SOUTH AFRICAN ART CLINICAL GUIDELINES 2019

ADOLESCENTS (≥ 10 YEARS) AND ADULTS

Third edition March 2022

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

or download our free SA HIV/TB Hotline App—scan QR code at bottom of poster

www.mic.uct.ac.za

ART ELIGIBILITY AND DETERMINING THE TIMEFRAME FOR ART INITIATION

WHO IS ELIGIBLE?

All people living with HIV, regardless of age, CD4 cell count and clinical stage. ART should be initiated within 7 days unless there is a reason to defer. Same day initiation is encouraged if client is clinically well and motivated

REASONS TO DEFER STARTING ART	WHEN TO START ART*
TB symptoms (cough, night sweats, fever, recent weight loss)	No TB: same day or within 7 days Confirmed DS-TB at non-neurological site: CD4 < 50 cells/µL: within 2 weeks of starting TB treatment CD4 ≥ 50 cells/µL: 8 weeks after starting TB treatment Confirmed DR-TB at non-neurological site: Start ART 2 weeks after TB treatment, once symptoms improved and TB treatment tolerated
Signs and symptoms of meningitis (headache, confusion, fever, neck stiffness or coma)	Investigate for meningitis before starting ART TBM (DS or DR): 4 - 8 weeks after starting TB treatment CM: 4 - 6 weeks after starting antifungal treatment
CrAg-positive with no symptoms or signs of meningitis	2 weeks after starting fluconazole
Other acute illnesses e.g. PJP or bacterial pneumonia	Defer ART for 1 - 2 weeks after commencing treatment for the infection
Clinical symptoms or signs of liver disease	Confirm liver disease using ALT and bilirubin. ALT > 120 IU/L with symptoms of hepatitis (nausea, vomiting, upper quadrant pain) and/or total serum bilirubin concentrations > 40 µmol/L: investigate and manage possible causes before starting ART

*Clients already on ART should NOT have their treatment interrupted upon diagnosis of the above conditions

BASELINE CLINICAL INVESTIGATIONS

- Recognise the client with respiratory, neurological, or abdominal danger signs
- Nutritional assessment (including weight and height)
- Screen for TB. If no symptoms consider TPT
- Meningitis
- Mental health issues/substance abuse
- Major chronic non-communicable diseases (NCDs) e.g. diabetes, hypertension, epilepsy
- Pregnancy or planning to conceive
- Symptom screen for sexually transmitted infections
- WHO clinical stage

BASELINE LABORATORY EVALUATION

TEST AND PURPOSE	INTERPRETATION / ACTION
Confirm HIV test result To confirm HIV status for those without documented HIV status	Ensure that the national testing algorithm has been followed
CD4 count (cells/µL) To identify eligibility for CPT and CrAg screening	Initiate CPT if CD4 < 200 or WHO stage 2, 3 or 4 If **CD4 < 100**, a reflex CrAg screening will be done automatically **CrAg-negative:** no fluconazole therapy required. Start ART **CrAg-positive:** the client will require treatment of the infection. All clients, including pregnant women, should be referred for a LP. Defer ART as above
Cervical cancer screening To identify women with cervical lesions	At baseline and thereafter every three years, if normal. If lesions present, refer for colposcopy and manage accordingly
HBsAg Identify hepatitis B co-infection	If positive, TDF-containing regimen is preferred. Exercise caution when stopping TDF due to risk of hepatitis flares
Creatinine and eGFR To detect renal insufficiency, and eligibility for TDF	Serum creatinine (SCr) is a waste product filtered by the kidneys; used to determine eGFR

Age/Pregnancy status	What must be measured?	Safe to use TDF
≥ 10 and < 16 years	eGFR using Counahan Barratt formula#	> 80 mL/min/1.73 m^2
Adult and adolescent ≥ 16 years	eGFR using MDRD equation as provided by the laboratory	> 50 mL/min/1.73m^2
Pregnant	Absolute creatinine level	< 85 µmol/L

