparatively less metabolic toxicity than alternative older ART regimens (that impair weight gain through toxicity) combined with an initial return-to-health phenomenon, and an obesogenic environment.[34-36] Given DTG-based ART regimens' numerous advantages over comparators, DTG should not be withheld out of concern for weight gain. Clinicians should instead provide proactive advice for preventing weight gain through diet and exercise, as significant weight gain is almost universal

after initiating antiretrovirals, and is progressive, especially among women. Evidence is accumulating for specific weight loss therapies such as glucagon-like peptide-1 (GLP-1) agonists, but these are likely to be unaffordable and currently out of reach of the vast majority of patients. There is no role for switching from DTG-containing regimens in patients gaining weight. See **Box 1**.

Common pitfall: Not starting DTG because of a fear of weight gain. Contrary to initial speculation, DTG does not appear to cause weight gain. Rather, physicians should alert patients to the possibility of weight gain when initiating any ART regimen, because of the return-to-health phenomenon and an obesogenic environment.

BOX 1: Advice on weight gain in patients on DTG-based regimens.

What the evidence suggests:

- Data from ADVANCE, NAMSAL and other high-quality trials show an association between dolutegravir and weight gain, particularly in women. In the ADVANCE cohort, median weight gain by 192 weeks was 5.8 kg for those on TDF/FTC/DTG compared to 3.3 kg for those on TDF/FTV/EFV.
- Most of the weight gain happens in the first year of starting DTG, and regardless of regimen, a component of the weight gain frequently represents a return-to-health phenomenon, whereby weight lost due to uncontrolled HIV is regained once HIV replication is suppressed.
- Subsequent analysis of the ADVANCE cohort revealed that the weight trajectory in patients on EFV had been determined largely by their genetics: those with a CYP2B6 genotype that enabled rapid metabolism of EFV had similar weight gain to participants in the DTG arm, intermediate EFV metabolisers gained almost no weight, and slow metabolisers (i.e., those with the highest serum EFV levels) lost weight.
- EFV is known to cause mitochondrial toxicity as well as inhibition of genes controlling adipogenesis and lipid accretion, reduced release of adipokines and increased pro-inflammatory catabolic cytokines. It may also mediate weight loss by neuropsychiatric adverse effects, by impairing appetite.
- Together, **these results suggest that the difference in weight gain seen between EFV and DTG in ADVANCE and similar trials is likely to be due to genetically-predisposed EFV-related toxicities impairing weight gain rather than DTG-mediated weight gain.**

Key management principles:

- Clinicians initiating or switching patient to DTG should take care not to unnecessarily imply that DTG "causes" weight gain, as this may lead to suboptimal treatment adherence in patients who do subsequently gain significant weight.
- The possibility of weight gain should be discussed by clinicians when starting all ART regimens, as obesity is an increasing problem in HIV care, particularly but not exclusively amongst women.
- Proactive advice for preventing weight gain through diet and exercise should be given to all patients starting or switching ART. Evidence is accumulating for specific weight loss therapies such as GLP-1 agonists, but these are likely to be unaffordable and out of reach of the vast majority of patients currently.
- Since the failure to gain weight in EFV-containing regimens is frequently mediated by toxic levels of EFV because of genetically slower drug metabolism, there is no current role for switching from DTG-containing regimens in patients gaining weight. In addition, drugs such as EFV are associated with inferior viral suppression rates compared to DTG.

Dosage and common adverse drug reactions of InSTIs are described in **Table 3**.

TABLE 3: Dosage and common adverse drug reactions of integrase strand transfer inhibitors available in Southern Africa.

Drug	Recommended dosage	Common or severe ADR
DTG	50 mg daily	Insomnia, headache and other CNS side-effects, gastrointestinal upset, **hepatitis and rash** (rare) can be accompanied by severe systemic hypersensitivity reaction
RAL	400 mg 12-hourly	Headache and other CNS side-effects, gastrointestinal upset, **hepatitis and rash** (rare), rhabdomyolysis (rare)

CNS, central nervous system; DTG, dolutegravir; RAL, raltegravir.
†Life-threatening reactions are indicated in **bold.**

Key drug-drug interactions with dolutegravir

Key drug-drug interactions involving DTG are summarised in **Table 4**.

In general, patients on rifampicin (RIF)-based tuberculosis regimens should receive DTG 12-hourly until 2 weeks after stopping RIF, as RIF decreases DTG drug levels. However, a large observational cohort study from Botswana suggested that HIV viral suppression rates were not statistically significantly different between those who received DTG 12-hourly and those who received it daily.[37] This was recently confirmed by a randomised placebo-controlled trial done in Cape Town (RADIANT-TB trial), where viral suppression rates at week 24 were 83% for both those given DTG 12-hourly and those who received the drug daily.[38] Thus, DTG may be given as a daily dose in patients on RIF who are on first-line DTG-based regimens. However, for those who have a prior history of treatment failure on a different regimen, in whom the companion NRTIs may not have full activity, there is still limited evidence on the optimal DTG dose. Pending further data, we suggest such patients continue to receive DTG 12-hourly.

TABLE 4: Key drug-drug interactions with dolutegravir.

Drug	Action required
Rifampicin (RIF)	Pending further data, for patients on DTG who have a history of virologic failure on a previous regimen, we suggest DTG be administered twice-daily (i.e. 50 mg 12-hourly) until 2 weeks after stopping RIF. For patients on DTG with no prior history of virological failure, no change in DTG dosing is required.
Metformin	Do not exceed metformin 500 mg 12-hourly.
Carbamazepine, phenytoin	Give alternative anticonvulsant (e.g. lamotrigine, topiramate or levetiracetam). If carbamazepine is used, then administer DTG 12-hourly.
Polyvalent cation-containing agents (e.g. antacids, laxatives, sucralfate, and iron, calcium and zinc supplements).	For magnesium-/aluminium-containing antacids, administer > 2 hours after or > 6 hours before DTG dose. For iron/calcium supplements, either take with food, otherwise apply intervals above. For pregnancy supplements, also apply timing intervals above.
Etravirine	Do not use DTG + etravirine together unless a boosted PI is also used in the combination

DTG, dolutegravir; RIF, rifampicin; PI, protease inhibitor

MODULE 4

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR CLASS OF ANTIRETROVIRAL DRUGS

Key points

- Efavirenz (EFV) remains an ART option for patients who tolerate DTG poorly, or where DTG is contraindicated or declined.
- EFV 400 mg is virologically non-inferior to EFV 600 mg and offers a somewhat improved side-effect profile. The 400 mg formulation is preferred in most instances, except for those patients receiving rifampicin (RIF)-based tuberculosis (TB) treatment, to whom 600 mg should be given.
- Rilpivirine (RPV) is another alternative but cannot be co-administered with RIF-based TB treatment, and should not be started in patients with a VL > 100 000 copies/mL.

Overview of non-nucleoside reverse transcriptase inhibitors

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) work by binding irreversibly to HIV's reverse transcriptase enzyme, which causes a conformational change in the enzyme's active site and impairs its functioning. The four NNRTIs currently available in Southern Africa are efavirenz (EFV), nevirapine (NVP), rilpivirine (RPV) and etravirine (ETR).

Individual non-nucleoside reverse transcriptase inhibitors

Efavirenz

Efavirenz (EFV) is available in 600 mg and 400 mg formulations, and both are now available as fixed dose combinations (FDC). EFV 600 mg is available in public sector programmes in South Africa and there is extensive clinical experience with the formulation. EFV 400 mg demonstrated non-inferior efficacy with moderately improved tolerability in the ENCORE1 study.[39] However, there are only limited pharmacokinetic data in pregnant patients, and in patients receiving RIF-based tuberculosis treatment. For most patients requiring EFV, EFV 400mg should be used unless they are also on RIF-based tuberculosis treatment, in which case EFV 600mg should be used.

EFV frequently causes neuropsychiatric effects in the first few weeks of therapy, typically presenting with insomnia, vivid dreams and dizziness. Both dysphoria and euphoria may occur. EFV may also cause a skin rash, which is usually mild. Patients starting EFV should be warned about these symptoms and reassured that they resolve in most patients continuing the drug after the first few weeks but, if not, an alternative can be substituted. Psychosis and Stevens-Johnson syndrome may occasionally occur. If the neuropsychiatric effects of EFV are not tolerated, then drug switching is recommended.

Recently, a late-onset encephalopathy syndrome has been linked to EFV.[40] This is characterised by a subacute encephalopathy and cerebellar dysfunction including ataxia, frequently presenting months to years after commencing EFV, and is associated with supratherapeutic EFV levels. Patients who are genetically slow metabolisers of EFV may be predisposed to this syndrome. Two common CYP2B6 polymorphisms linked to slow EFV metabolism have been shown to occur with increased frequency in patients of African descent.[41] This predisposition to toxic EFV levels may be further exacerbated in patients of low body weight and in those taking concomitant isoniazid, which inhibits an accessory EFV metabolism pathway via CYP2A6. Patients with a compatible clinical syndrome, in the absence of an alternative cause, should have plasma EFV levels measured and should be switched to a non-EFV-based regimen in the interim. Clinical improvement is typically seen within 10–21 days after stopping EFV.

EFV may also cause drug-induced hepatitis. A subset of these cases appears to occur relatively late, several months or even years after the drug has been initiated.[42] It is important that this diagnosis is

considered in the differential diagnosis of a subacute hepatitis syndrome.

Gynaecomastia can occur with the use of EFV.[43] This is not related to lipodystrophy. The onset occurs several months after initiation of ART, and it may be bilateral or unilateral. The mechanism appears to be related to oestrogen receptor activation in breast tissue by EFV.[44] It is important to exclude other common causes of gynaecomastia, such as other medications (including spironolactone, calcium channel blockers and metoclopramide). A serum testosterone test is useful in excluding hypogonadism as a cause. If serum testosterone is low, then other appropriate investigations should be done to identify the cause and be managed accordingly. If serum testosterone is normal, then EFV should be substituted for another drug. Resolution of gynaecomastia is generally slow, taking months, and may be incomplete in a small percentage.[45] It is therefore important to manage the expectations of the patient in this regard.

Rilpivirine

Another option in first-line ART is rilpivirine (RPV), a second-generation NNRTI. RPV is inexpensive and is available in fixed dose combination (FDC) combination on its own or as a with DTG. An important drawback is that it should not be started in patients with a VL > 100 000 copies/mL, as it is inferior to EFV in such patients.[46] RPV has a lower incidence of neuropsychiatric side-effects and rashes than EFV.[47] There are several important drug-drug interactions with RPV. Among other considerations, RPV cannot be co-administered with RIF or proton-pump inhibitors (PPIs). H2-receptor antagonists need to be administered 12 hours before or 4 hours after taking RPV. RPV must be taken with food to increase absorption.

Common pitfalls:

- Prescribing RPV without first checking baseline VL. RPV is less efficacious than comparator drugs when VL > 100 000 copies/mL.
- Forgetting that RPV needs to be taken with food.

Nevirapine

We do not recommend nevirapine (NVP) for new patients starting ART due to the severe toxicity that may be associated with its use. Although toxicity after the first 3 months of NVP treatment is unlikely, we also strongly recommend switching all

patients currently on NPV to a more robust once-daily regimen.

Etravirine

Etravirine (ETR) is a second-generation NNRTI that has been studied in treatment-experienced patients rather than in ART-naïve patients.[48] As is seen with RPV, ETR's activity is not affected by the first generation NNRTI's signature K103N resistance mutation.

Dosage and common adverse drug reactions of non-nucleoside reverse transcriptase inhibitors available in Southern Africa are described in **Table 5**.

Common pitfall: Immediately discontinuing an NNRTI in the case of a mild rash without systemic features. Such rashes often resolve if treatment is continued, though close monitoring is required.

Hypersensitivity with non-nucleoside reverse transcriptase inhibitors

Development of a rash is common in the first 6 weeks of therapy with an NNRTI; notably more severely and frequently with NVP. If the rash is accompanied by systemic features (e.g. fever, elevated alanine transaminase (ALT) or hepatitis), mucosal involvement or blistering, then the NNRTI should be discontinued immediately, and re-challenge must be avoided as these are features of life-threatening reactions. If the rash is mild and occurs without these features, then the NNRTI can be continued, and the rash can be treated symptomatically with antihistamines and possibly topical steroids. Systemic steroids should not be used. If there was a severe reaction to EFV or NVP, then we do not recommend switching to RPV or ETR – rather use DTG or a protease inhibitor (PI).

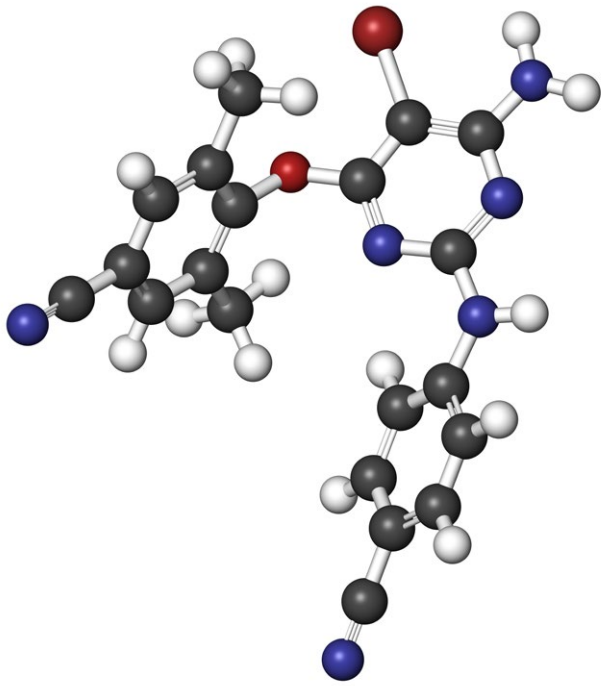


TABLE 5: Dosage and common adverse drug reactions of non-nucleoside reverse transcriptase inhibitors available in Southern Africa.

Drug	Recommended dosage	Common or severe ADR†
EFV	400 mg at night (600 mg at night if on RIF-based tuberculosis treatment)	CNS symptoms (vivid dreams, problems with concentration, dizziness, confusion, mood disturbance, psychosis, **late-onset encephalopathy), rash, hepatitis,** gynaecomastia
NVP	200 mg daily for 14 days and then 200 mg 12-hourly	**Rash, hepatitis**
RPV	25 mg daily with food	**Rash, hepatitis,** CNS symptoms (all uncommon)
ETR‡	200 mg 12-hourly	**Rash, hepatitis** (both uncommon)

ADR, adverse drug reaction; CNS, central nervous system; EFV, efavirenz; ETR, etravirine; NNRTI, non-nucleoside reverse transcriptase inhibitors; NVP, nevirapine; RPV, rilpivirine; RIF, rifampicin.
†, Life-threatening reactions are indicated in **bold**; ‡, NNRTI combinations to be avoided due to drug interactions include: (i) ETR + ATV/r and (ii) ETR + DTG unless a boosted PI is also used in the combination.

MODULE 5

PROTEASE INHIBITORS CLASS OF ANTIRETROVIRAL DRUGS

Key points

- Three protease inhibitor (PI) combinations are available in Southern Africa: lopinavir (LPV), atazanavir (ATV) or darunavir (DRV), each given with low-dose ritonavir (RTV; indicated as /r) for pharmacokinetic boosting.
- DRV has the highest barrier to resistance of any drug in this class and is the preferred PI.
- ATV and DRV offer a better side-effect profile than LPV.
- LPV/r is the only PI combination that can be used with RIF-based TB treatment, but the dose of LPV/r must be doubled. Apart from this indication, we recommend against LPV/r usage.

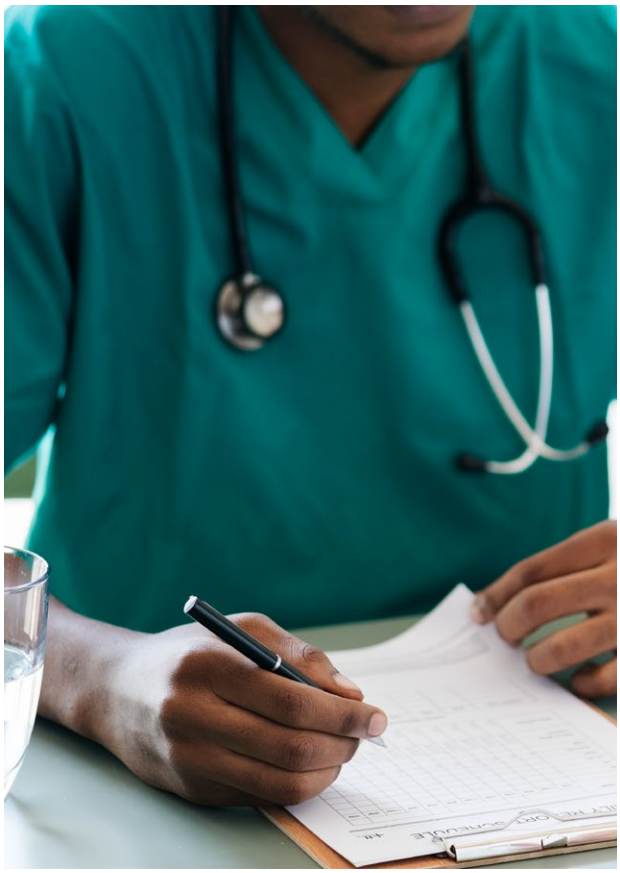
Overview of protease inhibitors

Protease inhibitors (PIs) are a class of agents that inhibit HIV's protease enzyme, which is required to cleave HIV's polyproteins into the final protein products that permit the production of infectious viral particles. Inhibition of this process results in immature, non-infectious virions.

Three PI combinations are registered for use in Southern Africa: lopinavir (LPV), atazanavir (ATV) and darunavir (DRV), each given with low-dose ritonavir (RTV; indicated as /r). All three primary drugs are now available in fixed-dose combination, coformulated with ritonavir in a single tablet. Atazanavir and darunavir are also available as separate tablets, to which ritonavir must be added.

RTV is a PI in its own right but is used principally as a pharmacokinetic 'booster'. As a potent inhibitor of CYP3A4, its use results in higher drug levels and prolonged half-lives of its companion PI. This allows for lower or less frequent PI dosing and decreases the chance of viral resistance developing. However, inhibition of CYP3A4, together with several other cytochrome P450 enzymes and p-glycoprotein, results in numerous drug-drug interactions with other medications. See **module 17**.

Common pitfall: Not using a drug interaction checker when prescribing PI-based ART or when prescribing new medication to patients taking PI-based ART. Clinically relevant drug-drug interactions are common with this class.



All PIs may be associated with cardiac conduction abnormalities (especially PR interval prolongation). This seldom results in clinically significant effects, but caution should be taken when co-prescribing other drugs that cause delayed cardiac conduction, such as macrolides or bedaquiline. All PIs are, to some degree, associated with metabolic side-effects. Elevated triglycerides (TG) and elevated low-density lipoprotein cholesterol (LDL-C) are class effects, although these side-effects are more marked with LPV/r than with other PI combinations.[49,50]

Dosing and common adverse drug reactions of protease inhibitors are described in **Table 6**.

Individual protease inhibitors

Darunavir

Darunavir (DRV) has the highest barrier to resistance of any PI, and for this reason is the preferred PI. The recommended dose of DRV depends on the presence or absence of DRV mutations, which can arise as a result of exposure to any of the PIs. For patients without any DRV mutations (including patients who are PI-naïve), the drug can be taken at a dose of DRV/r 800 mg/100 mg once daily. For patients who are switching to this regimen with a suppressed viral load, however, there is evidence that DRV/r 400 mg/100 mg once daily may be sufficient in this scenario.[51,52] For patients with mutations that confer any degree of resistance to DRV (e.g. I50V, L76V, I84V), the dose should be DRV/r 600 mg/100 mg twice daily. Compared with twice-daily dosing, once-daily dosing offers the benefits of reduced pill burden and better side-effect profile. **As with ATV, DRV cannot be co-prescribed with RIF-based TB treatment.**

Common pitfall: Prescribing ATV or DRV in patients receiving RIF-based TB treatment. LPV/r is the only PI combination that can be co-prescribed safely with RIF, but the dose of LPV/r must be adjusted as above.

Atazanavir

Atazanavir (ATV) is generally better tolerated than LPV and can be taken once daily. It has important drug interactions with drugs that reduce stomach acidity, such as PPIs. ATV may cause an unconjugated hyperbilirubinaemia as a result of inhibition of the hepatic enzyme UDP-glucuronosyltransferase. Though the hyperbilirubinaemia is harmless and does not reflect a drug-induced liver injury (DILI), a minority of patients will become visibly jaundiced, and this may require changing ART regimens for cosmetic reasons.

Common pitfall: Mistaking the unconjugated hyperbilirubinaemia sometimes seen with ATV use with a drug-induced liver injury (DILI). Conversely, it is equally important to note that ARVs can also cause a true DILI, and so a full liver function test panel should be checked to distinguish between the two possibilities.

Lopinavir

Lopinavir (LPV) is given twice-daily. This regimen has greater gastrointestinal side-effects than other PI combinations, and is associated with a worse metabolic profile. **In general, we recommend against LPV/r use.** However, LPV is the only PI that can be used concurrently with RIF-based TB treatment; the LPV/r dose has to be doubled in this instance to 800mg/200mg twice daily until 2 weeks after RIF has been stopped (see **module 18**).

Common pitfall: Forgetting to double the dose of LPV/r when starting RIF-based TB treatment.

TABLE 6: Dosage and common adverse drug reactions of protease inhibitor drugs available in Southern Africa.

Drug	Recommended dosage	Common or severe ADR
ATV/r††	300 mg/100 mg daily or 400/100 mg daily if given with EFV	Unconjugated hyperbilirubinaemia (visible jaundice in minority of patients), dyslipidaemia (low potential), renal stones (rare), **hepatitis**
LPV/r	400 mg/100 mg 12-hourly or 800 mg/200 mg 12-hourly if coadministered with RIF	Gastrointestinal upset, dyslipidaemia, **hepatitis**
DRV/r	800 mg/100 mg daily (if no DRV mutations) Consider 400 mg/100 mg daily (only if no DRV mutations and virally suppressed) 600 mg/100 mg 12-hourly if DRV mutations.	Gastrointestinal upset, rash, dyslipidaemia, **hepatitis** (uncommon). Contains sulphonamide moiety (use with caution in patients with sulpha allergy)

ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; RIF, rifampicin; ADR, adverse drug reaction
†Life-threatening reactions are indicated in bold. ††, Avoid the combination of ETR + ATV/r (due to drug interaction).

MODULE 6

INITIATION AND TIMING OF ANTIRETROVIRAL THERAPY

Key points

- Delays to starting ART should be minimised. Several studies have demonstrated that it is safe to initiate ART on the same day as diagnosis or on receipt of the CD4+ count result, with the chief benefit being improved retention in care.
- Screening for tuberculosis (TB), cryptococcal meningitis (CM) and other opportunistic infections prior to ART initiation is important since these conditions may necessitate delaying ART initiation.
- When a patient is virally suppressed and maintains adherence, HIV is not transmissible to their sexual partner/s. This is known as "Undetectable = Untransmittable (U=U)".

Overview

All patients who are diagnosed with HIV should be initiated on ART as soon as possible. Exceptions to this include patients presenting with cryptococcal meningitis (CM) or central nervous system tuberculosis (tuberculous meningitis (TBM) or tuberculoma) – see below.

Benefits of antiretroviral therapy in reducing morbidity and mortality

With ART-induced viral suppression, the CD4+ lymphocyte count usually increases, which is accompanied by a restoration of pathogen-specific immune function. For most patients, this results in a dramatic reduction in the risk of HIV-associated morbidity and mortality. For patients who start ART with preserved CD4+ counts, ART is able to prevent the decline in CD4+ count observed in untreated patients and thereby prevent clinical complications of HIV infection. The benefits in morbidity and mortality extend to patients with relatively preserved CD4+ counts. The START and TEMPRANO ANRS 12136 trials showed significant individual clinical benefit when starting ART immediately in patients with CD4+ counts > 500 cells/μL rather than deferring until a certain lower CD4+ threshold or clinical indication was met.[53,54]

Benefits of antiretroviral therapy in reducing transmission

The HPTN 052 trial showed that treating the HIV-positive partner in a serodifferent relationship with ART was associated with a 93% reduction in transmission risk to the HIV-negative partner, with the only linked transmissions occurring from partners without a suppressed VL.[55] Further evidence in serodifferent couples from the PARTNER, PARTNER2 and Opposites Attract trials have confirmed that HIV is not transmittable when the VL is suppressed and adherence is maintained.[56-58] "Undetectable = Untransmittable (U=U)" messaging is an important component of this. Community-level evidence has also demonstrated a reduction in HIV incidence as ART rollout is scaled up.[59,60] Therefore, early ART initiation has significant public health benefits.

Antiretroviral therapy in primary HIV infection

In patients who are diagnosed with HIV during acute seroconversion, we advise counselling and initiating ART as soon as possible. Expedited ART initiation is preferable as there is evidence that this may limit the size of the HIV reservoir.[61] Additional counselling once the patient is established on ART may be required for patients who start ART in this acute stage because there is limited time for extensive pre-ART counselling and there is often considerable psychological distress around this time.

Antiretroviral therapy initiation in 'elite controllers'

A minority of patients (< 1%) have very effective immune control of HIV infection and can control HIV viraemia at undetectable levels even in the absence of ART – termed 'elite controllers'.[62] While definitive data are lacking for this patient subgroup, we advise initiating ART in elite controllers

too, as indirect evidence suggests a potential benefit. Elite controllers still have evidence of chronic immune activation and inflammation that may drive non-infectious morbidities.[63] Elite controllers have also been shown to have a higher rate of hospitalisation than patients who are virologically controlled by ART.[64] Furthermore, a prospective study of HIV-positive 'controllers', who were able to control viral replication to < 500 copies/mL, showed that ART led to improvements in markers of immune activation and immune exhaustion, and a slightly improved self-reported quality of life.[65] This trial included elite controllers.

One important consideration in such patients is that careful attention should be paid to confirming the diagnosis of HIV before starting ART. These patients typically have a positive HIV ELISA test, undetectable HIV VL, CD4+ count in the normal range and are clinically well. The possibility of a false-positive HIV ELISA test should be excluded either by qualitative HIV DNA PCR or Western Blot assay. If the patient previously had a detectable VL, then this would also serve as confirmation. Such patients may need to be discussed with a laboratory virologist to assist with confirmation of HIV status.

Common pitfall: Not confirming the HIV status of an 'elite controller'. If such patients have been diagnosed with HIV based on an HIV ELISA or rapid detection test, then confirmation of their HIV status should be sought by additional testing methods to exclude the possibility of a false-positive result.

Commencing antiretroviral therapy at the first clinic visit

Several studies have demonstrated that it is possible to initiate ART safely on the same day as HIV diagnosis or reporting of the CD4+ count result.[66-68] These studies have demonstrated less overall loss to follow-up when ART is initiated immediately in selected patients. Now that treatment is recommended irrespective of CD4+ count, this same-day strategy should be considered as a means to improve retention in care.

Considerations when deciding to initiate ART on the same day as diagnosis:

- The patient should be motivated to start immediately.
- Same-day initiation is not an adherence support 'short cut'; ongoing support can occur in the days and weeks immediately after initiation.
- Patients starting TDF (who are the majority) should be contactable in the event of an eGFR < 50 mL/min/1.73m^2, and told to return to the clinic immediately.
- A serum/plasma CrAg test should be done in patients with **a CD4+ count < 200 cells/µL**; again, the patient should be contactable in the event of a positive result, and must be advised to return to the clinic immediately.
- Symptom screening for TB and CM before initiation of treatment remains important, and a positive screen requires further investigation prior to ART initiation.

Medical reasons to delay antiretroviral therapy initiation

Medical reasons to delay ART initiation are outlined in **Table 7**.

TABLE 7: Medical reasons to delay antiretroviral therapy initiation.

