PHC Chapter 11: Human immunodeficiency virus and acquired immune deficiency syndrome (HIV AND AIDS)

HIV infection in adults and adolescents (10-19 years old)

HIV INFECTION IN ADULTS AND ADOLESCENTS (10-19 YEARS OLD)

Consult the most recent HIV Guidelines from the National Department of Health.
https://www.knowledgehub.org.za/elibrary/national-consolidated-guidelines-management-hiv-adults-adolescents-children-and-infants

DESCRIPTION

HIV replicates in CD4 lymphocytes and monocytes, leading to progressive destruction of CD4 lymphocytes and impaired immunity.
Primary infection is characterised by:

» glandular fever-type illness
» maculopapular rash
» small orogenital ulcers

After primary infection, patients may have generalised lymphadenopathy and are usually asymptomatic for several years. Subsequently, if untreated, inflammatory skin conditions and an increased frequency of minor infections occur, followed by more severe infections (especially tuberculosis), weight loss and/or chronic diarrhoea. Eventually severe opportunistic infections, HIV-associated cancers, or other severe HIV manifestations develop, known as the Acquired Immune Deficiency Syndrome (AIDS).

DIAGNOSIS

» Provide adequate pre- and post-test counselling.
» Ensure patient confidentiality.
» A positive rapid HIV test in adults must be confirmed with a 2nd rapid test from a different manufacturer. If the screening and confirmation rapid test result differ, repeat the tests. If the repeated test series differ, do a laboratory test (usually ELISA).
» HIV antibodies are not detected during the 1st few weeks after infection. This is known as the window period.

PROGNOSIS

» Progression of HIV diseases is variable. The CD4 lymphocyte count and clinical features of immune suppression (see WHO staging below) both provide independent information on prognosis. Patients may be asymptomatic with very low CD4 counts or have severe clinical features with well-preserved CD4 counts. CD4 counts < 200 cells/mm^3 indicate severe immune suppression. All HIV-infected patients must have a CD4 count and WHO clinical staging done at diagnosis.
» All PLHIV are eligible for ART, irrespective of CD4 count or WHO stage. Patients should be counselled about the benefits and risks of early ART initiation, and encouraged to initiate ART as soon as feasible. However, should a patient elect to defer ART, the CD4 count should be repeated every 6 months until ART can be initiated.

South African modified WHO staging of HIV/AIDS for adults and adolescents

Clinical stage 1

» Asymptomatic.

» Persistent generalised lymphadenopathy.

Clinical stage 2
» Unexplained moderate weight loss (< 10% of presumed or measured body weight).
» Recurrent respiratory tract infections (sinusitis, otitis media and pharyngitis).
» Herpes zoster (shingles).
» Angular stomatitis.
» Recurrent oral ulceration.
» Papular pruritic eruption.
» Seborrhoeic dermatitis.
» Fungal nail infections.

Clinical stage 3
» Unexplained severe weight loss (> 10% of presumed or measured body weight).
» Unexplained chronic diarrhoea for > 1 month.
» Unexplained persistent fever (> 37.5ºC intermittent or constant for > 1 month).
» Persistent oral candidiasis (thrush).
» Oral hairy leukoplakia.
» Pulmonary TB.
» Severe bacterial infections (such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, or bacteraemia).
» Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis.
» Unexplained anaemia (< 8 g/dL), neutropaenia (< 0.5 × 109/L) and/or chronic thrombocytopaenia (< 50 × 109/L).

Clinical stage 4
» HIV wasting syndrome.
» Extrapulmonary tuberculosis.
» Pneumocystis pneumonia.
» Recurrent severe bacterial pneumonia.
» Chronic herpes simplex infection (orolabial, genital or anorectal of > 1 month duration or visceral at any site).
» Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs).
» Kaposi's sarcoma.
» Cytomegalovirus infection (retinitis or infection of other organs).
» Central nervous system toxoplasmosis.
» HIV encephalopathy.
» Extrapulmonary cryptococcosis including meningitis.
» Disseminated non-tuberculous mycobacterial infection.
» Progressive multifocal leukoencephalopathy.
» Chronic cryptosporidiosis.
» Chronic isosporiasis.
» Disseminated mycosis (extrapulmonary histoplasmosis or coccidiomycosis).
» Recurrent septicaemia (including non-typhoidal Salmonella).
» Lymphoma (cerebral or B cell non-Hodgkin).
» Invasive cervical carcinoma.
» Atypical disseminated leishmaniasis.

» Symptomatic HIV-associated nephropathy or symptomatic HIV-associated cardiomyopathy.

GENERAL MEASURES

» Patients and their families must be supported and encouraged to join support or peer groups.
» Counsel patients on methods to reduce the spread of HIV:
- use condoms during sexual intercourse
- ART in HIV-infected. See Section 11.1: Antiretroviral therapy.
- PrEP where indicated. See Section 11.11: Pre-exposure prophylaxis (PrEP)
- seek early treatment for sexually transmitted infections. See chapter 11: Sexually transmitted infections.
- safe handling of blood spills.

11.1 ANTIRETROVIRAL THERAPY, ADULTS AND ADOLESCENTS (10-19 YEARS OLD)

B24

Antiretroviral therapy (ART) suppresses viral replication (measured with the viral load test), increases the CD4 count and reduces HIV-associated diseases and death. ART guidelines are regularly updated, so it is important to consult the current National Guidelines.

ELIGIBILITY FOR ART

All adults with confirmed HIV infection, irrespective of CD4 count or WHO clinical stage.

Timing of ART initiation: *LoE: Ia*[1]

ART may be started on the day of diagnosis if the patient has no clinical contraindication, and the patient is willing to start after receiving pre ART counselling. For clinical indications for deferring ART initiation, see below.

Immediate initiation:

Initiate ART immediately in pregnancy and during breastfeeding if the patient has no clinical contraindication. *LoE:IIa*[2]

Clinical indications for deferring ART initiation:

Early ART initiation increases the risk of the immune reconstitution inflammatory syndrome (IRIS) (see Section 11.13.1: Immune Reconstitution Inflammatory Syndrome (IRIS)). Defer ART in patients with cryptococcal meningitis (see Section 11.3.4.2: Cryptococcal meningitis) or TB meningitis (see Section 10.17: Tuberculosis, extrapulmonary) as there is increased risk of mortality due to IRIS with early ART initiation (see below for timing).

TB co-infection:

» In TB co-infection, start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below):
- CD4 counts < 50 cells/mm^3: start ART within 2 weeks of starting TB treatment.

- CD4 count ≥ 50 cells/mm^3: defer ART until 8 weeks after starting TB treatment, which does not increase the risk of mortality and reduces the risk of deterioration due to the immune reconstitution inflammatory syndrome (IRIS).

LoE:Ia[3]

TB meningitis co-infection:

» In patients with TB meningitis (irrespective of CD4 count), defer ART until 8 weeks after starting TB treatment.

LoE:IIIa[4]

Cryptococcal meningitis co-infection:

» Defer ART until 4–6 weeks after starting antifungal treatment (earlier initiation has been shown to increase the risk of death). *LoE:IIIa*[5]

Positive cryptococcal antigen and no evidence for meningitis on LP:

» Defer ART until 2 weeks after initiating fluconazole

LoE:IVb[6]

PSYCHOSOCIAL INDICATORS OF READINESS FOR ART

It is essential that patients have good insight into the need for long-term therapy and high levels of adherence. Give careful attention to adherence planning. Encourage patients to disclose their HIV status to somebody to act as a treatment supporter. If this is not possible then the patient should join a support group.

Manage depression.

Active substance abuse/alcohol is an impediment to adherence and, where possible, should be addressed before initiating ART. *LoE:IIIb*[7]

ART REGIMENS

1ST LINE ART	
Treatment-naïve patients	Adults and adolescents ≥35kg: TDF + 3TC + DTG *LoE:IIa*[8] **Note**: DTG-based regimens are now recommended as first line ART in all adults and adolescents, including women of childbearing potential. *LoE:IIa*[9] Patients with TB: TDF + FTC + EFV OR (if EFV not available): TDF + 3TC + DTG *plus* additional dose of DTG 50mg 12 hours later. *LoE:IIIb*[10] (Also see section 6.8: HIV in pregnancy)
Contraindications/ intolerance to DTG	TDF + 3TC/FTC + EFV
Contraindications to EFV and DTG	Start protease inhibitor-based regimen: TDF + 3TC/FTC + ATV/r *LoE:IIb*[11]

	Note: if patient requires rifampicin-based TB treatment, substitute ATV/r for LPV/r 800/200 mg 12-hourly. The LPV/r can be switched to ATV/r two weeks after completion of TB therapy.
Contraindication to TDF » eGFR <50 mL/minute.	Replace TDF + 3TC/FTC with either ABC + 3TC (preferred) **or** AZT + 3TC *LoE:IIIb*[12]
Contraindication to TDF and ABC intolerance » eGFR <50 mL/minute. » Hypersensitivity.	AZT + 3TC with DTG **or** EFV
Note: In the unlikely scenario where there is intolerance/contraindication to all currently available NRTIs, an alternative dual-therapy regimen may be used, e.g. DTG + 3TC (if no resistance/intolerance to 3TC and VL <500 000 copies/mL) **or** EFV + LPV/r **or** DTG + LPV/r may be used. Consult a specialist. *LoE:IIb*[13]	
2ND LINE ART	
NNRTI-based 1st line regimen failure *(TDF+3TC/FTC+EFV/NVP)*	TDF + 3TC + DTG. *LoE:IIb*[14] If DTG contraindicated/ not tolerated and ***not*** on rifampicin-based TB treatment: TDF + 3TC/FTC + ATV/r *LoE:IIb*[15] If AZT and TDF contraindicated/ not tolerated (e.g. anaemia and renal impairment): ABC + 3TC + DTG
DTG- based 1st line regimen failure for >2 years *(TDF+3TC+DTG)* » Resistance testing for adults and adolescents failing a DTG-based regimen and who meet the definition of confirmed virological failure may be authorized by an expert on a case-by-case basis.	TDF + 3TC/FTC +ATV/r If HBsAg positive: ensure patient is on TDF-containing regimen. *LoE:IIb*[16]
Rifampicin-based TB treatment	If on DTG: Add DTG 50 mg - DTG needs to be given at a dose of 50 mg 12 hourly. If on ATV/r: Switch ATV/r to LPV/r 800/200 mg 12 hourly (i.e. double dose). **Note:** There is an increased risk of ALT/AST elevations and gastrointestinal disorders. Increase LPV/r dose graduallyover 1-2 weeks.
3RD LINE ART	
Any 2nd line regimen failure	Refer to a specialist. **Resistance to ATV/r or LPV/r and/or DTG must be shown on genotype antiretroviral**

	resistance test in order to qualify for 3rd line – this test is expensive and should only be done in patients with at least 2 years' exposure to a PI and objective evidence of good adherence. Application for 3rd line using the standard motivation form is required (available from TLART@health.gov.za or from https://www.righttocare.org/) – the regimen will be determined by an Expert Committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure.

ABC=Abacavir, ATV/r= Atazanavir/ritonavir, 3TC=Lamivudine, TDF=Tenofovir disoproxyl fumarate, AZT=Zidovudine, FTC=Emtricitabine, LPV/r=Lopinavir/ritonavir, DTG=Dolutegravir, EFV= Efavirenz

Table 11.1: ART regimens

Currently available ARV FDC preparations on contract:

- ABC 600 mg + 3TC 300 mg
- TDF 300 mg + FTC 200 mg
- AZT 300 mg + 3TC 150 mg
- LPV 100 mg + ritonavir 25 mg
- LPV 200 mg + ritonavir 50 mg
- TDF 300 mg + FTC 200 mg + EFV 600 mg
- TDF 300mg + DTG 50 mg + 3TC 300 mg
- ATV 300mg + ritonavir 100mg
- ABC 600mg + 3TC 300mg + DTG 50mg

Source: Contract circular HP13-2022ARV http://www.health.gov.za/

RE-INITIATING ART IN PATIENTS WHO HAVE INTERRUPTED TREATMENT

» Recommence previous regimen.
» Do VL, recommence ART regimen, repeat at 3-6 months.
» If VL does not to decrease to <1000 copies per mL at 6 months, manage virological failure according to the specific regiment (refer to ART regimens table).

