NEED HELP?

Contact the TOLL-FREE National HIV & TB Health Care Worker Hotline

0800 212 506 / 021 406 6782

Alternatively "whatsapp" or send an SMS or "Please Call Me" to 071 840 1572

www.mic.uct.ac.za

SOUTH AFRICAN ANTIRETROVIRAL TREATMENT GUIDELINES 2015

LATE ADOLESCENTS (> 15 YEARS) AND ADULTS

Third edition February 2018

WHO IS ELIGIBLE TO START ANTIRETROVIRAL TREATMENT (ART)

All **HIV positive patients**, regardless of CD4 count or clinical staging

TIMING OF ART INITIATION

ART should be started as soon as the patient is ready, within 2 weeks of the CD4 count being done, except:

FAST TRACK INITIATION (WITHIN 7 DAYS)	IMMEDIATE PRIORITY
• CD4 ≤ 200 cells/µL • WHO stage 4 disease, irrespective of CD4	• HIV-positive pregnant or breastfeeding women, unless they have active TB or a contraindication to first line ART

DELAY ART INITIATION IN THE FOLLOWING

ART is delayed until treatment is tolerated to allow improvement of symptoms, and prevent development of immune reconstitution inflammatory syndrome (IRIS)

Cryptococcal Meningitis (CM) prophylaxis (CLAT/CrAg +, **no** symptoms)	2 weeks after fluconazole treatment started
CM treatment (CLAT/CrAg + **plus** symptoms)	after 4-6 weeks on antifungal treatment
Tuberculosis (TB) with CD4 < 50	within 2 weeks on TB treatment
TB with CD4 > 50	within 2 - 8 weeks on TB treatment (8 weeks preferred)
TB meningitis	after 4-8 weeks on TB treatment

REGIMENS

1ST LINE

All **NEW PATIENTS**: • Pregnant and breastfeeding women • Adults (eGFR/CrCl > 50 mL/min), with or without HBV* or TB • Adolescents > 15 years AND > 40 kg AND CrCl** > 80 mL/min	**TDF + FTC (or 3TC) + EFV** Provided as fixed dose combination (FDC)
Currently on **d4T**-based regimen: Change d4T to TDF if **virally suppressed** and eGFR***/CrCl > 50 mL/min. If viral load (VL) > 1000 copies/mL, manage as potential treatment failure	**TDF** + FTC (or 3TC) + EFV
Adolescents# currently on (ABC or d4T) + 3TC + EFV: switch to FDC if > 15 years, weight > 40 kg, CrCl > 80 mL/min, no proteinuria and virally suppressed (VL done within the last 8 weeks)	FDC preferred
Adolescent < 40 kg and < 15 years	ABC + 3TC + EFV (Dose according to paediatric dosing chart)

ALTERNATIVE 1ST LINE REGIMENS

Contraindication to **EFV:** • Significant psychiatric co-morbidities **OR** • Intolerance to EFV **OR** • Where EFV may impair daily functioning e.g. shift workers	TDF + FTC (or 3TC) + **NVP**
Contraindication to **EFV** (see above) **and NVP** (see below) Don't initiate **NVP** if: • Baseline CD4 ≥ 250 for females • Baseline CD4 ≥ 400 in male patients	TDF + FTC (or 3TC) + **LPV/r**
Contraindication to **TDF:** • Renal disease (eGFR/CrCl < 50 mL/min) • The use of other nephrotoxic drugs e.g. aminoglycosides (kanamycin)	**ABC** + 3TC + EFV or (NVP)
Contraindication to **TDF and ABC** (previous hypersensitivity)	**AZT** +3TC + EFV (or NVP)

2ND LINE

Failing on a **TDF**-based 1st line regimen	Hepatitis B surface antigen (HBsAg) **negative**	AZT + 3TC + LPV/r
	HBsAg **positive**	TDF + AZT + 3TC + LPV/r
Failing on an **ABC**-based 1st line regimen		AZT + 3TC + LPV/r
Failing on a **d4T- or AZT**-based 1st line regimen		TDF + 3TC (or FTC) + LPV/r

ALTERNATIVE 2ND LINE REGIMENS

Patients with anaemia and renal failure	**ABC** + 3TC + LPV/r
Dyslipidaemia (total cholesterol > 6 mmol/L, fasting triglycerides > 5 mmol/L) OR gastrointestinal side-effects > 6 weeks on LPV/r OR cardio-vascular event risk > 20% OR established clinical cardiovascular disease	Switch LPV/r to **ATV/r**