#Counahan Barratt formula

$$eGFR\ (mL/min/1.73\ m^2) = \frac{height\ [cm] \times 40}{creatinine\ [\mu mol/L]}$$

	Adults and adolescents	Pregnant women
Haemoglobin (Hb) To detect anaemia	If Hb < 10 do FBC, and follow Primary Care Standard Treatment guidelines If Hb < 8 avoid AZT	If Hb < 10 initiate iron supplementation Refer if: Hb < 8 with symptoms of anaemia, or anaemia and ≥ 36 weeks pregnant, or no response to iron *Take note of DTG interaction with polyvalent cations, e.g. iron. See the interaction checker on the hotline app—scan QR code*
GeneXpert To diagnose TB	**Adults and adolescents**	**Pregnant women**
	Do GeneXpert only if client has symptoms of TB	Routinely done at first antenatal visit, regardless of symptoms

REGIMENS

RECOMMENDED FIRST-LINE IN NEW CLIENTS

Adults, **including pregnant clients,** adolescents ≥ 35 kg and ≥ 10 years of age	TLD
Client currently on **DS-TB treatment** at initiation of ART	TEE
Adolescents < 35 kg and children < 10 years	Refer to paed guidelines

SWITCHING STABLE CLIENTS ON A FIRST-LINE OR SECOND-LINE REGIMEN TO DTG

Warn the client of new side-effects that may be experienced when switching to DTG (insomnia, headache, gastrointestinal disturbances). These are usually mild and self-limiting.
If VL not done within the past 6 months, wait for next routine VL. Switch must only be made using a VL done within the past 6 months:

	Current regimen:	New regimen:
VL < 50	TDF + (FTC or 3TC) + (EFV or NVP)	TLD
	(AZT or ABC)[¥] + 3TC + (EFV or NVP)	(AZT or ABC) + 3TC + DTG
	AZT + 3TC + (LPV/r or ATV/r)[§]	AZT + 3TC + DTG
VL 50-999	Assess reason for elevated VL. Implement interventions and provide adherence support. Repeat VL in 3 months. If VL < 1000 – switch to DTG. If VL ≥ 1000 – **do not switch.** Refer to table – Virological and Immunological Response to ART	
Do not switch patients with a VL ≥ 1000 and/or patients on a non-standard second line regimen of TDF + 3TC/FTC + LPV/r or ABC + 3TC + LPV/r		

[§]Assess the reason for exclusion of TDF from the NRTI backbone. If TDF was excluded due to TDF-induced nephrotoxicity, continue using the same NRTI backbone. If TDF was excluded due to non-TDF related renal failure that has since resolved, then the use of TDF can be reconsidered. Before switching to TDF, ensure adequate renal function by checking eGFR/creatinine as outlined in the Baseline Laboratory Evaluation Table; [¥]Based on NDoH Poster: "Switching stable clients on first– and second-line ART to DTG-containing regimens", May 2021. Available at: https://tinyurl.com/2p85k3kc

SECOND- AND THIRD-LINE REGIMENS WITH CONFIRMED VIROLOGICAL FAILURE

REGIMEN	FIRST-LINE REGIMENS		SECOND-LINE REGIMENS	
	NNRTI-based Regimen	InSTI-based Regimen for > 2 years	PI/DTG-based Regimen for > 2 years	
	TDF + 3TC/FTC + **EFV/NVP**	**TDF** + 3TC/FTC + **DTG**	**AZT/TDF** + 3TC/FTC + **LPV/r or ATV/r or DTG**	
RESISTANCE TESTING	Resistance testing not required		Resistance testing not required	Resistance test required
RESISTANCE TEST RESULTS	Not applicable		Not applicable	No PI or InSTI resistance / PI or InSTI resistance
HBV CO-INFECTION	HBV-negative / HBV-positive		HBV-negative / HBV-positive	HBV-positive# or - negative
NEW REGIMEN	AZT + 3TC + DTG If DTG not suitable: AZT + 3TC + LPV/r	TDF + AZT + 3TC/FTC + DTG If DTG not suitable: TDF + 3TC/FTC + LPV/r	AZT + 3TC + LPV/r	TDF + 3TC/FTC + LPV/r
			Continue current regimen and address adherence. If intolerance to LPV/r is affecting adherence, discuss possible substitutions with an expert	Refer to third-line committee. Regimen will be determined by results of resistance test