LoE:IIIb[17]

MONITORING ON ART Standardised national monitoring for adults and adolescents with HIV	
At HIV Diagnosis	» A positive rapid HIV test must be confirmed with a 2nd rapid test from a different manufacturer. If the results differ, do an ELISA test. » WHO staging. » Check CD4 count. – CD4 <100 cells/mm^3: Check cryptococcal antigen (If positive, perform LP regardless of whether symptoms are present or not). *LoE:IVb*[18] – CD4 <200 cells/mm^3: Initiate cotrimoxazole prophylaxis. » Screen for mental health disorders, STIs, and NCDs. » Screen for TB symptoms (any one of cough, fever, night sweats, or weight loss). If positive, investigate for TB with a sputum Xpert MTB/RIF Ultra ®. Also do urine LAM if severely ill or CD4 ≤100 cells/mm^3. » In all pregnant women do sputum XpertMTB/RIF Ultra® at HIV diagnosis. *LoE:IIb*[19]
Prior to initiating ART	» If planning to use TDF: check creatinine (avoid TDF if eGFR <50 mL/minute). *LoE:IIIb*[20] » If planning to use AZT: Check Hb, and if abnormal, do FBC (avoid AZT if Hb <8 g/dl). » Check HBsAg (if positive, TDF should form part of the regimen).
On ART	» VL at 6 and 12 months after initiating ART and every 12 months thereafter, if virologically suppressed (VL<50 copies/mL) (See Figure 11.1). » CD4 at 12 months after initiating ART. Stop CD4 count monitoring when >200 cells/mm^3 and virologically suppressed. However, if virological or clinical failure occurs, check CD4 count as cotrimoxazole may need to be commenced/recommenced. Repeat CD4 count every 6 months if VL remains > 1000 copies/mL » If on TDF: creatinine at 3, 6 and 12 months after initiation, and every 12 months thereafter. » If on AZT: FBC and differential count at 3 and 6 months after initiating AZT, then every 12 months. » ALT if symptoms of hepatitis develop. » If on a protease inhibitor (PI): Fasting cholesterol and triglycerides at 3 months after initiating PI.

Table 11.2: Monitoring for adults and adolescents with HIV on ART

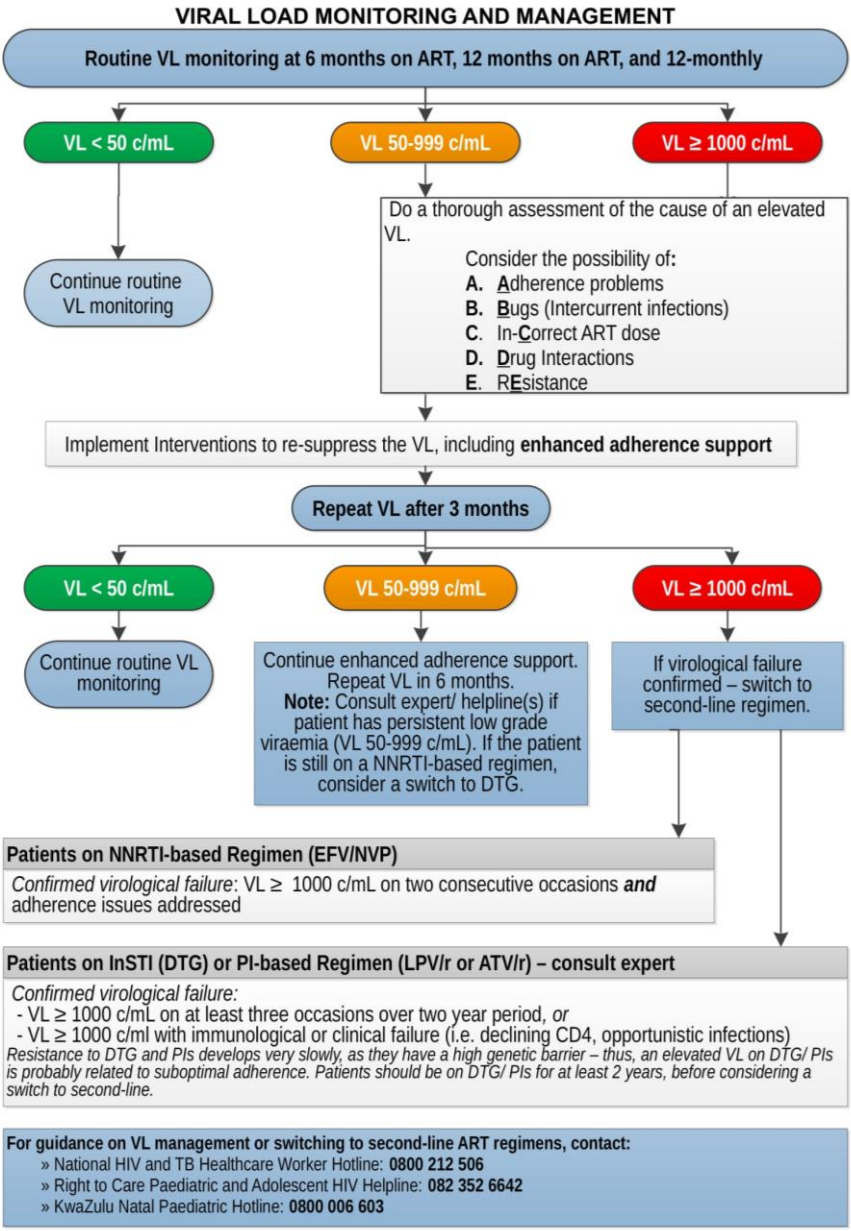

Figure 11.1: Viral load monitoring and management

LoE:IIIb[21]

ART: DOSING AND IMPORTANT ADVERSE EFFECTS

Generic name	Class	Usual dose	Renal adjusted dose	Important adverse drug reactions and timing
Tenofovir (TDF)	NRTI	300 mg daily	Avoid in renal impairment (eGFR <50 mL/min)	» Acute kidney injury (rare - weeks to months). » Decline in eGFR (months to years) » Fanconi syndrome (rare – months to years) » Reduced bone mineral density (months to years).
Abacavir (ABC)	NRTI	600 mg daily	Dose adjustment not required	» Hypersensitivity reaction (1 to 6 weeks): fever, rash, constitutional symptoms, gastrointestinal symptoms and respiratory symptoms.
Zidovudine (AZT)	NRTI	300 mg 12 hourly	eGFR <10 mL/min: 300 mg daily	» Anaemia, neutropenia (weeks to months). » Gastro-intestinal upset. » Headache. » Myopathy (rare). » Hyperlactataemia / steatohepatitis (medium risk - months). » Lipoatrophy (months to years).
Lamivudine (3TC)	NRTI	300 mg daily (or 150 mg 12 hourly)	eGFR 10-50 mL/min: 150 mg daily CrCl <10 mL/min: 50 mg daily	» Anaemia due to pure red cell aplasia (rare).
Emtricitabine (FTC)	NRTI	200 mg daily	eGFR 30-50 mL/min: 200 mg every 2 days eGFR 15-29 mL/min: 200 mg every 3 days eGFR <15 mL/min: 200 mg every 4 days	» Palmar hyperpigmentation. » Anaemia due to pure red cell aplasia (rare). *LoE:IVb*[22]
Efavirenz (EFV)	NNRTI	600 mg at night	Dose adjustment not required	» Central nervous system symptoms: vivid dreams, problems with concentration, confusion, mood disturbance, psychosis (days to weeks). » Encephalopathy, often with cerebellar features (uncommon – months to years). » Rash (1 to 6 weeks). *LoE:IVb*[23] » Hepatitis (weeks to months) » Gynaecomastia.
Lopinavir/ ritonavir	Boosted PI	400/100 mg 12-hourly	Dose adjustment not required	» Gastrointestinal upset. » Dyslipidaemia (weeks). » Rash and/or hepatitis (1 to 6 weeks).

(LPV/r)		**OR** 800/200 mg daily (only if PI-naïve)		
Atazanavir/ ritonavir (ATV/r)	Boosted PI	300 mg with ritonavir 100 mg daily	Dose adjustment not required	» Unconjugated hyperbilirubinaemia (common, but benign). » Dyslipidaemia (low risk). » Hepatitis (rare - 1 to 6 weeks). » Renal stones (uncommon).
Dolutegravir (DTG)	InSTIs	50 mg once daily	Dose adjustment not required	» Hypersensitivity (rare, weeks) » Insomnia (common) » Headache (common) » Other neuropsychiatric symptoms » Nausea, diarrhea (common) » Hepatitis (uncommon) » Increase in serum creatinine due to inhibition of creatinine secretion by DTG; this is clinically insignificant as glomerular filtration rate is not reduced but will modestly affect eGFR which is determined using serum creatinine.

Table 11.3: Dosing and important adverse effects associated with ART

The time-onset information with respect to adverse drug reactions (ADRs) serves as an estimate. Patients may present with ADRs with the onset deviating from that indicated in the table. InSTI: integrase strand transfer inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

LoE:IIIb[24]

ART: DRUG-DRUG INTERACTIONS

Information can be accessed from:

» https://www.hiv-druginteractionslite.org/checker
» http://www.mic.uct.ac.za/ and download the ARV/EML interaction checker.
» Package inserts.

ART INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR ADMINISTRATION			
Class	**ARV**	**Interaction with rifampicin**	**Dose of ARV with rifampicin**
NRTI	3TC/FTC/TDF/ AZT/ABC	No clinically significant pharmacokinetic interactions	No dose adjustment required.
NNRTI	EFV	Non-significant change (EFV concentrations may increase in patients who are genetic slow metabolisers of EFV due to inhibition by isoniazid (INH)	No dose adjustment required (600 mg at night).
InSTI	DTG	Significant reduction in concentration of DTG	Increased dose frequency to 50 mg 12 hourly.*
PI	LPV/r	LPV plasma concentrations significantly decreased	Double the dose of LPV/r to 800/200 mg 12-hourly. **Note: There is an increased risk of ALT/AST elevations and gastrointestinal disorders. Increase dose gradually over 1-2 weeks.**
	All other PIs	Marked reduction in PI concentrations	Do not prescribe concomitantly – replace rifampicin with rifabutin 150 mg daily.

Continue increased dose for 2 weeks after rifampicin is stopped, then decrease to usual dose.

Table 11.4: ART interactions with rifampicin and dose-adjustment recommendations *LoE:IIIb*[25]

In patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with rifabutin (doctor prescribed) – see Adult Hospital Level STGs and EML. section 10.1: Antiretroviral therapy.

DRUG INTERACTIONS WITH DOLUTEGRAVIR		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Preparations containing polyvalent cations (Mg^{2+}, Ca^{2+}, Fe^{2+}, Al^{3+}, Zn^{2+}) Antacids Sucralfate Mineral supplements	Significant reduction in concentration of DTG	Magnesium- and aluminum-containing preparations should be taken 6 hours before or 2 hours after DTG Calcium- and iron- containing preparations can be taken with DTG together with food.

		Note: Iron and calcium should be taken at least 4 hours apart from one another.
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in DTG concentration	Avoid co-administration if possible. Consider valproate or lamotrigine. *For carbamazepine:* Double DTG dose to 50 mg 12 hourly.
Metformin	Significant increase in metformin concentration	Administer metformin to a maximum of 500 mg 12 hourly.
Rifampicin	Significant reduction in DTG concentration	Double DTG dose to 50 mg 12 hourly.

Table 11.5: Drug interactions with DTG *LoE:IIIb*[26]

DRUG INTERACTIONS WITH BOOSTED PIs		
Interacting medicine	**Effect of co-administration**	**Recommendation**
Substrates of cytochrome P450 3A4 (e.g. most statins, calcium channel blockers, most SSRIs, most benzodiazepines)	Significant increase in concentrations of CYP3A4 substrates	Avoid co-administration or use lower doses of CYP3A4 substrates (always consult interaction resources)
Anticonvulsants: Carbamazepine Phenobarbital Phenytoin	Significant reduction in concentration of PI	Avoid co-administration. Consider valproate or lamotrigine.
Proton pump inhibitors	Significant reduction in ATV concentration	Avoid co-administration. *LoE:IIIb*[27]
Rifampicin	Significant reduction in PI concentration	Double LPV/r dose. Avoid co-administration of other PIs (replace rifampicin with rifabutin)

Table 11.6: Drug interactions with boosted PIs

REFERRAL

Second-line ART regimen failures.