3RD LINE

Failing any 2nd line regimen	Specialist referral - Regimen should be chosen according to genotype resistance testing, managed by an expert panel. Third line drugs will be managed centrally

WHEN TO DO RESISTANCE TESTING

- On a PI-based regimen for more than 2 years, and failing (VL > 1000); **AND**
- Tolerability, drug-drug interactions and adherence has been addressed by assessing pharmacy refills, pill counts, diary entries and thorough counselling; **AND**
- 6 months after adherence was addressed VL is still > 1000

*HBV = hepatitis B virus **CrCl = creatinine clearance ***eGFR = estimated glomerular filtration rate

#Please note that the Cockroft-Gault formula does NOT apply to children or adolescents. Using it in these groups will result in an incorrect CrCl. Please call the hotline for further information

MONITORING AT DIAGNOSIS OF HIV

	PURPOSE & INTERPRETATION/ACTION
Confirm HIV status	To confirm HIV positive status in clients who present without documented proof of positive HIV status. Ensure that the national testing algorithm has been followed
Baseline CD4 count and **WHO clinical staging**	Assess timing of ART and appropriate prophylactic treatment: Initiate co-trimoxazole prophylactic treatment (CPT) if WHO stage 2,3 or 4 and/or HIV/TB co-infection or CD4 < 200. If CD4 < 100, eligible for CrAg/CLAT
Pregnancy	Identify women who should be initiated immediately, opportunity to offer appropriate family planning
TB symptoms	Identify TB/HIV co-infection and timing of ART initiation on TB treatment
Mantoux / Tuberculin Skin Test (TST)	Assess need for Isoniazid prophylactic treatment (IPT) – see section on IPT
CrAg/CLAT if baseline **CD4 < 100**	**If CLAT negative**: Start ART **If CLAT positive and asymptomatic**: Start fluconazole 800 mg daily for 2 weeks, then fluconazole 400 mg daily for 2 months, followed by fluconazole 200 mg daily for a minimum of 1 year in total. Discontinue when patient has had two CD4 counts > 200 cells/µL taken at least 6 months apart; Start ART 2 weeks into antifungal treatment **If CLAT positive and symptomatic (symptoms include: headache, confusion)**: Refer to hospital urgently for lumbar puncture to exclude cryptococcal meningitis

Other investigations: Screen for other STIs (sexually transmitted infections), hepatitis B, syphilis, major non-communicable diseases, measure weight (and height in adolescents)

MONITORING PRIOR TO INITIATION OF ART

Initiating **Tenofovir (TDF) - Serum creatinine (SCr) & Creatinine clearance (CrCl)**

To detect renal insufficiency - serum creatinine (SCr) is a waste product filtered by the kidneys used to determine eGFR/CrCl

If eGFR value is not provided by laboratory - calculate CrCl:

Adolescent < 16 years:

$$\text{CrCl (mL/min)} = \frac{\text{height (cm)}}{\text{SCr (µmol/L)}} \times 40$$

Adult/adolescent > 16 years (non-pregnant):

$$\text{CrCl (mL/min)} = \frac{\text{140 - age (years)} \times \text{weight (kg)}}{\text{SCr (µmol/L)}}$$

Females: multiply CrCl x 0.85*

TDF can be initiated if eGFR/CrCl > 50 mL/min

If CrCl is **abnormal (< 50 mL/min):**

Check urine dipstix for proteinuria and repeat SCr after 1 month. Refer to specialist if renal dysfunction is persistent

Doses for ARVs may need to be adjusted for renal impairment

Tenofovir is contraindicated and should NOT be started in the following:

eGFR/CrCl ≤ 50 mL/min in adults and adolescents > 16 years, or CrCl ≤ 80 mL/min in adolescents < 16 years

eGFR and CrCl cannot be calculated during **pregnancy.** If SCr ≥ 85 µmol/L don't use TDF and refer urgently

THE FOLLOWING TESTS SHOULD BE DONE IF FDC (TDF+FTC+EFV) CANNOT BE USED:

Initiating **AZT** – Haemoglobin (Hb) or Full blood count (FBC)	To detect anaemia/neutropenia **Hb > 8g/dL** – can use AZT **Hb ≤ 8g/dL** - do NOT use AZT (use alternative)
Initiating **NVP** – Alanine Transaminase (ALT)	To detect liver dysfunction **ALT < 100 units/L** – can use NVP **ALT > 100 units/L** – discuss with specialist or call HIV & TB hotline
Initiating **LPV/r** – **Fasting cholesterol and triglycerides**	To identify clients with contraindications to LPV/r or at risk of LPV/r related hyperlipidaemia **Cholesterol > 6 mmol/L or triglycerides > 5 mmol/L** – consider using atazanavir/ritonavir (ATV/r) instead of LPV/r

MONITORING ON ART

At every visit:

- Screen for TB, WHO clinical staging, STI, pregnancy/planning to conceive and major non-communicable diseases
- Measure weight (and height in adolescents)
- Ask about side effects

TEST	PURPOSE & INTERPRETATION/ACTION
CD4 (cells/µL) At 12 months on ART, then annually if clinically indicated	To monitor immune response to ART, and eligibility for co-trimoxazole prophylaxis **CD4 < 200**: co-trimoxazole should be initiated/continued; patient should be on ART. If not, prioritise for initiation **CD4 > 200 on two or more occasions** at least 6 months apart: Stop monitoring, stop CPT and stop fluconazole prophylaxis
Viral load (copies/mL) At months 6, 12 and then annually	VL > 1000: Check adherence, tolerability, drug-drug interactions and assess psychological issues **On NNRTI-regimen (e.g. EFV, NVP)**: Repeat VL 2 months later – if VL still > 1000: Check hepatitis B status (if not done previously and TDF is part of 1st line) and consider switching to 2nd line **On PI-based regimen (e.g. LPV/r, ATV/r)**: Repeat VL after 6 months. See section on genotyping if VL consistently > 1000 VL 400 - 1000: Assess adherence carefully. Repeat VL in 6 months, and manage accordingly VL < 400: Repeat VL as per guideline. Patient is doing well

Remember to LOOK at results as soon as they come back from the laboratory and ACT on them as soon as possible

IF ON	PURPOSE & INTERPRETATION/ACTION
TDF - SCr and eGFR at months 3, 6, 12, and then annually	To detect TDF-toxicity: See section above on "MONITORING PRIOR TO INITIATION OF ART" for interpretation and management
AZT – FBC at month 3, 6 and then annually	To detect AZT toxicity: **Hb > 8 or Neutrophils > 1.5 x 10^9/L**- Continue AZT ; **Hb < 8 or Neutrophils < 1.5x 10^9/L** - Do NOT use AZT. Switch to alternative; **Neutrophils < 1 x 10^9/L** - Stop co-trimoxazole
NVP / EFV / LPV/r – ALT if rash or symptoms of hepatitis develop while on EFV/NVP – ALT monthly on double dose LPV/r and TB therapy	To detect liver toxicity: **ALT 40 – 100**: repeat ALT in 2 weeks **ALT 100 – 200**: repeat ALT in one week. If symptoms of hepatitis or jaundice – stop relevant drugs, do hepatitis screen and full LFT. Do INR if patient is jaundiced **ALT > 200:** Stop relevant drugs, do hepatitis screen and full LFT. INR should also be done in patients with jaundice
LPV/r - Fasting cholesterol and triglycerides (TG) at month 3, and annually if clinically indicated	Total Cholesterol > 6 mmol/L : Switch to ATV/r TG > 5 mmol/L: Switch to ATV/r Manage hyperlipidaemia with dietary modifications and appropriate statins if indicated (avoid simvastatin, consider low dose atorvastatin, max dose 10 mg/d)
HBsAg Do test when switching from TDF	HBsAg positive: Continue TDF (see section on 2nd line) HBsAg negative: No need for TDF

Based on the National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the Management of HIV in Children, Adolescents and Adults National Department of Health, South Africa, April 2015 and Standard Treatment Guidelines and Essential Medicines List for South Africa, Hospital Level Adults, 2015. Updated November 2016 to incorporate the National Test and Treat protocol implemented by NDoH, Sep 2016.