Reason	Action
Diagnosis of CM	Defer ART for 4–6 weeks after start of antifungal treatment.
Diagnosis of TBM or tuberculoma	Defer ART until 4–8 weeks after start of TB treatment.
Diagnosis of TB at non-neurological site	Defer ART up to 2 weeks after start of TB treatment if CD4$^+$ count ≤ 50 cells/µL and up to 8 weeks if CD4$^+$ count > 50 cells/µL.
Headache	Investigate for meningitis before starting ART.
TB symptoms (cough, night sweats, fever, recent weight loss)	Investigate for TB before starting ART.
Significantly abnormal LFTs (ALT > 200 U/L or jaundice) or acute kidney injury that is expected to resolve soon	Investigate and address the cause before starting ART, including other drugs causing DILI and acute kidney injury.

ART, antiretroviral therapy; ALT, alanine transaminase; CM, cryptococcal meningitis; DILI, drug-induced liver injury; LFTs, liver function tests; TB, tuberculosis; TBM, tuberculous meningitis.

Tuberculosis

Decisions regarding the timing of ART in patients with TB should generally be based on the CD4+ count.

- **CD4+ count ≤ 50 cells/µL:** ART should be regarded as urgent, with the aim to start therapy within 2 weeks following the commencement of TB treatment. A meta-analysis of randomised controlled trials (RCTs) has demonstrated that this approach reduces mortality.[69] It is advised to commence ART once it is clear that the patient's TB symptoms are improving and that TB therapy is tolerated. The exception to this is in the case of CM or TBM (see below). It is important to book an ART initiation date and track the patient if they do not return in order to decrease loss to follow-up in this high-risk group.
- **CD4+ count > 50 cells/µL:** ART can be delayed to start within the first 8 weeks after starting TB treatment, but no later. However, if the patient has other serious opportunistic infections, then ART should be initiated within 2 weeks after TB treatment is started (with the exception to this being CM or central nervous system tuberculosis). The longer delay before commencing ART in this group is anticipated to reduce the risk of immune reconstitution inflammatory syndrome (IRIS) (see **module 26**). The aforementioned meta-analysis of RCTs did not show a higher risk of AIDS progression/mortality in this group when ART initiation was delayed until approximately 8 weeks after starting TB treatment, but did show a reduced risk of TB-IRIS.[69]

Tuberculous meningitis

Patients with tuberculous meningitis (TBM) are an exception to the above: starting ART immediately or at 2 months following diagnosis was shown to have similarly high mortality, with more complications in the immediate group.[70] We recommend starting ART 4–8 weeks after TBM diagnosis.

There are important potential drug interactions and shared side-effects when ART is co-administered with TB therapy (see **module 18**). When ART is commenced, patients should be warned that TB symptoms or signs may temporarily worsen, and new features may occur in the first 3 months as a result of TB-IRIS (see **module 26**).

Cryptococcal disease

For patients with CM, the optimal time to start ART is 4–6 weeks from the time of starting CM treatment. The COAT (Cryptococcal Optimal ART Timing) trial demonstrated significantly higher mortality in patients who started ART in hospital 1–2 weeks after CM diagnosis than in those starting 5–6 weeks after diagnosis.[71]

For patients diagnosed with cryptococcal antigenaemia who have CM excluded by lumbar puncture (LP), ART can be commenced immediately.

Patients commenced on ART prior to a positive reflex CrAg result should be referred immediately for LP to exclude CM. In patients with a negative cerebrospinal fluid (CSF) CrAg result (i.e. CM is excluded), ART can be continued, and fluconazole pre-emptive therapy should be initiated. However, in patients with a positive CSF CrAg result (i.e. with cryptococcal meningitis), we recommend temporary ART interruption. ART may be reinitiated after 4 weeks of CM therapy.

*For further details refer to the **2019 Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons.***

Starting ART in patients with other opportunistic infections and acute illnesses

In the case of most opportunistic infections (OIs) and acute illnesses (e.g. pneumocystis or bacterial pneumonia), the aim should be to initiate ART within 2 weeks of the patient commencing treatment for that infection.[72] In patients with severe Kaposi's sarcoma and lymphoma, or other severe HIV-associated conditions such as immune thrombocytopenia (ITP) or thrombotic thrombocytopenic purpura (TTP), ART counselling should be expedited and ART should be initiated as soon as possible.

It is imperative that patients initiated on ART while in hospital are adequately linked to care after discharge.[73]

In patients with HIV admitted to hospital and unable to take oral medications, e.g. patients in the intensive care unit (ICU):

- If the patient is receiving ART, then this should be continued – through nasogastric tube (NGT) if necessary – and only interrupted if the gastrointestinal tract is not functional (e.g. ileus).
- If the patient is not yet receiving ART, then it should not be commenced if the reason for admission is an acute critical illness or injury. There are several potential problems associated with commencing ART in this setting, including a lack of adequate counselling, gastrointestinal dysfunction, renal dysfunction, malabsorption and possible development of resistance.
- There are no intravenous options for ART. In patients admitted to the ICU for prolonged periods, ART initiation in the unit should be considered after multi-organ failure has resolved. Certain ART preparations should not be administered via NGT. In general, paediatric syrups can be administered via NGT. A pharmacist should always be consulted regarding which ART drugs can be administered via NGT and how to do this.

MODULE 7

BASELINE INVESTIGATIONS

Confirming the diagnosis of HIV

Prior to the initiation of lifelong ART, it is recommended that HIV infection is confirmed with two different testing methods, at least one of which should be a laboratory-based test. Acceptable combinations include:

- Rapid detection test + enzyme-linked immunosorbent assay (ELISA)
- Rapid detection test + viral load (VL)
- ELISA + VL

However, awaiting confirmatory testing should not be a reason to delay ART initiation. Note that a VL may be undetectable in < 1% of patients not receiving ART,[62] i.e. **'elite controllers'.**

Baseline investigations

Baseline investigations for ART are summarised in **Table 8.**

Symptom screen

We also advise a symptom screen for:

- **Tuberculosis (TB):** patients should be asked about cough, weight loss, fever, night sweats and possible TB contacts. A positive symptom screen is an indication for a chest X-ray and urine lipoarabinomannan (LAM) test, in addition to the sputum GeneXpert MTB/RIF testing which is now routinely recommended in patients able to produce sputum, even in the absence of symptoms.

If the patient's symptom screen is positive for TB, then ART should be deferred until the results of the GeneXpert, and/or LAM are known. Delays in this process should, however, be kept to a minimum.

- **STI symptom screen:** patients should be asked about urethral/vaginal discharges and genital ulcers. If present, investigate further and offer pathogen-directed treatment. The management of STIs is beyond the scope of this guideline; for further detail, please consult the **2022 Southern African HIV Clinicians' Society Guideline for the Management of Sexually-transmitted Infections.**

TABLE 8: Summary of baseline investigations for antiretroviral therapy.

Investigation	Comment
$CD4^+$ count	If CD4+ count < 200 cells/μL, then CPT is required, and sCrAg testing needs to be performed.
Baseline VL	Can also serve as a confirmatory HIV test.
ALT	If raised, then will need workup and may influence ART regimen choice.
Creatinine (eGFR)	Avoid TDF if eGFR < 50 mL/min/1.73m^2, and avoid TAF/FTC combinations if eGFR < 30 mL/min/1.73m^2. Other NRTIs, except ABC, require dose adjustment if CrCl < 50 mL/min/1.73m^2.
HBsAg	See **module 20**.
Syphilis serology	
Chlamydia trachomatis and *Neisseria gonorrhoea* NAAT	Perform even in the absence of symptoms, as infection is frequently asymptomatic. Use first-void urine in men, and either self- or clinician-directed vaginal or endocervical swab (preferred) or else first-void urine in women. See **SAHCS 2022 guideline for the Management of Sexually-transmitted Infections** for further details.
sCrAg	Only required in patients with a CD4+ count < 200 cells/μL. If sCrAg-positive, exclude CM by LP. See section on CM management (**module 27**) for further details.
Urine LAM	For those with signs and symptoms of TB, or those who are seriously ill, or with a low CD4 count (< 200 cells/μL for inpatients or < 100 cells/μL for outpatients)
Sputum GeneXpert MTB/RIF	For patients able to produce sputum, even in the absence of a positive symptom screen.

ABC, abacavir; ALT, alanine transaminase; eGFR, estimated glomerular filtration rate; CM, cryptococcal meningitis; CPT, cotrimoxazole preventive therapy; HBsAg, hepatitis B surface antigen; NAAT, nucleic acid amplification test; LP, lumbar puncture; sCrAg, serum/plasma cryptococcal antigen; SAHCS, Southern African HIV Clinicians Society; TDF, tenofovir disoproxil fumarate; VL, viral load.

VIRAL LOAD

HIV viral load (VL) monitoring is key to the success of ART. Decisions to change ART made on the basis of virological failure, rather than on clinical or immunological failure alone, have been shown to result in better patient outcomes.[74] If the VL is undetectable, then the virus cannot mutate and develop resistance. A sustained VL < 50 copies/mL is associated with the most durable benefit. A suppressed VL also prevents transmission of HIV to contacts: Undetectable = Untransmittable (U=U).

Timing of HIV viral load monitoring in the nonpregnant patient starting ART.

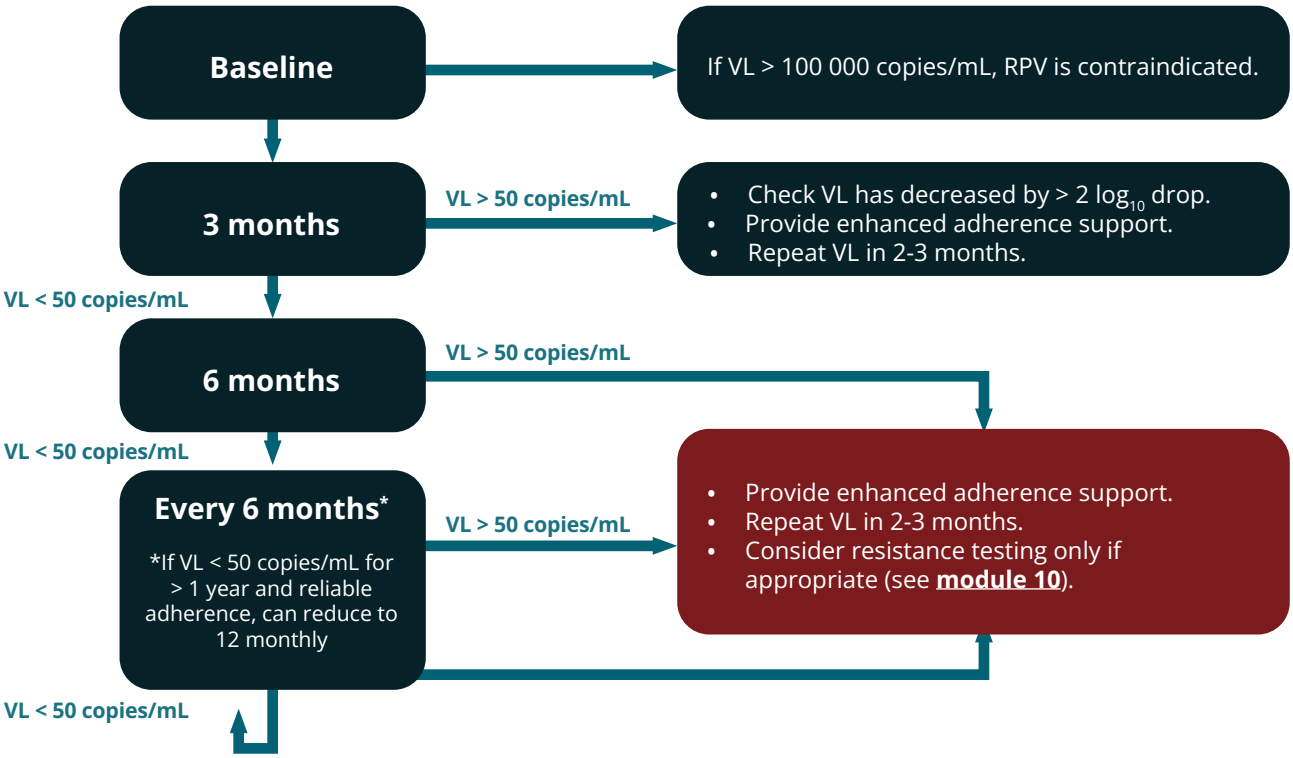


FIGURE 2: Timing of viral load monitoring of the patient starting ART. For patients with a viral load > 50 copies/mL on two consecutive occasions, refer to text. For the timing of viral loads in pregnant women, consult the pregnancy module. (RPV, rilpivirine; VL, viral load)

We recommend a **baseline VL** for the following reasons:

1. The 3-month VL can then be compared with the baseline VL to detect > 2 $\log_{10}$ drop, and if this has not occurred, then it allows for early adherence intervention.
2. It confirms the diagnosis of HIV (antibody tests may very rarely give a false-positive result).
3. In rare cases where RPV is considered as initial therapy, it may guide selection (RPV should not be used if VL > 100 000 copies/mL)

A **3-month VL** is desirable to detect adherence problems early, before resistance develops. A subset of patients who start ART with a very high VL may not be fully suppressed at 3 months despite 100% adherence, but such patients would have had a > 2 $\log_{10}$ drop in VL from baseline if adherence is optimal and there is no resistance. Therefore, the 3-month result should be interpreted in relation to the baseline VL. (For instance, if the baseline viral load is 100,000 copies/mL, then the viral load should be down to 1000

copies/mL or less at 3 months). All patients who have a detectable VL at 3 months should receive additional adherence interventions. In general, a patient's VL declines fastest on InSTI-based regimens.

If the 3-month VL is undetectable, then VL monitoring is recommended at 6 months and every 6 months thereafter. In patients who have an undetectable VL for > 12 months, and who demonstrate reliable adherence and follow-up, it may be acceptable to reduce the frequency of VL monitoring to 12-monthly.

If the VL is > 50 copies/mL at any stage, then this should be an indication for urgent action. The patient should receive counselling and interventions should be implemented to improve adherence. A repeat measurement of VL should then be done in 2–3 months.

Interpreting viral load results

Virological criteria for treatment success

Treatment success is defined as a decline in VL to < 50 copies/mL within 6 months of commencing ART, and sustained thereafter. A VL > 50 copies/mL is robustly associated with subsequent virological failure.[75,76] Sustained viral replication, even at these low levels, can lead to the accumulation of resistance mutations (although this has not yet been definitively established in the case of dolutegravir).

Virological criteria for treatment failure

Treatment failure is defined as a confirmed VL > 1000 copies/mL on two consecutive measurements taken 2–3 months apart. The implication of this depends on the regimen the patient is on. Patients on DTG-based therapy as their initial ART regimen are extremely unlikely to have developed resistance at the point of treatment failure, but this is not necessarily true of other regimens, or of DTG-based regimens when there has been a history of failure with a prior ART regimen.

Viral blips

Isolated detectable HIV VLs < 1000 copies/mL, followed by an undetectable VL, are termed 'viral blips' and alone are not a reason to change the ART regimen.

- Viral blips can be caused by immune activation (such as from an acute infection), variability in the laboratory testing thresholds, or intermittent poor adherence. Provided they are infrequent, and the viral load returns to being undetectable at the next measurement, they are not regarded as consequential.

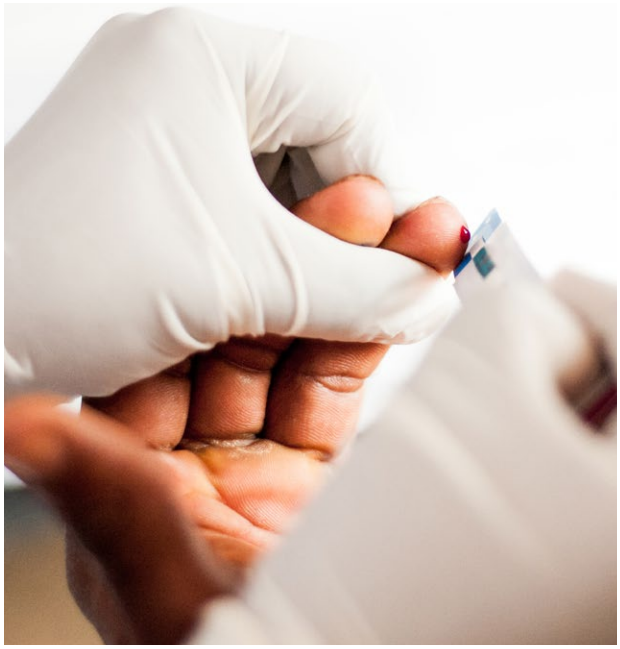
Reasons for a high viral load

A high VL can be attributed to one or more of these three factors:

- Inadequate patient adherence (most commonly). This may sometimes be out of the patient's control (e.g. stock-outs, unplanned facility closure). See **Table 28**.
- Resistance to the prescribed ART – including both acquired and transmitted drug resistance.
- Inadequate ART drug levels as a result of altered pharmacokinetics, such as absorption difficulties, or drug-drug interactions.

These explanations are not mutually exclusive. For instance, inadequate patient adherence may lead to the development of drug resistance.

Transmitted drug resistance is only likely to be a concern for the rare patients who initiate therapy on an NNRTI, as by far the commonest transmitted mutation is K103N, which has little effect on viral fitness and can therefore persist in the population even in the absence of drug pressure.[77] Transmitted drug resistance to other drug classes is unusual and often of minimal clinical importance; therefore first-line therapy with a DTG-based regimen is unlikely to be affected by this phenomenon.



MODULE 9

CD4+ CELL COUNT

Key points

- The role of CD4+ count testing is to establish whether CTX prophylaxis, sCrAg testing and urine LAM testing is required, and to identify patients with advanced HIV disease who may need closer follow-up to monitor for opportunistic infections and other HIV-related complications. See the Southern African HIV Clinicians Guidelines for hospitalised adults with Advanced HIV Disease **here**.
- Monitoring ART efficacy is best established using VL, not CD4+ count.
- Once the CD4+ count is > 200 cells/µL, repeat CD4 count testing is of no value unless the patient subsequently develops virologic or clinical failure.
- If CD4+ count does not rise despite viral suppression, the ART regimen does not need to be altered. This phenomenon may reflect an 'immunological discordant response to ART'; although if the patient is unwell, then other secondary causes should be sought. Cotrimoxazole prophylaxis is indicated with immunological discordant CD4+ count of < 200 cells/ µL.[78]

Role of CD4+ count monitoring

A CD4+ count < 200 cells/µL indicates the need for CTX prophylaxis, principally to prevent *Pneumocystis jirovecii* pneumonia, although CTX is also active against other opportunistic pathogens, including *Toxoplasma gondii, Cystoisospora belli* and *Nocardia* spp. A baseline CD4+ count < 200 cells/µL is also an indication to reflexly perform sCrAg testing, and urine LAM testing should be offered at baseline if the CD4+ count is < 200 for outpatients, or < 100 for inpatients, even in the absence of TB symptoms or overt clinical illness. If the CD4+ count is > 200 cells/µL at baseline or it increases above this threshold on ART, then CD4+ testing can be stopped, since therapeutic monitoring on ART is best accomplished with VL, not CD4+ count or clinical criteria. However, if virologic or clinical failure occurs, then the CD4+ count should be repeated, as CTX prophylaxis should be commenced if the count drops to < 200 cells/µL on ART.

Common pitfall: Routinely checking CD4+ counts if the previous result was >200 cells/µL. This is unnecessary unless virological or clinical failure subsequently occurs.

Timing of CD4+ count measurements

CD4+ counts should be performed:

- At baseline (to guide decisions about CTX prophylaxis).
- Every 6 months thereafter if the previous CD4+ count was < 200 cells/µL.
- If a patient experiences virological failure (to assess the need to restart CTX prophylaxis).

Common pitfall: Not checking a CD4+ count in a patient with virological failure.

CD4+ count response

In patients who start ART with an abnormally low CD4+ count, the CD4+ count typically increases rapidly in the first month of ART, by ~75–100 cells/µL, with a more gradual rise thereafter (50–100 cells/µL per year).[79] Most patients achieve a CD4+ count > 500 cells/µL after several years of ART, provided that the VL remains suppressed. However, CD4+ count responses are highly variable and may fail to increase despite virological suppression in about 10–20% of patients.[80,81] Such patients have a delayed or absent CD4+ count response to ART despite viral suppression, which is termed an **'immunological discordant response to ART', previously, 'immune non-responders'**. Certain studies suggest that older patients are at higher risk of this response. There is no evidence that such patients benefit from a change in ART regimen; therefore, the same regimen should be continued. CTX prophylaxis should be continued if the CD4+ count remains < 200 cells/µL. There is evidence that the prognosis of such patients is worse

than in those who have a CD4+ response, but better than that of patients experiencing both virological and immunological failure.[81] If patients with an immunological discordant response to ART are clinically unwell, then TB or lymphoma should be considered as the cause of persistent CD4+ lymphopenia. CD4+ counts may remain stable in the presence of incomplete viral suppression in patients receiving ART until the VL is high (approximately ≥ 10 000 copies/mL).[82]

Common pitfall: Confusing an 'immunological discordant response to ART' with treatment failure. There is no role for changing ART if the VL is suppressed.

Figure 3 outlines the suggested approach to patients with low CD4+ counts despite a suppressed viral load on ART.

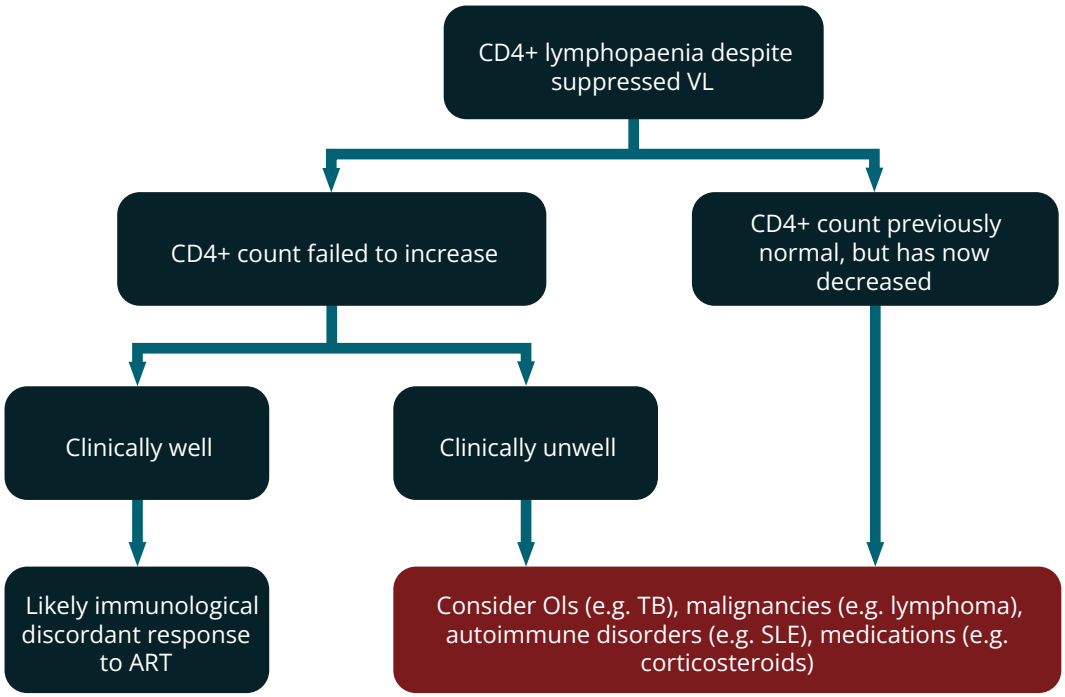


FIGURE 3: Suggested approach to patients with low CD4+ counts despite a suppressed viral load on ART.

(ART; antiretroviral therapy; CD4+, cluster of differentiation 4; OIs, opportunistic infections; SLE, systemic lupus erythematosus; TB, tuberculosis; VL, viral load).

MODULE 10

RESISTANCE AND GENOTYPING

Key points

- Adherence is the key to preventing drug resistance.
- In the era of robust DTG- and PI-based regimens, and where TDF and FTC/3TC can be recycled across multiple regimens, the role of resistance testing is more limited than previously.
- Resistance testing may not detect archived mutations to particular drugs if the patient is not receiving these drugs at the time of resistance testing.

Overview

As a result of transcription errors and recombination, HIV that is replicating can accumulate mutations that lead to drug resistance. Durable viral suppression by ART is required to limit the chances of drug resistance developing. Intermittent drug adherence, as opposed to a total lack of ART, provides a greater opportunity for resistance to develop, by exposing replicating virus to sub-therapeutic ART drug concentrations. Similarly, drug-drug interactions may result in prolonged exposure to sub-therapeutic drug levels and hence the opportunity for drug resistance to develop.

ARV drug resistance mutations are summarised in **Table 9.**

TABLE 9: ARV drug resistance mutations.

Drug	Key mutations selected
3TC or FTC	Selects for M184V, which compromises both 3TC and FTC and slightly impairs the activity of ABC, but increases susceptibility to AZT and TDF.
TDF	Selects for K65R, which compromises TDF and ABC but increases susceptibility to AZT. TDF also selects for K70E, which causes low-level resistance to TDF, ABC, and possibly 3TC/FTC.
ABC	Selects for L74V, which compromises ABC. May also select for K65R, which compromises TDF and ABC but increases susceptibility to AZT. Selects for Y115F, which decreases its susceptibility.
AZT	Selects for TAMs, which may ultimately compromise all NRTIs.
EFV or NVP	Selects for K103N, which causes high-level resistance to EFV and NVP. Also selects for Y181C and other NNRTI mutations which cause resistance to EFV, NVP, RPV and ETR.
RPV	Selects for several mutations, including E138K, which compromise its susceptibility.
PIS	Multiple mutations usually required before seeing a decrease in susceptibility, especially for LPV and DRV, and cross-resistance between the PIs is common. ATV selects for I50L, which causes high-level resistance to ATV but not to the other PIs.
RAL	Selects for Q148H/K/R, Y143C and N155H, which cause resistance to RAL and, in certain combinations, to DTG.
DTG	Very rarely selects resistance if InSTI-naïve, provided it is coupled to at least one other fully active drug. In patients with prior RAL or cabotegravir exposure, mutations such as Q148H may cause decreased DTG susceptibility when combined with additional mutations. In contrast, R263K and G118R occur significantly more often in ART-experienced INSTI-naïve persons with VF while receiving a DTG-containing regimen.

3TC, lamivudine; ABC, abacavir; ATV, Atazanavir; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; ETR, etravirine; DTG, dolutegravir; FTC, emtricitabine; InSTI, integrase strand transfer inhibitor; LPV, lopinavir; NVP, nevirapine; PIs, protease inhibitors; RAL, raltegravir; RPV, rilpivirine; TAMs, thymidine analogue mutations; NRTIS, nucleoside reverse transcriptase inhibitors; TDF, tenofovir disoproxil fumarate.

When to perform a resistance test

Baseline resistance test

A baseline resistance test is not generally indicated. We recommend a baseline resistance test to guide first-line regimen choice only where there is a recent history of sexual exposure to a person with known resistance to the InSTI drug class, or where pre-exposure prophylaxis (PrEP) with a cabotegravir-containing regimen has been taken within the past year. A resistance test is no longer indicated for patients with breakthrough infection while taking oral PrEP, as FTC/3TC and TDF/TAF can be recycled in subsequent ART regimens regardless of resistance.

Resistance testing at treatment failure

Resistance testing is generally only possible if the VL is > 500 copies/mL. However, in the era of DTG- and PI-based therapy, we generally recommend it only be performed with a 2-3 consecutive VL > 1000 copies/mL, which would satisfy the definition of virological failure.

TABLE 10: Recommendations for resistance testing in the case of treatment failure.