#Ideally clients who are HBsAg-positive should be on a TDF-based regimen if feasible

IMPORTANT DRUG INTERACTIONS BETWEEN ARVs AND TB MEDICINES**

Interacting medicines	Interaction	Management
Rifampicin and DTG	Rifampicin decreases DTG levels	If no integrase inhibitor mutations present, increase DTG dose to 50 mg twice daily. Avoid DTG if integrase inhibitor mutations present
Rifampicin and LPV/r	Rifampicin decreases LPV levels. Increases ALT/AST	Dosage adjustment required. Monitor liver function. The dose of LPV/r should be doubled slowly over 2 weeks (to 800/200 mg bd). Monitor ALT while increasing the dose at weekly intervals, and then monthly while on double dose
Rifampicin and other PIs	Rifampicin decreases ATV, and DRV levels. Increases ALT/AST	Avoid concurrent use with ATV/r and DRV/r as dose adjustment not established. Consider rifabutin 150 mg daily as an alternative
Bedaquiline (BDQ) and EFV	EFV decreases BDQ levels. Also additive risk of QT prolongation	Avoid combination. Phone the hotline to discuss switching EFV to DTG or LPV/r
Linezolid and AZT	Additive mitochondrial and haematotoxicity	Linezolid and AZT should not be used together

**This list is not exhaustive. Download the free SA HIV/TB Hotline app for a complete interaction checker – scan QR code:

Based on the 2020 National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and PMTCT, 2020; Updated 2022 based on NDoH circular reference 2021/06/29/EDP/01

This publication was supported under funding provided by the Global Fund to Fight AIDS, Tuberculosis and Malaria through the National Department of Health of South Africa and the NDoH Pharmacovigilance Centre for Public Health Programmes. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the Global Fund or the National Department of Health of South Africa

FOLLOW-UP MONITORING IN CLIENTS ON ART

CLINICAL ASSESSMENT AND RESPONSE

- Weight
- Screen for TB and other OIs
- WHO clinical staging
- Screen for pregnancy and ask if planning to conceive
- Ask about side-effects, especially sleep and gastrointestinal disturbances

VIROLOGICAL AND IMMUNOLOGICAL RESPONSE TO ART

TEST	ACTION/INTERPRETATION
CD4 count At 1 year on ART	Repeat CD4 6 monthly **only** if CD4 < 200 **or** VL ≥ 1000 Stop CD4 monitoring if VL < 1000 and CD4 > 200. Stop CPT if CD4 > 200
Viral Load (VL) Month 6, 12 and then 12-monthly if VL suppressed	

VL	RESPONSE
≥ 1000	Do thorough assessment of the cause of an elevated VL: Consider adherence problems, intercurrent infections, incorrect ART dose, drug interactions and resistance. Implement interventions, including adherence support. Do HBsAg if not done previously and currently on TDF-based treatment. Repeat VL in 3 months If VL still ≥ 1000 and on **NNRTI** regimen: Consider switching to second-line if virological failure confirmed, i.e. VL ≥ 1000 on 2 consecutive occasions and adherence issues addressed If VL still ≥ 1000 and on **PI-based or InSTI (DTG)** regimen: Consider switching if virological failure confirmed, i.e. VL ≥ 1000 on at least 3 occasions over the course of 2 years, or VL ≥ 1000 with signs of immunological or clinical failure (i.e. declining CD4 and/or opportunistic infections)
50 – 999	Do thorough assessment of the cause of an elevated VL. Consider adherence problems, intercurrent infections, incorrect ART dose, drug interactions and resistance. Implement interventions, including adherence support. Repeat VL after 3 months. If VL 50 - 999 again, repeat in 6 months. For < 50 or ≥ 1000 follow table
< 50	Continue routine VL monitoring and routine adherence support. Client is doing well