11.2 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN ADULTS

11.2.1 COTRIMOXAZOLE PROPHYLAXIS

Z29.2 + (B24)

DESCRIPTION

Primary prophylaxis reduces the probability of developing many infections, e.g.:

- » pneumocystis pneumonia
- » toxoplasmosis
- » bacterial pneumonia
- » bacteraemia
- » cystoisosporiasis

Indications for primary prophylaxis:
» WHO Clinical stage 2, 3 or 4.
» CD4 count < 200 cells/mm^3. *LoE:IIIb*[28]

MEDICINE TREATMENT

Prophylaxis
- Cotrimoxazole, oral, 160/800 mg daily. *LoE:IIb*[29]

Note:
» Once the CD4 >200 cells/mm^3 discontinue prophylaxis. If the CD4 count was >200 cells/mm^3 when cotrimoxazole was commenced (e.g. patients with TB) continue for 6 months (See Section 17.3.4.2.4: Pneumocystis pneumonia for secondary prophylaxis).
» Cotrimoxazole hypersensitivity is common and usually presents as a maculopapular rash. If there are systemic features or mucosal involvement associated with the use of cotrimoxazole, stop the medicine immediately and permanently and refer the patient to hospital.

LoE:IIIb[30]

11.2.2 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Z29.2 + (B24)

PLHIV are more susceptible to TB infection than HIV-uninfected people at any CD4 count. TPT is an effective intervention for reducing the incidence of TB in PLHIV.

Eligibility
All adult PLHIV, irrespective of CD4 count and ART status.

Exclusions
» suspected or confirmed TB
» liver disease
» previous MDR- or XDR-TB
» painful peripheral neuropathy
» alcohol use disorder

Note:
» Exclude TB before initiating TPT by screening for the following:
  - cough (any duration)
  - cever
  - weight loss
  - night sweats
» Do not start TPT if any of the above symptoms are present. These patients require further investigation for active TB.

Start TPT together with ARVs:
- TPT, e.g.: *LoE:IIb*[31]
- Isoniazid, oral, 300 mg daily for 12 months.

Note: Ideally start TPT together with ARVs. However, if a rifapentine-containing TPT regimen is available, it should only be initiated together with an EFV-based ART regimen. A rifapentine-containing TPT regimen can be used with a DTG-based ART regimen in patients who are already virally suppressed. Do not use in patients on protease inhibitor-based ART, or in women on oral or hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen].* *LoE:IIb*[32]

ADD

- Pyridoxine, oral, 25 mg once daily for 12 months.
  - Educate patients on the symptoms of hepatotoxicity (nausea, vomiting, yellow eyes, brown urine, and pain in right upper quadrant).
  - Instruct patient to present early if any of these symptoms arise.
  - Follow patients up monthly for the first 3 months.

In pregnant women, starting ART:

» If CD4 >350 cells/mm^3. » Defer TPT until after delivery.	» If CD4 ≤350 cells/mm^3. » Exclude active TB with symptom screen and TB Xpert MTB/RIF Ultra ®, then give TPT. *LoE:IIIa*[33]

11.3 OPPORTUNISTIC INFECTIONS, TREATMENT IN ADULTS

11.3.1 APHTHOUS ULCERS IN HIV INFECTION

K12.0 + (B24)

DESCRIPTION

Painful ulcers in the mouth, except the gums, hard palate and dorsum of the tongue.
Minor ulcers (< 1 cm diameter) usually heal within 2 weeks.
Major ulcers (> 1 cm diameter) are very painful, often very deep, and persistant. Major ulcers generally resolve rapidly on ART.
Herpes simplex, histoplasmosis and mycobacteria may also present with major mucosal ulcers.

MEDICINE TREATMENT

Minor aphthous ulcers:

- Tetracaine 0.5 %, oral, topical, applied every 6 hours.
  - Apply a thin layer on the affected areas only.

REFERRAL

Major aphthous ulcers for further diagnostic evaluation.

11.3.2 CANDIDIASIS, ORAL

B20.4

See Section 1.2: Candidiasis, oral (thrush).

- Commence ART.

11.3.3 CANDIDIASIS, OESOPHAGEAL

B20.4

DESCRIPTION

Infection of the oesophagus with candida, a fungus causing oral thrush.
Patients with oral thrush who have pain or difficulty on swallowing may have oesophageal candidiasis.
See Section 1.2: Candidiasis, oral (thrush).

GENERAL MEASURES

Maintain hydration.

MEDICINE TREATMENT

- Fluconazole, oral, 200 mg daily for 14 days.
- Commence ART within 7 days (unless patient has cryptococcal or TB meningitis). See section: 11.1 Antiretroviral therapy, adults.

LoE:IIIb[34]

REFERRAL

» Inability to swallow.
» Frequent relapses.
» Poor response to fluconazole.

11.3.4 CRYPTOCOCCOSIS

B20.5

DESCRIPTION

A life-threatening fungal infection caused by the fungus Cryptococcus. The fungi remain inactive unless a person's immune system is weakened, such as in transplant recipients or persons with untreated HIV.

INVESTIGATIONS

» All ART-naïve patients with CD4 < 100 cells/mm^3 should have a serum cryptococcal antigen (CrAg) test done (unless confirmed diagnosised of cryptococcal infection).
» All patients with a positive serum CrAg test should have a lumbar puncture (LP) to exclude cryptococcal meningitis. The CSF is tested for cryptococcal meningitis by CSF CrAg.

LoE:IIa[35]

MEDICINE TREATMENT

<u>If CSF CrAg positive:</u>
Refer for amphotericin B, IV (induction phase) - See Adult Hospital STGs and EML, Section 10.2.4: Cryptococcosis.
Patients may be down referred for secondary prophylaxis; see maintenance phase, below.

<u>If there is any delay in performing LP, start oral fluconazole therapy:</u>

- Fluconazole, oral, 1200 mg immediately.

LoE:IVb[36]

<u>No symptoms present and CSF CrAg negative (LP):</u>

Induction phase

- Fluconazole, oral 1200 mg daily for 14 days.

LoE:IIIb[37]

Consolidation phase

Follow with:

- Fluconazole, oral, 800 mg daily for 8 weeks.

Maintenance phase

- Fluconazole, oral, 200 mg daily.
  - **Continue for at least 1 year provided that the CD4 count increases to >200 cells/mm^3 on ART. If the CD4 count does not increase continue treatment indefinitely.**

LoE:IIIb[38]

- Commence ART: See section 10.1: Antiretroviral therapy.
  - Cryptococcal meningitis: After 4–6 weeks after starting antifungal therapy.
  - Asymptomatic cryptococcosis: After completion of the induction phase i.e. at 2 weeks after starting antifungal therapy.

LoE:IIIb[39]

CAUTION

» Fluconazole is potentially teratogenic when used during the 1st trimester, but pregnant women should be counselled that the benefits of fluconazole likely outweigh the risks in the management of cryptococcosis.

» All pregnant women <20 weeks gestation exposed to fluconazole should have an ultrasound scan to detect congenital abnormalities. *LoE:IIIb*[40]

» Although fluconazole is excreted into breast milk at concentrations similar to maternal plasma concentrations, the dose that the infant is exposed to with doses <400 mg is similar to the dose used in systemic treatment in infants. Even for higher doses, the benefits will likely outweigh the risks, though this can be discussed with a specialist.

LoE:IVb[41]

REFERRAL

» If LP unavailable: Refer all serum CrAg positive patients for LP

» If LP available:
  - Refer all patients with CSF CrAg positive (cryptococcal meningitis).
  - Refer all symptomatic patients with CSF CrAg negative (non-meningeal cryptococcosis).

» All patients with complications.

11.3.5 DIARRHOEA, HIV-ASSOCIATED

B20.8 + (A07.2-3)

DESCRIPTION

Diarrhoea that persists for > 2 weeks.
Often associated with wasting.
Diarrhoea persisting for 4 weeks is a WHO stage 3 condition (if there is weight loss or fever it is stage 4).

Send stool sample to look for ova, cysts and parasites in all cases.
Note: A negative stool specimen does not exclude *Cryptosporidium*. If cryptosporidium infection is suspected, request specific laboratory testing for the parasite.

MEDICINE TREATMENT

If stool is negative for parasites or shows *Cryptosporidium*:

- Loperamide, oral, 2 mg as required.
  - Maximum 8 mg daily.
- Commence ART.

If stool shows *Isospora belli*:

- Cotrimoxazole, oral, 320/1600 mg (4 tablets) 12 hourly for 10 days.
  - Followed by 160/800 mg (2 tablets) daily until CD4 > 200 cells/mm^3 on ART.
- Commence ART.

REFERRAL

Stool contains blood or mucus.

11.3.6 ECZEMA, SEBORRHOEIC

See section 5.8.3: Dermatitis, seborrhoeic.

11.3.7 FUNGAL NAIL INFECTIONS

B20.5

This is common in PLHIV and can involve multiple nails. Treatment is not generally recommended because it is mostly of only cosmetic importance and therefore the risk of systemic therapy is not warranted. It generally resolves when patient is on ART.

11.3.8 FUNGAL SKIN INFECTIONS

B20.5

See Section 5.5: Fungal infections of the skin.

11.3.9 GINGIVITIS, ACUTE NECROTISING ULCERATIVE

See Section 1.3.3: Necrotising periodontitis.

11.3.10 HERPES SIMPLEX ULCERS, CHRONIC

B20.3 + (B00.1-2)

DESCRIPTION

Painful ulcers due to herpes simplex virus, involving the skin around the anogenital area or in and around the mouth and nostrils in patients with advanced HIV infection. Ulcers persist for weeks and may be several centimetres in diameter.

GENERAL MEASURES

Keep affected areas clean with soap and water or diluted antiseptic solution.

MEDICINE TREATMENT

- Antiviral (active against herpes simplex) e.g.: *LoE: IIIb*[42]
- Aciclovir, oral, 400 mg 8 hourly for 7 days.
- Commence ART.

Pain:

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

REFERRAL
» No response to therapy.
» Frequent recurrences

11.3.11 HERPES ZOSTER (SHINGLES)
B20.3 + (B02.0-3/B02.7-9)

DESCRIPTION
Painful vesicular rash in a dermatomal distribution, usually presenting as a band on one side of the body, due to recrudescence of the varicella-zoster virus that causes chickenpox. The surrounding skin is inflamed and the vesicles often contain cloudy fluid. Secondary bacterial infection is very uncommon.
The elderly and HIV-infected are most affected.
Severe pain can occur after shingles has healed (post-herpetic neuralgia).
Shingles is less infectious than varicella and isolation is not warranted.

MEDICINE TREATMENT
<u>If fresh vesicles are present:</u>
- Antiviral (active against herpes zoster) e.g.:
- Aciclovir, oral, 800 mg five times daily for 7 days (4 hourly missing the middle of the night dose). *LoE:IIa*[43]

<u>If secondary infection is present:</u>
ADD
- Flucloxacillin, oral, 500 mg 6 hourly for 5 days.

Pain:
- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

<u>If inadequate pain relief</u>
ADD
- Tramadol, oral, 50 mg 6 hourly (Doctor prescribed).

For prolonged pain occurring after shingles has healed (post-herpetic neuralgia), or if pain not responding to paracetamol and tramadol:
- Amitriptyline, oral, 25 mg at night.
  - Increase dose to 50 mg after two weeks if needed.
  - Increase further to 75 mg after a further two weeks if needed.

REFERRAL
» Involvement of the eye.
» Disseminated disease (many vesicles extending beyond the main area).
» Features of meningitis (headache and neck stiffness).
» Severe post-herpetic neuralgia not responding to amitriptyline.

11.3.12 PAPULAR PRURITIC ERUPTION

L29.8

DESCRIPTION

Itchy inflamed papules at different stages of evolution. Healed lesions are often hyperpigmented. The itch is difficult to manage. May flare after starting ART, but generally improves as the CD4 count increases. It is essential to exclude scabies.

GENERAL MEASURES

Minimise exposure to insect bites, e.g. by regularly dipping pets.

MEDICINE TREATMENT

- Cetirizine, oral, 10 mg daily.
- Hydrocortisone 1%, topical cream, applied twice daily for 7 days.
  - Apply sparingly to the face.

11.3.13 PNEUMONIA, BACTERIAL

See Section 17.3: Respiratory infections.

11.3.14 PNEUMONIA, PNEUMOCYSTIS

See Section 17.3.4.2.4: Pneumocystis pneumonia.

11.3.15 TOXOPLASMOSIS

B20.8

Initial diagnosis can only be made at hospital level.

MEDICINE TREATMENT

- Cotrimoxazole, oral, 320/1600 mg 12 hourly for 4 weeks.
  - Then 160/800 mg 12 hourly for 12 weeks.

