

SOUTH AFRICAN ART CLINICAL GUIDELINES 2019

ADOLESCENTS (≥ 10 YEARS) AND ADULTS

Second version April 2020

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

ART ELIGIBILITY AND DETERMINING THE TIMEFRAME FOR ART INITIATION	
WHO IS ELIGIBLE?	
All people living with HIV (PLHIV) 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	
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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?				
≥ 10 and < 16 years	eGFR using Counahan Barratt formula [#]				
Adult and adolescent ≥ 16 years	eGFR using MDRD equation as provided by the laboratory				
Pregnant	Absolute creatinine level				
	Safe to use TDF				
	> 80 mL/min/1.73 m ²				
	> 50 mL/min/1.73m ²				
	< 85 μmol/L				
#Counahan Barratt formula					
$eGFR (mL/min/1.73 m^2) = \frac{\text{height [cm]} \times 40}{\text{creatinine } [\mu\text{mol/L}]}$					
Haemoglobin (Hb) To detect anaemia	<table border="1"> <thead> <tr> <th>Adults and adolescents</th> <th>Pregnant women</th> </tr> </thead> <tbody> <tr> <td>If Hb < 10 do FBC, and follow Primary Care Standard Treatment guidelines If Hb < 8 avoid AZT</td> <td>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 drug interactions under key points</td> </tr> </tbody> </table>	Adults and adolescents	Pregnant women	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 drug interactions under key points
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GeneXpert To diagnose TB	<table border="1"> <thead> <tr> <th>Adults and adolescents</th> <th>Pregnant women</th> </tr> </thead> <tbody> <tr> <td>Do GeneXpert only if client has symptoms of TB</td> <td>Routinely done at first antenatal visit, regardless of symptoms</td> </tr> </tbody> </table>	Adults and adolescents	Pregnant women	Do GeneXpert only if client has symptoms of TB	Routinely done at first antenatal visit, regardless of symptoms
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REGIMENS			
RECOMMENDED FIRST-LINE IN NEW CLIENTS			
Adult women and adolescent girls ≥ 35 kg and ≥ 10 years Provide information on risks and benefits of TEE and TLD to allow client to make an informed choice. Document that woman has been counselled and consents to receive DTG	Not pregnant	Not childbearing potential	TLD
	Pregnant	Childbearing potential, not wanting to fall pregnant, provide contraception	TLD
		Childbearing potential, wanting to conceive	TEE
Adult men and adolescent boys ≥ 35 kg and ≥ 10 years of age	First 6 weeks of gestation	TEE	
	After 6 weeks gestation	TLD	
Client currently on DS-TB treatment at ART initiation			TEE
SWITCHING CLIENTS WHO ARE STABLE ON A FIRST-LINE REGIMEN TO DOLUTEGRAVIR			
Latest VL (copies/mL) result (within the past 6 months):			
<ul style="list-style-type: none"> If VL not done within the past 6 months, wait for next routine VL Only switch a stable pregnant woman on ART from EFV to DTG if her VL is < 50 copies/mL AND she is more than 6 weeks pregnant 			
VL < 50	Discuss benefits and risks of switching and the use of contraception in women of childbearing potential. If client chooses to switch to DTG:		
	Current regimen:	New regimen:	
	TDF + (FTC or 3TC) + (EFV or NVP)	TLD	
	(AZT or ABC) [†] + 3TC + (EFV or NVP)	(AZT or ABC) + 3TC + DTG	
VL ≥ 50	Do not switch. Refer to section on viral load monitoring. If the repeat VL after 3 months is ≤ 999, then a switch to DTG can be considered		

[†]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

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 <u>not</u> required	Resistance testing <u>not</u> required	Resistance test required		
RESISTANCE TEST RESULTS	Not applicable		No PI or InSTI resistance		
HBV CO-INFECTION	HBV-negative	HBV-positive	HBV-negative	HBV-positive	HBV-positive [#] or - negative
NEW REGIMEN	AZT + 3TC + DTG [∞]	TDF + AZT + 3TC/FTC + DTG [∞]	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 ^β
	If DTG not suitable: AZT + 3TC + LPV/r	If DTG not suitable: TDF + 3TC/FTC + LPV/r	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; [∞]Before DTG initiation, all women and adolescent girls of childbearing potential must be appropriately counselled on the potential risk of neural tube defects with DTG use around conception and within the first 6 weeks of pregnancy; ^βWhether remaining on DTG, or switching to DTG, ensure at least one active NRTI in the DTG-containing regimen

KEY POINTS ON THE USE OF DTG vs EFV	
	Dolutegravir
Resistance	<ul style="list-style-type: none"> Provides rapid viral suppression High genetic barrier to resistance
Side-effects	<ul style="list-style-type: none"> Side-effects are mild and uncommon Weight gain Insomnia
Interactions[∞]	<ul style="list-style-type: none"> Drug interactions with rifampicin, metformin, some anticonvulsants and polyvalent cations (Mg²⁺, Fe²⁺, Ca²⁺, Al³⁺, Zn²⁺) No interaction with hormonal contraceptives
Pregnancy	<ul style="list-style-type: none"> DTG may increase the risk of neural tube defects (NTDs) if used in the first six weeks of pregnancy
	Efavirenz
Resistance	<ul style="list-style-type: none"> Low genetic barrier to resistance
Side-effects	<ul style="list-style-type: none"> Neuropsychiatric side-effects
Interactions[∞]	<ul style="list-style-type: none"> No significant interaction with rifampicin Drug interactions with hormonal contraceptives, and many other medicines metabolised by the liver
Pregnancy	<ul style="list-style-type: none"> Safe in pregnancy

[∞]For more information on drug-drug interactions contact the National HIV- & TB HCW hotline at 0800 212 506

Based on the 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates, Updated March 2020

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FOLLOW-UP MONITORING IN CLIENTS ON ART									
CLINICAL ASSESSMENT AND RESPONSE									
<ul style="list-style-type: none"> Weight Screen for TB and other OIs WHO clinical staging 	<ul style="list-style-type: none"> 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	<table border="1"> <thead> <tr> <th>VL</th> <th>RESPONSE</th> </tr> </thead> <tbody> <tr> <td>≥ 1000</td> <td>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 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)</td> </tr> <tr> <td>50 – 999</td> <td>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</td> </tr> <tr> <td>< 50</td> <td>Continue routine VL monitoring and routine adherence support. Client is doing well</td> </tr> </tbody> </table>	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. 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
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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 with 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 TG 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 (0800 212 506)

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 for 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; ART = antiretroviral therapy; 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; 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; 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; TC = Total cholesterol; TG = Triglycerides; VL = viral load