DO THE FOLLOWING TESTS IF THE CLIENT IS ON THE DRUG THAT MAY CAUSE THE ADVERSE EVENT

DRUG	TEST	FREQUENCY	ACTION/INTERPRETATION
TDF	Creatinine	Month 3, 6 and 12. Then 12-monthly	See creatinine and eGFR section at baseline laboratory testing
AZT	FBC + differential WCC	At months 3 and 6, thereafter if clinically indicated	Hb > 8 g/dL: Continue AZT Hb ≤ 8 g/dL: Use alternative – consult with expert
PI-based regimen (LPV/r, ATV/r, DRV/r)	Cholesterol + triglycerides (TGs)	At month 3, if above acceptable range, do fasting cholesterol and TGs	To monitor PI-related metabolic side-effects. Consult with specialist if fasting cholesterol and TGs still above acceptable range
TB treatment **or** NVP **or** EFV	ALT	Signs/symptoms of hepatitis (e.g. nausea, vomiting, jaundice)	If ALT is abnormal, refer to specialist or phone the HIV hotline

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 OR 800 mg/100 mg daily (depending on mutations)	Normal dose	Normal dose
Dolutegravir (DTG)	**No integrase inhibitor mutations:** 50 mg daily. If also on rifampicin: boosting of DTG required. The dosing frequency of DTG should be increased to 50 mg 12 hourly. If on TLD FDC, then add DTG 50 mg 12 hours after TLD. Continue boosting until 2 weeks after rifampicin discontinued **Integrase inhibitor mutations present:** 50 mg twice daily. If also on rifampicin, avoid DTG	Normal dose	Normal dose
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
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: Clients on a rifampicin-containing TB regimen: Increase LPV/r to 800/200 mg twice daily slowly over 2 weeks with ALT monitoring. Continue double dose until 2 weeks after stopping rifampicin	Normal dose	Normal dose
Raltegravir (RAL)	400 mg twice daily	Normal dose	Normal dose
Tenofovir (TDF)	300 mg once daily	Avoid use	Avoid use
Zidovudine (AZT)	300 mg twice daily	Normal dose	300 mg daily

3TC = lamivudine; **ABC** = abacavir; **ALT** = Alanine transaminase; **ART** = antiretroviral therapy; **AST** = Aspartate transaminase; **ATV/r** = atazanavir and ritonavir; **AZT** = zidovudine; **CM** = cryptococcal meningitis; **CPT** = cotrimoxazole preventive therapy; **CrAg** = cryptococcal antigen; **DR** = drug-resistant; **DS** = drug-sensitive; **DTG** = dolutegravir; **DRV/r** = darunavir and ritonavir; **EFV** = efavirenz; **eGFR** = estimated glomerular filtration rate; **FBC** = full blood count; **FTC** = emtricitabine; **HBV** = hepatitis B virus; **HBsAg** = hepatitis B surface antigen; **InSTI** = Integrase strand transfer inhibitor; **LPV/r** = lopinavir and ritonavir; **LP** = lumbar puncture; **NRTI** = nucleoside reverse transcriptase inhibitor; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **NVP** = nevirapine; **paed** = paediatric; **PI** = protease inhibitor; **OI** = opportunistic infection; **PJP** = *Pneumocystis jirovecii* pneumonia; **TB** = Tuberculosis; **TBM** = Tuberculosis meningitis; **TDF** = tenofovir; **TLD** = tenofovir + lamivudine + dolutegravir; **TEE** = tenofovir + emtricitabine + efavirenz; **TG** = Triglycerides; **TPT** = TB preventive therapy; **VL** = viral load; **WCC** = white cell count