Secondary prophylaxis

- Cotrimoxazole, oral 160/800 mg daily.
  - Continue until the CD4 count has risen to >200 cells/mm^3 on ART.
- Commence ART.

11.3.16 TUBERCULOSIS (TB)

See Section 17.4: Pulmonary tuberculosis (TB).

11.4 HIV AND KIDNEY DISEASE

N04.9/N05.9/N17.9 + (B24)

DESCRIPTION

Various forms of kidney disorders are described among PLHIV.
Early detection of HIV kidney disease may be beneficial in an attempt to protect the kidney from further disease progression and for adjusting the dose of relevant medicines (See table: Antiretroviral medicines: Dose and common adverse drug reactions, section: 11.1 Antiretroviral therapy, adults).
Screen all patients for renal disease at time of HIV diagnosis.

Patients at high risk or susceptible for HIV renal disease include:
» CD4 count < 200 cells/mm^3.
» History of nephrotoxic medications.
» Comorbidity such as diabetes mellitus, hypertension, or hepatitis C virus co-infection.

Screening for renal disease in HIV
» Tests should include:
  - Urine dipstix for haematuria and proteinuria.
  - Serum creatinine and eGFR.
» If there is no evidence of kidney disease at the initial evaluation, repeat screening annually.
» Monitor creatinine/eGFR on initiation and at months 3, 6, 12 and then 12 monthly for patients receiving tenofovir.

REFERRAL
» Patients with persistent significant proteinuria (1+ or more).
» Unexplained haematuria on 2 consecutive visits
» Estimated eGFR < 60 mL/min.

HIV INFECTION IN CHILDREN (<10 YEARS OLD)

DESCRIPTION

HIV is a retrovirus affecting immune cells, especially CD4 T-lymphocytes. In advanced HIV disease the body loses its ability to fight infections and this is characterised by organ damage, opportunistic infections, malignancies and very low CD4 counts.

In infants and children, most infection is transmitted from mother to child. In adolescents and adults sexual spread is the usual cause.

Infants born of HIV-infected mothers may be:

» HIV-infected,
» HIV-exposed uninfected, or
» HIV-exposed, unknown infection status (at risk of becoming HIV-infected).

For the purpose of the ART guidelines:

» Children <10 years of age: follow the paediatric antiretroviral therapy (ART) guidelines.
» Adolescents (10–19 years of age): follow the adult ART guidelines. *LoE:IIIb*[44]

DIAGNOSIS IN CHILDREN

Testing must be done with counselling of parent/legal guardian/primary caregiver and, where appropriate, the child. The appropriate consent/assent should be obtained.

WHEN AND HOW TO TEST IN CHILDREN

Which test

Child <18 months of age

HIV PCR test: Always confirm with 2nd HIV PCR test if the first test is positive. Do not delay ART initiation; start ART with the first positive result.

Child ≥ 18 months of age

HIV rapid or ELISA test: If 1st rapid test is positive, confirm the result with:

» A HIV PCR test if infant between 18-24 months
» A second rapid test using a kit of a different manufacturer, and preferably on a different blood specimen if infant is > 24 months.
» HIV rapid tests may be less reliable in children with advanced disease. If clinical findings suggest HIV infection but the rapid test is negative, send a further specimen of blood to the laboratory for HIV ELISA testing. If HIV status is still unclear, do an HIV PCR test.

When to test HIV-exposed children (See section: 11.5 The HIV-exposed infant).

» Birth (HIV PCR).
» Repeat at 10-week visit (HIV PCR).
» Repeat at 6-month visit (HIV PCR)
» At any time when clinical signs indicate possible HIV infection.
» 6 weeks after breastfeeding has stopped.
» Do Universal HIV rapid/ELISA test at 18 months (HIV rapid test for ALL children regardless of HIV exposure, except in those who previously tested HIV positive and are on ART). *LoE:IIIb*[45]

Also perform PCR testing AT BIRTH on:
» Infants born to mothers who were on TB treatment for active TB during their pregnancy.
» Infants with congenital pneumonia.
» Infants with clinical features suggestive of HIV infection.
» High risk infants requiring urgent HIV diagnosis.

If the HIV PCR result is not available at discharge, the mother must return within 1 week for the result.

» If the HIV PCR result is negative, repeat at 10 weeks:
  - If HIV PCR result at 10–18 weeks, or an age-appropriate test 6 weeks after breastfeeding has stopped, is still negative, perform HIV rapid test at 18 months of age.
  - If positive at any time, start infant ART.

Note:
» Negative tests do not exclude HIV infection until 10-18 weeks after birth and 6 weeks after exposure to other risk of HIV infection (including breastfeeding).
» Discuss children with discordant HIV test results with an expert.
» Do not repeat HIV rapid/ELISA tests in children on established ART.

Also perform age-appropriate testing at any time:
» Parental request to test the child.
» HIV-infected father or sibling.
» Death of mother, father or sibling.
» Mother's HIV status and her whereabouts are unknown.
» Clinical features suggest HIV infection.
» Infant has acute severe illness.
» Breastfed infant of newly diagnosed HIV-infected breastfeeding mother.
» IMCI classification of SUSPECTED SYMPTOMATIC HIV INFECTION or POSSIBLE HIV INFECTION (see below).
» TB diagnosis, history of TB treatment or new TB exposure.
» Suspicion of sexual assault.
» Wet-nursed/breastfed infant fed by a woman of unknown or HIV-infected status (and repeat age-appropriate test 6 weeks later).
» Children considered for adoption or fostering.

Newborn child whose mother is of unknown HIV status, has died or is not available due to abandonment or other reasons:
» Perform both infant HIV PCR and HIV rapid tests. Initiate PMTCT as for high risk exposure.
» Perform age-appropriate HIV testing in an HIV-uninfected child at any other time if clinical symptoms suggest HIV infection.

Clinical indications that HIV infection should be considered in a child are:
» If the mother is HIV-infected or if the mother's HIV status is not known.
» If the child was HIV PCR-negative but was subsequently breastfed.
» If a child has any of the following features:
  - Rapid breathing or chest indrawing now ("Pneumonia").
  - Persistent diarrhoea now or in the past.

- Ear discharge now or in the past.
- Low weight for age/height or unsatisfactory weight gain.
- ≥ 2 enlarged glands of: neck, axilla or groin.
- Oral thrush.
- Parotid enlargement.

All infants/children accessing care should have their HIV exposure status (recent maternal HIV status) and/or HIV status determined.
Women who previously tested HIV-positive should not be retested.
Where mothers tested negative in pregnancy, maternal HIV status should be determined 3-monthly whilst breastfeeding.

WHO clinical staging of HIV and AIDs for infants and children
https://www.who.int/hiv/pub/guidelines/arv2013/annexes/WHO_CG_annex_1.pdf

Adapted WHO clinical staging of HIV and AIDS for infants and children For persons ≤15 years of age with confirmed laboratory evidence of HIV infection
Clinical Stage 1 » asymptomatic » persistent generalised lymphadenopathy (PGL)
Clinical Stage 2 » unexplained persistent weight loss » hepatosplenomegaly » papular pruritic eruptions » extensive human papilloma virus infection » extensive molluscum contagiosum » fungal nail infections » recurrent oral ulcerations » lineal gingival erythema (LGE) » unexplained persistent parotid enlargement » herpes zoster » recurrent or chronic RTIs, i.e. » otitis media » otorrhoea » sinusitis
Clinical Stage 3 » moderate unexplained malnutrition (not adequately responding to standard therapy) » unexplained persistent diarrhoea (14 days or more) » unexplained persistent fever (above 37.5°C, intermittent or constant, for longer than one month) » persistent oral candidiasis (after first 6-8 weeks of life) » oral hairy leukoplakia » acute necrotising ulcerative gingivitis/periodontitis » lymph node TB » pulmonary TB » severe recurrent bacterial pneumonia » chronic HIV-associated lung disease including bronchiectasis » symptomatic lymphoid interstitial pneumonitis (LIP) » unexplained anaemia (< 8 g/dL), and or neutropaenia (< 500/mm3) and/or thrombocytopaenia (< 50 000/mm3) for more than one month
Clinical Stage 4 » unexplained severe wasting, stunting or severe malnutrition not adequately responding to standard therapy » pneumocystis pneumonia

- recurrent severe presumed bacterial infections, e.g.
  - empyema
  - bone or joint infection
  - pyomyositis
  - meningitis
- *but* excluding pneumonia
- chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration or visceral at any site)
- extrapulmonary TB
- Kaposi's sarcoma
- oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
- CNS toxoplasmosis (outside the neonatal period)
- HIV encephalopathy
- CMV infection (CMV retinitis or infections of organs other than liver, spleen or lymph nodes; onset at age one month of more)
- extrapulmonary cryptococcosis including meningitis
- any disseminated endemic mycosis, e.g.
- extrapulmonary histoplasmosis
- coccidiomycosis
- chronic cryptosporidiosis
- chronic isosporiasis
- disseminated non-tuberculous mycobacteria infection
- HIV associated recto-vaginal fistula
- cerebral or B cell non-Hodgkin lymphoma
- progressive multifocal leukoencephalopathy (PML)
- HIV-associated cardiomyopathy or HIV-associated nephropathy

Table 11,7: WHO clinical staging for infants and children

11.5 THE HIV-EXPOSED INFANT

Z20.6

DESCRIPTION

An infant whose mother is HIV-infected, or in whom HIV infection has not been confirmed or excluded.

Transmission of HIV infection from mother to child may occur during pregnancy, during delivery or via breastfeeding. Transmission of infection from mother to child can be effectively prevented with a very high success rate by means of suppressing the mother's VL and giving ARVs to the infant.

If the mother's VL is not suppressed the risk of breast milk transmission remains significant.

When to test HIV-exposed children

- Birth (HIV PCR).
- For recommendations on when to perform additional tests, refer to the guidance on "When to Test" (See section above: HIV infection in children).

Feeding advice

- Exclusive breastfeeding is strongly recommended for the 1st 6 months, after which the nutritional needs of the child will require the introduction of complementary foods, while breastfeeding continues
- Mothers whose 2nd or 3rd line regimens are failing should not breastfeed. However, a sustainable supply of formula must be provided.

» If women are switched from 1st to 2nd line therapy during pregnancy or breastfeeding, consult with a practitioner experienced and knowledgeable of the factors informing the feeding option decision.
» Mothers on effective ART should be encouraged to breastfeed as the advantages of breastfeeding exceed the risks of HIV transmission.
» Use of flash pasteurisation or Pretoria pasteurisation to reduce HIV transmission is supported but may pose significant barriers to successful breast milk feeding due to the effort involved.

MEDICINE TREATMENT

Mother

The PMTCT plan starts with initiation of ART in the mother (either pre or post conception). See Section 6.8: HIV in pregnancy.

Infant

Thereafter, the HIV-exposed infant may be classified into one of the following categories which determines the appropriate infant prophylaxis regimen:
» Low risk.
» High risk.
» Unknown risk, e.g. abandoned infant (manage as high risk). *LoE:IIa*[46]

Situation	Comment
<u>Low Risk</u> (at birth) • **NVP** at birth and then daily for 6 weeks.	
Mother is on lifelong ART, and VL <1000 copies/ml (most recent VL taken during the last 12 weeks, *prior to delivery*) **or** Maternal VL <1000 copies/ml *at delivery*	» HIV testing* – Do HIV PCR at birth. – Do HIV PCR at 10 weeks. – Do HIV PCR at 6 months. – Do infant HIV testing 6 weeks' post-cessation of breastfeeding (either HIV PCR or ELISA depending on age). » Encourage maternal ART adherence.
<u>High Risk</u> (at birth) • **NVP daily for at least 12 weeks (until maternal VL< 1000 copies/mL) and AZT 12 hourly for 6 weeks.**** ○ (initiate as soon as possible) *LoE:IIIa*[47]	
Mother is on lifelong ART, and VL >1000 copies/ml (most recent VL taken during the last 12 weeks, *prior to delivery*) **or** Maternal VL >1000 copies/ml at delivery. **or** Mother with no VL result in the last 12 weeks. **or** Mother not on ART.	» If new maternal HIV diagnosis, initiate ART (see Section 6.8: HIV in pregnancy). » If mother on ART with elevated VL, encourage ART adherence, and/or switch to second line to suppress maternal VL as a matter of urgency (see Section 6.8: HIV in pregnancy). » HIV testing* – Do infant HIV PCR at birth/ immediately, if infant tests HIV PCR+, do repeat HIV PCR test and initiate ART immediately. – Do HIV PCR at 10 weeks. – Do HIV PCR at 6 months.