	DTG-based therapy	PI-based therapy	NNRTI-based therapy
Resistance testing criteria	• Patient on regimen for > 2 years, OR • Patient recently exposed to drug-drug interaction that would have lowered DTG drug levels significantly, OR • Patient known to have prior InSTI resistance. • DTG monotherapy inadvertently taken.	• Patient is on regimen for > 2 years, OR • Patient recently exposed to drug-drug interaction that would have lowered PI drug levels significantly, OR • Patient known to have prior PI resistance.	• Not routinely required (see text for more information).
Resistance test required	*Integrase* gene (may be possible to do without testing *protease* and reverse *transcriptase* gene, depending on laboratory).	*Protease* gene (almost always done in conjunction with *reverse transcriptase* gene)	*Reverse transcriptase* gene (almost always done in conjunction with *protease* gene)

Dolutegravir-based therapy

Resistance to DTG as part of initial ART is extremely rare. DTG resistance in those with a prior history of treatment failure is less so; approximately 1-3% of patients developed resistance in this scenario within 1-3 years in clinical trials.[22,83,84] In most scenarios, we recommend testing for integrase gene resistance only when a patient with virological failure has been on DTG for > 2 years. Exceptions that may warrant earlier *integrase* gene testing include when a patient has virological failure following a drug-drug interaction that would have substantially decreased DTG concentrations (e.g. magnesium supplementation at the same time as DTG for a prolonged period), a patient with known previous *integrase* resistance, or a patient with exposure to DTG monotherapy.

Protease inhibitor-based therapy

For PI-based regimens, sufficient resistance mutations to cause virological failure typically take at least 2 years to develop; therefore, in most cases, we recommend only performing a resistance test after the patient has been on a PI-based regimen for at least this long. Exceptions include exposure to sub-therapeutic PI drug levels as a result of drug-drug interactions (e.g. not doubling the dose of LPV/r when using RIF-based TB treatment), and those with known previous PI resistance.

NNRTI-based therapy

A resistance test at failure of NNRTI-based therapy is not routinely recommended. The EARNEST and SELECT trials showed that without the use of a resistance test to decide which NRTIs to use in second-line therapy, virological outcomes were good and equivalent to a boosted PI + RAL regimen.[85,86] However, where resources permit, resistance testing may offer some advantages:

- A resistance test may offer reassurance that some first-line NRTIs can be safely recycled (e.g. ABC) if they are shown to be susceptible. Note, however, that TDF and FTC/3TC can be safely and effectively recycled even in the face of high-level resistance, and thus testing for resistance to these agents is of little or no value.[4]
- A resistance test may identify drug resistance to drugs (such as second-generation NNRTIs) that may be important to identify should the patient require third-line ART in future.

Ordering a resistance test

Most labs offer combined *reverse transcriptase* (RT) and *protease* (PR) resistance testing with the optional addition of *integrase* (IN) resistance testing on request. For patients on an integrase inhibitor-based regimen, it may be possible to request *integrase* testing alone without RT/PR testing, depending on the lab, which reduces the cost of resistance testing. In these patients, identifying resistance to TDF or 3TC/FTC via RT testing is no longer be of relevance since they can be recycled in subsequent regimens without significant loss of efficacy, and hence RT testing is not indicated.

Guide to interpreting a resistance test

Current commercial tests have been licensed for specimens with a VL of at least 1000 copies/mL. Nevertheless, many in-house assays can detect VLs of 500–1000 copies/mL. In general, most commercial HIV resistance tests detect mutations if they are present in > 10–20% of the HIV subpopulations in the sample.87

Common pitfall: Performing a resistance test in patients with a low or undetectable VL. Commercial assays may not be successful in samples where the VL is < 500–1000 copies/mL.

A key concept in interpreting resistance tests is **archived resistance**. After reverse transcription from its RNA template, HIV inserts a DNA copy of itself into the host genome. Some of the cells that HIV infects are extremely long-lived, and essentially provide an 'archive' of HIV variants over time. **Thus, mutations that are known to have been present at one point in time can be assumed to be present for the lifetime of the patient, even if they are not visible on the patient's latest resistance test.**

A second key concept is that of the **wild-type virus**, which is the naturally-occurring HIV strain free of drug-resistance mutations. In most cases, this form of the virus replicates more efficiently than viral strains that have acquired resistance. Therefore, when drug pressure is removed, the wild-type forms of the virus will predominate, even though the resistant strains have been archived and can become predominant again later if the drug pressure subsequently changes in ways favourable to these strains.

- A prominent exception to this is the signature mutation of EFV and NVP, namely K103N, which imposes no significant fitness cost on the virus. Even after these drugs are stopped, the K103N strains may persist at detectable levels for several years.
- Resistance testing should, therefore, only be performed when the patient is still taking their ART regimen, or up to a maximum of 4 weeks after discontinuation.
- The absence of any identified resistance mutations implies that non-adherence is the cause for a raised VL. This does not exclude the possibility of archived resistance however, which may only become detectable once the patient is back on ART that suppresses the wild-type strain.
- Any significant drug resistance mutations identified by resistance testing can be assumed to be present for the lifetime of the patient, even if subsequent resistance testing fails to show these mutations (e.g. as a result of worsened adherence or an ART switch). Therefore, where a patient has had more than one resistance test, the results of all resistance tests should be combined.
- Conversely, it is only possible to identify mutations reliably for drugs that the patient was currently taking when the resistance testing was performed, and for drugs affected by cross-

resistance. 'Susceptible' results to drugs for which there is no drug pressure may be unreliable due to archived resistance if the patient has been exposed to that drug or certain drugs of the same class in the past.

Common pitfall: Performing a resistance test in the absence of drug pressure. If a patient has interrupted or discontinued therapy for more than a few weeks, there is little purpose for a resistance test. In this scenario, it is highly likely that replication of wild-type virus will overtake and obscure any resistant strain, rendering mutations undetectable by conventional resistance tests.

BOX 2: Worked example of resistance testing.

A patient was prescribed 3TC + TDF + EFV. When the patient failed this regimen after 1 year, new onset renal failure was also diagnosed. The patient was switched to 3TC + ABC + DTG. After 2 years, the patient failed this regimen too, therefore resistance testing was performed. The results showed the following:

3TC/FTC:	Resistant
TDF:	Susceptible
ABC:	Low-level resistance
AZT:	Susceptible
EFV:	Resistant
DTG:	Susceptible

Interpretation:

- Since the patient was receiving 3TC + ABC + DTG at the time of resistance testing, it is possible to interpret the results reliably for these drugs.
- EFV shows resistance, despite the patient not receiving the drug at the time of testing. This phenomenon is relatively common with the K103N mutation.
- TDF shows susceptibility. The patient was previously exposed to TDF, however. Although it is possible that none of the patient's HIV strains have evolved TDF resistance, the patient was not receiving the drug at the time of resistance testing. Consequently¬, the possibility of archived resistance to TDF cannot be excluded. However, in this case any archived resistance is unlikely to be of clinical significance, since several studies have demonstrated that recycling TDF in the face of resistance acquired during first line therapy is either non-inferior or superior to switching to AZT.

MODULE 11

INITIAL ANTIRETROVIRAL THERAPY REGIMENS FOR THE PREVIOUSLY UNTREATED PATIENT

Key points

- In ART-naïve patients, the preferred initial regimen is 3TC (300 mg) or (FTC 200 mg) + TDF (300 mg) + DTG (50 mg) daily – available as a once-daily, one-tablet FDC.
- In patients with renal impairment (eGFR < 50 ml/min/1.73m^2), the alternative regimen is 3TC + ABC + DTG.

Preferred initial antiretroviral therapy regimen

The preferred initial regimen for previously untreated patients is summarised in **Table 11**.

TABLE 11: Preferred initial ART regimen for previously untreated patients.

First drug	Second drug	Third drug
TDF 300 mg daily	3TC 300 mg daily **or** FTC 200 mg daily	DTG 50 mg daily

3TC, lamivudine; DTG, dolutegravir; FTC, emtricitabine; TDF, tenofovir

There are no significant interactions between NRTIs and rifampicin (RIF); however, InSTIs, NNRTIs, PIs and maraviroc (MVC) all exhibit drug interactions with RIF. DTG can be used in patients receiving RIF, but a dose adjustment to 50mg twice daily until two weeks after stopping RIF is advised.[88] There is evidence from a Phase 2 trial and an observational cohort that standard DTG dosing with RIF (50mg daily) achieves similar virological suppression to dose adjustment in patients on first-line regimens (see **module 17**). Other drug-drug interactions with DTG are discussed in **module 3** and **module 17**.

Patients should be advised to take TLD in the morning given the potential side-effect of insomnia, but if it is more convenient for the patient to take at night this will be tolerated in most patients.

Reasons for this preferred regimen are:

- This combination is available as a once-daily, one-tablet FDC from several suppliers.
- TDF is preferred over ABC because the risk of hypersensitivity reactions with ABC (HLA-B*5701 testing is not widely available in SA); studies show lower VL suppression with ABC when baseline VL is > 100 000 copies/mL (although not confirmed in a meta-analysis);[13] and lower cost.
- 3TC and FTC are regarded as interchangeable in terms of efficacy and safety.
- DTG is preferred over RAL and RPV because of its higher resistance barrier.[89] RAL also requires twice-daily dosing and is not co-formulated in FDC. DTG is preferred over EFV and PIs because superior efficacy and tolerability were demonstrated in first-line clinical trials.[19,20]
- There is an increasing prevalence of pre-treatment resistance to NNRTIs in South Africa (> 10% in some studies) which may compromise efficacy of EFV-based regimens.[90]

Alternative initial antiretroviral therapy regimens

Alternatives regimens for the previously untreated patient are summarised in **Table 12**. We only recommend an NNRTI regimen in patients who do not tolerate DTG.

TABLE 12: Recommended alternative initial antiretroviral therapy regimens in specific clinical situations where TDF + 3TC (or FTC) + DTG cannot be used.	
Scenario	**Alternative regimen**
Renal impairment at baseline (eGFR < 50 mL/min/1.73m^2)	ABC + 3TC + DTG† or TAF + 3TC + DTG† if eGFR 30-50 mL/min/1.73m^2
Renal impairment develops due to TDF	ABC + 3TC + DTG
Patient is intolerant of DTG side-effects	TDF + 3TC (or FTC) + EFV, or TDF + 3TC (or FTC) + RPV
Pure red cell aplasia develops due to 3TC/FTC	TDF + DTG (can consider adding AZT when Hb has recovered) (or RPV + DTG, provided VL is suppressed)

3TC, lamivudine; ABC, abacavir; AZT, zidovudine; CrCl, creatinine clearance rate; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; Hb, haemoglobin; RPV, rilpivirine; TDF, tenofovir; VL, viral load.
† In such patients, if renal function subsequently improves (eGFR > 50 mL/min/1.73m^2), then they can be switched to TDF + 3TC + DTG with creatinine monitoring.

Key points about some of these alternative regimens can be found in **Table 13**.

TABLE 13: Alternative initial ART regimens for the previously untreated patient if DTG or TDF not tolerated.	
Regimen	**Notes**
TDF + 3TC (or FTC) + EFV	• EFV can be used at 600 mg nocte or 400 mg nocte. • EFV 400 mg dose is associated with fewer side-effects and less LTFU.[39] • There are insufficient data to recommend the EFV 400 mg dose in pregnant patients and patients receiving RIF although small-cohort studies have suggested that adequate concentrations are achieved in these patients.[91,92]
TDF + 3TC (OR FTC) + RPV	• RPV cannot be used in patients receiving RIF. • RPV should not be used in initial therapy when baseline VL is > 100 000 copies/mL due to worse virologic outcomes.
ABC + 3TC + DTG	• International guidelines recommend HLA-B*5701 testing before prescribing ABC because a negative result rules out the risk of hypersensitivity reaction. However, this genotype is very rare in people of African descent and is thus probably not indicated in these patients. • In patients of non-African descent, HLA-B*5701 testing should be considered if ABC is to be used, though access to this test is limited in Southern Africa.

3TC, lamivudine; ABC, abacavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LTFU, loss to follow-up; RIF, rifampicin; RPV, rilpivirine; TDF, tenofovir; VL, viral load.

Considerations for two-drug first-line regimen of dolutegravir + lamivudine

Dolutegravir + lamivudine was shown to have non-inferior efficacy to a three-drug regimen in RCTs.[93] However, these trials did not include patients with a VL > 500 000 copies/mL. Furthermore, virological suppression was lower in patients with a CD4+ count ≤ 200 cells/µL. Therefore, we do not routinely recommend this regimen unless neither TDF nor ABC can be used. Importantly, hepatitis B must be excluded before considering this regimen as patients with hepatitis B must receive TDF + 3TC (or FTC) to prevent rapid emergence of 3TC/FTC resistance.

Common pitfall: Assuming all newly diagnosed patients are ART- naïve. In South Africa, many patients who present as newly diagnosed and report no prior treatment exposure have actually been on treatment before. Take a full, non-judgemental history from every "newly diagnosed" patient to ascertain if they may be returning to care after treatment interruption as this may impact management plans.

MODULE 12

MANAGEMENT OF PATIENTS CURRENTLY RECEIVING FIRST-LINE THERAPY

Key points

- Patients currently on TDF + FTC/3TC + EFV or NVP regimens should be switched to TLD **regardless of whether their VL is suppressed or not**. Ensure that those that are virally unsuppressed receive enhanced adherence support.
- The typical criteria of two VL measurements greater than a certain threshold despite an adherence intervention to define virological failure and direct a switch to second-line are not appropriate for DTG-based first-line regimens. Rather, in patients started on a first-line DTG regimen, we recommend switching to second-line therapy only if there is demonstrated DTG resistance.

Patients currently on an efavirenz-, or nevirapine-based first-line regimen

In contrast to previous guidelines, we now advise that patients currently on TDF +FTC/3TC and EFV or NVP be switched to TLD regardless of whether their VL is suppressed or not suppressed. There are multiple lines of evidence supporting this recommendation:

- In the SINGLE trial, DTG was superior to EFV in first-line ART.[94]
- DTG has a higher barrier to resistance than NNRTIs which improves the likelihood of sustained virologic suppression.[94] In an observational study among patients who were virologically suppressed those who did not switch to TLD from non-DTG regimens were significantly more likely to lose virological suppression.[95]
- In patients who have an unsuppressed VL and have developed NRTI mutations, there is evidence that a DTG-based regimen is virologically superior to a LPV/r based regimen,[96] and that TLD is equivalent to a DRV/r-[83,97] or an ATV/r-based[98] regimen.
- Maintaining TDF in second-line is superior to switching to AZT,[83,97] hence we no longer recommend an NRTI switch from TDF to AZT in patients switching to second-line from a failing TDF + FTC/3TC + NNRTI, but rather using TLD.

A subset of patients switched from EFV to DTG may experience weight gain. This is experienced in patients who are slow metabolisers of EFV and therefore have higher drug exposures while on EFV. The weight gain is not directly caused by DTG but is rather due to the removal of the effect of EFV causing weight loss in the context of a lifestyle that promotes weight gain. Patients should be informed about this phenomenon. We do not recommend switching back to EFV, but rather a focus on diet and exercise interventions (see **module 3**).

An additional benefit of switching from NVP to DTG is switching from a twice-daily to once-daily regimen, potentially facilitating improved adherence.

In patients currently on an ABC + 3TC + EFV/NVP due to renal impairment or previous TDF nephrotoxicity or patients found to have renal impairment (eGFR < 50 mL/min/1.73m^2) when the switch is being considered, then TDF cannot be used, and the options are:

If the VL is suppressed:

- TAF + FTC + DTG (if eGFR 30 – 50 mL/min/1.73m^2). If available, TAF may be used as a standalone drug as part of a regimen if eGFR is > mL/min/1.73m^2)
- ABC + 3TC + DTG

If the VL is not suppressed:

- TAF + FTC + DTG (if eGFR 30 – 50 mL/min/1.73m^2)
- ABC + 3TC + DTG
- ABC + 3TC + DRV/r

In patients who develop acute kidney injury while on TDF and are switched to ABC, but where TDF was not the cause of the injury, when the eGFR has normalised, it is important to a switch back to the original TDF-based regimen rather than remaining on an ABC-based regimen.

It is important to note that the trials demonstrating the virological efficacy of a DTG or boosted PI regimen with compromised NRTIs have not included regimens with ABC + 3TC as the NRTI combination and therefore there is no direct evidence to support the virological efficacy of ABC + 3TC with DTG or PIs when both ABC and 3TC are compromised by resistance mutations. ABC has a different resistance mutation profile compared to TDF, and therefore caution needs to be taken in extending the findings of the EARNEST, SECOND LINE, SELECT, NADIA, VISEND and ARTIST trials to ABC + 3TC second-line regimens. Given this lack of data and a possible risk that virological failure could be more frequent compared with TLD in second-line, **patients should be closely monitored on second-line regimens of ABC + 3TC + PI *or* ABC + 3TC + DTG.**

Clinicians should consider switching virologically suppressed patients on RPV + two NRTI regimens from RPV to DTG, because of DTG's higher barrier to resistance, but there is no direct evidence comparing the virological efficacy of DTG versus RPV first-line regimens. Patients experiencing virologic failure on a RPV-based regimen should be switched to a DTG-based regimen (TLD if eGFR > 50 ml/min/1.73m^2).

Another option in patients who are virologically suppressed (VL < 50 copies/mL) while receiving a regimen of NNRTI + two NRTIs, and who have never experienced virological failure, is a switch to the two-drug combination of DTG + RPV. Data from two clinical trials (SWORD I and II)[99] show that this regimen maintains virological suppression as a switch strategy in patients who have not previously experienced virological failure. This should not be done in patients who have chronic hepatitis B as TDF and 3TC (or FTC) should always form part of their treatment. Hepatitis B surface antigen status should therefore always be tested before making this switch.

Patients started on a dolutegravir-based first-line regimen

Such patients should have their VL measured 6–12-monthly (see **modules 8 and 15**). We have previously used the criteria of two VL measurements > 1000 copies/mL despite an adherence intervention to define virological failure and the need to switch from first- to second-line ART. This was appropriate for patients on NNRTI-based first-line regimens because of the low barrier to resistance of the NNRTI class. However, considerations are very different with DTG-based first-line regimens. In several clinical trials of DTG in first-line therapy, no DTG resistance has been described despite some patients having virological failure; and in clinical practice very few cases of DTG resistance have been described worldwide when the drug has been used as part of a three-drug first-line regimen.[89] Therefore, it would be inappropriate to use the same criteria for switching to second-line ART for DTG as it is likely that most patients with two unsuppressed VLs will not have resistance and rather require improved adherence on the same first-line regimen to achieve suppression. For that reason, we only recommend switching from first-line DTG-based ART to second-line if resistance testing demonstrates DTG resistance.

Until further data are available, in patients with an unsuppressed VL on DTG -based first-line ART, we recommend enhanced adherence counselling. The tolerance of the regimen should also be addressed as the regimen may need to be switched due to side-effects. Integrase resistance testing should be considered in these situations:

- Previous DTG monotherapy (DTG resistance has been more frequently described in this situation)[89]
- Patient on DTG-based a regimen for > 2 years and 2-3 recent VLs consecutively > 1000 copies/mL (despite adherence interventions, 100% pharmacy refills and self-reported adherence)
- Prolonged period of exposure to a co-medication that has a drug-drug interaction that reduces exposure to DTG.

If a resistance test is performed, then this should include sequencing of the integrase region and should be limited to the integrase region if the laboratory makes this option available. The clinician should **only switch from a DTG-based first-line regimen to second-line therapy if DTG resistance is detected**. The choice of drugs in second-line are discussed in **module 13**.

These recommendations are based on accumulated information on the resistance barrier to DTG to date suggesting that DTG resistance is extremely rare when the drug is used in a three-drug first-line regimen. These recommendations may be updated when more data become available regarding incidence and risk factors for DTG resistance with more widespread use in routine clinical practice.

Figure 4 outlines the virological monitoring of patients on DTG-based first-line ART and the recommended response to results.

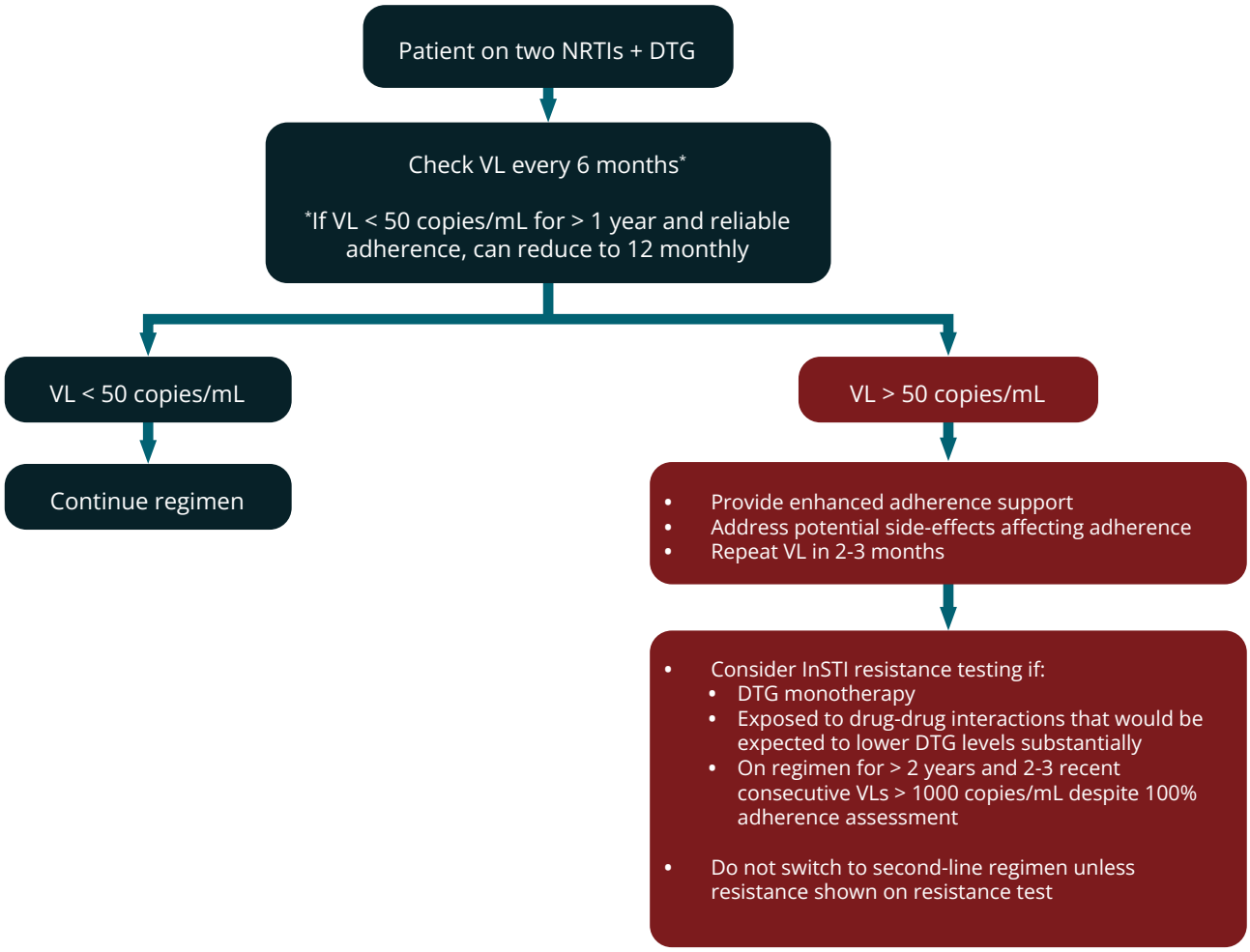


FIGURE 4: Virological monitoring of patients receiving DTG-based first-line ART and response to results.

(DTG, dolutegravir; NRTIs, nucleoside reverse transcriptase inhibitors; VL; viral load)

MODULE 13

MANAGEMENT OF PATIENTS STARTING OR CURRENTLY RECEIVING SECOND-LINE THERAPY

Key points

- In patients failing a TDF + FTC/3TC + EFV or NVP first-line regimen, the second-line should be TDF + 3TC/FTC + DTG (TLD).
- In patients with renal impairment or prior TDF nephrotoxicity failing an NNRTI regimen, options are TAF + FTC + DTG (if eGFR > 30 mL/min/1.73m^2), ABC + 3TC + DTG, ABC + 3TC + DRV/r or ABC + 3TC + ATV/r.
- In patients failing TLD first-line with documented DTG resistance (rare) the second-line should be TDF + FTC/3TC + DRV/r.
- We advise DRV/r 800 mg/100 mg once daily as the first choice PI if a PI is used in second-line therapy.

Recommendations for patients failing a first-line regimen

Failed first-line regimen of two NRTIs + NNRTI

Table 14 summarises the recommended second-line regimen to start in patients who have failed a first-line regimen consisting of two NRTIs + NNRTI.

TABLE 14: Recommended second-line regimen in patients who have failed a first-line regimen of two NRTIs + NNRTI.

Failing first-line regimen	Advised second-line regimen
TDF + 3TC (or FTC) + NNRTI	TDF + 3TC + DTG
Patients with renal impairment or prior TDF nephrotoxicity	TAF + FTC + DTG (if eGFR > 30mL/min/1.73m^2) or ABC + 3TC + DTG or ABC + 3TC + DRV/r or ABC + 3TC + ATV/r

Based on the results of the DAWNING trial, it is preferable to use a DTG-based regimen rather than a LPV/r regimen in second-line therapy.[22] In this trial, a second-line regimen of DTG + two NRTIs was superior in terms of virological suppression due to better tolerance than LPV/r + two NRTIs in patients who had failed a first-line regimen of NNRTI + two NRTIs. All patients enrolled in this trial had a resistance test performed at entry and had to have at least one fully active NRTI to be eligible.

Since the DAWNING trial, three trials have demonstrated the virological efficacy of maintaining the same NRTI backbone of TDF + 3TC from first- to second-line ART and only switching EFV to DTG. In the NADIA trial at 96 weeks, 92% of patients on second-line TLD has VL < 400 copies/mL, the same as patients on second-line TDF + 3TC + DRV/r. In this trial, maintaining TDF + 3TC from first- to second-line was superior in terms of VL suppression at 96 weeks, compared to switching the NRTI backbone to AZT + 3TC. Excellent virological outcomes were seen in patients with resistance to both TDF and 3TC on second-line TLD.[83] In the VISEND trial, 83% of participants on second-line TLD had a VL < 1000 copies/mL at 48 weeks which was similar to patients on AZT + 3TC + ATV/r (82%) and higher than in patients on AZT + 3TC + LPV/r (69%).[98] In stages 1 and 2 of the ARTIST trial conducted in South Africa, 82-86% of patients on second-line TLD had a VL < 50 copies/mL at 24 weeks.[100,101]

If a boosted PI is used in second line (e.g. if DTG is not tolerated) we recommend DRV/r 800/100mg once

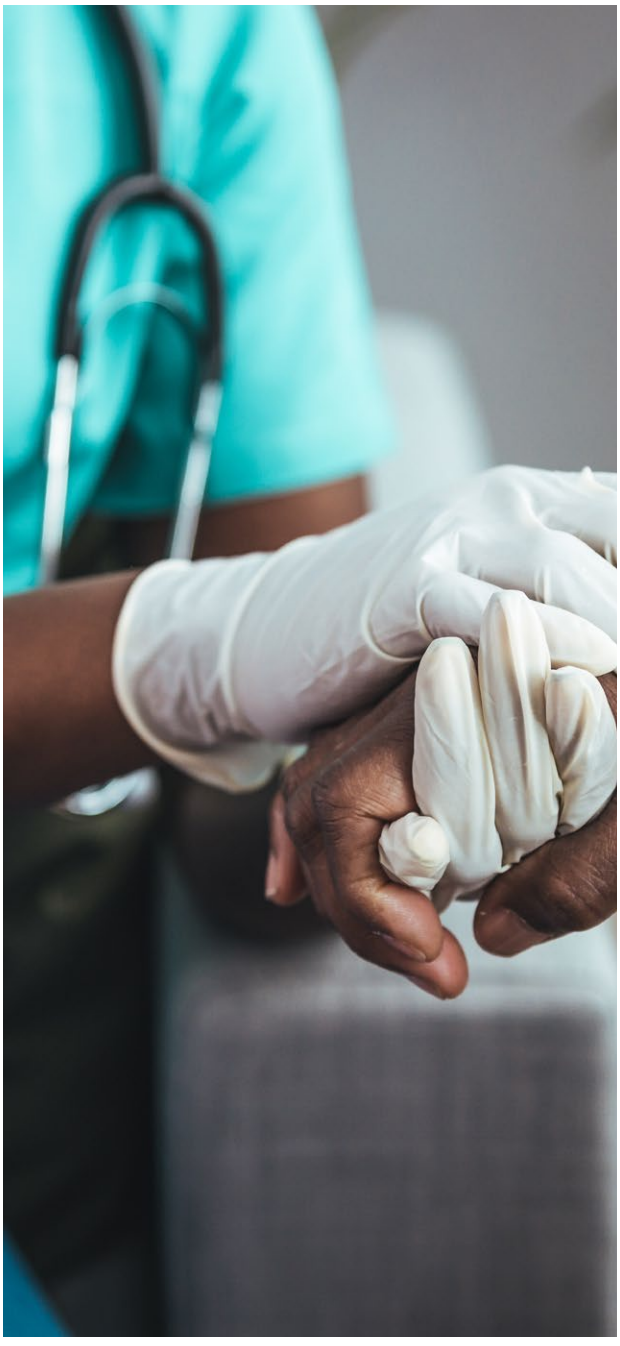
daily as the PI of choice. It is associated with fewer gastro-intestinal side effects than LPV/r and is not associated with unconjugated hyperbilirubinaemia like ATV/r. It also has a higher genetic barrier to resistance than LPV/r or ATV/r. The second choice PI advised is ATV/r which has fewer gastro-intestinal side effects than LPV/r. **LPV/r is only advised if a PI is required, and the patient is on RIF-based TB treatment** – in this situation LPV/r should be double dosed at 800/200mg twice daily. ATV/r and DRV/r should not be co-administered with RIF.

