# 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<br>Confirmed DS-TB at non-neurological site:<br>CD4 < 50 cells/μL: within 2 weeks of starting TB treatment<br>CD4 ≥ 50 cells/μL: 8 weeks after starting TB treatment<br>Confirmed DR-TB at non-neurological site:<br>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<br>TBM (DS or DR): 4 - 8 weeks after starting TB treatment<br>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**<br>To confirm HIV status for those without documented HIV status | Ensure that the national testing algorithm has been followed |
| **CD4 count (cells/μL)**<br>To identify eligibility for CPT and CrAg screening | Initiate CPT if CD4 < 200 or WHO stage 2, 3 or 4<br>If **CD4 < 100** a reflex CrAg screening will be done automatically<br>**CrAg-negative:** no fluconazole therapy required. Start ART<br>**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**<br>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**<br>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**<br>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)**<br>To detect anaemia | If Hb < 10 do FBC, and follow Primary Care Standard Treatment guidelines<br>If Hb < 8 avoid AZT | If Hb < 10 initiate iron supplementation<br>Refer if: Hb < 8 with symptoms of anaemia, or anaemia and ≥ 36 weeks pregnant, or no response to iron<br>*Take note of DTG drug interactions under key points* |
| **GeneXpert**<br>To diagnose TB | 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

| | | | |
|---|---|---|---|
| **Adult women and adolescent girls ≥ 35 kg and ≥ 10 years**<br>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 |
| | | Childbearing potential, not wanting to fall pregnant, provide contraception | TLD |
| | | Childbearing potential, wanting to conceive | TEE |
| | Pregnant | First 6 weeks of gestation | TEE |
| | | After 6 weeks gestation | TLD |
| **Adult men and adolescent boys** ≥ 35 kg and ≥ 10 years of age | | | 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):

- 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 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[∞]<br>If DTG not suitable:<br>AZT + 3TC + LPV/r | TDF + AZT + 3TC/FTC + DTG[∞]<br>If DTG not suitable:<br>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[β] | 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; [β]Whether 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 | Efavirenz |
|---|---|---|
| **Resistance** | • Provides rapid viral suppression<br>• High genetic barrier to resistance | • Low genetic barrier to resistance |
| **Side-effects** | • Side-effects are mild and uncommon<br>• Weight gain<br>• Insomnia | • Neuropsychiatric side-effects |
| **Interactions[ϖ]** | • Drug interactions with rifampicin, metformin, some anticonvulsants and polyvalent cations ($Mg^{2+}$, $Fe^{2+}$, $Ca^{2+}$, $Al^{3+}$, $Zn^{2+}$)<br>• No interaction with hormonal contraceptives | • No significant interaction with rifampicin<br>• Drug interactions with hormonal contraceptives, and many other medicines metabolised by the liver |
| **Pregnancy** | • DTG may increase the risk of neural tube defects (NTDs) if used in the first six weeks of pregnancy | • Safe in pregnancy |

[ϖ]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

- 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**<br>At 1 year on ART | Repeat CD4 6 monthly **only** if CD4 < 200 **or** VL ≥ 1000<br>Stop CD4 monitoring if VL < 1000 and CD4 > 200. Stop CPT if CD4 > 200 |
| **Viral Load (VL)**<br>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. Repeat VL in 3 months<br>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<br>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<br>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<br>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<br>**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<br>NB: Clients on a rifampicin-containing TB regimen:<br>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