	– Do infant HIV testing 6 weeks post-cessation of breastfeeding (either HIV PCR or rapid test depending on age). » Encourage maternal ART adherence. » If maternal VL ≥ 1000 copies/ml continue infant NVP prophylaxis.
<u>High Risk</u> (during breastfeeding) **NVP daily for at least 12 weeks (until maternal VL<1000 copies/mL) and AZT 12 hourly for 6 weeks.** o Initiate as soon as possible.	
Breastfeeding mother newly diagnosed HIV positive > 72 hours after delivery. Mother on ART with latest VL > 1000 copies/ml during breastfeeding.	» If new maternal HIV diagnosis, initiate ART (see Section 6.8: HIV in pregnancy). » If mother on ART with elevated VL, encourage ART adherence, and/or switch to second line to re-suppress maternal VL as a matter of urgency (see Section 6.8: HIV in pregnancy). » Do immediate infant HIV PCR*. » If infant currently breastfeeding, or has breastfed in the last week: provide high-risk infant prophylaxis. » If breastfeeding never started or stopped > 1 week ago: no prophylaxis needed. » Repeat HIV PCR 6 weeks after stopping NVP » Do all other routine HIV tests according to the age and schedule for HIV exposed infants*. » See algorithm below: Management of high maternal VL after delivery.
UNKNOWN RISK (abandoned/orphaned infant) • **NVP daily for 6 weeks and AZT 12 hourly for 6 weeks.** o Initiate as soon as possible. *LoE:IIa*[48]	
Unknown maternal status because orphaned or abandoned. (Treat all as high-risk HIV-exposed infants)	» Do an HIV PCR* and HIV rapid test » Start high risk infant prophylaxis for 6 weeks. » Repeat HIV PCR at 10 weeks of age, or 4 weeks after stopping NVP* » Do all other routine HIV tests according to the age and schedule for HIV-exposed infants*. » See algorithm below: Management of infant of unknown risk (abandoned infant).

Note:

* If infant tests HIV-positive at any stage, confirm positive result, stop any ART prophylaxis, and initiate ART. See Section 11.6: Management of HIV-infected children.

**High-risk infants who are exclusively formula fed from birth: give NVP daily for 6 weeks and AZT 12 hourly for 6 weeks. *LoE:IIIb*[49]

Table 11.8: Infant prophylaxis for HIV

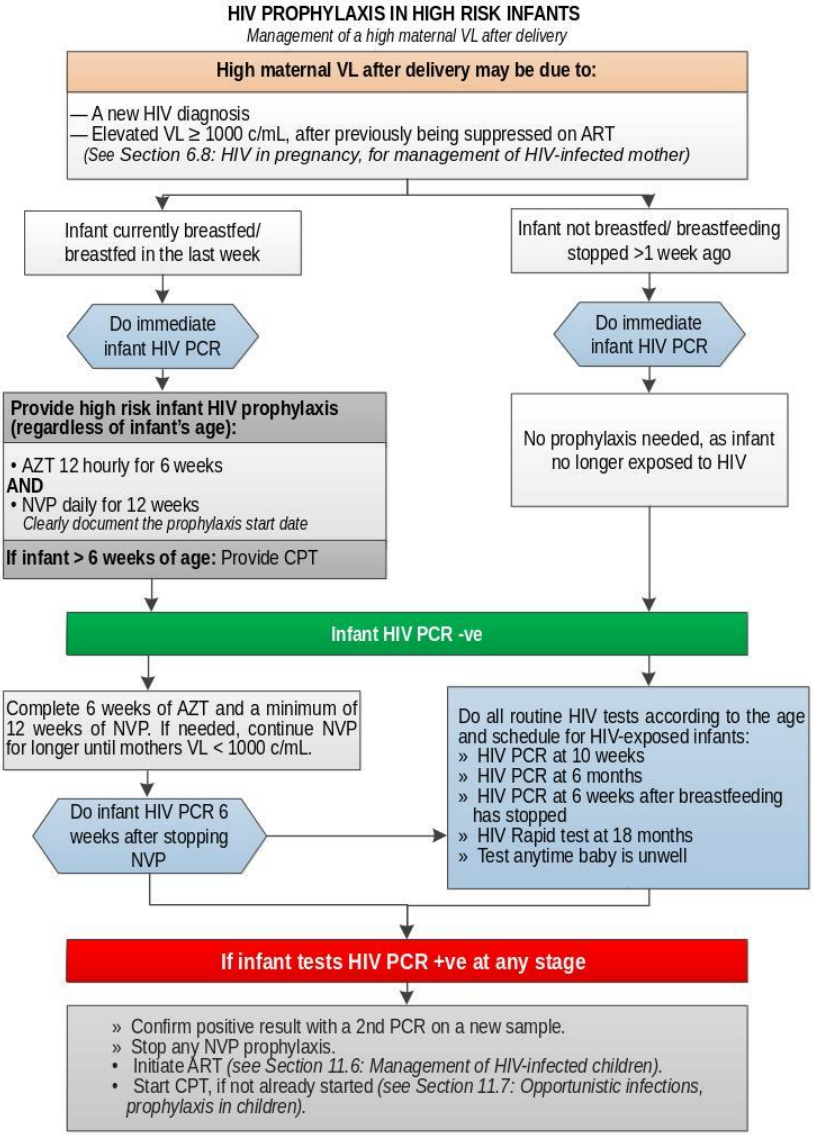

Figure 11.2: HIV prophylaxis in HIV-exposed infant at high risk after delivery

LoE:IIIb[50]

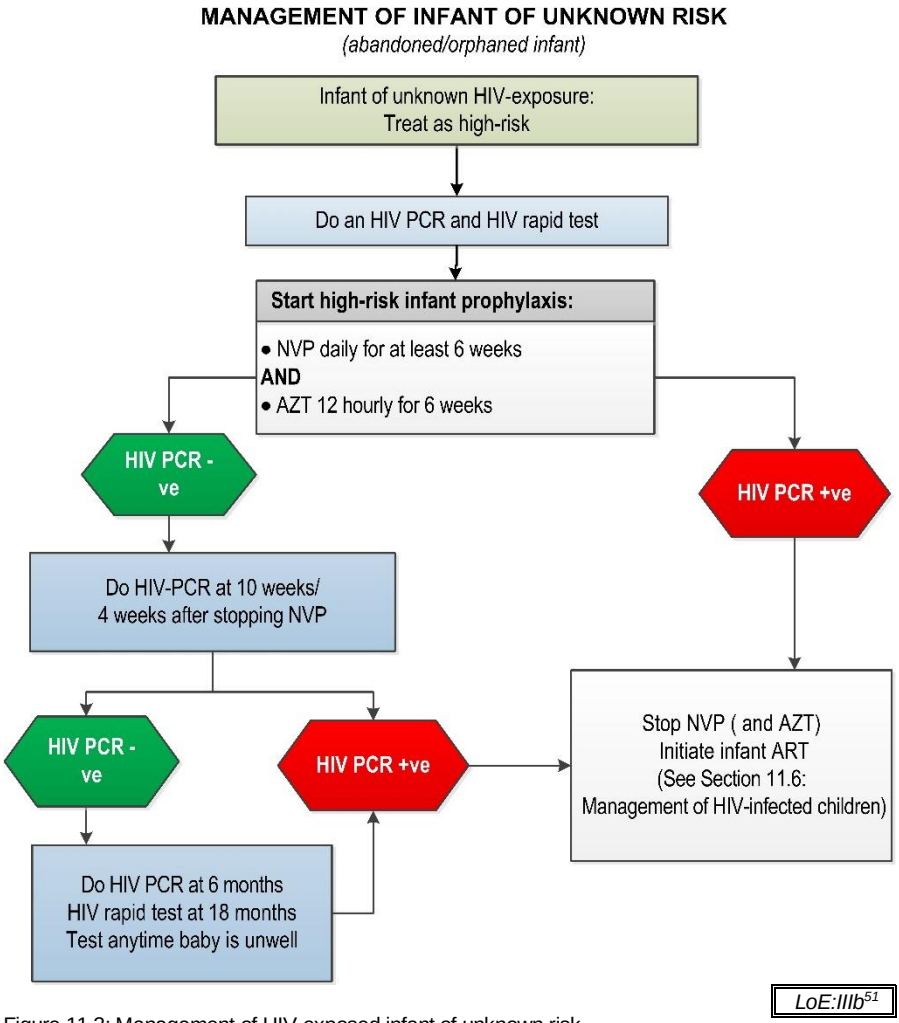

Figure 11.3: Management of HIV-exposed infant of unknown risk

Non-breastfeeding mother diagnosed HIV positive > 72 hours after delivery:
Do not start NVP. Perform an HIV test on infant and if positive initiate ART.

Infant PMTCT dosages:
Daily prophylaxis for 6 or 12 weeks administered to infants, as indicated above:
» Give 1st dose as soon as possible after birth.
» If baby vomits: Repeat dose once only.
» If infant HIV PCR is positive at any time, stop prophylactic ARV, confirm with 2nd PCR and initiate/refer for ART, while awaiting 2nd PCR result.

» Continue normal breastfeeding and start cotrimoxazole prophylaxis if > 6 weeks of age.

Nevirapine (NVP) dose for infant on PMTCT:

Newborns ≥ 2 kg and infants:

- Nevirapine, oral, 4 mg/kg daily.

Weight kg	Dose mg	Syrup 10 mg/mL	Age Months
> 2–2.5 kg	10 mg	1 mL	Birth–6 weeks
> 2.5–3.5 kg	12.5 mg	1.25 mL	
> 3.5–5 kg	17.5 mg	1.75mL	> 6 weeks–6 months

Children >6 months of age requiring prophylaxis should use treatment doses. See the Paediatric Hospital STGs and EML, section 9.1.3 The HIV Infected Infant/Child or the dosing table pg 23.8. *LoE:IIIb*[52]

Zidovudine (AZT) dose for infant on PMTCT:

Newborns ≥ 2 kg and infants:

- Zidovudine, oral, 4mg/kg/dose 12 hourly.

Weight kg	Dose mg	Syrup 10 mg/mL	Age Months
2–2.499kg	10mg	1 mL	Birth–6 weeks
≥ 2.5 kg	15 mg	1.5 mL	
≥ 2.5–7 kg	60 mg	6 mL	> 6 weeks–6 months

Children >6 months of age requiring prophylaxis should use treatment doses. See dosing table, pg 23.9. *LoE:IIIb*[53]

Cotrimoxazole prophylaxis (CPT)

Initiation:

» High-risk HIV-exposed or infected infants, starting from 6 weeks of age.

Note: Low-risk HIV-exposed infants with a negative birth PCR do not need CPT (unless subsequently confirmed HIV-infected).

Discontinuation: *LoE:IIIa*[54]

» If 10-week PCR is negative and;
  - mother is virally suppressed – discontinue CPT.
  - mother is not virally suppressed or engaged in mixed feeding – continue CPT until mother is virally suppressed or mixed feeding has stopped.

» *If HIV-infected:* See Section: 11.6 Management of HIV-infected children (<10 years).

REFERRAL

Mother declines infant ARV prophylaxis.

11.6 MANAGEMENT OF HIV-INFECTED CHILDREN (<10 YEARS)

B24

DESCRIPTION

HIV-infected child: An infant/child in whom HIV infection has been confirmed with two age-appropriate tests. See Section 11.5. The HIV-exposed infant.

GENERAL AND SUPPORTIVE MEASURES

» Identify a caregiver who can supervise the child's treatment.
» Link the HIV interventions to the regular well infant visits/nutritional care. Ensure the road to health booklet is correctly completed and used to reflect and guide care.

Counselling is a vital part of the successful care of children with HIV infection and their families. Specific matters requiring attention are:

» The implications of the disease to the family.
» Implications of treatment and understanding of the condition and its care.
» The disclosure process within the family and extended family should be encouraged. Besides the caregiver, help from the family is often useful.
» Disclosure to the child appropriate to age and maturity with the parents' support.
  - Find out what the child understands of their illness and what they would like to know.
  - Disclosure should be child led in terms of information required, language used and educational/emotional readiness.
  - Anticipate the effects of disclosure on the child, family and other contacts such as friends and school colleagues.
  - Ensure that in disclosure the child is constantly reassured of the parents'/caregivers' love.