Failed first-line regimen of two NRTIs + dolutegravir

The second-line regimen to commence in patients who have failed a first-line regimen of two NRTIs + DTG is provided in **Table 15**.

TABLE 15: Recommended second-line regimen in patients who have failed a first-line regimen of two NRTIs + DTG.

Failing first-line regimen	Second-line regimen advised
Two NRTIs + DTG	Two NRTIs + DRV/r (usually TDF + 3TC or FTC + DRV/r) Only switch to second-line if resistance test shows DTG resistance.



If patients experience virological failure on a first-line DTG-based regimen, then we do not recommend switching to second-line therapy unless a resistance test is performed and demonstrates DTG resistance. This is because DTG is a very robust drug and resistance is very rare when used in triple-drug combination first-line therapy. Therefore, it is far more likely a VL > 50 copies/mL is due to adherence problems rather than resistance. If DTG resistance is demonstrated, then we then advise a regimen of two NRTIs + DRV/r. Usually this would be TDF + 3TC or FTC + DRV/r unless there is renal impairment or prior TDF nephrotoxicity. The NADIA trial reported high rates of virological success of this regimen and no development of PI resistance, even when there was resistance to both TDF and 3TC.[83]

Patients currently established on protease inhibitor-based second-line therapy

We recommend switching patients currently on a second-line LPV/r regimen, to a TLD regimen, particularly in patients experiencing gastrointestinal or other side-effects including dyslipidaemia. This switch will simplify the regimen and reduce pill burden. Clinical trials data[22] suggests better outcomes on a second-line DTG regimen compared with a second-line LPV/r regimen, driven by better tolerance. This recommendation is regardless of current VL, but see note of caution below.

There is direct evidence from the 2SD trial[102] that patients suppressed on a second-line PI regimen switched to a DTG second-line regimen maintained suppression equivalent to those randomised to continue the PI regimen (suppression remained >90%

in both arms). In patients currently on a second-line ATV/r or DRV/r-based regimen, a switch to TLD could be considered, particularly in patients experiencing gastrointestinal or other side-effects. Trial findings suggest equivalent second-line outcomes with a TLD regimen and a DRV/r based-regimen[83] and an ATV/r-based regimen.[98] However, switching to TLD may reduce side effects and pill burden.

Patients who have renal impairment or prior tenofovir nephrotoxicity and who are on a LPV/r second-line regimen could be switched to TAF + FTC + DTG (if eGFR > 30 mL/min/1.73m^2) or ABC + 3TC + DTG, to reduce side effects and provide a once daily regimen. It is important to note that the same direct evidence of virological efficacy for ABC + 3TC + DTG in second-line does not exist, as for TLD and, therefore, VL of patients should be monitored closely. In patients who have renal impairment or prior tenofovir nephrotoxicity, who are on DRV/r or ATV/r second line regimens we recommend maintaining their current regimen unless they are not tolerating the PI in which case one of the two regimens above could be considered.

Patients in whom caution should be applied before switching from a second-line PI regimen to a DTG regimen is those who have been on the PI regimen for more than 2 years and with 2 or more consecutive VL measurements above 1000 copies/mL. Such patients should have a resistance test done before switching as they may require a more robust regimen that includes DRV/r if they have acquired PI resistance mutations (see **module 14**).

Patients currently established on AZT + 3TC + DTG second-line therapy

Based on the findings of the NADIA trial, patients on AZT + 3TC + DTG second-line therapy should be switched to TLD. NADIA demonstrated that at 96 weeks TDF/3TC was superior to AZT/3TC as an NRTI backbone in second-line in terms of virological suppression. This appeared to be the case regardless of NRTI mutational profile present at first-line failure.[83] If a patient has been on AZT + 3TC + DTG for over 2 years and has had 2 or 3 VL measurements > 1000 copies/mL then an integrase resistance test could be considered before switching to ensure there is still susceptibility to DTG.

MODULE 14

THIRD-LINE ANTIRETROVIRAL THERAPY

Key points

- For a patient with a detectable VL on second-line therapy for < 2 years, intensified adherence counselling and support are required rather than a switch to a third-line therapy.
- For a patient on a second-line regimen for > 2 years with 2 or 3 VL measurements > 1000 copies/mL within a 6-month period **despite adherence interventions that have been assessed to be satisfactory**, then a resistance test should be performed.
- The choice of the third-line regimen should be made in conjunction with an HIV expert, based on treatment history and resistance test(s) result.

Management of patients with a detectable viral load on second-line therapy and initiation of third-line therapy

In a patient who has been on a second-line regimen for ≥ 2 years, if there are two or three VL measurements > 1000 copies/mL in a 6-month period despite adherence interventions, **and adherence is assessed to be satisfactory** (e.g. 100% pharmacy claims over 6 months), then a resistance test should be performed. If a patient who has been on second-line therapy for < 2 years is found to have a detectable VL, then a resistance test should not be performed; rather, the regimen should be reviewed with a view to making it more tolerable and convenient to facilitate adherence, and intensified adherence counselling and support provided. For a patient on a PI regimen, this will usually involve switching them to TLD, unless TDF is contraindicated (see **module 13**).

It is unlikely that significant resistance to a PI or DTG will have developed within 2 years. The exceptions include: a patient who in error was not prescribed LPV/r double dosing with concurrent RIF use who subsequently demonstrates a detectable VL, and a patient who has been taking an incorrectly low dose of medication. Such patients are eligible for resistance testing even if they have been on second-line therapy for < 2 years.

There should be documented PI or DTG resistance before switching to a third-line regimen. Resistance tests should be interpreted by an expert in conjunction with a full ART history. In many patients failing second-line regimens, there are no PI (or DTG) mutations found on resistance testing. In these patients, improved adherence is required rather than switching to a third-line regimen. Such patients should be switched to a simple and tolerable regimen to facilitate better adherence, which will usually be TLD unless TDF is contra-indicated in a patient currently on a PI regimen.

Figure 5 outlines indications for performing resistance testing in patients on second-line ART regimens.

Patients who fail a LPV/r or ATV/r second-line regimen and are found to have PI resistance

In most patients who experience virological failure on a second-line LPV/r or ATV/r regimen with low-, intermediate- or high-level resistance to the PI (i.e. Stanford Score > 14) a switch to TLD is recommended provided DRV is reported as fully susceptible and there has been no prior DTG failure. TLD will be an effective regimen in most patients even if TDF + 3TC resistance is present, based on evidence from the NADIA, VISEND and ARTIST trials.[83,98,100] For the minority of patients who will go on to fail this third-line TLD regimen and develop DTG resistance then TDF + 3TC + DRV/r would be an appropriate subsequent regimen provided DRV is still fully active.

We therefore recommend avoiding switching to TLD alone after second-line ATV/r or LPV/r regimen failure if there is DRV cross-resistance reported on the resistance test. If DRV is reported as low- or

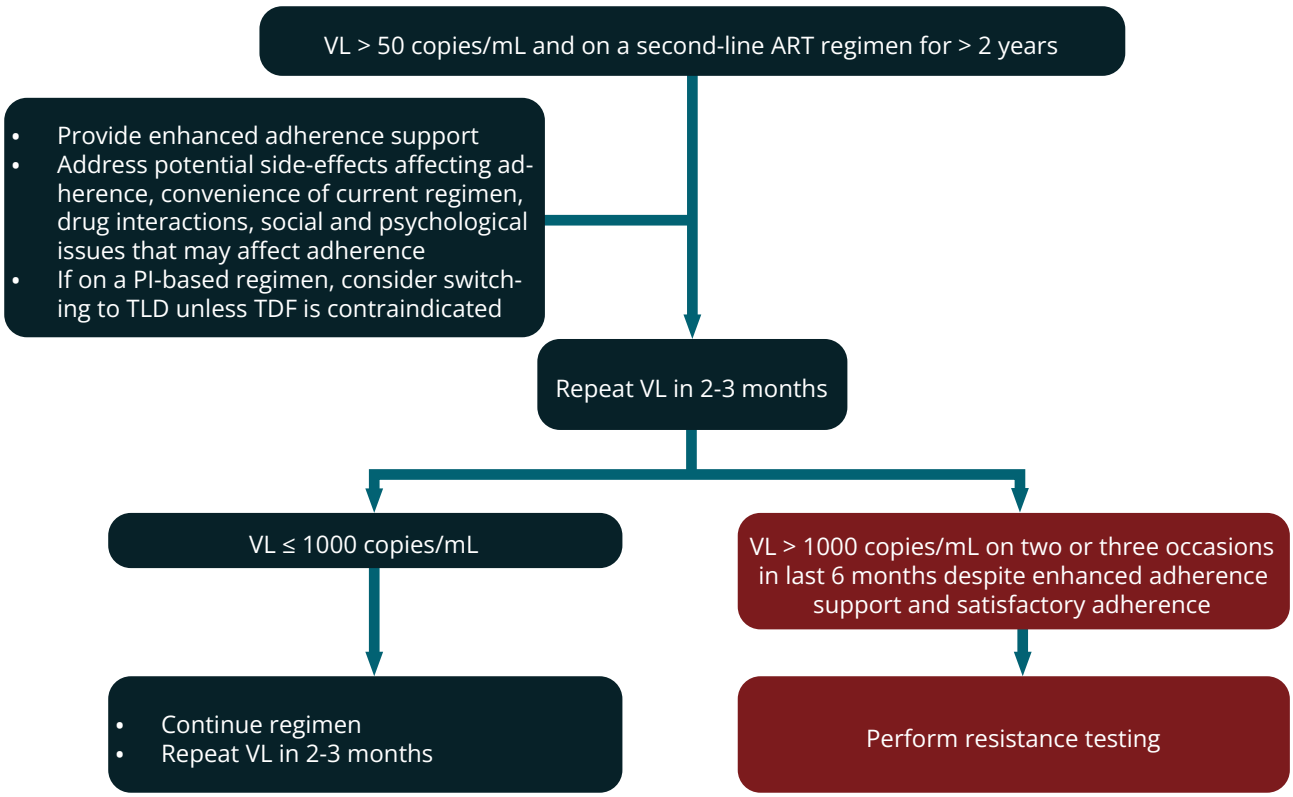


FIGURE 5: Indications for performing resistance (genotype) testing in second-line antiretroviral therapy.

(ART, antiretroviral therapy; DTG, dolutegravir; LPV/r, ritonavir-boosted lopinavir; PI, protease inhibitor, VL, viral load.)

intermediately susceptible on this resistance test (i.e. Stanford score 15-59), we rather recommend TLD plus DRV/r 600/100mg twice daily to provide a more robust regimen, because there is no fully active regimen available if the third-line regimen fails (**Figure 6**). If patients in this category cannot take TDF (renal impairment or prior TDF nephrotoxicity) the regimen should be discussed with an HIV expert.

Patients who fail a DTG second-line regimen and are found to have DTG resistance

The usual option for patients who fail a DTG second-line regimen and are found to have DTG resistance is TDF + 3TC + DRV/r. However, if they are found to have PI resistance or are strongly suspected to have archived PI resistance, they may require additional drugs and treatment should be discussed with an HIV expert. Patients with renal impairment or prior TDF nephrotoxicity will also need an alternative regimen, and this should be discussed with an HIV expert.

In patients failing a second-line DTG regimen who have not failed a PI-regimen previously, it can be assumed that DRV/r is fully active and can be used at 800 mg/100 mg daily. Based on the results of the NADIA trial,83 it can be concluded that a TDF + 3TC + DRV/r regimen will be an active regimen with a high barrier to PI resistance even if there is resistance to the two NRTIs (TDF and 3TC).

Certain patients with long or complicated treatment histories may require additional drugs in their regimen and should be discussed with an HIV expert. These may include:

- RPV or ETV (provided Stanford score for the drug is <30). Because most patients are not receiving a NNRTI at the time of failing second-line therapy, when a genotype resistance test is typically performed, prior NNRTI mutations related to

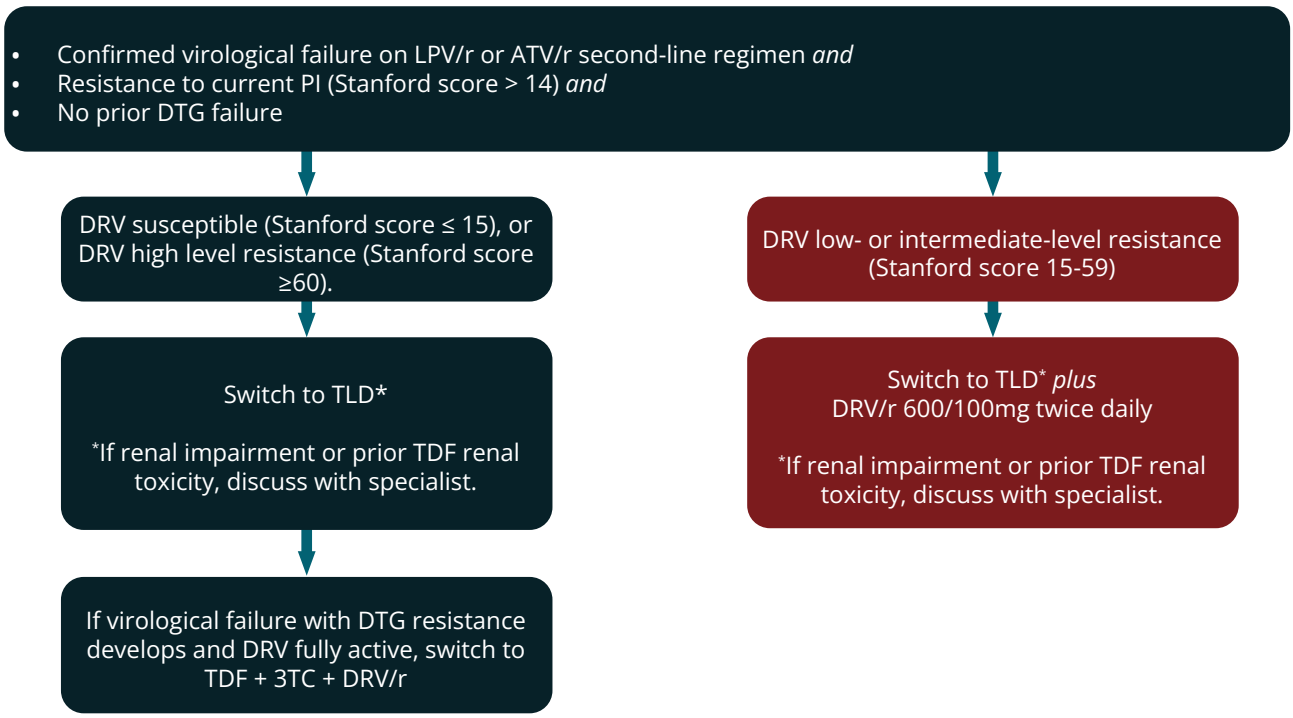


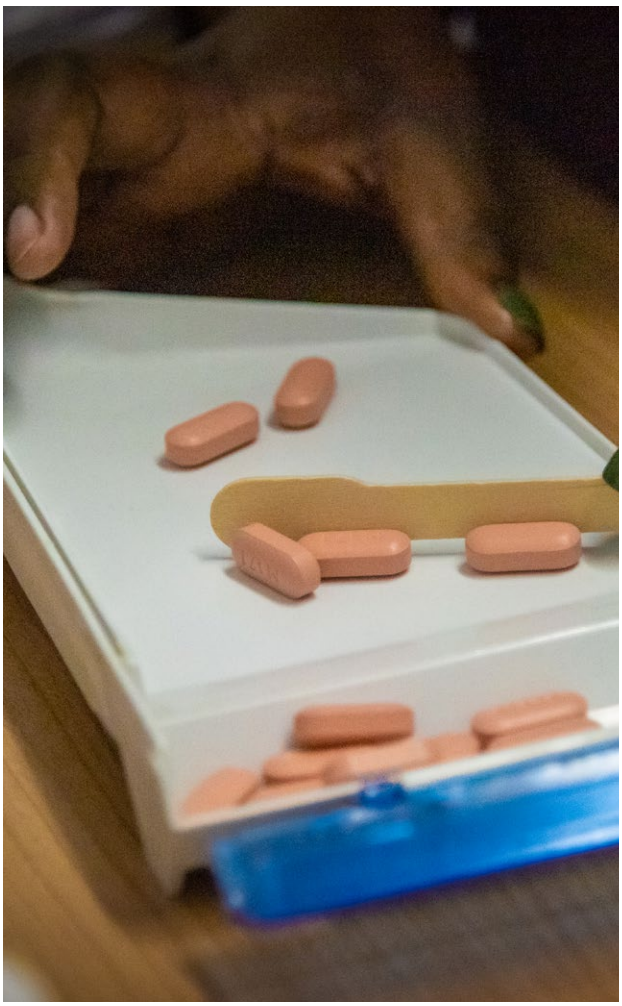
FIGURE 6: Indications for performing resistance (genotype) testing in second-line antiretroviral therapy.

ART, antiretroviral therapy; DTG, dolutegravir; LPV/r, ritonavir-boosted lopinavir; PI, protease inhibitor, VL, viral load.

first-line NNRTI failure may be archived at this time. Therefore, it is difficult to be certain from the resistance test performed at second-line failure, whether ETR/RPV are still active; however, data from South Africa suggest that the majority of patients who have failed NVP or EFV do not have high levels of resistance to ETR/RPV.[103]

- MVC (a CCR5 blocker) is a consideration in third-line therapy; however, it is extremely costly and can only be used after a tropism test demonstrates that the patient's circulating virus has sole tropism for the CCR5 co-receptor. MVC should only be considered when there is intermediate- or high-level resistance to all PIs, all NNRTIs and all NRTIs, and there is not full susceptibility to DTG.
- RAL may still be active in patients with DTG resistance depending on the specific resistance mutations in the integrase region. Its use should be guided by resistance test report.

Decisions regarding third-line therapy need to be individualised in consultation with an HIV expert, taking into account treatment history (which drugs and classes the patient previously failed) and previous and current resistance test results.



Patients currently on third-line therapy

Given the new evidence regarding the efficacy of TLD with compromised NRTIs, it may be possible to simplify the regimens of certain patients currently on multi-drug third-line regimens to improve adherence. This should only be done after a careful review of treatment history and all genotype results with an HIV expert. If the regimen is simplified to TLD, it must be ensured that a follow-on regimen is still available should that regimen fail and DTG resistance develop. This would typically require DRV to be fully susceptible. Simplification of DRV 600/100mg 12-hourly to 800/100mg once daily to reduce pill burden can also be considered if prior resistance tests demonstrated a Stanford score for DRV of 0.

Adherence counselling before third-line therapy

Specific adherence counselling should be provided for patients preparing to start third-line ART, with a frank discussion that this regimen may be their last option for the foreseeable future.

Additional points and explanatory notes

- Patients with a DRV score of 0 on Stanford Score (and no DRV mutations, see **module 5**) can take DRV/r 800 mg/100 mg once daily.
- Patients with prior virological failure on RAL and/or with a DTG score > 0 on integrase resistance testing **should receive DTG 50 mg twice daily.**
- We generally advise the continuation of NRTIs in the third-line regimen, even if there is documented NRTI resistance. 3TC (or FTC) resistance with the M184V mutation impairs viral replication, as does TDF resistance with the K65R mutation.
- In the SAILING trial, in treatment-experienced patients, a DTG regimen proved superior to RAL and fewer patients in the DTG arm developed treatment-emergent InSTI resistance.[104] **Consequently, we no longer recommend use of RAL in third-line therapy unless DTG is not tolerated or based on resistance test result.** We also recommend switching patients currently using RAL in third-line therapy to DTG, due to its higher barrier to resistance.[104] If such patients have a suppressed VL, then they can be switched to standard dose DTG 50 mg daily, but if they are not virologically suppressed, then we recommend a resistance test with a request for integrase sequencing, before switching. If there are InSTI mutations present that are associated with partially reduced susceptibility to DTG, then the DTG dose should be 50 mg twice daily if DTG is used.
- If viral suppression is not achieved on third-line therapy, there is still benefit in continuing failing ART, because of the residual partial activity and 'crippling' effect of such ART. 'Crippling' describes mutant viruses often having a lower replicative capacity. Provided that the VL can be maintained at < 10 000 copies/mL, the CD4+ count will usually be maintained or even increase.[82]

MODULE 15

LABORATORY MONITORING OF THE EFFICACY AND SAFETY OF ANTIRETROVIRAL THERAPY

Key points

- ART efficacy is monitored with VL and CD4+ count – discussed in **modules 8 and 9.**
- The key efficacy endpoint in ART is sustained virological suppression with a VL < 50 copies/mL.
- CD4+ count monitoring can be stopped when the CD4+ count is > 200 cells/μL and the VL is suppressed. But repeat CD4+ to guide management if there is virological failure or clinical failure, or if the viral load rebounds above 10 000 copies/mL due to adherence challenges. Also repeat CD4+ count if a patient returns to care after interruption of ART.
- Creatinine monitoring is advised in patients on TDF, and full blood count in patients on AZT.
- In most patients taking PIs, only one lipid measurement is advised (at 3 months) unless dyslipidaemia is diagnosed, or other cardiovascular risk factors are present.

In patients on TDF who are admitted to hospital, it is important to check creatinine (eGFR) even if it does not fall within these monitoring guidelines. This is because intercurrent illnesses with dehydration or sepsis may be associated with deterioration in renal function, in which TDF may act as a co-factor.

Table 17 lists the laboratory investigations and their frequency advised for monitoring of ART safety.

TABLE 17: Standard laboratory monitoring of patients after commencement of antiretroviral therapy.

Test†	When		Comments
	Baseline	Ongoing	
VL	Yes	At 3, 6 and 12 months and then 6-12 monthly	If the VL is undetectable for > 12 months, can reduce to 12-monthly monitoring.
CD4+ count	Yes	At 6 and 12 months and then 6-monthly At virological/clinical failure	Can be stopped if CD4+ > 200 cells/μL and virologically suppressed. Repeat CD4+ if a patient returns to care after treatment interruption to guide management.
ALT	Yes	No	If baseline ALT is normal, routine monitoring of ALT is not required. If baseline ALT is abnormal or the patient is on other hepatotoxic drugs, continue to monitor
Creatinine (eGFR)	Yes	At 3 months, 6 months and then 6-12 monthly	Also at 1 and 2 months in high-risk patients. If symptoms of tubular wasting (e.g. muscle weakness), then also check potassium and phosphate levels
FBC + differential count	Yes	Monthly for the first 3 months, then at 6 months	Only for patients on AZT-containing regimens.
TC and TG (ideally fasting)	Not routinely	At 3 months	Only for patients on a PI-containing regimen. If normal at 3 months, reassess only if other cardiovascular risk factors are present.

ALT, alanine transaminase; AZT, zidovudine; eGFR, estimated glomerular filtration rate; FBC, full blood count; NVP, nevirapine; TC, total cholesterol; TG, triglycerides; VL, viral load.
† These tests should also be done when clinically indicated, based on the discretion of the clinician.

Common pitfall: Not monitoring the VL at least annually. If VL is not monitored, this can result in delayed detection of ART failure and required interventions resulting in clinical deterioration and increased risk of HIV transmission.

MODULE 16

PATIENTS WHO RETURN AFTER STOPPING ANTIRETROVIRAL THERAPY

Key points

- Many patients return to care after treatment interruption when they experience clinical deterioration – screening for opportunistic infections should be performed.
- VL measurement should be performed 3 months after ART re-initiation.
- The majority of patients returning to care should be re-initiated on tenofovir/lamivudine/dolutegravir (TLD) unless there is a reason not to use one of these drugs or the patient requires a more robust third line regimen.

Patients receiving ART may interrupt their treatment for a variety of reasons (e.g. treatment fatigue, denial, life event, depression, new job, relocation). Many patients return to care after an interruption, often precipitated by clinical deterioration. Patients who have clinical symptoms of an opportunistic infection (OI) when returning to care should be investigated and, if appropriate, started on treatment for the infection before restarting ART. In particular, patients should be screened for symptoms of meningitis and for TB symptoms when returning to care. Reasons for delaying ART re-initiation are the same as for delaying initiation in ART-naïve patients (see **module 6**). Patients who are asymptomatic when they return to care can be re-initiated on ART the same day with appropriate counselling. A counselling plan should be implemented to ensure retention in care going forward and to address reasons for disengagement in a non-judgemental manner.

We recommend performing a CD4+ count when the patient returns to care (to guide OI prophylaxis) and a VL measurement 3 months after re-initiation of ART. If this VL is suppressed, then VL monitoring could revert to annually. If it is not suppressed, follow standard guidance in response to the result (see **module 8**). If the patient is restarted on TDF then an eGFR should also be checked at baseline and at 3 months.

The majority of patients returning to care should be re-initiated on TDF/3TC/DTG (TLD). This is supported by data demonstrating the virological efficacy of TLD in first- and second-line ART, and the convenience of a well-tolerated single daily tablet in patients with prior adherence problems.

Patients who should not be restarted on TLD include:

- Patients with renal impairment or prior nephrotoxicity due to TDF. These patients should be recommenced on ABC/3TC/DTG **or** ABC/3TC/DRV/r **or** ABC/3TC/ATV/r, **or** TAF/FTC/DTG if eGFR > 30mL/min/1.73m^2.
- Patients previously on a third-line regimen including DRV/r. These patients should be restarted on the same regimen although, in consultation with an HIV expert, consideration could be given to rationalising the regimen to fewer drugs after review of their treatment history and prior resistance tests.

Common pitfall: Performing a resistance test after an ART treatment interruption of > 4 weeks. Such testing is of limited value. Many resistance mutations are overtaken by wild-type virus when ART is stopped and thus the resistance test may not accurately reflect the true resistance pattern.

MODULE 17

DRUG-DRUG INTERACTIONS

Key points

- Whenever patients start or switch antiretroviral (ARV) drugs or start new concomitant medications, it is important to evaluate for potential drug interactions.
- Many drugs and drug classes have clinically significant drug-drug interactions with ARVs.
- There are also important drug interactions between several ARVs.
- It is important to consult a regularly-updated database to assess whether drugs can be co-administered and whether a dose adjustment is required.
- Herbal medications may also have interactions with ART drugs (e.g. St John's Wort, garlic), but data on herb-drug interactions are very limited.
- Certain over-the-counter products (such as multivitamin products) contain polyvalent cations that may interact with DTG.