DOSAGE

ANTIRETROVIRAL	USUAL ADULT DOSE	DOSE ADJUSTMENT IN RENAL IMPAIRMENT	
		eGFR 10 - 50 mL/min	eGFR < 10 mL/min
Abacavir (ABC)	300 mg twice daily OR 600 mg once daily	Normal dose	Normal dose
Atazanavir + ritonavir (ATV/r)	300 mg/100 mg once daily	Normal dose	Normal dose
Darunavir + ritonavir (DRV/r)	600 mg/100 mg twice daily	Normal dose	Normal dose
Dolutegravir (DTG)	**No integrase inhibitor mutations:** 50 mg daily. If also on rifampicin, use 50 mg twice daily **Integrase inhibitor mutations present:** 50 mg twice daily. If also on rifampicin, avoid DTG	eGFR > 30: No dose adjustment; eGFR < 30: No data, use with caution	
Efavirenz (EFV) (Swallow tablet whole)	600 mg daily (or 400 mg if < 40 kg); usually given at night	Normal dose	Normal dose
Emtricitabine (FTC)	200 mg once daily (not available as single agent)	Not applicable	Not applicable
Etravirine (ETR)	200 mg twice daily	Normal dose	Normal dose
Lamivudine (3TC)	150 mg twice daily OR 300 mg once daily	150 mg daily	50 mg daily
Lopinavir + ritonavir (LPV/r) (Swallow tablet whole)	400 mg/100 mg twice daily NB: Patients on a rifampicin-containing TB regimen: Increase LPV/r to 800/200 mg twice daily – see table: Patients with concomitant TB	Normal dose	Normal dose
Nevirapine (NVP)	200 mg daily for 2 weeks*, then 200 mg twice daily	Normal dose	Normal dose
Raltegravir (RAL)	400 mg twice daily	Normal dose	Normal dose
Stavudine (d4T)	30 mg twice daily	15 mg twice daily	15 mg daily
Tenofovir (TDF)	300 mg once daily	Avoid use	Avoid use
Zidovudine (AZT)	300 mg twice daily	Normal dose	300 mg daily

*Do not use nevirapine lead-in dose in patients already on rifampicin or if patient has been on efavirenz for more than 2 weeks; Do not increase the dose to 200 mg twice daily in the presence of a rash. Delay increase until rash stabilises or switch to alternative drug e.g. EFV

PATIENTS WITH CONCOMITANT TB

Patients already on ART:

- Continue ART throughout TB treatment
- EFV-based regimens are generally preferred to NVP-based regimens in adolescents and adults with active TB on 1st line ART regimens
- Patients on LPV/r and rifampicin concomitantly should have their LPV/r dose doubled slowly over two weeks (to 800/200 mg twice a day). Monitor ALT while increasing the dose at weekly intervals, and then monthly while on double dose
- If the patient is on an ATV/r containing regimen, then rifampicin should be replaced with rifabutin 150 mg daily
- Patients requiring streptomycin/kanamycin/amikacin avoid TDF, unless renal function is monitored weekly. AZT, d4T or ABC can be used in these patients
- Patients on third line ARVs should be discussed with an expert or the HIV hotline for management of drug interactions

Remember: Patients on TB medication and ARVs are taking a large number of tablets. Do pre-emptive counselling to improve adherence

Patients not yet on ART:

- Patients who present with TB with a CD4 > 50 cells/µL, with no other serious HIV conditions (e.g. Kaposi's sarcoma or HIV encephalopathy) should start ART 2-8 weeks after starting TB treatment (preferably at 8 weeks, to avoid IRIS). If CD4 < 50, start ART within 2 weeks
- If patients need to start ARV therapy and are on rifampicin, and efavirenz is contraindicated, (e.g. psychosis or previous adverse reaction to efavirenz) start nevirapine, but do not use lead-in dose

ISONIAZID PREVENTION THERAPY (IPT)

Eligibility criteria:	Contra-indications to IPT:	Dose of IPT:
• HIV positive **AND** • Never had IPT before **AND** • Active TB excluded	• Excessive alcohol use • Active TB disease • Active liver disease • Peripheral neuropathy • History of adverse reactions to isoniazid • Patients who completed MDR- or XDR-TB treatment	Isoniazid 5 mg/kg daily (max 300 mg daily) Vitamin B6 25 mg daily

Adult patients who have completed TB treatment where there is documented proof of bacteriological cure, can be started on IPT immediately if they meet the above criteria. IPT and ART may be started on the same day. If a patient is already on ART and requires IPT, start IPT as soon as possible.

TST needs to be done to confirm duration of IPT. If TST is not available at initiation of IPT, then it should be done within ONE month of initiation of IPT. If it comes back positive, extend IPT to 36 months. If negative, change according to table below

Duration of IPT:	TST not done	TST negative	TST positive
Pre-ART (regardless of CD4)	6 months	No IPT	36 months
Patients on ART	12 months	12 months	36 months

Date Published: November 2015
Second edition: November 2016
Third edition: February 2018