Treatment of mothers, caregivers and other family members:

» Always ask about the caregiver's health, and the health of other family members.
» Ensure that mothers and other family members have timeous access to medical care including ART.
» Encourage breastfeeding in all mothers with HIV-infected children, with introduction of complementary foods from 6 months of age.
» At every visit ask about TB contacts and symptoms in children and their caregivers.

STANDARDISED NATIONAL MONITORING FOR INFANTS & CHILDREN WITH HIV

AT INITIAL DIAGNOSIS OF HIV	PURPOSE
Verify HIV status.	To ensure that national testing algorithm has been followed.
Document weight, height, head circumference (< 2 years of age) and development.	To monitor growth and development.
Screen for TB symptoms.	To identify TB and HIV co-infection
Do CD4 count.	To determine eligibility for cotrimoxazole prophylaxis (CPT)
Hb or FBC if available.	To detect anaemia or neutropaenia.
AT INITIATION OF ART (BASELINE)	**PURPOSE**
Hb or FBC.	If < 8 g/dL: Manage appropriately.
CD4 count (if not performed in last 6 months).	Baseline assessment.
ALT (If jaundiced or on TB treatment).	To detect liver dysfunction.
ON ART	**PURPOSE**
Height, weight, head circumference (if child < 2 years) and development.	To monitor growth and development. Adjust dosing at each visit according to weight gain.
Clinical assessment including medicine-related adverse events.	To monitor response to ART and detect adverse effects.

CD4: At 1 year on ART, and then every 6 months until meets criteria to stop cotrimoxazole. Thereafter stop CD4 count monitoring if patient remains virologically supressed. If not virologically supressed monitor CD4 count every 6 months.	To monitor response to ART. Stop cotrimoxazole prophylaxis if indicated.
Viral load: At month 6 on ART, after 12 months on ART, then every 12 months.	To monitor viral response to ART. To identify treatment failure and adherence problems. For management of an elevated VL, see algorithm, below: Monitoring and management of viral loads.
Hb or FBC at months 3 and 6 if on AZT. Thereafter, repeat if clinically indicated	To identify AZT-related anaemia.
If on PI-based regimen: Cholesterol + triglyceride at month 3. If above acceptable range, do fasting cholesterol and TGs; and if still above acceptable range consult with doctor/specialist.	To monitor for PI-related metabolic side effects.

Table 11.9: Monitoring for infants and children with HIV on ART *LoE:IIIb*[55]

MEDICINE TREATMENT

Prophylaxis for opportunistic infections

See Section 11.7 Opportunistic infections, prophylaxis in children

Immunisation, deworming and vitamin A programme

» Continue deworming and vitamin A programme as in the HIV-uninfected child.
» Continue immunisation as in the HIV-uninfected child (See Section 13.3: Vaccines for routine administration), except do not give birth BCG vaccine.

Nutritional support

Treat specific nutritional deficiencies appropriately.

Antiretroviral therapy

Initiation of ART in well, infants shown to be PCR-positive should be carried out at PHC level.

The preparation of the child and family to start ART is critical to the success of the treatment. Failure to achieve adherence and understanding may lead to resistance and adversely affect the prognosis of the child.

Eligibility for ART

Clinical criteria

» Confirmation of diagnosis of HIV infection, irrespective of CD4 count/percentage or WHO clinical stage. *LoE:IIIb*[56]

AND

» No indications for deferral i.e. TB, Cryptococcal meningitis, other relevant opprtunitistic infections or No medical contraindication (e.g. major organ dysfunction). If medical contraindications are present refer to hospital for rapid review and planning.

Social issues that must be addressed to ensure successful treatment

These are extremely important for success and impact on adherence. Social challenges should be overcome and not be barriers to care. Adherence to treatment must at least be considered probable. Disclosure to another adult living in the same house is encouraged so that there is someone else who can assist with the child's treatment. However, absence of disclosure should not preclude ART initiation.

» Mandatory component: At least one identifiable caregiver able to supervise the child and/or administer medication. All efforts should be made to ensure that the social circumstances of vulnerable children (e.g. orphans) be addressed to facilitate treatment.
» Adherence:
  - High levels of adherence are required for adequate virological response and prevention of viral resistance. This can be achieved with regular education and support.
  - All efforts to encourage this level of adherence should be made.
  - Viral load measurements are useful for monitoring adherence.
  - Sensitive, age-appropriate disclosure facilitates adherence.
» Mother and other family members should be assessed and treated.

Requirements before ART is initiated:

The child's family (parents, caregivers) should understand:

» ART is life-long.
» The prognosis of the condition (treated and untreated).
» Medicines' adverse effects and modes of action, and the risk and implications of developing resistance, if incorrectly used.
» That all medicines should be given - if two ARVs are missing from the medicine regimen, stop treatment until they are all available again.

ART regimens

» Are chosen according to age, weight, expected adverse effects, efficacy and prior antiretroviral exposure.
» Adjust the dosage of ART according to weight, during follow up visits.
» Do not change regimens or move to 2nd line therapy without clear guidance from a paediatric expert, as unnecessary loss of effective regimens can shorten life expectancy. Adherence problems must be addressed thoroughly before switching to a 2nd or 3rd line regimen.
» Single medicine substitutions may only be made when medicine-specific adverse effects are encountered, on condition that virological suppression is documented and the matter is discussed with a practitioner experienced in child ART.

FIRST-LINE REGIMEN	
Infants < 4 weeks or < 3 kg: Consult paediatric expert on treatment regimen and dosage, or refer.	
If weight 3–19.9 kg, and child ≥ 4 weeks of age and ≥ 42 weeks gestational age:	ABC + 3TC + LPV/r.
If weight ≥ 20 to < 35 kg or < 10 years of age:	ABC + 3TC + DTG
If weight ≥ 35 kg AND ≥10 years of age	TDF + 3TC + DTG

Table 11.10: First-line ART regimens for infants and children *LoE:IIIb*[57]

General ART comments

» Switch to tablets or capsules from pellets, syrups or solutions as soon as possible.
» Fixed-dose combinations are preferred to single agents.
» If available, use daily dose regimens.

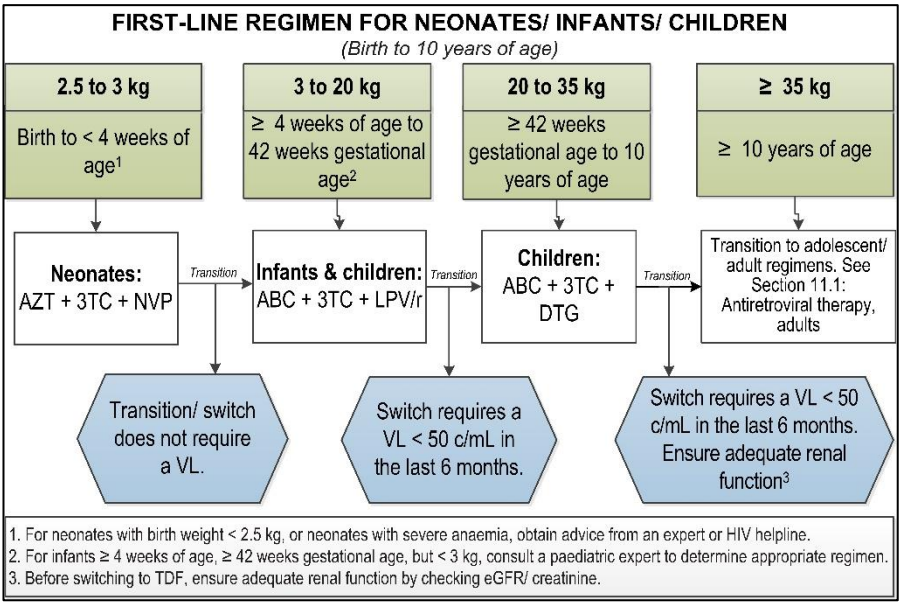

Figure 11.4: First-line paediatric ART-switching algorithm for neonates/infants/children

LoE:IIIb[58]

ADJUSTMENT OF PREVIOUS FIRST-LINE REGIMENS	
EFV-containing first-line regimens: *(See algorithm, below: first-line regimen for neonates/ infants/ children)*.	Weight > 20 kg: – If VL is < 50 c/mL: Change EFV to DTG. – If VL is 50-999 c/mL: o Investigate cause of elevated VL and provide enhanced adherence support. o Repeat VL in 3 months o If VL remains <1000 c/mL, switch EFV to DTG – If VL > 1000 c/mL at any stage o Manage as virological failure. If VL remains high after enhanced adherence, refer for consideration of a change in regimen. Weight < 20 kg: Children that do not yet qualify for DTG (< 20kg), but who are already on EFV-containing regimen with a suppressed VL should remain on their EFV-containing regimen until they can switch to DTG (weight reaches 20 kg), or until an unsuppressed VL mandates an earlier switch to a LPV/r-containing second-line regimen

Transitioning between different regimens for children: *(See algorithm, above: first-line regimen for neonates/ infants/ children).*	<u>If child reaches weight of 20 kg:</u> – Transition from LPV/r to DTG – Transition requires VL < 50 c/mL in last 6 months <u>If child reaches weight of ≥ 35 kg and ≥ 10 years of age:</u> – Switch from ABC to TDF – Ensure adequate renal function – Transition requires VL < 50 c/mL in last 6 months

Table 11.11: Adjustment of previous 1st line ART regimens for infants and children

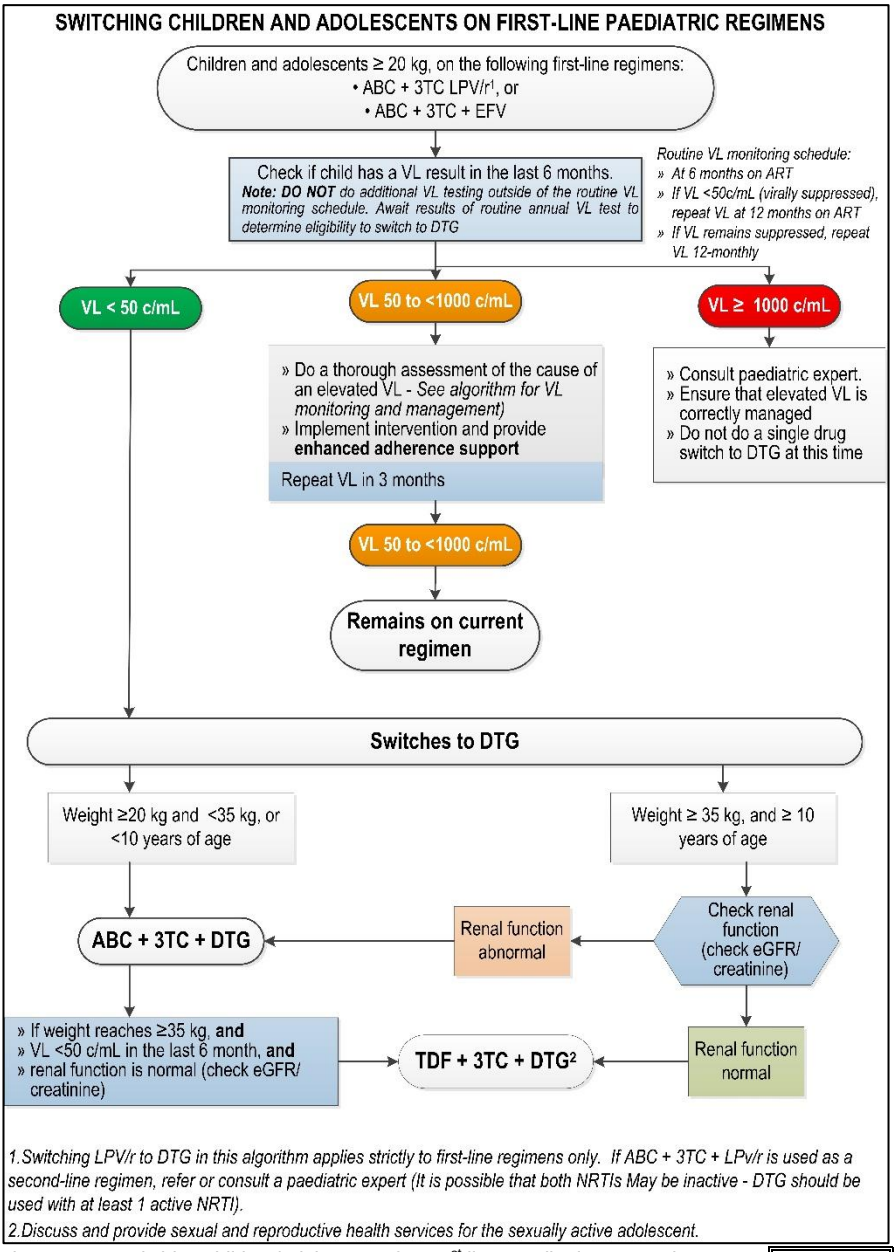

Figure 11.6: Switching children/adolescents from 1st-line paediatric ART regimens *LoE:IIIb*[59]

Initiating ART in children (the 6 steps/IMCI child NIMART)

(These steps are taken from the IMCI nursing protocol. Doctors may obtain further guidance from the Paediatric Hospital Level EML and STGs).