Mechanisms of drug interactions

There are two main mechanisms of drug-drug interactions:

Pharmacodynamic interactions occur when one drug influences the action of another drug without altering its concentrations. Such interactions may be beneficial, if drug effects are additive or synergistic; or harmful, if drug effects are antagonistic. Additive toxicity is also a pharmacodynamic interaction (e.g. AZT and linezolid both cause myelosuppression and should not be co-administered).

Pharmacokinetic interactions occur when a perpetrator drug alters the concentrations of a victim drug by affecting its absorption, distribution, metabolism or excretion. Inhibition is a direct chemical effect when a drug binds to the active site of drug-metabolising enzyme or drug transporter – typically only one or a few enzymes or transporters are inhibited. Inhibition is maximal when the inhibiting drug reaches steady state and wanes rapidly when the inhibiting drug is stopped. Strong inhibitors (e.g. ritonavir, clarithromycin, itraconazole) can cause marked increases in concentrations of victim drugs, resulting in toxicity. Induction results in transcriptional activation of many genes involved in drug metabolism and transport, which takes about 2 weeks to be maximal and wanes over a similar time. Strong inducers (e.g. RIF, carbamazepine, phenytoin) can cause marked decreases in concentrations of victim drugs, resulting in reduced efficacy. Pharmacokinetic interactions are occasionally beneficial (e.g. RTV markedly increases the concentrations of other PIs to increase their antiviral efficacy). Data on herb-drug interactions are very limited – both St John's Wort and garlic are known inducers. Clinically significant pharmacokinetic interactions require dose adjustment of the victim drug or, if the interaction is severe, avoiding co-administration with the perpetrator drug.

Overview of drug-drug interactions by antiretroviral class

- **NRTIs** are generally neither victims nor perpetrators of clinically significant pharmacokinetic interactions. An exception is TAF, which may be the victim of inducers (see **module 2**).
- **PIs:** RTV is a potent inhibitor of the key cytochrome P450 enzyme 3A4 (CYP3A4) and the drug efflux transporter P-glycoprotein. It also induces several other drug-metabolising enzymes and drug transporters. Therefore, RTV-boosted PIs are frequent perpetrators of pharmacokinetic interactions but can also be victims of such interactions when co-administered with strong inducers – co-administration with strong inhibitors does not add significantly to the inhibition by RTV. ATV/r requires an acid pH in the stomach for absorption and it should, therefore, be taken 2 hours before or 1 hour after antacids, and administration with PPIs should be avoided.

- **NNRTIs** differ by individual drug. EFV is a moderate inducer. RPV can be the victim when co-administered with strong inducers. Although inhibitors increase exposure to RPV, it is seldom necessary to dose-adjust. ETR induces CYP3A4 and also inhibits two CYP enzymes; it can also be the victim when co-administered with strong inducers.
- **InSTIs:** Polyvalent cations (calcium, magnesium, iron, aluminium, zinc) bind to InSTIs, reducing their absorption. InSTIs should be taken 2 hours before or 6 hours after polyvalent cations. However, calcium and iron can be co-administered with InSTIs if taken with a meal, but not in a fasted state. InSTIs are victim drugs when co-administered with strong inducers. InSTIs are not perpetrator drugs; however, DTG inhibits an efflux transporter important in the elimination of metformin. As such, the metformin dose should not exceed 500 mg 12-hourly in a patient taking DTG.

There are many important pharmacokinetic drug interactions between ARVs and other drugs, as well as between different ARVs. Some of these drug-drug interactions are discussed in other modules of these guidelines (e.g. interactions with RIF in **module 18**).

The full list of all potential drug interactions is extensive and beyond the scope of these guidelines, and knowledge of drug interactions is constantly evolving. Clinicians are, therefore, advised to seek reliable information on drug-drug interactions when using non-standard ART regimens and when drugs are co-administered, using one or more of the resources listed in **Box 3.**

BOX 3: Contacts and resources for seeking reliable information on drug-drug interactions.

- Package inserts of ARVs and concomitant drugs
- UCT MIC HIV & TB Hotline: 0800 212 506 or 021 406 6782 or SA HIV & TB HCW Hotline App: **SA HIV & TB HCW Hotline App | Medicines Information Centre (uct.ac.za)**
- University of Liverpool HIV Drug Interactions Checker: **https://www.hiv-druginteractions.org/checker**
- Aid for AIDS clinical guidelines contain tables giving advice on drug-drug interactions: **http://www.aidforaids.co.za/dp_clin.php**
- University of Cape Town (UCT) Medicines Information Centre (MIC) has a regularly updated table of interactions between ARVs and drugs used in the public sector (essential medicines list): **http://www.mic.uct.ac.za/**

Common pitfalls:

- **Not checking for interactions between concomitant drugs and current or newly initiated ARVs.** Concomitant drugs may need dose adjustment or discontinuation when ART is switched, e.g. switching from a moderate inducer (EFV) to a strong inhibitor (PI/r), or from either of these to DTG.
- **Not considering marked increases in statin considerations when used concomitantly with PIs.** There are major interactions between PIs and many statins resulting in marked increases in statin concentration. Low-dose atorvastatin (not exceeding 10 mg, which will give equivalent exposure to about 60 mg) can be used with PIs, but simvastatin cannot be used.
- Not counselling patients on DTG about drug-drug interactions that can occur with polyvalent cation-containing over-the-counter medications (including antacids, laxatives, multivitamins and pregnancy supplements).

MODULE 18

TUBERCULOSIS

Key points

- Rifampicin (RIF) is a potent inducer of certain drug-metabolising enzymes and drug transporters and reduces exposure to drugs in the InSTI, NNRTI and PI classes, necessitating dose adjustments of certain of these drugs.
- LPV/r is the only PI that can be used with RIF, but the LPV/r dose needs to be doubled.
- Rifabutin (RFB) can be used with all PIs, but a RFB dose adjustment is required.
- Several side-effects are shared between ARVs and TB drugs including gastrointestinal intolerance, hepatotoxicity, drug rashes, myelosuppression and neuropsychiatric side-effects.

Considerations for antiretroviral therapy in the context of tuberculosis

Tuberculosis (TB) is the most frequent concomitant infection affecting people with HIV (PWH) in Southern Africa. Patients may be diagnosed with TB at entry or re-entry into HIV care, or diagnosed with active TB while on ART. Studies in South Africa have suggested that TB incidence remains higher in patients who are virally suppressed on long-term ART compared with HIV-negative people living in the same community, possibly because of persisting defects in anti-mycobacterial immunity. The co-treatment of HIV and TB is complex because of: (i) drug-drug interactions (discussed below); (ii) TB-IRIS (see **module 26**); and (iii) shared side-effects (discussed below). These issues, which have recently been reviewed,[105] affect decisions regarding the timing of ART in ART-naïve patients with TB (see **module 6**).

Certain ART regimens need to be modified for compatibility with rifampicin (RIF). RIF is a critical component of the drug-sensitive TB regimen that substantially reduces the risk of relapse after completing TB treatment.

There are no significant interactions between NRTIs and RIF; however, InSTIs, NNRTIs, PIs and MVC all exhibit drug interactions with RIF. DTG can be used in patients receiving RIF, but a dose adjustment to 50mg twice daily is advised in most cases (**Table 18**).[88] A recent phase 2 clinical trial in South Africa38 and observational data from Botswana[106] showed that virologic outcomes were similar in patients who remained on standard dose DTG (50mg daily) compared with those in whom dose was adjusted to 50mg twice daily. Standard dosing of DTG with RIF is therefore an option, but we do not advise this in patients who have previously failed a regimen and may have NRTI resistance as this dosing strategy has not been evaluated in this patient group.
EFV is the preferred NNRTI for use with RIF. NVP was previously recommended as an alternative in patients with contraindications to EFV (e.g. psychosis), but it carries a higher risk of virological failure when used with RIF and given the availability of the InSTI class, NVP is no longer recommended. RPV and ETR cannot be used with RIF.

The plasma concentrations of all PI/r are reduced to subtherapeutic ranges with RIF. Dose adjustment of LPV/r can overcome this induction (see **Table 18**), but there is a risk of hepatotoxicity; therefore, patients require counselling and ALT should be monitored frequently.[107,108] Gastrointestinal side effects are frequent with LPV/r double dosing.

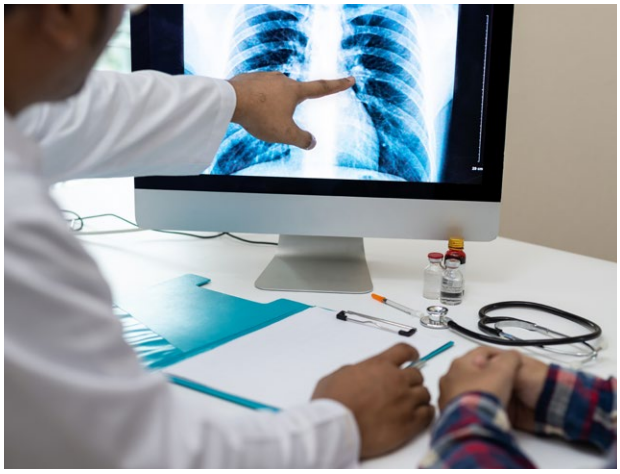


TABLE 18: Antiretroviral drug interactions with rifampicin and recommendations for co-administration.			
Class	**ART drug**	**Interaction**	**Dose of ART drug with RIF**
NRTI	All in class	No significant pharmacokinetic interactions.†	No dose adjustment required
NNRTI	EFV	Mild reduction in EFV concentrations INH increases EFV concentrations in genetic slow metabolisers (~20% of South Africans), who already have high EFV concentrations – this can result in toxicity.	No dose adjustment required (600 mg nocte)
	ETR and RPV	Marked reduction in concentrations	Do not prescribe concomitantly with RIF
PI/r	LPV/r	LPV plasma concentrations significantly decreased	Double the dose of LPV/r to 800 mg/200 mg 12-hourly. There is an increased risk of hepatotoxicity with this strategy. The dose adjustment can be made gradually over 1–2 weeks. Dose adjustment should be continued for 2 weeks after RIF is stopped. This regimen is associated with increased gastrointestinal side-effects.
	All other PI/r	Marked reduction in PI concentrations	Do not prescribe concomitantly
InSTI	RAL	Reduction in concentrations	Dose increase to 800 mg 12-hourly
	DTG	Significant reduction in concentrations	Dosing frequency increased to 50 mg 12-hourly. For patients on first-line TLD, standard (daily) dosing can be used
CCR5 blocker	MVC	Reduction in concentrations	Increase MVC dose to 600 mg twice daily when co-administered with RIF in the absence of a potent CYP3A4 inhibitor

ART, antiretroviral therapy; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; InSTI, integrase inhibitor (integrase strand transfer inhibitor); LPV, lopinavir; LPV/r, ritonavir-boosted lopinavir; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI/r, ritonavir-boosted protease inhibitors; RAL, raltegravir; RIF, rifampicin; RPV, rilpivirine.
† RIF reduces TAF concentration in the blood but the intracellular TFV-dp concentration remains adequate, and so no dose adjustment is needed.

An alternative approach is to replace RIF with rifabutin (RFB) in patients taking a PI/r. However, RFB is not co-formulated with other TB drugs, and the evidence base for RFB in the treatment of TB is much less substantial than for RIF.[109] There is also uncertainty regarding the optimal dose of RFB with PI/r; these guidelines recommend 150 mg daily (**Table 19**) for efficacy reasons, but careful monitoring for toxicity is required (ALT, neutrophil count and visual symptoms at least monthly).[110] RFB may be considered in patients who are not tolerating co-treatment with double-dose LPV/r and RIF-based TB treatment (i.e. patients unable to tolerate the increased LPV/r dose due to hepatotoxicity or gastrointestinal side-effects) or in ART-experienced patients on a regimen that is not compatible with RIF (e.g. third-line ART with DRV/r). In most patients on RIF-based TB treatment, however, a DTG regimen rather than a PI should be used, except in patients who are intolerant of DTG and those on third-line requiring both DTG and DRV/r.

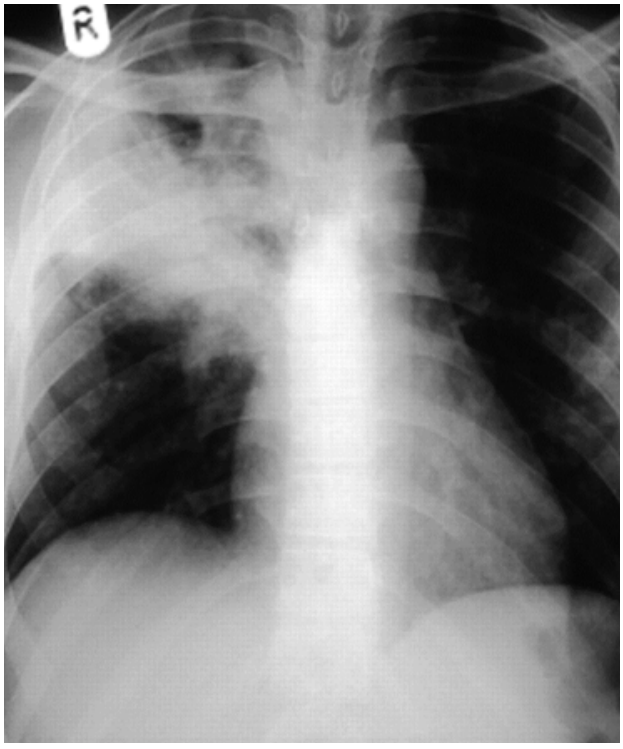


TABLE 19: Dosage of antiretroviral drugs and rifabutin when prescribed concomitantly.		
ARV drug	**ART dosage**	**RFB dosage**
EFV	No change	Increase to 450 mg/day
InSTI class	No change	300 mg/day
ATV or PI/r	No change	Decrease to 150 mg/day (monitor ALT, neutrophils and visual symptoms at least monthly)
RPV	Do not co-administer **or** increase RPV to 50 mg daily	300 mg/day (or 150 mg/day with PI/r)
ETR	Preferably avoid, but if used, then standard doses of ETR	300 mg/day (or 150 mg/day with PI/r)

ALT, alanine transaminase; ART, antiretroviral therapy; ATV, atazanavir; EFV, efavirenz; ETR, etravirine; InSTI, integrase strand transfer inhibitor; PI/r, ritonavir-boosted protease inhibitor; RFB, rifabutin; RPV, rilpivirine; RTV, ritonavir.

TABLE 20: Shared side-effects of ART and TB treatment.		
Side-effects	**ART**	**TB treatment**
Nausea	AZT, PIs	Pyrazinamide, ethionamide, PAS
Hepatitis	EFV, PIs (NRTIs can cause steatohepatitis)	RIF, RFB, INH, pyrazinamide, bedaquiline and many second-line TB drugs, including quinolones
Renal impairment	TDF	Aminoglycosides, RIF (rare)
Rash	EFV, RAL, DTG	RIF, RFB, INH, pyrazinamide, ethambutol, streptomycin and many second-line TB drugs, including quinolones
Neuropsychiatric complications	EFV, DTG	Terizidone/cycloserine, quinolones, INH
Prolonged QTc	RPV	Bedaquiline, quinolones, clofazimine, delamanid
Myelosuppression	AZT	RFB and linezolid

ART, antiretroviral therapy; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; INH, isoniazid; NRTIs, nucleoside reverse transcriptase inhibitors; PAS, Para-aminosalicylic acid; PIs, protease inhibitors; RAL, raltegravir; RFB, rifabutin; RIF, rifampicin; RPV, rilpivirine; TB, tuberculosis; TDF, tenofovir; QTc, corrected QT interval

Common pitfall:

- **Co-administering RIF with LPV/r, but not adjusting the dose of LPV/r.** This results in subtherapeutic LPV concentrations and development of PI resistance.
- **Combining linezolid and AZT.** These drugs should not be combined because both can cause bone marrow suppression (especially anaemia and neutropenia).

MODULE 19

PREGNANCY AND BREASTFEEDING

Key points

- Virological suppression on ART is essential for maternal health, and to prevent HIV transmission to the infant. An elevated VL > 50 copies/mL in a pregnant or breastfeeding woman requires urgent action. Focus should be given to retaining these women in long-term care.
- Standard first-, second- and third-line regimens should be used in women who are pregnant or breastfeeding.

Note: It is beyond the scope of these guidelines to provide comprehensive guidance for the management of pregnant women; however, it is important to note that women of reproductive age are disproportionately affected by HIV and HIV remains a major contributor to maternal deaths in South Africa (48.1% of women who died in the 2017 - 2019 triennium were living with HIV).[111] Key recommendations relating to the mother are included, but providers are encouraged to refer to national guidelines (see **Box 4**). All women should be linked to routine antenatal care when pregnancy is confirmed.

BOX 4: South African national guidelines for the prevention of vertical transmission of HIV.
NOTE: The 2019 PMTCT guidelines are currently being updated. Be sure to use the latest version.

South African National Department of Health. Guideline for the Prevention of Mother to Child Transmission of Communicable Infections. Pretoria, South Africa: National Department of Health, 2019.
PMTCT Guideline 10-2019.indd (sahivsoc.org)

South African National Department of Health 2023 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates April 2023.

Maternal health is central to healthy infants and is an essential focus of vertical transmission prevention (VTP) services: advanced HIV disease results in life-threatening opportunistic infections, leading to miscarriage, stillbirth, premature delivery, and maternal death.

An elevated VL > 50 copies/mL in a pregnant or breastfeeding woman requires urgent action. In well-functioning VTP programmes, a significant proportion of infections in infants result from undetected seroconversion during pregnancy and breastfeeding. Repeated HIV testing is essential and should occur at every routine antenatal visit (i.e. eight visits in all) and throughout breastfeeding for women testing negative.

Vertical transmission of HIV

Overall, the risk of vertical transmission of HIV is ~40% in the absence of any intervention. Timing of such transmission is as follows: in utero – 5% (with increasing risk in the third trimester); during delivery – 15–20%; up to 24 months of breastfeeding – 20%.

The time of highest risk coincides with delivery, which spans a matter of hours. The risk during 24 months of breastfeeding is slightly higher, but over a significantly greater timespan. Breastfeeding should not be stopped because of a new diagnosis of HIV, or an elevated VL in a woman already on ART. Instead, initiation of ART and management of raised VL (together with infant prophylaxis) are

interventions to make breastfeeding 'safer'. In low-resource settings, breastfeeding is recommended for at least 24 months, irrespective of the maternal HIV status. Current estimates place ART continuation rates at approximately 63% at 18 months postpartum, highlighting the need for improved postnatal retention in care to ensure success in VTP interventions.

Antiretroviral therapy for women of reproductive age, and during pregnancy and breastfeeding

All HIV-positive pregnant and breastfeeding women should be initiated on lifelong ART, ideally the same day that pregnancy is confirmed. **Standard first-, second- and third-line regimens should be used in women who are pregnant or breastfeeding** (**modules 11–14**). The postpartum period is a crucial window for ART retention when women may disengage from care, contributing to disease progression, increased risk of HIV transmission, and potential drug resistance.

Regarding DTG use in pregnancy, it is now clear that DTG is safe for use in women of reproductive age, regardless of reproductive plans, and in all gestational ages during pregnancy. We previously recommended that women be counselled regarding the potential risks of neural tube defects (NTDs) with the use of DTG in pregnancy. However, continuously emerging data has shown that there is no statistically significant increase in the risk of NTDs in infants of mothers using DTG (see **module 3**).[112] In addition DTG has been shown to be an effective drug in pregnancy with more frequent viral suppression at delivery.[32,33,113] For a detailed discussion on the use of DTG in pregnancy refer to the commentary released by SAHCS in July 2021: **https://sahivsoc.org/Files/DTG%20commentary%20220721.pdf**

Other points regarding ART in pregnancy:

- EFV-based regimens should be avoided given the preference for DTG-based regimens in pregnancy. However, in the rare case of DTG intolerance, EFV 600 mg is a safe and effective regimen for use by women of reproductive age, including during the time from conception to the end of the first trimester. There are insufficient data to recommend routine use of EFV 400 mg in pregnant women.
- Commonly used eGFR calculations are not validated in pregnant women, therefore avoid TDF if serum creatinine ≥ 85 µmol/L.
- Dose adjustment of ART during pregnancy is only indicated for women taking both TDF and ATV/r during the second or third trimester; the ATV/r dose should be increased from 300 mg/100 mg to 400 mg/100 mg.

Particular importance should be placed on the drug-drug interactions between DTG and divalent cation-containing medication in pregnancy, since pregnant women frequently receive iron or calcium supplements and/or magnesium-/aluminium-containing antacids (see **module 17**).

Patients returning to care in pregnancy after interrupting a first-line NNRTI regimen or those exposed to previous VTP regimens should be put directly on a DTG-based regimen, rather than retrying an NNRTI-regimen (see also **module 16**). As per the current PMTCT guidelines, women not already on ART at the time of labour or delivery should commence TLD immediately and also receive an additional single dose of NVP 200 mg before delivery of the baby. An HIV test should be performed on all women at the time of delivery if their HIV status is unknown or previously negative. Women who are newly diagnosed with HIV during the breastfeeding period may continue breastfeeding, provided maternal ART and infant prophylaxis are initiated and adherence support given.

Note: all HIV-exposed infants should receive infant prophylaxis post-partum, as guided by the latest national PMTCT guidelines: **PMTCT Guideline 10-2019.indd (sahivsoc.org)** (Note: these guidelines are currently being updated. Ensure to refer to the latest version)

Table 21 details the recommended timing of VL monitoring during pregnancy, delivery and breastfeeding.

TABLE 21: Timing of viral load monitoring during pregnancy, delivery and breastfeeding.				
Period	**ART initiation in pregnancy**	**Already on ART at diagnosis of pregnancy**	**Previously taken ART, not currently on treatment (ART interruption, ART for PMTCT)**	**Newly diagnosed HIV infection during delivery or breastfeeding**
Antenatal	VL at baseline and after 3 months of ART: if > 28 weeks' gestation, then repeat VL at delivery	VL at first ANC visit	VL at initiation of DTG-based regimen; repeat VL 3 months later (change in VL determines management)	-
Delivery	All women need VL measurement at delivery; review result at day 3–6 postnatal visit			-
Postnatal, up to the end of breastfeeding	At 6 months postpartum, then VL 6-monthly until 6 weeks after cessation of breastfeeding			VL after 3 months on ART, then 6-monthly during breastfeeding until 6 weeks after cessation of breastfeeding

ANC, antenatal care; ART, antiretroviral therapy; DTG, dolutegravir; VTP, vertical transmission prevention; VL, viral load.

Other key recommendations:

- All pregnant women should be screened at every visit for sexually transmitted infections (STIs) and treated as needed.
- All pregnant and breastfeeding women should be screened for TB at every visit. A sputum for TB GeneXpert is recommended for all women at pregnancy confirmation, regardless of their TB symptom screen. If the TB screen is negative and the woman has a CD4+ count < 350 cells/μL, consider TB-preventive therapy (see **module 27**).
- Pregnant women frequently experience vomiting, which can result in viral rebound due to reduced absorption and sub-therapeutic ARV drug levels. Screen for, and actively manage, vomiting in women on ART during pregnancy.
- Women are at high risk of low adherence or disengaging from care in the post-natal period. Provide support to women during this time, particularly if there are other risk factors including depression, teenage pregnancy, gender-based violence or socioeconomic challenges.

Common pitfall:

- **Not performing VL monitoring at the appropriate time.** See **Table 21** for the appropriate monitoring intervals.
- **Not acting on an elevated VL urgently.** VL results should be fast-tracked, and women failing their current regimen identified early and, if necessary, a regimen switch made without delay.
- **Failing to identify a pregnant or breastfeeding woman with advanced HIV disease** and/or not providing appropriate prophylaxis and OI screening. All pregnant and breastfeeding women should have a known CD4+ count, whether known on ART, newly diagnosed or returning to treatment.

MODULE 20

LIVER DISEASE

Key points

- There is no single blood test for accurate quantification of liver impairment.
- Child-Pugh class C liver disease may require dose adjustment for some ART drugs.
- ATV can cause jaundice due to elevation of unconjugated bilirubin (indirect) which is benign.
- The combination of TDF (or TAF) + 3TC (or FTC) + DTG is regarded as least hepatotoxic.

Antiretroviral dose adjustments

Table 22 outlines dose adjustments for the relevant ART drugs in patients with Child-Pugh class C liver impairment[1].

TABLE 22: Prescribing antiretroviral therapy in liver impairment.

Class	Drug	Prescribing notes
NRTI	TDF	No dose adjustment necessary
	3TC	No dose adjustment necessary
	FTC	No dose adjustment necessary
	AZT	Decrease dose by 50% or double dosage interval in significant liver disease
	ABC	Reduce dose to 200 mg twice daily in mild liver disease (Child-Pugh score 5-6). No clinical data in patients with moderate-severe liver disease, so not routinely recommended unless judged necessary.
InSTI	DTG	No data on recommendation for those with severe liver disease (Child-Pugh class C)
	RAL	No dose adjustment necessary
PI	DRV	Use with caution or avoid in significant liver disease
	ATV	Avoid in severe liver disease
	LPV/r	LPV is highly metabolised in the liver and concentrations may be increased in patients with hepatic impairment Therapeutic drug monitoring should be done if available
NNRTI	EFV	Not recommended in severe liver disease
	ETR	Use with caution in severe liver disease
	RPV	Use with caution in severe liver disease (Child-Pugh class C) – dose recommendation not established
CCR5 blocker	MVC	Concentrations likely to be increased with liver impairment

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; ARVs, antiretrovirals; AZT, zidovudine; CCR5, C-C chemokine receptor type 5; DTG, dolutegravir; DRV, darunavir; EFV, efavirenz; ETR, etravirine; FTC, emtricitabine; InSTI, integrase strand transfer inhibitor; LPV, lopinavir; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; RAL, raltegravir; RPV, rilpivirine; TDF, tenofovir disoproxil fumarate.

[1]The Child-Pugh score consists of five clinical features and is used to assess the prognosis of chronic liver disease and cirrhosis. Five factors (total bilirubin level, serum albumin, and international normalized ratio, or INR, degree of ascites and hepatic encephalopathy) are graded into a composite score and divided into 3 classes. Class C represents a score of 10-15 and is associated with a 45% one-year survival (https://www.ncbi.nlm.nih.gov/books/NBK542308/)

Concomitant hepatitis B and HIV

Key points

- All patients with HIV should be screened for active hepatitis B virus (HBV) – hepatitis B surface antigen (HBsAg) screening is an appropriate test.
- The HBV VL correlates with disease progression and is used to monitor anti-HBV therapy.
- All children and adults eligible for HBV vaccination should be vaccinated.
- ART drugs with anti-HBV activity are TDF (or TAF) + 3TC (or FTC).
- For all HIV-positive HBsAg-positive patients, the ART regimen should include TDF (or TAF) + 3TC (or FTC).
- Using 3TC without TDF to treat concomitant HBV/HIV leads to HBV resistance in most patients.
- Interruption of TDF (or TAF) and/or 3TC (or FTC) has been associated with flares of life-threatening hepatitis in patients with hepatitis B.
- For patients with chronic HBV infection and chronic kidney disease, options include TAF (down to eGFR of 15 ml/min/1.73m^2 or for those on intermittent haemodialysis) and/or adjustment of the dosing frequency of TDF. If renal function is severe or deteriorates with TDF (or TAF), then 3TC monotherapy or other drugs with anti-HBV activity should be considered.

Hepatitis B virus (HBV) is a common concomitant infection with HIV in Southern Africa, with significant implications for progression to cirrhosis, as well as for treatment options. Access to vaccination, laboratory resources and treatment options are to some extent limited in Southern African countries, and each recommendation below should each be considered in the light of its local context.

Concomitant HBV/HIV is associated with:

- an increased risk of chronic liver disease
- a higher HBV VL
- an increased risk of drug-induced hepatotoxicity
- a flare of hepatitis within 3 months of commencing ART (due to HBV-related IRIS, which is difficult to differentiate from drug hepatotoxicity)

Drugs directed against HBV that have no or minimal anti-HIV activity (e.g. entecavir and telbivudine) are largely unavailable or extremely expensive in our region. Instead, it is usually necessary to use ART drugs that also have anti-HBV activity: TDF (or TAF) + 3TC (or FTC). As with HIV, these drugs suppress HBV, but do not eradicate it. Effective treatment prevents or slows progression to cirrhosis. For all HIV-positive hepatitis B surface antigen (HBsAg)-positive patients, the ART regimen should include TDF (or TAF) + 3TC (or FTC). Using 3TC without including TDF/TAF leads to the development of HBV resistance in 80–90% of patients within 5 years of treatment.[114] If a patient switches to a second-line ART regimen (to treat HIV), then tenofovir (either TDF or TAF) + 3TC (or FTC) should be continued to suppress HBV infection, as interruption of tenofovir and/or 3TC/FTC has been associated in case reports with flares of life-threatening hepatitis in case reports.[115] **The second-line ART regimen should be shaped around these two drugs.**

In patients with HBV and chronic kidney disease, the following options can be considered for hepatitis B treatment:

- TAF + FTC/3TC (preferred). When coformulated with 3TC/FTC, TAF can be given down to a minimum eGFR of 30 mL/min/1.73m^2. However, if given as a separate tablet, TAF can be administered down to an eGFR of 15 mL/min/1.73m^2, as well as to patients on chronic haemodialysis. Dose-adjusted 3TC can be given with this (see **module 21**).
- TDF may be considered with dosing frequency adjustment based on eGFR (**Table 23**) and with more frequent monitoring.
- If renal dysfunction is severe or renal function deteriorates with TDF, then 3TC monotherapy or other drugs with anti-HBV activity should be considered.
- For information on the management of partners of those with HBV see the National guidelines for the management of viral hepatitis **here**.

TABLE 23: Suggested TDF dose adjustment in patients with hepatitis B and renal dysfunction if TAF not available. Use TAF- preferentially if eGFR between 30 and 50 ml/min/1.73 m^2	
eGFR (mL/min/1.73 m^2)	**Suggested dose of TDF**
≥ 50	Usual dose
30–49	300 mg every 48 hours
10–29	300 mg every 72–96 hours
< 10	Avoid (consider 3TC monotherapy, or other drugs with anti-HBV activity)
Haemodialysis	300 mg every week (dose after dialysis, on dialysis days)

3TC, lamivudine; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate.

Common pitfall:

- **Not continuing with a combination of TDF (or TAF) + 3TC (or FTC) when switching to second-line ART.** The second-line ART regimen should be shaped around these two drugs.
- **Using 3TC without including TDF or TAF in the treatment of HIV/HBV co-infected patients.**
- **Not reviewing other causes of liver disease in patients with concomitant hepatitis B and counselling them about risks (e.g. alcoholic liver disease)**

MODULE 21

RENAL DISEASE

Antiretroviral drug dose adjustment in renal disease

Key points

- Renal function in chronic kidney disease is best estimated by the CKD EPI equations, rather than by the Cockroft-Gault or MDRD calculations.
- Renal function in AKI is defined by absolute creatinine level.
- For haemodialysis, the ART prescribed should be taken after dialysis.

In people with HIV (PWH) on chronic haemodialysis, there are a number of important ART considerations. The NRTI class is eliminated through the kidneys, thus most NRTIs require dose adjustment as per **Table 24.**

Note that there is good evidence that 3TC can be given without dose adjustment down to an eGFR of 30 ml/min/1.73m^2.[116] Below this, a dose 150mg can be given down to an eGFR of 15 ml/min/1.73m^2. For those with an eGFR <15 ml/min/1.73m^2, some experts still recommend that the lowest available tablet dose of 150 mg 3TC daily be used (including in patients on dialysis) so as to avoid having to use the liquid formulation of 3TC, and because of the favourable safety profile and lack of data to suggest 3TC dose-related toxicity. This is particularly relevant if the 3TC liquid formulation is unavailable or not tolerated.

If available, TAF is preferred as part of a coformulated regimen in cases where eGFR is >30 ml/min/1.73m^2. When used as a separate tablet, it can be given down to an eGFR of 15 ml/min/1.73m^2, and to patients on hemodialysis.

TABLE 24: Antiretroviral drug dose adjustments in chronic kidney disease‡

Drug	eGFR (ml/min/1.73m^2) §			Haemodialysis (dosage after dialysis)	Peritoneal dialysis
	30-50	15–30	< 15		
TDF	**Avoid**	**Avoid**	**Avoid**	300 mg once weekly	Unknown
TAF	Unchanged	Unchanged*	**Avoid**	Unchanged*	Unknown
ABC	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
3TC	Unchanged	150 mg daily	50 mg daily‡	50 mg first dose, thereafter 25 mg daily‡	50 mg first dose, thereafter 25 mg daily‡
AZT	Unchanged	Unchanged	300 mg daily	300 mg daily	300 mg daily
NNRTIs	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
PIs	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged
InSTIs	Unchanged	Unchanged	Unchanged	Unchanged	Unchanged

3TC, lamivudine; ABC, abacavir; ART, antiretroviral therapy; AZT, zidovudine; eGFR, estimated glomerular filtration rate; InSTIs, integrase strand transfer inhibitors; MDRD, modification of diet in renal disease; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; TDF, tenofovir disoproxil fumarate.

†, This table was developed and modified from: (i) Bartlett JG, Gallant JE, Pham PA (eds). Medical Management of HIV Infection. 2009-2010. 15th ed. Baltimore, MD: John Hopkins University Press, 556 pp;(ii) Gilbert DN, Moellering RC, Eliopoulos GM, et al. (eds). The Sanford Guide to Antimicrobial Therapy 2012. 42nd ed., 232 pp; and (iii) HIV Medicine Association of the Infectious Diseases Society of America. Clinical Practice Guideline for the Management of Chronic Kidney Disease in Patients Infected With HIV: 2014 Update. Clin Infect Dis 2014;59(9):e96-e138.
*, When coformulated with 3TC/FTC, a minimum eGFR of 30 ml/min/1.73m^2 is recommended instead (and the drug should not be used in patients on haemodialysis either) to avoid administering excess of the 3TC/FTC component.
‡, Some experts recommend that the lowest available tablet dose of 150 mg 3TC daily be used in patients with advanced renal disease (eGFR < 10 mL/min/1.73m^2) and patients on dialysis so as to avoid having to use the liquid formulation of 3TC, and because of the favourable safety profile and lack of data to suggest 3TC dose-related toxicity. This is particularly relevant if the 3TC liquid formulation is unavailable or not tolerated.
§, Most laboratories report the eGFR calculated using a variation of the MDRD formula. This result should be used (in place of a self-calculated CrCl) to make decisions regarding dose modification.

Antiretroviral drug choice and dosing in patients on chronic haemodialysis

Key points

- Patients with HIV may develop end-stage renal failure owing to HIV-associated nephropathy or an HIV-unrelated cause, necessitating chronic haemodialysis.
- TDF can be used in patients on chronic haemodialysis, but with once-weekly dosing which can be difficult for patients to remember.
- When administered as a separate tablet, TAF can be used without adjusting the dose in patients on chronic haemodialysis. However, when coformulated with 3TC/FTC, this is not recommended.
- AZT is generally avoided because of anaemia associated with renal failure.
- InSTIs and NNRTI drugs do not require dose adjustment.
- ATV concentrations are reduced in patients on haemodialysis to a greater degree than LPV concentrations.
- ART drugs taken once daily, or the evening doses of drugs taken twice daily, should be given after haemodialysis session on dialysis days, to prevent the drug from being dialysed out.
- Patients on chronic haemodialysis should be reviewed by an HIV-expert at least 6-monthly, to monitor treatment efficacy and side-effects and to adjust the regimen when needed.

We recommend the following first-line option for patients on chronic haemodialysis: ABC (600 mg daily) + 3TC (50 mg first dose and thereafter 25 mg daily) + DTG (50 mg daily). On the days when haemodialysis is performed, the drugs should be given after the haemodialysis session. Note also that some experts recommend giving the lowest available tablet dose of 3TC (i.e. 150 mg) in this scenario (see above).

Common pitfall: Not giving daily doses or the evening doses of a twice-daily regimen after the haemodialysis session on dialysis days, to prevent the drug from being dialysed out.

Antiretroviral therapy in patients with acute kidney injury

Key points

- In patients with acute kidney injury (AKI), NRTI dose adjustments should be implemented based on of the eGFR.
- TDF should be interrupted even if it is not thought to be the cause of the AKI.
- TAF coformulated with 3TC/FTC can be used in patients with renal dysfunction, provided eGFR > 30 ml/min/1.73m^2.
- Re-challenge with tenofovir (TDF or TAF) may be considered in patients 1-month post-resolution of AKI if tenofovir was not the cause and renal function returns to normal.
- In patients with AKI who are not yet receiving ART, initiation with an alternate regimen can be considered (avoiding TDF) or delayed by not more than 2 weeks if follow-up is assured.
- Once renal function is improving (creatinine on the downward trend), standard NRTI doses should be reintroduced to avoid under-dosing.

In patients with acute kidney injury (AKI), NRTI dose adjustments should be implemented (see **Table 24**). TDF should be interrupted even if it is not thought to be the cause of the AKI. Care should be taken to identify other drugs which may affect renal function (including supplements and traditional medicines), such as aminoglycoside antibiotics, nonsteroidal anti-inflammatory drugs, co-trimoxazole and iodinated radiocontrast; these drugs should be avoided where possible, including temporary discontinuation.

Once there is clear evidence that renal function is improving (creatinine is on a downward trend), standard NRTI doses should be reintroduced to avoid under-dosing. In patients with AKI who are not yet receiving ART, initiation can proceed with an alternate regimen (e.g. ABC/3TC/DTG) if there is reasonable assurance of patient follow-up. If ART initiation is delayed, it should not be delayed for more than 2 weeks, to avoid any increase in mortality. If renal function does not show any improvement after treating an acute event (e.g. sepsis) and this persists beyond 3 months, then the patient should be assessed for chronic kidney disease and referred to a physician who can evaluate and investigate further.

Common pitfalls:

- Not stopping TDF in AKI.
- Performing other NRTI dose adjustment in patients with AKI.
- Not restarting ART once the AKI episode has improved/resolved.

MODULE 22

MENTAL HEALTH

Key points

- Common mental disorders (CMDs), including depression, anxiety and substance use disorders are highly prevalent in people with HIV (PWH).
- CMDs are often undiagnosed or undertreated in HIV-positive individuals due to patient and staff stigma and low mental health literacy. Untreated CMDs may undermine adherence and contribute to loss to follow up.
- HIV clinicians should be familiar with tools used for screening of CMDs and be able to treat (using psychotropic medication or counselling) or refer appropriately.
- DTG may cause insomnia, headache and neuropsychiatric side-effects, including suicidality.
- Consider avoiding EFV- and RPV- based regimens in patients with a psychiatric illness as these drugs can exacerbate psychiatric symptoms and may be associated with suicidality.

Mental or psychiatric disorders (including severe mental illness and common mental disorders) are associated with lower or non-adherence to ART, leading to challenges in care engagement and poorer HIV treatment outcomes. There is a higher prevalence of depression in HIV-positive individuals, with a reported range of 20–40% vs. 10% in the general population.[117] Substance and alcohol use disorders are also highly prevalent, as is traumatic stress, often in the context of gender based violence.

Despite the high mental disorder prevalence and their impact on outcomes, a significant treatment gap remains with up to 75% of PLWH not receiving adequate diagnosis or treatment. Factors include stigma towards PLWH with a co-morbid mental disorder, and reluctance on the part of clinicians to engage with patients on what might be perceived to be time-consuming or specialised interviews.

The most prevalent conditions, including depression, the anxiety disorders and substance abuse can be readily diagnosed with semi-structured clinical interviews, or validated brief instruments, such as the PHQ-2 or PHQ-9, the GAD-7, the K-10, and the AUDIT (for alcohol use disorder).[118-121] All have been validated in South African HIV care settings and clinicians should familiarise themselves with these tools, and refer to local guidelines as required. Suicidality remains a common concern, and may require additional assessment.

DTG may cause insomnia, headache and neuropsychiatric side-effects. EFV frequently causes neuropsychiatric effects in the first few weeks of therapy, typically presenting with insomnia, vivid dreams and dizziness. Both dysphoria and euphoria may occur. The majority of patients who experience neuropsychiatric features of EFV do so within the first 2–6 weeks, and thereafter the drug is better tolerated. Late neurological syndromes, including ataxia, are however described (see **module 4**). Recent data suggest that EFV significantly impairs cognition compared to DTG.[122,123] Psychosis may occasionally occur.

Clinicians in primary care should be familiar with first-line anti-depressant prescribing, the details of which are beyond the scope of these guidelines. Fluoxetine is safe and effective, as is citalopram. Basic counselling including problem-solving approaches and motivational interviewing are increasingly being taught to counsellors and nurses in HIV care. Referral to registered counsellors and psychologists can be used when first-line care fails.

Common pitfalls:

- Not screening for common mental health conditions such as depression and anxiety in patients initiating ART.
- Unnecessarily delaying ART initiation while providing first line mental health care in patients with psychiatric disorders.
- Not warning patients starting ART about potential neuropsychiatric symptoms. Patients must be informed about potential side-effects.

MODULE 23

MALARIA

Key points

- There are several drug interactions between antimalarial agents and ART drugs.
- No artemether-lumefantrine dose adjustment is recommended for patients taking PIs or InSTIs.
- EFV has a significant drug interaction with artemether-lumefantrine (Coartem) such that artemether (and its active metabolite) and lumefantrine concentrations are lowered, which can lead to failure of antimalarial therapy. Consider extending the course of artemether-lumefantrine to 6 days if administered concurrently with EFV.
- PIs and NNRTIs exhibit several interactions with atovaquone-proguanil (Malanil) such that atovaquone concentrations are reduced – atovaquone-proguanil is best avoided in patients receiving these drugs.
- There are no significant drug interactions between InSTIs (DTG) and antimalarial drugs.
- Quinine is best avoided in patients on PIs or NNRTIs.

No significant drug interactions are predicted between InSTIs and antimalarial drugs.

However, there are several drug interactions between antimalarials and other ART classes (see **Table 25**). EFV significantly lowers the concentrations of artemether (and its active metabolite) and lumefantrine (the two components of Coartem), which is likely to increase the risk of failure of antimalarial therapy. There is no clear guidance on how to overcome this interaction, but some experts recommend repeating the 3-day course of artemether-lumefantrine (i.e. treat for 6 days). Boosted PIs dramatically increase the plasma concentrations of lumefantrine, but a dose reduction is not recommended, as the toxicity threshold of lumefantrine seems to be high. Close monitoring for toxicity is recommended when co-administering artemether-lumefantrine with ART.

Among drugs used for malaria chemoprophylaxis, there are no clinically significant pharmacokinetic interactions between ARVs and mefloquine or doxycycline. However, mefloquine and EFV both cause frequent neuropsychiatric side-effects; therefore, doxycycline is the preferred chemoprophylactic agent for patients receiving EFV. There are several interactions with atovaquone-proguanil (Malanil) however. Atovaquone concentrations are reduced by PIs and EFV, and also likely by NVP. Proguanil concentrations are also reduced by PIs and EFV. Use of atovaquone-proguanil is therefore best avoided in patients receiving PIs or NNRTIs.

TABLE 25. Important drug-drug interactions between antimalarial agents and antiretroviral drugs.

Drug	Antimalarial agent	Direction of interaction	Recommendation
InSTI	Artemether-lumefantrine	No interaction	Safe to co-administer
	Atovaquone-proguanil	No interaction	Safe to co-administer
EFV	Artemether-lumefantrine	↓ artemether and lumefantrine concentrations	Use but consider repeating the 3-day course of artemether-lumefantrine
	Atovaquone-proguanil	↓ atovaquone and proguanil concentrations	Avoid co-administration
PI/r	Artemether-lumefantrine	↑ lumefantrine concentrations	No dose adjustment necessary
	Atovaquone-proguanil	↓ atovaquone and proguanil concentrations	Avoid co-administration

ART, antiretroviral therapy; EFV, efavirenz; InSTI, integrase strand transfer inhibitor; NVP, nevirapine; PI/r, ritonavir-boosted protease inhibitor.

Common pitfalls:

- Not advising patients receiving ART on chemoprophylaxis for malaria when travelling to malaria-endemic areas.
- Not including malaria in the differential diagnoses in PLHIV presenting with an acute illness.
- Not providing ART recipients with intravenous artesunate or artemether-lumefantrine for malaria treatment despite the potential drug interactions.

MODULE 24

ANTIRETROVIRAL DRUG-INDUCED LIVER INJURY

Key points

- All ART classes have been associated with hepatotoxicity and cause injury through an idiosyncratic reaction as the mechanism of injury.
- Alanine transaminase (ALT) elevations > 5x the upper limit of normal (ULN) are significant in the absence of symptoms.
- In the presence of symptoms of hepatitis, ALT elevations > 2.5x ULN are significant.
- Patients on EFV may present with a delayed DILI many months after commencing therapy.
- Re-challenge is best avoided. It may only be considered in select cases in consultation with a specialist.
- If severe hepatitis occurs, or any hepatitis together with a rash, fever or systemic reaction, then re-challenge with NNRTIs, ABC or co-trimoxazole (CTX) should not be attempted.
- Atazanavir can cause jaundice through indirect hyperbilirubinemia. This is not a symptom of DILI and ATV only needs to be discontinued if the appearance of jaundice is bothersome.

An ALT test should be performed in all patients at ART initiation. Repeat ALT testing is indicated in those who develop symptoms or signs suggestive of hepatitis. All ARV classes have been associated with hepatotoxicity – most commonly NNRTIs. Mild ALT elevations occur commonly and in general are transient. ALT elevations > 5X the upper limit of normal (ULN) are significant in the absence of symptoms. In the presence of symptoms of hepatitis, ALT elevations > 2.5X ULN are also significant. In such patients, potentially hepatotoxic ARVs should be switched to alternative agents. Management guidelines are provided in **Table 26.**

Re-challenge is best avoided. It may only be considered in select cases in consultation with a specialist. If hepatitis requiring hospitalisation occurs, or any hepatitis with rash, fever, or other systemic manifestation, a specialist opinion should be sought. In this situation re-challenge with NNRTIs, ABC or CTX should not be attempted.

In patients with severe hepatitis or jaundice, features of hepatic encephalopathy (i.e. features of hepatic failure) must be clinically assessed and the international normalised ratio (INR) and serum glucose checked.

Mild elevation of canalicular enzymes is common in PLHIV and does not represent DILI. If there is a sustained significant canalicular enzymes, the concentration of canalicular enzymes is more significantly elevated than that of ALT, or if conjugated bilirubin is elevated, then an ultrasound of the liver should be considered to exclude biliary obstruction.

ATV is associated with isolated unconjugated hyperbilirubinaemia (drug-induced Gilbert's syndrome). In these patients, all other liver function tests (LFTs) are normal, and there are no other symptoms of hepatitis. Although this is a benign condition (it does not reflect liver injury, but isolated competitive inhibition of the enzyme in the liver which conjugates bilirubin), it is often cosmetically unacceptable to patients, necessitating a switch from ATV to an alternate drug.

While EFV has been recognised as an infrequent cause of DILI, a novel pattern has been recognised.[42] Among such patients, many had a particularly severe pattern of liver injury at liver biopsy (termed 'submassive necrosis', and associated with severe jaundice and a raised INR). The overall mortality was 11%. While EFV-related DILI is likely to be uncommon, clinicians should be aware of its particular features:

- It usually occurs 3–6 months after starting EFV (e.g. longer than expected with TB medication or NVP).
- There are no associated features of hypersensitivity (e.g. drug rash) and jaundice is often the first symptom rather than abdominal symptoms.
- LFTs normalise several months after stopping EFV (median resolution > 6 months).

We do not advise routine LFT monitoring in patients on ART, as there is no evidence that this would result in earlier detection of DILI or improve outcomes. Instead, patients who develop symptoms and signs of hepatitis (nausea, vomiting, right-sided abdominal pain, jaundice) should have LFTs done and managed accordingly.

Many other drugs can cause hepatotoxicity, notably anti-tuberculous agents (including prophylactic isoniazid) and azoles. CTX is an uncommon cause of hepatitis, often as part of a systemic hypersensitivity reaction. In addition to medications, patients may be taking herbal supplements, alcohol or other substances, which can cause, or exacerbate, liver disease.

Recommendations for the management of DILI in patients receiving TB treatment have been published by the Southern African HIV Clinicians Society in 2013 (see **here**) and will be updated in 2023/24.[124] If there are concerns about management of TB treatment in the setting of DILI a specialist opinion should be sought.

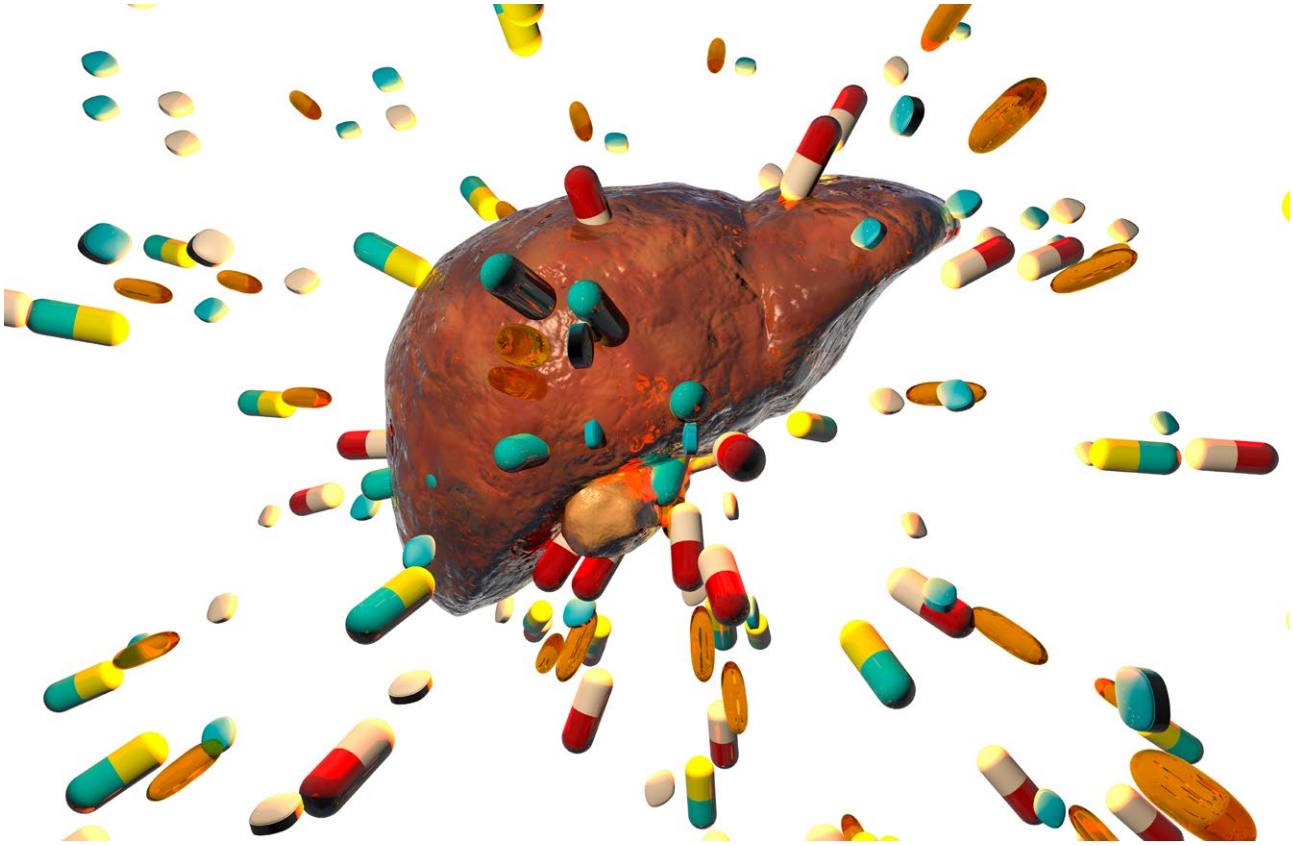
TABLE 26: Guidelines for managing hepatotoxicity.

Elevation	ULN†		
	< 2.5 × ULN	2.5–5 × ULN	> 5 × ULN
ALT	Repeat at 1–2 weeks	Repeat at 1 week	Discontinue relevant drug(s)
Bilirubin	Repeat at 1 week	Discontinue relevant drug(s)	Discontinue relevant drug(s)

ALT, alanine transaminase; ULN, upper limit of normal.
†, Any elevations with symptoms or signs of hepatitis (nausea, vomiting, right upper quadrant pain, jaundice) should be regarded as an indication to discontinue the relevant drugs.

Common pitfalls:

- **Failing to recognise other drugs, herbal supplements and alcohol as a potential cause of hepatotoxicity in patients taking ART and other hepatotoxic drugs.**
- **Performing routine LFT monitoring in patients on ART, in an attempt to detect DILI earlier.** There is no evidence to support this approach.



MODULE 25

DYSLIPIDAEMIA

Key points

- DTG does not significantly affect cholesterol.
- Routine monitoring of lipids is not required unless the patient is on a PI regimen.
- PIs can cause hypertriglyceridaemia and elevated low-density lipoprotein (LDL) cholesterol. Lipids should be assessed routinely after 3 months on a PI regimen.
- ATV/r and DRV/r are associated with less significant lipid abnormalities than LPV/r.
- EFV can cause elevated total cholesterol and mild hypertriglyceridaemia.

PIs can cause hypertriglyceridaemia and elevated LDL cholesterol. ATV/r and once-daily DRV/r (800 mg DRV/100 mg once daily) are associated with less severe dyslipidaemia than other boosted PIs; AZT can cause mild hypertriglyceridaemia, and EFV can cause elevated total cholesterol and mild hypertriglyceridaemia. We suggest that total cholesterol and triglycerides should be assessed routinely after 3 months on a PI regimen (see **module 15**). If normal at this stage, then reassessment should be performed only in those with cardiovascular risk factors. Diet and lifestyle modification should always be advised. Diet is more effective for controlling hypertriglyceridaemia than hypercholesterolaemia. Other cardiovascular risk factors should be addressed. Clinicians should consider and investigate secondary causes of hypertriglyceridaemia and hypercholesterolaemia (e.g. diabetes, nephrotic syndrome, alcohol use and hypothyroidism).

If patients receiving LPV/r develop significant dyslipidaemia but still require a PI, they should be switched to DRV/r or ATV/r, rather than adding lipid-lowering therapy. However, lipid-lowering therapy is indicated in patients with persistent elevations despite switching to DRV/r or ATV/r. Note though that many patients on a PI should be switched to DTG as described in **module 13**. DTG has a more favourable lipid profile than PIs.

Marked hypertriglyceridaemia (> 10 mmol/L) can cause pancreatitis and requires urgent treatment with diet modification (restrict total triglyceride intake to < 30 g/day), fibrates and switching LPV/r to DRV/r, ATV/r or DTG (fibrates can be stopped after 1 month, followed by reassessment within 4–6 weeks).

Indications for statin therapy in HIV-positive patients should be the same as in HIV-negative patients, using the Framingham heart disease risk score. Generally, in young patients with isolated elevated cholesterol but no other cardiovascular risk factors, a threshold of total cholesterol > 7.5 mmol/L (or LDL cholesterol > 5.0 mmol/L) should be used for initiating statin therapy; and, if feasible, the patient should be referred to a lipid clinic for investigation. In patients with cardiovascular risk factors (e.g. smoking, diabetes, hypertension), decisions should be made using the **Framingham heart disease risk score**. All patients with established atherosclerotic disease (coronary, cerebral or peripheral) or familial hypercholesterolaemia should be started on statin treatment. In addition, type 2 diabetics should also be started on a statin if they have chronic kidney disease, or if they are older than 40 years of age (or have had diabetes for more than 10 years) and have one or more additional cardiovascular risk factors.[125]

Many statins have interactions with PIs that can lead to potentially toxic statin concentrations, with the exception of pravastatin and fluvastatin. Atorvastatin concentrations are significantly raised by PIs, but low doses (maximum 20 mg daily) can be used with monitoring for symptoms of myalgia. Lovastatin and simvastatin should not be co-administered with PIs, as their concentrations are dramatically increased, and severe rhabdomyolysis has been reported. We also advise against the use of rosuvastatin with PIs due to a complex drug-drug interaction: PIs increase the plasma concentrations of rosuvastatin while reducing their efficacy in the liver. If in doubt, consult a reliable resource for information on drug-drug interactions (see **Box 3**).