1. Record patient details and history
2. Decide if the child has confirmed HIV infection (see testing above).
3. Decide if the caregiver is able to give ART (If not, refer to appropriate level to ensure ability to take ART effectively and safely).
4. Decide if a nurse should initiate ART (i.e. NIMART suited patient).
   a. If any of the following are present refer:
      - Fast breathing.
      - TB.
      - Weight < 3 kg.
      - General danger signs or severe disease evident.
5. Assess and record baseline information.
   b. Record the following information:
      - Weight and height.
      - Head circumference in children < 2 years of age.
      - Assess for malnutrition and anaemia.
      - Feeding assessment and feeding problems.
      - Development.
      - Consider and screen for TB.
      - WHO clinical stage.
      - Laboratory results: Hb, CD4 count and percentage.
   c. If SEVERE MALNUTRITION, SEVERE ANAEMIA or TB refer to next level of care.
   d. If POSSIBLE TB provide appropriate follow up.
   e. If Hb < 10 g/dL (but not severe anaemia) treat as per IMCI. Do not delay ART. Send appropriate laboratory tests but do not wait for results to start ART.
6. Start ART:
   f. If weight 3–20 kg, and child > 4 weeks of age and > 42 weeks gestational age:
      - ABC + 3TC + LPV/r.
   g. If weight > 20 to < 35 kg or < 10 years of age: *LoE:IIIb*[60]
      - ABC + 3TC + DTG.
   h. Continue (or start) cotrimoxazole prophylaxis.
   i. Follow up after 1 week:
      - To check ability to adhere.
      - To check outstanding laboratory results.
      - To resolve any problems that may have arisen.

Then proceed to long term follow up (the 7 steps/IMCI child NIMART).

(These steps are taken from the IMCI nursing protocol. Doctors may obtain further guidance from the Paediatric Hospital Level EML and STG, 2017).

Assess for problems:

1. Ask if there are any problems.
   a. Check for any danger signs.
   b. Check for ART danger signs:
      - Severe skin rash.

- Difficulty breathing or severe abdominal pain.
- Yellow eyes.
- Fever, vomiting, rash.

c. Check for any other symptoms.
d. Consider TB/ask if there has been TB contact and examine at each visit.

2. Monitor progress on ART:
   a. Record weight (and height every 3 months).
   b. Assess development every 6 months.
   c. Assess adherence and record (ask mother, self-assessment, record correct number of pills remain, watch body language).
   d. Assess for side effects. If present manage according to guidelines or refer:
      - yellow eyes
      - nausea and vomiting
      - fever
      - sleep disturbances
      - anxiety
      - lipoatrophy
      - rash
      - diarrhoea
      - headache
      - nightmares
      - tingling or numbness
   e. Assess clinical progress.
   f. Monitor blood results.
   g. Indications for referral to a doctor include:

Not gaining weight for 3 months.
Regression of milestones.
Failure to attain milestones.
Poor adherence after adherence counselling.
Significant side effects despite appropriate management.
Deterioration of clinical stage.
CD4 count significantly dropping.
Detectable VL, despite adherence counselling.
Fasting total cholesterol > 4.43mmol/L.
Fasting TG > 5.6 mmol/L.

3. Provide further ART:
   a. Continue treatment if stable and no significant side effects.
      Note: Check dose is correct for current weight and adjust accordingly.
4. Provide other treatments:
   a. Continue cotrimoxazole prophylaxis until: 1–5 year: CD4% > 25%; or if > 5 years: CD4 > 350 cells/mm^3; on two tests at least 3–6 months apart.
5. Provide routine care:
   a. Check immunisations, vitamin A, deworming etc. have all been done.
6. Counsel the mother/caregiver:
   a. Use the visit to check mother's knowledge and need for support.
   b. Check if family and mother are receiving own necessary care.
7. Arrange further follow up:
   a. Arrange follow up in 1 month (more frequently if other problems are present).

Treatment failure

» VL is the most sensitive method to detect ART failure.
» Virological failure can be defined as a measurable viral load, despite optimal adherence and optimal dosing over a 4-month period. Clinical and immunological deterioration are late features of ART failure.

» The most common cause of treatment failure is poor adherence. Adherence must be addressed before switching to 2nd-line therapy.

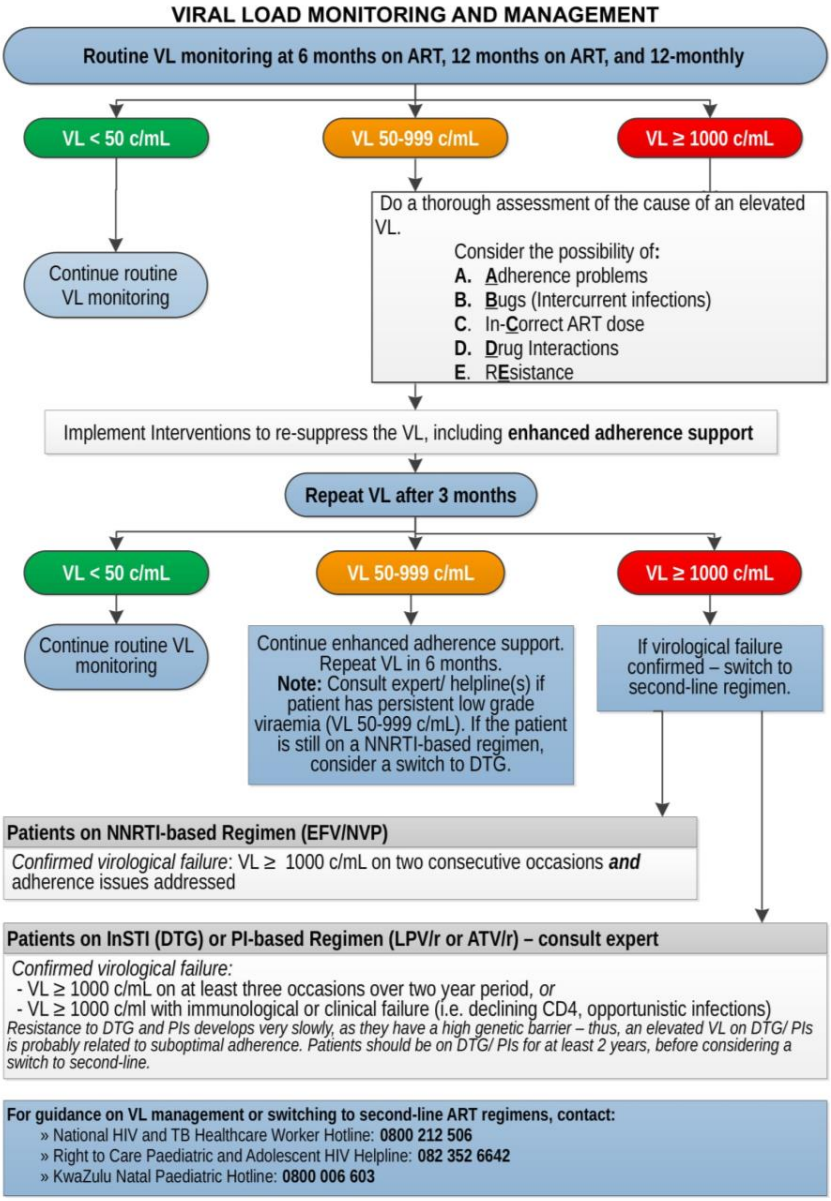

Figure 11.7: Viral load monitoring and management

LoE:IIIb[61]

Side effects:

	Continue ART with careful monitoring. Get expert advice.	**Consider stopping treatment URGENTLY. Consult expert urgently.**
Symptomatic hyperlactataemia/lactic acidosis	Lactate: 2–5 mmol/L with no signs or symptoms	Lactate > 5 mmol/L, **or** acidosis, **or** signs or symptoms.
Anaemia	Hb: 7.0–9.9 g/dL	Hb < 7g/dL, **or** cardiac failure.
Neutropaenia	0.4–1.2 X 10^9/L	< 0.4 X 10^9/L
Increased liver enzymes and hepatitis	< 9.9 X upper normal limit	≥ 10.0 X upper normal limit
Increased serum triglycerides	1.54–8.46 mmol/L	≥ 8.47 mmol/L
Increased total cholesterol	4.43–12.92 mmol/L	≥ 12.93 mmol/L
Skin reactions	» diffuse maculopapular rash, or » dry desquamation	Vesiculation, **or** ulcers, **or** exfoliative dermatitis, **or** Stevens-Johnson syndrome, **or** erythema multiforme, **or** moist desquamation, **or** elevated ALT, **or** elevated AST.
Lipoatrophy (Subcutaneous fat loss of the face, extremities and/or buttocks. Caused by NRTIs, in particular ddI, d4T and sometimes AZT. ABC, TDF, FTC, 3TC are less likely to cause lipoatrophy).	» Look for and respond to clinical features of lipoatrophy. » Change regimen to include NRTIs less likely to cause lipoatrophy e.g. replace d4T or AZT with ABC or TDF (FDC preferred, where possible). » Seek specialist advice for switching if not virologically suppressed.	Not an indication to stop ART.
Other side effects: » peripheral neuropathy » myopathy » abdominal pain » nausea and vomiting » pancreatitis » headache	Clinical evaluation. **Discuss all cases with an HIV clinician, before interrupting therapy**.	

» fatigue » sedative effect » sleep disturbance » confusion » abnormal thinking » possible teratogenicity	

Table 11.12: Side-effects associated with ART use in infants and children

Note: Children may occasionally need to change a medicine from the first line regimen to one from the second line regimen because of intolerance or a serious adverse reaction. There is no need to change an entire regimen for a single adverse drug reaction.

» A single drug substitution can only be made if the viral load is undetectable or if the change is made in the first six months of starting a regimen.
» Refer or consult a doctor with antiretroviral experience. *LoE:IIIb*[62]