Common pitfalls:

- **Not routinely assessing lipids while the patient is receiving PI-based ART.**
- **Failure to recognise that many statins have interactions with PIs that lead to toxic statin concentrations.**
- **Monitoring of LDL cholesterol in patients on a high-dose statin for secondary prevention.** Such monitoring is not necessary.

MODULE 26

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Key points

- Approximately 10–20% of patients who start ART with advanced immunosuppression experience immune reconstitution inflammatory syndrome (IRIS) in the first few months of treatment.
- Two forms of IRIS have been recognised, namely unmasking and paradoxical IRIS.
- IRIS is most frequently described in association with tuberculosis (TB) and cryptococcal meningitis (CM).
- InSTIs are not associated with an increased risk for TB-IRIS in clinical trials.
- Early ART initiation (defined as 1–4 weeks after anti-tuberculous therapy) doubles the risk of TB-IRIS compared with late ART initiation (defined as 8–12 weeks after anti-tuberculous therapy), but ART should not be delayed for this reason.
- There is no confirmatory diagnostic test for IRIS.
- In most instances, ART is continued in cases of IRIS, unless IRIS is life-threatening (e.g. neurological involvement in TB-IRIS with new focal findings or depressed level of consciousness).
- Corticosteroids have been shown to reduce morbidity and improve symptoms in paradoxical TB-IRIS.

Approximately 10–20% of patients who start ART with advanced immunosuppression experience clinical deterioration during the first few months due to IRIS.[126] Most presentations of IRIS occur within the first 3 months of ART. Two forms are recognised:

- **Unmasking IRIS** occurs in patients who have an unrecognised opportunistic infection (OI) when ART is initiated, and who then present with exaggerated inflammatory features of that infection during early ART due to it being 'unmasked' by recovering immunity.
- **Paradoxical IRIS** occurs in patients who are being treated for an OI when they start ART, but who develop an immune-mediated worsening or recurrence of features of that infection after starting ART.

IRIS is most frequently described in association with TB and CM. Skin conditions such as molluscum contagiosum and Kaposi's sarcoma may also worsen due to IRIS. The diagnosis of IRIS can be difficult, mainly because there is no confirmatory diagnostic test. Diagnosis relies on recognition of the characteristic clinical presentation, ensuring that OIs are correctly diagnosed, and excluding alternative causes for deterioration, such as drug resistance (e.g. multidrug-resistant TB). Case definitions for TB and cryptococcal IRIS have been published.[127,128] It is important to ensure that the underlying OI is treated appropriately. ART should be continued unless the IRIS is life-threatening (e.g. neurological involvement in TB-IRIS with depressed level of consciousness). Corticosteroids have been shown to reduce morbidity and improve symptoms in paradoxical TB-IRIS,[129] and can be used in mycobacterial and fungal forms of IRIS when other causes of deterioration have been excluded, and particularly when IRIS features are severe.

For paradoxical TB-IRIS, prednisone can be commenced at a dose of 1.5 mg/kg/day and weaned over 4 weeks, but a longer course may be required if symptoms recur on weaning.[130] Steroids should not be used in patients with Kaposi's sarcoma, as administration may be associated with worsening of disease and increased risk of mortality.

Common pitfalls:

- **Using steroids in patients with Kaposi's sarcoma, herpes infections and active hepatitis B.**
- **Not counselling patients with advanced HIV disease about the potential for IRIS when initiating ART.**

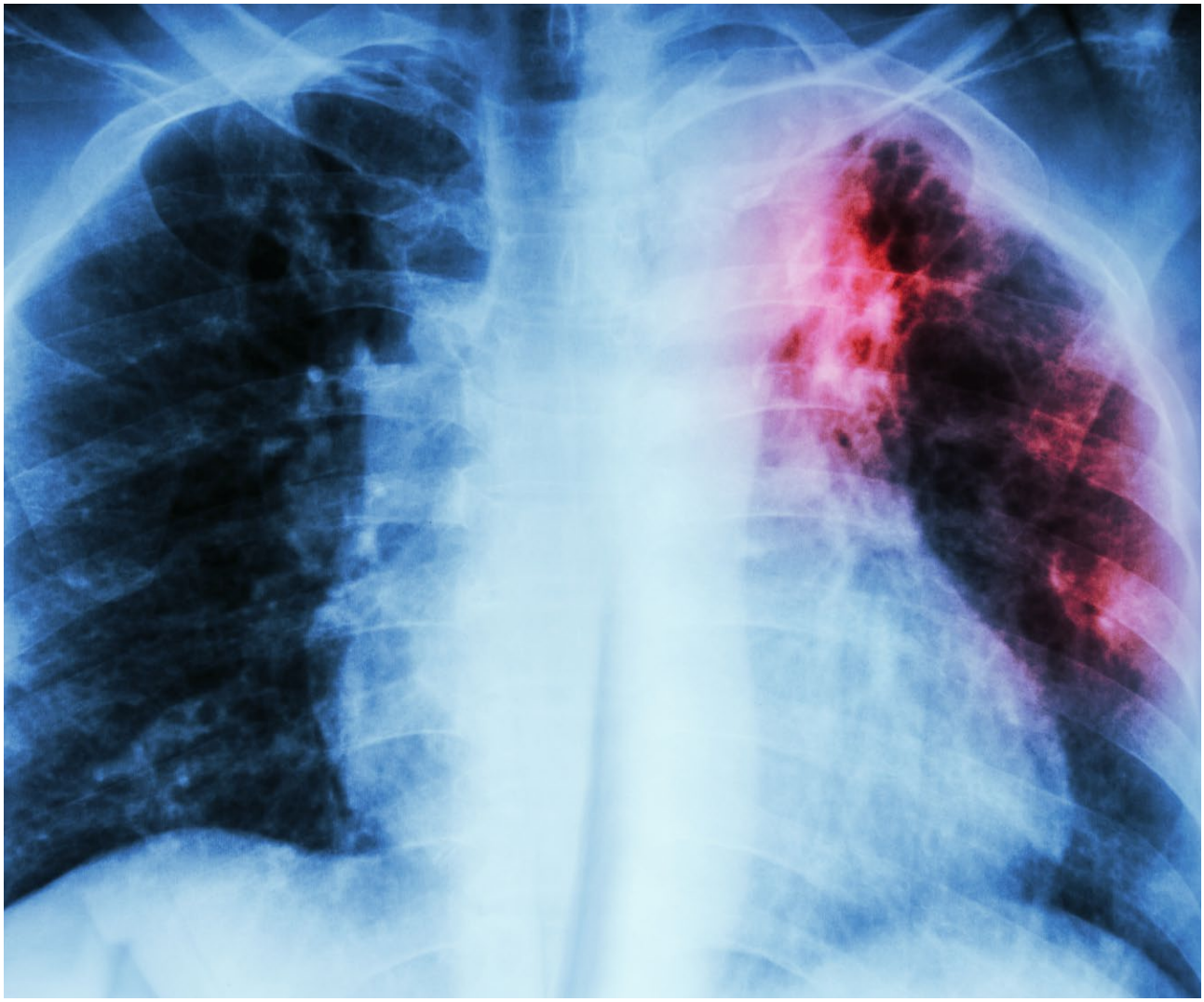
Prophylactic prednisone

Key points

- Patients with active TB and who are improving on TB therapy with a CD4+ count ≤ 100 cells/µl, upon starting ART can be initiated on prednisone 40 mg daily for 14 days followed by 20 mg daily for 14 days to prevent paradoxical TB-IRIS.
- The use of prednisone in this context is not associated with excess risk of severe infections, cancers or adverse events.

The use of prophylactic prednisone for the prevention of paradoxical TB-associated IRIS in adults with a CD4+ count ≤ 100 cells/µl has been shown in a randomised trial to be associated with a 30% lower relative incidence of TB-IRIS.[131] Importantly, this did not cause an excess risk of severe infections or cancers. The recommended prednisone regimen is 40 mg daily for 14 days, followed by 20 mg daily for 14 days, and the prednisone should be started concurrently with ART. However, certain patient groups should be excluded from receiving prednisone, including patients with Kaposi's sarcoma and patients with RIF-resistant TB, or whose TB has not improved prior to starting ART.

Common pitfall: Using prophylactic prednisone in patients who are not improving on TB therapy. Refer these patients to an HIV-expert for a full assessment and management.



MODULE 27

PROPHYLAXIS FOR TB AND CRYPTOCOCCAL MENINGITIS

Key points

- The use of appropriate prophylaxis (primary or secondary) is an essential part of HIV care.
- The three most essential forms of prophylaxis and pre-emptive treatment to consider are cotrimoxazole prophylaxis, TB preventative treatment, and pre-emptive cryptococcal treatment for patients with a positive serum cryptococcal antigen (if cryptococcal meningitis has been ruled out).
- Local and international guidelines should be consulted for both asymptomatic and symptomatic patients.

Cotrimoxazole primary prophylaxis

Prophylactic cotrimoxazole (CTX) is indicated for HIV-positive patients with a CD4+ count < 200 cells/μL, or with WHO stage 3 or 4 conditions (including TB). CTX offers protection against Pneumocystis jirovecii, toxoplasmosis, isosporiasis and certain bacterial infections. The recommended dose is 160/800 mg daily. Patients who develop a hypersensitivity reaction to CTX can be given dapsone instead, although this is best avoided if the reaction to CTX was life-threatening. CTX can be discontinued once the patient's CD4+ count is > 200 cells/μL.

CTX is a common cause of cutaneous and systemic hypersensitivity reactions, indistinguishable from hypersensitivity reactions to ART drugs. CTX should be interrupted when treating mild suspected NNRTI cutaneous hypersensitivity rashes, and permanently discontinued if severe hypersensitivity reactions occur. If CTX is prescribed for secondary prophylaxis or used for primary prophylaxis in those with severe immunosuppression, then an alternative should be substituted.

Common pitfall: Prescribing CTX for newly diagnosed HIV-positive patients with a CD4+ count > 200 cells/μL.

Cryptococcal antigen screening and pre-emptive treatment

Key points

- Cryptococcal antigen (CrAg) screening should be done for all patients with a CD4+ count <200 cells/μL who are initiating or re-initiating ART.
- Reflex laboratory screening is the preferred approach in South Africa.
- Lumbar puncture (LP) is recommended for all patients with a new positive CrAg screening test.

Screening for subclinical cryptococcal disease has been shown to have a benefit in reducing mortality in HIV-positive patients with a CD4+ count < 200 cells/μL. It is recommended that HIV-positive adults and adolescents (≥ 10 years) with a CD4+ count < 200 cells/μL be screened for cryptococcal antigenaemia (CrAg) on serum or plasma by reflex laboratory testing (preferred) or clinician-initiated testing. If clinician-initiated testing is performed, then it is recommended that screening should be restricted to patients without prior cryptococcal disease who are initiating or re-initiating ART. For patients with a new positive CrAg result and a LP that excludes the diagnosis of CM, oral fluconazole alone as induction therapy should be given (1200 mg daily for 2 weeks). In these patients with a negative CSF CrAg result, ART can be started immediately with fluconazole. Patients diagnosed with CM should be managed as per the latest **Southern African HIV Clinicians' Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update.**

Common pitfall: Not performing an LP in all patients who are newly diagnosed as CrAg positive. The absence of any symptoms of meningitis does not exclude CM; approximately one in three patients with asymptomatic antigenaemia have concurrent CM.

Tuberculosis preventive therapy (TPT)

Key points

- Tuberculosis preventive therapy (TPT) should be started at ART initiation or added to the treatment regimen of patients already on ART who have not yet received TPT, once active TB disease has been excluded.
- There is no need to test for latent TB prior to commencing TPT.
- TPT can be administered in the form of 12 months of isoniazid ("12H"), 3 months of weekly isoniazid and rifapentine ("3HP"), or 1 month of daily isoniazid and rifapentine ("1HP"), all given with pyridoxine for the duration of the TPT. These three options appear equally efficacious, but the shorter regimens are associated with a slightly lower incidence of hepatotoxicity than 12H.
- TPT is recommended for pregnant women, but as 3HP and 1HP have not been adequately studied in pregnancy, pregnant women should take 12H instead.

Clinical trials have shown that tuberculosis preventive therapy (TPT) has an additive effect with ART in preventing incident TB in patients with HIV.[132,133] In a South African trial, there was a 37% reduction in incident TB when patients receiving ART were prescribed IPT (vs. placebo) for 12 months.[132] This benefit applied irrespective of tuberculin skin test (TST) status, and the trial included patients established on ART.

Newer alternative but more costly regimens for TPT consist of the combination of rifapentine and isoniazid. These have the benefit that they can be administered for much shorter durations. 3HP and 1HP are shorter duration regimens for TPT that contain rifapentine in addition to isoniazid. 3HP is given for 3 months in weekly doses (12 doses) and 1HP is given for 1 month in daily dosing. Both 3HP[134] and 1HP[135] are non-inferior to IPT in terms of preventing TB, and the shorter regimens may provide a benefit in terms of treatment completion and hepatotoxicity. Rifapentine, just like rifampicin is a potent liver enzyme inducer and therefore concomitant use can result in drug-drug interactions. A pharmacokinetic study of the effect of rifapentine on dolutegravir did not justify the need for dose-adjustment when using it weekly in patients who were suppressed at the time of the start of dolutegravir start.[136]

The ACTG A5372 trial showed that DTG needs to be given twice daily for 28 days if co-administered with rifapentine.[137] Rifapentine also affects the metabolism of common ARV drugs most affected by CYP induction such as all protease inhibitors (PIs) including LPV/r, and some non-nucleoside reverse transcriptase inhibitors (NNRTIs), including nevirapine.[138]

All patients receiving ART should be considered for TPT after having been screened for active TB using a symptom screen, urine LAM, sputum GXP and/or chest X-ray where appropriate (see **2023 National Guidelines** for more information).[139] In patients receiving TPT, monitoring for neuropathy and hepatitis symptoms should be performed. Routine ALT monitoring is not indicated, but ALT should be tested if hepatitis symptoms occur. Patients receiving a long course of isoniazid should receive pyridoxine (vitamin B6) concurrently.

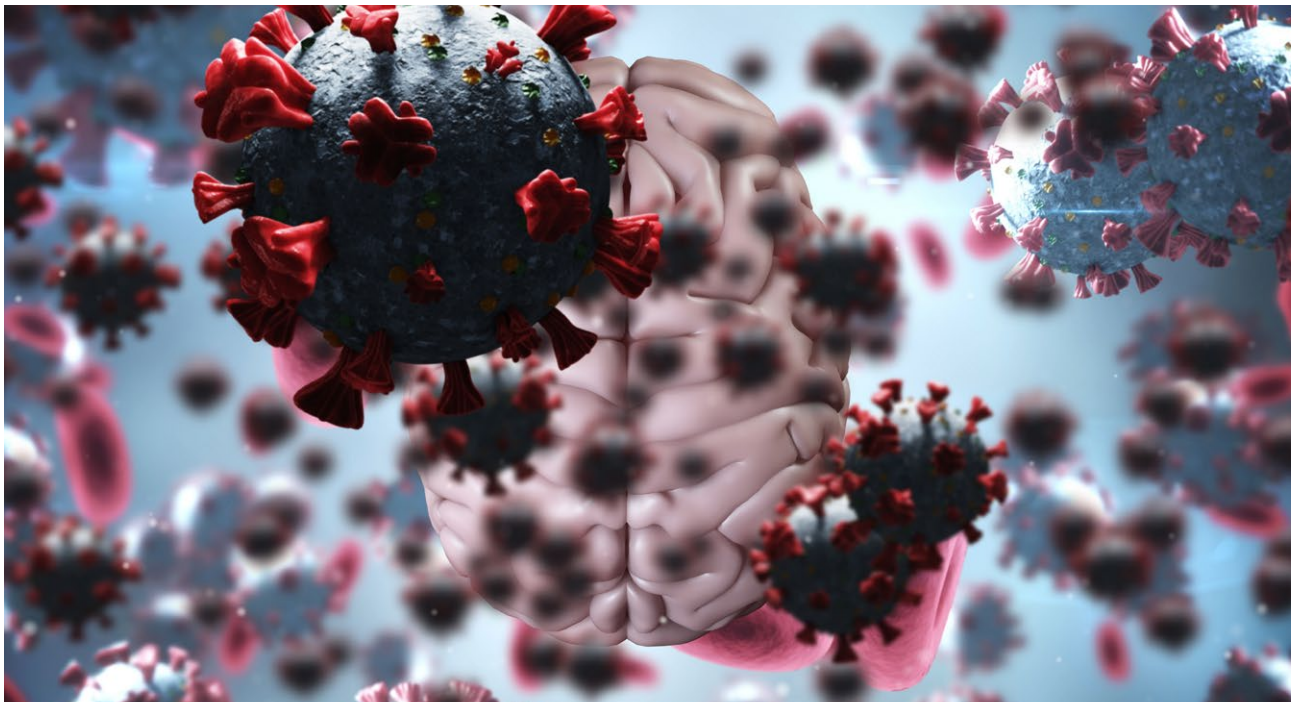
There is conflicting data as to the safety of isoniazid prophylaxis in pregnancy. A trial of IPT in pregnant women receiving ART, the TB APPRISE study, showed that IPT resulted in worse pregnancy outcomes.[140]

However, this was not confirmed in a larger observational studies, including one from the Western Cape, which showed that IPT use was associated with better pregnancy outcomes, and that incident TB was reduced in women on IPT who had CD4 counts <350 cells/l.[141] Current WHO and South African National Department of Health guidelines recommend 12H for pregnant women living with HIV, regardless of CD4 count. Studies are underway to determine the safety of rifapentine in pregnancy, with preliminary data showing no need for dose adjustment in pregnancy.[142] In the interim, use of rifapentine is not recommended in pregnancy, and thus 12H is the only regimen recommended for pregnant women.

The 2023 South African national guidelines for the treatment of TB infection in people living with HIV are summarised in **Table 27**. The full guideline should be consulted for further guidance (see **here**).

TABLE 27: Recommended regimens for people living with HIV

Scenario	Recommended regimen for adults >50kg
Initiating DTG-based ART	12H: isoniazid 300mg daily for 12 months
On DTG-based ART but viral load not suppressed	12H: isoniazid 300mg daily for 12 months
On ART (any regimen) and virally suppressed	3HP: rifapentine 900mg weekly + isoniazid 900mg weekly for 12 weeks
Pregnant women	12H: isoniazid 300mg daily for 12 months



MODULE 28

ADHERENCE

Patient readiness for antiretroviral therapy

Key points

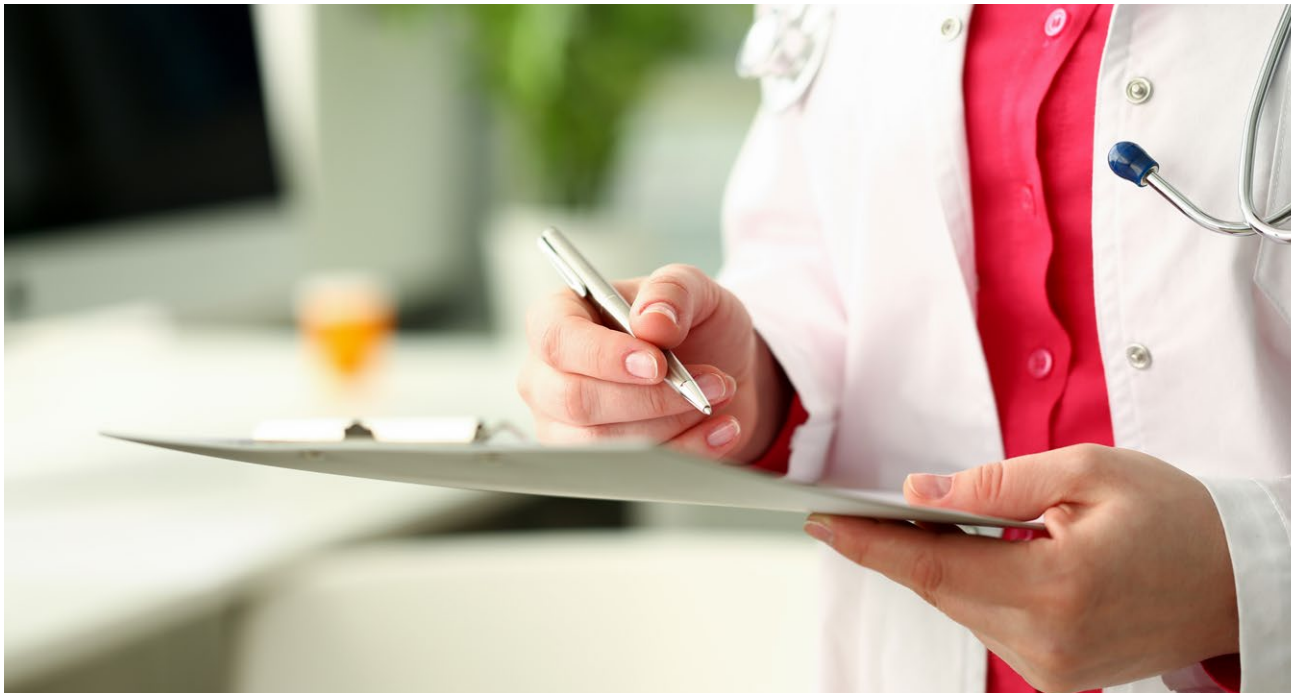
- Each patient commencing ART needs to be prepared for taking lifelong ART.
- Barriers to adherence (e.g. depression, alcohol use, non-disclosure or food security) and any misconceptions about HIV and ART must be identified.
- Patients must be educated about the importance of viral load suppression.
- Longer term adherence and avoiding treatment fatigue can be encouraged through patient-centred care, multi-month dispensing and counselling about Undetectable = Untransmittable (U=U).

Preparing patients for lifelong ART with good adherence is a critical component of achieving long-term efficacy, preventing treatment resistance and reducing transmission. Previously two or three counselling visits, staggered close together, were required before ART could be initiated. However, it is now considered acceptable to perform some of the counselling during early ART rather than delaying same-day initiation (as described in **module 6**). Counselling about U=U is an important part of adherence counselling and should be emphasised.

Delays in commencing ART should be avoided. In addition, to aid prompt ART initiation, there is a move towards Provider-Initiated Counselling and Testing (PICT) rather than the patient needing to wait for a counselling appointment. During PICT, the provider doing the HIV test also provides the necessary counselling prior to testing.

Common pitfalls:

- **Delaying ART because the patient has not completed 2-3 counselling visits or not disclosed their HIV status.** Patients can be initiated on ART on the same day as diagnosis or soon thereafter, with additional counselling performed during early ART.



Support and counselling

Key points

- Success of ART hinges on how well the tablets are taken; at least 90%, preferably more, of treatment doses need to be taken.
- Support should be provided to ensure high levels of treatment adherence.
- None of the commonly used first- and second-line ART regimens have meaningful food restrictions.
- Delayed dosing is rarely a problem; even if out by many hours, most of the drugs have long half-lives, and patients should be encouraged and supported to take their dose once they remember to do so in these instances.
- Disclosure is not a prerequisite for ART.
- Heavy alcohol use may affect adherence and may potentiate ART hepatotoxicity and other hepatic pathology; however, responsible alcohol use is not prohibited in patients established on or starting ART.
- A non-judgmental approach which is supportive and patient-centred is essential to address chronic adherence issues.

During counselling, patients should be provided with the following information:

- The benefits of ART
- That ART is life-long therapy
- The importance of good adherence
- Side-effects relevant to their ART regimen, including what to do and who to contact if serious side-effects occur
- The importance of viral load monitoring on ART and viral load suppression
- A roadmap of follow-up visits and what to expect at each visit
- The benefits of treatment as prevention to reduce transmission (e.g. VTP and U=U)

The patient should be informed about the benefits of ART and that side-effects are usually minor and transient, or manageable. The patient should be given a treatment plan, specifying the drugs to be used (with names and details including the appearance of each drug, when and how they are to be taken, and a brief indication of anticipated side-effects and toxicity).

Counselling should also ensure the patient has a good understanding of HIV (the virus, the potential clinical complications and transmission), and should cover safer-sex practices and address issues related to reproductive health (i.e. family planning, contraception, condom use and pregnancy). Clinicians should check family-planning choices at follow-up visits and ensure adequate access to safe and effective contraception. It is important to discuss U=U and ensure that the patient understands the concept and that ART will only prevent onward transmission if there is optimal adherence with VL suppression.

Common mental disorders and substance use should be screened for actively and managed promptly (see **module 22**). A personal treatment plan should be formulated for each patient, specifying medication storage, strategies for missed doses and how to integrate taking medication into their daily routine. The patient must be made aware and be reminded of their follow-up visits and the importance of these.
Disclosure of HIV status (to a partner, trusted friend and family/household members) should strongly be encouraged as it is an important determinant of treatment adherence and assists in the provision of patient-directed support. Disclosure may also identify opportunities for HIV screening and support. Ensure sensitivity in situations where disclosure may have harmful consequences, particularly for women (e.g. intimate partner violence). However, when disclosure is not possible, insisting on it may cause the patient to disengage. In this case, the patient should be encouraged to join a support group and/or identify a treatment 'buddy'. Clinicians should ensure that they have the correct contact details of their patient as well as the contact details of a person who has been disclosed to/their treatment buddy.

Neither disclosure nor support group participation are prerequisites for good adherence, and they should not be a reason for deferring ART.

The causes of poor adherence are often complex and linked to social issues. Common causes are outlined in **Table 28**.

TABLE 28: Possible reasons for poor adherence.		
Individual	**Provider**	**Medication**
• Depression • Alcohol or substance use • Non-disclosure • Inadequate treatment literacy • Adolescence • Recent pregnancy • Food security • Work-related issues (e.g. shift work) • Social problems (stigma and poor social support networks)	• Stock-outs • Inaccessible clinics (both in place and time) • Poor communication (not patient-centred) • Stigma • Too frequent/inaccessible clinic visits	• High pill burden • Frequent dosing (> once per day) • Adverse effects • Cost (for cash-paying patients)

Common pitfall:

- **Not informing patients of the benefits of ART.** This includes not only reduced mortality and morbidity, but also prevention of HIV transmission.
- **Not informing patients that side-effects are usually minor and transient, or manageable.**
- **Not advising patients on how to deal with delayed dosing.**
- **Not providing patients with a treatment plan specifying the drugs to be used.**
- **Not considering ongoing costs of monitoring and treatment in patients in private/cash paying patients.** This includes those with annual medical aid benefits that may run out. These patients should be effectively and timeously transferred to a public facility to avoid possible treatment interruption.

REFERENCES

1. Maartens G. 'Covering the tail'after stopping efavirenz-based antiretroviral therapy. *Southern African Journal of HIV Medicine.* 2020;21(1):1-2.
2. Majluf Cruz A, Luna Castaños G, Treviño Pérez S, Santoscoy M, Nieto Cisneros L. Lamivudine induced pure red cell aplasia. *American journal of hematology.* 2000;65(3):189-191.
3. Cohen K, Viljoen C, Njuguna C, Maartens G. Emtricitabine-associated red cell aplasia. *AIDS*. 2019;33(6):1095-1096.
4. Paton NI, Musaazi J, Kityo C, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. *Lancet HIV*. Apr 20 2022.
5. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat.* 2011;2011:354908.
6. Venter WDF, Fabian J, Feldman C. An overview of tenofovir and renal disease for the HIV-treating clinician. *South Afr J HIV Med.* 2018;19(1):817.
7. Pilkington V, Hughes SL, Pepperrell T, et al. Tenofovir alafenamide vs. tenofovir disoproxil fumarate: an updated meta-analysis of 14894 patients across 14 trials. *Aids*. Dec 1 2020;34(15):2259-2268.
8. Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet.* Jun 27 2015;385(9987):2606-2615.
9. Mallon PW, Brunet L, Hsu RK, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. *J Int AIDS Soc.* Apr 2021;24(4):e25702.
10. Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. L*ancet HIV.* Oct 2020;7(10):e666-e676.
11. Schafer JJ, Sassa KN, O'Connor JR, Shimada A, Keith SW, DeSimone JA. Changes in Body Mass Index and Atherosclerotic Disease Risk Score After Switching From Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide. *Open Forum Infect Dis.* Oct 2019;6(10):ofz414.
12. Cerrone M, Alfarisi O, Neary M, et al. Rifampicin effect on intracellular and plasma pharmacokinetics of tenofovir alafenamide. *Journal of Antimicrobial Chemotherapy*. 2019;74(6):1670-1678.
13. Cruciani M, Mengoli C, Malena M, et al. Virological efficacy of abacavir: systematic review and meta-analysis. *J Antimicrob Chemother*. Dec 2014;69(12):3169-3180.
14. D. A. D. Study Group, Sabin CA, Worm SW, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet*. Apr 26 2008;371(9622):1417-1426.
15. Ribaudo HJ, Benson CA, Zheng Y, et al. No risk of myocardial infarction associated with initial antiretroviral treatment containing abacavir: short and long-term results from ACTG A5001/ALLRT. *Clin Infect Dis*. Apr 1 2011;52(7):929-940.
16. Dean L. Abacavir therapy and HLA-B* 57: 01 genotype. 2018.
17. Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir versus twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. Nov 2013;13(11):927-935.
18. You J, Wang H, Huang X, et al. Therapy-Emergent Drug Resistance to Integrase Strand Transfer Inhibitors in HIV-1 Patients: A Subgroup Meta-Analysis of Clinical Trials. *PLoS One*. 2016;11(8):e0160087.
19. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. Nov 7 2013;369(19):1807-1818.
20. Molina JM, Clotet B, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir for treatment-naive adults with HIV-1 infection (FLAMINGO): 96 week results from a randomised, open-label, phase 3b study. *Lancet HIV*. Apr 2015;2(4):e127-136.
21. Orrell C, Hagins DP, Belonosova E, et al. Fixed-dose combination dolutegravir, abacavir, and lamivudine versus ritonavir-boosted atazanavir plus tenofovir disoproxil fumarate and emtricitabine in previously untreated women with HIV-1 infection (ARIA): week 48 results from a randomised, open-label, non-inferiority, phase 3b study. *Lancet HIV*. Dec 2017;4(12):e536-e546.

22. Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. *Lancet Infect Dis.* Mar 2019;19(3):253-264.

23. Cevik M, Orkin C, Sax PE. Emergent Resistance to Dolutegravir Among INSTI-Naïve Patients on First-line or Second-line Antiretroviral Therapy: A Review of Published Cases. *Open Forum Infect Dis*. Jun 2020;7(6):ofaa202.

24. Schramm B, Temfack E, Descamps D, et al. Viral suppression and HIV-1 drug resistance 1 year after pragmatic transitioning to dolutegravir first-line therapy in Malawi: a prospective cohort study. *Lancet HIV*. Aug 2022;9(8):e544-e553.

25. Turkova A, White E, Mujuru HA, et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children. N Engl J Med. Dec 30 2021;385(27):2531-2543.

26. Zash R, Holmes L, Diseko M, et al. Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. *N Engl J Med.* Aug 29 2019;381(9):827-840.

27. Zash RH, LB; Diseko, M; Jacobson, D; Mayondi, G; Mabuta, J; Mmalane, M; Gaolathe, T; Lockman, S; Makhema, J; Shapiro, R. Update on neural tube defects with antiretroviral exposure in the Tsepamo Study, Botswana. *AIDS 2022.* Montréal, Canada2022.

28. Chouchana L, Beeker N, Treluyer JM. Is There a Safety Signal for Dolutegravir and Integrase Inhibitors During Pregnancy? *J Acquir Immune Defic Syndr*. Aug 1 2019;81(4):481-486.

29. Pereira GFM, Kim A, Jalil EM, et al. Dolutegravir and pregnancy outcomes in women on antiretroviral therapy in Brazil: a retrospective national cohort study. *Lancet HIV.* Jan 2021;8(1):e33-e41.

30. Kintu K, Malaba TR, Nakibuka J, et al. Dolutegravir versus efavirenz in women starting HIV therapy in late pregnancy (DolPHIN-2): an open-label, randomised controlled trial. *Lancet HIV*. May 2020;7(5):e332-e339.

31. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet.* Apr 3 2021;397(10281):1276-1292.

32. Patel K, Huo Y, Jao J, et al. Dolutegravir in Pregnancy as Compared with Current HIV Regimens in the United States. *New England Journal of Medicine.* 2022;387(9):799-809.

33. Malaba TR, Nakatudde I, Kintu K, et al. 72 weeks post-partum follow-up of dolutegravir versus efavirenz initiated in late pregnancy (DolPHIN-2): an open-label, randomised controlled study. *The Lancet HIV.* 2022;9(8):e534-e543.

34. Griesel R, Maartens G, Chirehwa M, et al. CYP2B6 Genotype and Weight Gain Differences Between Dolutegravir and Efavirenz. *Clin Infect Dis.* Dec 6 2021;73(11):e3902-e3909.

35. Griesel R, Kawuma AN, Wasmann R, et al. Concentration-response relationships of dolutegravir and efavirenz with weight change after starting antiretroviral therapy. *Br J Clin Pharmacol*. Mar 2022;88(3):883-893.

36. Griesel R, Maartens G, Chirehwa M, et al. CYP2B6 genotype and weight gain differences between dolutegravir and efavirenz. *Clinical Infectious Diseases*. 2021;73(11):e3902-e3909.

37. Modongo C, Wang Q, Dima M, et al. Clinical and Virological Outcomes of TB/HIV Coinfected Patients Treated With Dolutegravir-Based HIV Antiretroviral Regimens: Programmatic Experience From Botswana. *J Acquir Immune Defic Syndr.* Oct 1 2019;82(2):111-115.

38. Griesel R, Hill A, Meintjes G, Maartens G. Standard versus double dose dolutegravir in patients with HIV-associated tuberculosis: a phase 2 non-comparative randomised controlled (RADIANT-TB) trial. *Wellcome Open Research*. 2021;6.

39. Encore Study Group, Carey D, Puls R, et al. Efficacy and safety of efavirenz 400 mg daily versus 600 mg daily: 96-week data from the randomised, double-blind, placebo-controlled, non-inferiority ENCORE1 study. *Lancet Infect Dis*. Jul 2015;15(7):793-802.

40. Variava E, Sigauke FR, Norman J, et al. Brief Report: Late Efavirenz-Induced Ataxia and Encephalopathy: A Case Series. *J Acquir Immune Defic Syndr*. Aug 15 2017;75(5):577-579.

41. Sinxadi PZ, Leger PD, McIlleron HM, et al. Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in South Africa. *Br J Clin Pharmacol.* Jul 2015;80(1):146-156.

42. Sonderup MW, Maughan D, Gogela N, et al. Identification of a novel and severe pattern of efavirenz drug-induced liver injury in South Africa. *AIDS.* Jun 1 2016;30(9):1483-1485.

43. Jover F, Cuadrado JM, Roig P, Rodriguez M, Andreu L, Merino J. Efavirenz-associated gynecomastia: report of five cases and review of the literature. *Breast J.* May-Jun 2004;10(3):244-246.

44. Sikora MJ, Rae JM, Johnson MD, Desta Z. Efavirenz directly modulates the oestrogen receptor and induces breast cancer cell growth. *HIV Med.* Oct 1 2010;11(9):603-607.

45. Njuguna C, Swart A, Blockman M, et al. Cases of antiretroviral-associated gynaecomastia reported to the National HIV & Tuberculosis Health Care Worker Hotline in South Africa. *AIDS Res Ther.* 2016;13:40.

46. Cohen CJ, Molina JM, Cassetti I, et al. Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials. *AIDS*. Mar 27 2013;27(6):939-950.

47. Behrens G, Rijnders B, Nelson M, et al. Rilpivirine versus efavirenz with emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV-1-infected patients with HIV-1 RNA </=100,000 copies/mL: week 96 pooled ECHO/THRIVE subanalysis. *AIDS Patient Care STDS*. Apr 2014;28(4):168-175.

48. Katlama C, Clotet B, Mills A, et al. Efficacy and safety of etravirine at week 96 in treatment-experienced HIV type-1-infected patients in the DUET-1 and DUET-2 trials: SAGE Publications Sage UK: London, England; 2010.

49. Cohen C, Nieto-Cisneros L, Zala C, et al. Comparison of atazanavir with lopinavir/ritonavir in patients with prior protease inhibitor failure: a randomized multinational trial. *Curr Med Res Opin*. Oct 2005;21(10):1683-1692.

50. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. *AIDS.* Aug 24 2009;23(13):1679-1688.

51. Venter WDF, Moorhouse M, Sokhela S, et al. Low-dose ritonavir-boosted darunavir once daily versus ritonavir-boosted lopinavir for participants with less than 50 HIV RNA copies per mL (WRHI 052): a randomised, open-label, phase 3, non-inferiority trial. *Lancet HIV*. Jul 2019;6(7):e428-e437.

52. Molina JM, Gallien S, Chaix ML, et al. Low-dose ritonavir-boosted darunavir in virologically suppressed HIV-1-infected adults: an open-label trial (ANRS 165 Darulight). *J Antimicrob Chemother*. Aug 1 2018;73(8):2129-2136.

53. Insight Start Study Group, Lundgren JD, Babiker AG, et al. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *N Engl J Med*. Aug 27 2015;373(9):795-807.

54. Temprano Anrs Study Group, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822.

55. Cohen MS, Chen YQ, McCauley M, et al. Antiretroviral Therapy for the Prevention of HIV-1 Transmission. *N Engl J Med.* Sep 1 2016;375(9):830-839.

56. Rodger AJ, Cambiano V, Bruun T, et al. Sexual Activity Without Condoms and Risk of HIV Transmission in Serodifferent Couples When the HIV-Positive Partner Is Using Suppressive Antiretroviral Therapy. *JAMA*. Jul 12 2016;316(2):171-181.

57. Rodger AJ, Cambiano V, Bruun T, et al. Risk of HIV transmission through condomless sex in serodifferent gay couples with the HIV-positive partner taking suppressive antiretroviral therapy (PARTNER): final results of a multicentre, prospective, observational study. *Lancet*. Jun 15 2019;393(10189):2428-2438.

58. Bavinton BR, Pinto AN, Phanuphak N, et al. Viral suppression and HIV transmission in serodiscordant male couples: an international, prospective, observational, cohort study. *Lancet HIV*. Aug 2018;5(8):e438-e447.

59. Johnson LF, Meyer-Rath G, Dorrington RE, et al. The effect of HIV programs in South Africa on national HIV incidence trends, 2000–2019. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2022;90(2):115-123.

60. Vandormael A, Akullian A, Siedner M, de Oliveira T, Bärnighausen T, Tanser F. Declines in HIV incidence among men and women in a South African population-based cohort. *Nature communications*. 2019;10(1):5482.

61. O'Brien M, Markowitz M. Should we treat acute HIV infection? *Curr HIV/AIDS Rep*. Jun 2012;9(2):101-110.

62. Okulicz JF, Lambotte O. Epidemiology and clinical characteristics of elite controllers. *Current Opinion in HIV and AIDS*. 2011;6(3):163-168.

63. Krishnan S, Wilson EM, Sheikh V, et al. Evidence for innate immune system activation in HIV type 1-infected elite controllers. *J Infect Dis.* Mar 2014;209(6):931-939.

64. Crowell TA, Gebo KA, Blankson JN, et al. Hospitalization Rates and Reasons Among HIV Elite Controllers and Persons With Medically Controlled HIV Infection. *J Infect Dis*. Jun 1 2015;211(11):1692-1702.

65. Li JZ, Segal FP, Bosch RJ, et al. ART reduces T cell activation and immune exhaustion markers in HIV controllers. *Clin Infect Dis*. May 25 2019.

66. Amanyire G, Semitala FC, Namusobya J, et al. Effects of a multicomponent intervention to streamline initiation of antiretroviral therapy in Africa: a stepped-wedge cluster-randomised trial. *Lancet HIV.* Nov 2016;3(11):e539-e548.

67. Pilcher CD, Ospina-Norvell C, Dasgupta A, et al. The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a US Public Health Setting. *J Acquir Immune Defic Syndr*. Jan 1 2017;74(1):44-51.

68. Rosen S, Maskew M, Fox MP, et al. Initiating Antiretroviral Therapy for HIV at a Patient's First Clinic Visit: The RapIT Randomized Controlled Trial. *PLoS Med.* May 2016;13(5):e1002015.

69. Uthman OA, Okwundu C, Gbenga K, et al. Optimal Timing of Antiretroviral Therapy Initiation for HIV-Infected Adults With Newly Diagnosed Pulmonary Tuberculosis: A Systematic Review and Meta-analysis. *Ann Intern Med*. Jul 7 2015;163(1):32-39.

70. Torok ME, Yen NT, Chau TT, et al. Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)--associated tuberculous meningitis. *Clin Infect Dis.* Jun 2011;52(11):1374-1383.

71. Boulware DR, Meya DB, Muzoora C, et al. Timing of antiretroviral therapy after diagnosis of cryptococcal meningitis. *N Engl J Med*. Jun 26 2014;370(26):2487-2498.

72. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One*. 2009;4(5):e5575.

73. Ford N, Patten G, Rangaraj A, Davies M-A, Meintjes G, Ellman T. Outcomes of people living with HIV after hospital discharge: a systematic review and meta-analysis. *The Lancet HIV*. 2022;9(3):e150-e159.

74. Tucker JD, Bien CH, Easterbrook PJ, et al. Optimal strategies for monitoring response to antiretroviral therapy in HIV-infected adults, adolescents, children and pregnant women: a systematic review. *AIDS*. Mar 2014;28 Suppl 2:S151-160.

75. Hermans LE, Moorhouse M, Carmona S, et al. Effect of HIV-1 low-level viraemia during antiretroviral therapy on treatment outcomes in WHO-guided South African treatment programmes: a multicentre cohort study. *Lancet Infect Dis*. Feb 2018;18(2):188-197.

76. Laprise C, de Pokomandy A, Baril JG, Dufresne S, Trottier H. Virologic failure following persistent low-level viremia in a cohort of HIV-positive patients: results from 12 years of observation. *Clin Infect Dis*. Nov 2013;57(10):1489-1496.

77. Chimukangara B, Lessells RJ, Rhee SY, et al. Trends in Pretreatment HIV-1 Drug Resistance in Antiretroviral Therapy-naive Adults in South Africa, 2000-2016: A Pooled Sequence Analysis. *EClinicalMedicine*. Mar 2019;9:26-34.

78. Lilian RR, Rees K, Mabitsi M, McIntyre JA, Struthers HE, Peters RP. Baseline CD4 and mortality trends in the South African human immunodeficiency virus programme: Analysis of routine data. *Southern African journal of HIV medicine*. 2019;20(1):1-10.

79. Smith CJ, Sabin CA, Lampe FC, et al. The potential for CD4 cell increases in HIV-positive individuals who control viraemia with highly active antiretroviral therapy. *AIDS*. May 2 2003;17(7):963-969.

80. Loutfy MR, Genebat M, Moore D, et al. A CD4+ cell count <200 cells per cubic millimeter at 2 years after initiation of combination antiretroviral therapy is associated with increased mortality in HIV-infected individuals with viral suppression. *J Acquir Immune Defic Syndr*. Dec 2010;55(4):451-459.

81. Tuboi SH, Pacheco AG, Harrison LH, et al. Mortality associated with discordant responses to antiretroviral therapy in resource-constrained settings. *J Acquir Immune Defic Syndr*. Jan 2010;53(1):70-77.

82. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet*. Jul 3-9 2004;364(9428):51-62.

83. Paton NI, Musaazi J, Kityo C, et al. Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial. *The Lancet HIV*. 2022.

84. Moore CL, Turkova A, Mujuru H, et al. ODYSSEY clinical trial design: a randomised global study to evaluate the efficacy and safety of dolutegravir-based antiretroviral therapy in HIV-positive children, with nested pharmacokinetic sub-studies to evaluate pragmatic WHO-weight-band based dolutegravir dosing. *BMC infectious diseases*. 2021;21(1):1-14.

85. Paton NI, Kityo C, Hoppe A, et al. Assessment of second-line antiretroviral regimens for HIV therapy in Africa. *N Engl J Med*. Jul 17 2014;371(3):234-247.

86. La Rosa AM, Harrison LJ, Taiwo B, et al. Raltegravir in second-line antiretroviral therapy in resource-limited settings (SELECT): a randomised, phase 3, non-inferiority study. *Lancet HIV*. Jun 2016;3(6):e247-258.

87. WHO HIV drug resistance report 2012. Available here: **https://www.hst.org.za/publications/NonHST%20Publications/9789241503938_eng.pdf**

88. Dooley KE, Kaplan R, Mwelase N, et al. Dolutegravir-Based Antiretroviral Therapy for Patients Co-Infected with Tuberculosis and Hiv: A Multicenter, Noncomparative, Open-Label, Randomized Trial. *Clin Infect Dis.* Mar 28 2019.

89. Rhee SY, Grant PM, Tzou PL, et al. A systematic review of the genetic mechanisms of dolutegravir resistance. *J Antimicrob Chemother*. Nov 1 2019;74(11):3135-3149.

90. Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. *Lancet Infect Dis*. Mar 2018;18(3):346-355.

91. Lamorde M, Wang X, Neary M, et al. Pharmacokinetics, Pharmacodynamics, and Pharmacogenetics of Efavirenz 400 mg Once Daily During Pregnancy and Post-Partum. *Clin Infect Dis.* Aug 16 2018;67(5):785-790.

92. Kaboggoza JP, Wang X, Neary M, et al. A Lower Dose of Efavirenz Can Be Coadministered With Rifampicin and Isoniazid in Tuberculosis Patients. *Open Forum Infect Dis*. Feb 2019;6(2):ofz035.

93. Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet*. Jan 12 2019;393(10167):143-155.

94. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir–lamivudine for the treatment of HIV-1 infection. *New England Journal of Medicine.* 2013;369(19):1807-1818.

95. Esber A, Dear N, Shah N, et al. Brief Report: Virologic Impact of the Dolutegravir Transition: Prospective Results From the Multinational African Cohort Study. *JAIDS Journal of Acquired Immune Deficiency Syndromes*. 2022;91(3):285-289.

96. Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. *The Lancet Infectious Diseases*. 2019;19(3):253-264.

97. Paton NI, Musaazi J, Kityo C, et al. Dolutegravir or darunavir in combination with zidovudine or tenofovir to treat HIV. *New England Journal of Medicine*. 2021;385(4):330-341.

98. Mulenga L, Fwoloshi S, Mweemba A. Dolutegravir with recycled nRTIs is noninferior to PI-based ART: VISEND trial. Paper presented at: The 29th Conference on Retroviruses and Opportunistic Infections2022.

99. Llibre JM, Hung CC, Brinson C, et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies. Lancet. Mar 3 2018;391(10123):839-849.

100. Meintjes G. Antiretroviral therapy in second-line: investigating tenofovir-lamivudine-dolutegravir (ARTIST): a randomised controlled trial. 2022.

101. Zhao Y, Griesel R, Omar Z, et al. Initial supplementary dose of dolutegravir in second-line antiretroviral therapy: a non-comparative, double-blind, randomised placebo-controlled trial. *Clinical Infectious Diseases*. 2023.

102. Penner J, Ombajo L, Nkuranga J, et al. Switching treatment-experienced, integrase inhibitor-naïve, virally suppressed HIV-1 infected adults from ritonavir-boosted protease inhibitors to dolutegravir: design, methods, and baseline results of a randomized, open-label, non-inferiority trial. *F1000Research.* 2022;11(881):881.

103. Stevens WS, Wallis CL, Sanne I, Venter F. Will etravirine work in patients failing nonnucleoside reverse transcriptase inhibitor-based treatment in southern Africa? *J Acquir Immune Defic Syndr*. Dec 2009;52(5):655-656.

104. Cahn P, Pozniak AL, Mingrone H, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. *Lancet*. Aug 24 2013;382(9893):700-708.

105. Meintjes G, Brust JCM, Nuttall J, Maartens G. Management of active tuberculosis in adults with HIV. *Lancet HIV*. Jul 2019;6(7):e463-e474.

106. Modongo C, Wang Q, Dima M, et al. Clinical and virological outcomes of TB/HIV co-infected patients treated with dolutegravir-based HIV antiretroviral regimens: Programmatic experience from Botswana. *Journal of acquired immune deficiency syndromes (1999)*. 2019;82(2):111.

107. la Porte CJ, Colbers EP, Bertz R, et al. Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob Agents Chemother*. May 2004;48(5):1553-1560.

108. Decloedt EH, Maartens G, Smith P, Merry C, Bango F, McIlleron H. The safety, effectiveness and concentrations of adjusted lopinavir/ritonavir in HIV-infected adults on rifampicin-based antitubercular therapy. *PLoS One.* 2012;7(3):e32173.

109. Davies G, Cerri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. *Cochrane Database Syst Rev*. Oct 17 2007(4):CD005159.

110. Hennig S, Svensson EM, Niebecker R, et al. Population pharmacokinetic drug-drug interaction pooled analysis of existing data for rifabutin and HIV PIs. *J Antimicrob Chemother.* May 2016;71(5):1330-1340.

111. *National Committee on the Confidential Enquiries into Maternal Deaths. Saving Mothers 2017-2019: Seventh triennial report on confidential enquiries into maternal deaths in South Africa.* 2020.

112. Updated South African ART guidelines for use of dolutegravir (DTG) in pregnant women and women of childbearing potential (WOCP) Southern African HIV Clinicians Society (SAHCS); 2021.

113. Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *The Lancet.* 2021;397(10281):1276-1292.

114. Benhamou Y, Bochet M, Thibault V, et al. Long term incidence of hepatitis B virus resistance to lamivudine in human immunodeficiency virus–infected patients. *Hepatology.* 1999;30(5):1302-1306.

115. Chang M-L, Liaw Y-F. Hepatitis B flares in chronic hepatitis B: pathogenesis, natural course, and management. *Journal of hepatology.* 2014;61(6):1407-1417.

116. Fischetti B, Shah K, Taft DR, Berkowitz L, Bakshi A, Cha A. Real-world experience with higher-than-recommended doses of lamivudine in patients with varying degrees of renal impairment. Paper presented at: Open Forum Infectious Diseases2018.

117. van Coppenhagen B, Duvenage HS. Prevalence of depression in people living with HIV and AIDS at the Kalafong Provincial Tertiary Hospital Antiretroviral Clinic. *S Afr J Psychiatr*. 2019;25:1175.

118. Bhana A, Rathod SD, Selohilwe O, Kathree T, Petersen I. The validity of the Patient Health Questionnaire for screening depression in chronic care patients in primary health care in South Africa. *BMC psychiatry.* 2015;15:1-9.

119. Petersen I, Bhana A, Fairall LR, et al. Evaluation of a collaborative care model for integrated primary care of common mental disorders comorbid with chronic conditions in South Africa. *BMC psychiatry*. 2019;19:1-11.

120. Bhana A, Mntambo N, Gigaba S, et al. Validation of a brief mental health screening tool for common mental disorders in primary healthcare. *South African Medical Journal*. 2019;109(4):278-283.

121. Grant M, Petersen I, Mthethwa L, Luvuno Z, Bhana A. Accuracy of a community mental health education and detection (CMED) tool for common mental disorders in KwaZulu-Natal, South Africa. *International Journal of Mental Health Systems*. 2022;16(1):44.

122. Chan P, Yoon B, Colby D, et al. Immunological, cognitive and psychiatric outcomes after initiating EFV-and DTG-based antiretroviral therapy during acute HIV infection. *Clin Infect Dis*. 2022:ciac466.

123. Chan P, Yoon B, Colby D, et al. Immunological, Cognitive, and Psychiatric Outcomes After Initiating Efavirenz-and Dolutegravir-based Antiretroviral Therapy During Acute Human Immunodeficiency Virus Infection. *Clinical Infectious Diseases*. 2023;76(3):e718-e726.

124. Jong E, Conradie F, Berhanu R, et al. Consensus statement: Management of drug-induced liver injury in HIV-positive patients treated for TB. 2013. 2013-09-17 *2013*;14(3):7.

125. SEMDSA Type 2 Diabetes Guidelines Expert Committee. SEMDSA 2017 Guidelines for the Management of Type 2 diabetes mellitus. 2017. **https://www.semdsa.org.za/images/647-4385-1-PB.pdf.**

126. Murdoch DM, Venter WD, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. *AIDS research and therapy*. 2007;4:1-10.

127. Haddow LJ, Colebunders R, Meintjes G, et al. Cryptococcal immune reconstitution inflammatory syndrome in HIV-1-infected individuals: proposed clinical case definitions. *The Lancet infectious diseases.* Nov 2010;10(11):791-802.

128. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *The Lancet infectious diseases*. Aug 2008;8(8):516-523.

129. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS.* Sep 24 2010;24(15):2381-2390.

130. Meintjes G, Sonderup MW. A practical approach to the diagnosis and management of paradoxical tuberculosis immune reconstitution inflammatory syndrome. *Continuing Medical Educatio*n. 2011;29(10):410-417.

131. Meintjes G, Stek C, Blumenthal L, et al. Prednisone for the Prevention of Paradoxical Tuberculosis-Associated IRIS. *N Engl J Med*. Nov 15 2018;379(20):1915-1925.

132. Rangaka MX, Wilkinson RJ, Boulle A, et al. Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet.* Aug 23 2014;384(9944):682-690.

133. Group TAS, Danel C, Moh R, et al. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med*. Aug 27 2015;373(9):808-822.

134. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. *New England Journal of Medicine*. 2011;365(23):2155-2166.

135. Swindells S, Ramchandani R, Gupta A, et al. One month of rifapentine plus isoniazid to prevent HIV-related tuberculosis. *New England Journal of Medicine*. 2019;380(11):1001-1011.

136. Dooley KE, Savic R, Gupte A, et al. Once-weekly rifapentine and isoniazid for tuberculosis prevention in patients with HIV taking dolutegravir-based antiretroviral therapy: a phase 1/2 trial. *The Lancet HIV*. 2020;7(6):e401-e409.

137. Marjorie Z. Imperial AL, Rodney Dawson, Yoninah Cramer, Sue Rosenkranz, Susan Swindells, Irina Gelmanova, Anchalee Avihingsanon, Roberto C. Arduino, Wadzanai Samaneka, Kelly Dooley, Rada Savic, Anthony T. Podany. DTG PK in people with HIV receiving daily 1HP for Latent TB treatment *Conference on Retroviruses and Opportunistic Infections* (CROI)2022.

138. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV. : U.S. Department of Health and Human Services, Panel on Antiretroviral Guidelines for Adults and Adolescents.; 2021.

139. Getahun H, Kittikraisak W, Heilig CM, et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource-constrained settings: individual participant data meta-analysis of observational studies. *PLoS Med*. Jan 18 2011;8(1):e1000391.

140. Gupta A, Montepiedra G, Aaron L, et al. Isoniazid Preventive Therapy in HIV-Infected Pregnant and Postpartum Women. *N Engl J Med*. Oct 3 2019;381(14):1333-1346.

141. Kalk E, Heekes A, Mehta U, et al. Safety and Effectiveness of Isoniazid Preventive Therapy in HIV-Positive Pregnant Women on Art: An Observational Study using Linked Population Data. *Clin Infect Dis*. Jan 4 2020.

142. Mathad JS, Savic R, Britto P, et al. Pharmacokinetics and Safety of 3 Months of Weekly Rifapentine and Isoniazid for Tuberculosis Prevention in Pregnant Women. *Clinical Infectious Diseases*. 2022;74(9):1604-1613.

Website: www.sahivsoc.org

Telephone: +27 (0) 11 728 7365

Email: sahivcs@sahivcs.org