<table>
<tr><th colspan="6">ANTIRETROVIRAL MEDICINE DOSAGES BY WEIGHT BANDS</th></tr>
<tr><th></th><th colspan="2">Abacavir
(ABC)</th><th colspan="2">Lamivudine
(3TC)</th><th>Dolutegravir
(DTG)</th><th>Efavirenz
(EFV)</th></tr>
<tr><td>Target dose</td><td colspan="2">8 mg/kg 12 hourly
OR
≥ 10 kg:
16 mg/kg once daily</td><td colspan="2">4 mg/kg 12 hourly
OR
≥ 10 kg:
8 mg/kg once daily</td><td>By weight band once daily</td><td>By weight band once daily</td></tr>
<tr><td>Available formula-tions</td><td colspan="2">Sol. 20 mg/mL
Tab 60 mg (scored, dispersible)
Tab 300 mg (not scored),
ABC/3TC 600/300 mg.</td><td colspan="2">Sol. 10 mg/mL
Tab 150 mg (scored),300 mg;
Tab ABC/3TC 600/300 mg</td><td>Tab 50 mg</td><td>Caps 50,200 mg
Tabs 50,200, 600 mg (not scored)</td></tr>
<tr><td>Weight Kg</td><td colspan="6">Currently available tablet formulations of ABC (except 60 mg), EFV, and DTG must be swallowed whole and not chewed, divided or crushed.</td></tr>
<tr><td>< 3</td><td colspan="6">Consult with a clinician experienced in paediatric ARV prescribing for neonates (< 28 days of age) and infants weighing < 3 kg</td></tr>
<tr><td>3–4.9</td><td colspan="2">2 mL 12 hourly</td><td colspan="2">2 mL 12 hourly</td><td rowspan="4">Don't use if < 20 kg</td><td>Don't Use < 10kg or < 3 years</td></tr>
<tr><td>5–6.9</td><td colspan="2">3 mL 12 hourly</td><td colspan="2">3 mL 12 hourly</td><td rowspan="3"></td></tr>
<tr><td>7–9.9</td><td colspan="2">4 mL12 hourly</td><td colspan="2">4 mL 12 hourly</td></tr>
<tr><td rowspan="2">10–13.9</td><td colspan="2">Choose only one option</td><td colspan="2">Choose only one option</td><td rowspan="2">1x200* cap/tab at night</td></tr>
<tr><td>6 mL 12 hourly
OR
2x60* tabs
12 hourly</td><td>12 mL daily
OR
4x60* tabs daily</td><td>6 mL
12 hourly</td><td>12 mL daily</td></tr>
<tr><td>14–19.9</td><td>8 mL 12 hourly
OR
2.5x60* tabs
12 hourly</td><td>1x300* tab daily
OR
15 mL daily</td><td>8 mL
12 hourly
OR
½x150* tab 12 hourly</td><td>1x150* tab daily
OR
15 mL daily</td><td rowspan="3">1x200* cap/tab + 2x50* cap/tab at night</td></tr>
<tr><td>20–22.9</td><td rowspan="2">10 mL 12 hourly
OR
3x60* tabs
12 hourly</td><td>20 mL daily
OR
1x300*+ 1x60* tab daily</td><td rowspan="2">1x150* tab 12 hourly
OR
15 mL
12 hourly</td><td rowspan="2">30 mL daily
OR
1x300* tab daily
OR
2x150* tab daily</td><td rowspan="5">1x50 mg tab once daily</td></tr>
<tr><td>23-24.9</td><td>20 mL daily
OR
1x300*+ 2x60* tabs daily</td></tr>
<tr><td>25–29.9</td><td rowspan="4">1x300* tab
12 hourly</td><td rowspan="4">2x300 tabs daily
OR
1 x ABC/3TC 600/300* tab daily</td><td rowspan="4">1x150 tab 12 hourly</td><td rowspan="4">2x150* tabs daily
OR
1x300* tab daily
OR
1 x ABC/3TC 600/300* tab daily</td><td rowspan="3">2x200* caps/tab at night</td></tr>
<tr><td>30–34.9</td></tr>
<tr><td>35–39.9</td></tr>
<tr><td>> 40</td><td>600 tab at night</td></tr>
</table>

*dosage in mg Sol: solution Tab: tablet Cap: capsule

For standard dosing of abacavir, see dosing table - pg 23.1; efavirenz - see dosing table pg 23.4; lamivudine - see dosing table pg 23.6; lopinavir/ritonavir - see dosing table pg 23.7; ritonavir - see dosing table pg 23.9

LoE:IIIb[63]

Table 11.13: ART dosing tables for infants and children

<table>
<tr><th colspan="6">ANTIRETROVIRAL MEDICINE DOSAGES BY WEIGHT BANDS</th></tr>
<tr><td></td><td colspan="4">Lopinavir/ritonavir
(LPV/r)</td><td>Ritonavir (r)
boosting</td></tr>
<tr><td>Target dose</td><td colspan="4">300/75mg/m2/dose LPV/r
12 hourly</td><td rowspan="2">ONLY as booster for LPV/r when on rifampicin
12 hourly
(0.75xLPV dose
12 hourly)</td></tr>
<tr><td>Available formula-tions</td><td colspan="4">Pellets 40/10 mg per capsule
Sol. 80/20 mg/mL
Adult Tabs 200/50 mg,
Paeds Tabs 100/25 mg</td></tr>
<tr><td>Weight Kg</td><td colspan="4">Currently available tablet formulations of LPV/r must be swallowed whole and not chewed, divided or crushed.</td><td>Sol: 80 mg/mL</td></tr>
<tr><td>< 3</td><td colspan="4">Consult with a clinician experienced in paediatric ARV prescribing for neonates (< 28 days of age) and infants weighing < 3 kg</td><td></td></tr>
<tr><td rowspan="2">3–4.9</td><td colspan="4">Choose one option</td><td rowspan="2">1 mL 12 hourly</td></tr>
<tr><td colspan="2">2 caps 12 hourly</td><td colspan="2">1 mL 12 hourly</td></tr>
<tr><td>5–5.9</td><td colspan="2">2 caps 12 hourly</td><td colspan="2" rowspan="2">1.5 mL 12 hourly</td><td rowspan="3">1.5 mL 12 hourly</td></tr>
<tr><td>6–6.9</td><td colspan="2" rowspan="2">3 caps 12 hourly</td></tr>
<tr><td>7–9.9</td></tr>
<tr><td>10–13.9</td><td colspan="2">4 caps 12 hourly</td><td colspan="2">2 mL 12 hourly</td><td>1.5 mL 12 hourly</td></tr>
<tr><td rowspan="2">14–19.9</td><td colspan="4">Choose one option</td><td rowspan="2">2 mL12 hourly</td></tr>
<tr><td>Either
5 caps
12 hourly</td><td>OR
2.5 mL
12 hourly</td><td>OR
2 x 100/25* tabs
12 hourly</td><td>OR
1 x200/50* tab
12 hourly</td></tr>
<tr><td>20–22.9</td><td rowspan="2">Either
6 caps
12 hourly</td><td rowspan="2">OR
3 mL
12 hourly</td><td>OR
2x100/25* tabs
12 hourly</td><td>OR
1x200/50* tab
12 hourly</td><td rowspan="2">2.5 mL 12 hourly</td></tr>
<tr><td>23-24.9</td><td>OR
1x200/25* tabs
12 hourly</td><td>OR
1x200/50* tab
12 hourly</td></tr>
<tr><td>25–29.9</td><td>Either
6 caps
12 hourly</td><td>OR
3.5 mL 12 hourly</td><td rowspan="2">OR
3x100/25* tabs
12 hourly</td><td rowspan="2">OR
1x200/50* tab
+1x100/25* tab
12 hourly</td><td rowspan="2">3 mL 12 hourly</td></tr>
<tr><td>30–34.9</td><td>Either
8 caps
12 hourly</td><td>OR
4 mL
12 hourly</td></tr>
<tr><td>35–39.9</td><td rowspan="2">Either
10 caps 12 hourly</td><td rowspan="2">OR
5 mL
12 hourly</td><td colspan="2" rowspan="2">OR
2x200/50* tabs
12 hourly</td><td rowspan="2">4 mL 12 hourly</td></tr>
<tr><td>> 40</td></tr>
</table>

*dosage in mg Sol: solution Tab: tablet Cap: capsule

For standard dosing of abacavir, see dosing table - pg 23.1; efavirenz - see dosing table pg 23.4; lamivudine - see dosing table pg 23.6; lopinavir/ritonavir - see dosing table pg 23.7; ritonavir - see dosing table pg 23.9.

Table 11.13 (continued): ART dosing tables for infants and children

Instructions to administer LPV/r pellets to children are:

- Hold the capsule at both ends and, twisting in opposite directions, pull apart to pour out the pellets inside the capsule.
- Add the pellets (from the required number of capsules) to a spoonful of food a little at a time. For example, porridge can be used (must be at room temperature)
- Do not stir, crush, or dissolve the pellets: rather sprinkle over the food.
- Use only a small amount of food, to ensure child can consume all the pellets. Discard food with pellets after 2 hours.
- The capsule can be discarded with usual waste. *LoE:IIIb*[64]

11.7 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN CHILDREN

Z29.2 + (B24)

Cotrimoxazole prophylaxis

Initiation

» All HIV-infected infants (< 1 year), starting from 6 weeks of age.
» Any child 1–5 years of age with CD4% < 25%.
» Any child > 5 years of age with CD4 count < 200 cells/mm3.

- Cotrimoxazole, oral, once daily (everyday). See dosing table, pg 23.4.

Discontinuation

» HIV-infected child > 1 year of age whose immune system is fully reconstituted on ART (i.e. 1–5 year: CD4% > 25% or > 5 years: CD4 count > 200 cells/mm^3 on two tests at least 3–6 months apart).
» Child is HIV-infected with PJP infection: after treatment, continue cotrimoxazole prophylaxis until 5 years of age. *LoE:IIIb*[65]

TB prophylaxis

See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.

Immunisation

Continue immunisation as in the HIV-uninfected child (See Section 13.3: Vaccines for routine administration), except do not give birth BCG vaccine, if confirmed HIV positive diagnosis - commence ART.

11.8 OPPORTUNISTIC INFECTIONS, TREATMENT IN CHILDREN

11.8.1 CANDIDIASIS, ORAL (THRUSH), RECURRENT

B20.4

MEDICINE TREATMENT

- Nystatin suspension, oral, 100 000 IU/mL, 0.5 mL after each feed.
  - Keep in contact with the affected area for as long as possible prior to swallowing.
  - In the older child, ask child to swirl in the mouth, prior to swallowing.
  - In the infant, advise caregiver to apply to front of the mouth and spread over the oral mucosa with a clean finger.
  - Continue for 48 hours after resolution of symptoms.

If there is oral candidiasis and the child cannot swallow, this indicates the presence of oesophageal candidiasis. See Section 11.8.2: Candidiasis, oesophageal.

11.8.2 CANDIDIASIS, OESOPHAGEAL

B20.4

MEDICINE TREATMENT

- Fluconazole, oral, 6 mg/kg once daily for 21 days. See dosing table, pg 23.5.

11.8.3 DIARRHOEA, HIV-ASSOCIATED

See Section 2.9: Diarrhoea.

11.8.4 PNEUMONIA

See Section 17.2: Respiratory infections.

11.8.5 MEASLES AND CHICKENPOX

Refer all patients.

11.8.6 SKIN CONDITIONS

These are common and include scabies, seborrhoeic eczema and others.
See Chapter 5: Skin conditions.
If no response to care as directed in the chapter, refer.

11.8.7 TUBERCULOSIS (TB)

A15.0-3/A15.7-8/A16.0-2/A16.7-8/B20.0

DESCRIPTION

TB and HIV are often comorbid conditions. Exclude TB in all patients before starting ART. See Section 17.4.2: Pulmonary tuberculosis, in children.

Re-evaluate the risk for TB and TB contact at each visit on history (including contact history) and clinical examination.

TB should be considered early in non-resolving pneumonias.
Tuberculin tests are often not reliable and a negative test does not exclude TB.
If TB is suspected but cannot be proven, refer early for diagnostic evaluation.

MEDICINE TREATMENT

TB prophylaxis Z29.2 + (B24)

Give TB prophylaxis to all HIV-infected children in whom no evidence of TB disease is present and who are:

» Exposed to a close contact with infectious pulmonary TB or
» TST-positive (only the 1st time a positive TST is shown).

- Isoniazid, oral, 10 mg/kg/dose once daily for 6 months.
  - Maximum dose 300 mg daily.
  - See Section 17.4.2.1: TB chemoprophylaxis/Isoniazid preventive therapy (IPT) in children.

Repeat course if an HIV-infected patient, irrespective of age, is re-exposed to a TB contact at any point after completing TB treatment or prophylaxis.

If patient has been exposed to a known MDR or XDR-TB source case or the contact case has failed standard TB treatment, refer.

TB treatment

<u>If the child is not yet on ART:</u>

» Commence TB treatment first. Follow with ART, usually after 2–8 weeks:
  - 2 weeks if CD4 < 50 cells/mm^3

- 8 weeks if CD4 > 50 cells/mm^3

» Check ALT before commencing ART. If the ALT is raised, discuss this with an expert as it may not be an absolute contra-indication to treatment.
» Be aware of the possibility of Immune Reconstitution Inflammatory Syndrome (IRIS).

If the child is already on ART:

» Commence TB treatment taking into consideration possible medicine interactions.

If the child needs to take concomitant ART and rifampicin:

» Dolutegravir: use DTG 12 hourly.
» Efavirenz: use the normal recommended dosage as per dosing table on pg 23.4.
» Abacavir and lamivudine: no dose adjustment required.
» Lopinavir/ritonavir: Add additional ritonavir to ensure an equal dose in mg of lopinavir and ritonavir while on rifampicin. For example, for each mL of LPV/r solution (80/20 mg/mL), add 0.75 mL of ritonavir solution (80 mg/mL). See dosing table, pg 23.9.
» Avoid using double-dose lopinavir/ritonavir solution in young children. If ritonavir powder is not available, consult an expert.
» Give pyridoxine (vitamin B6) to all children on TB and ART, to avoid development of peripheral neuropathy.

11.9 DEVELOPMENTAL DELAY OR DETERIORATION

Refer children with cognitive (learning problems) and motor delays for assesment and neurodevelopmental rehabilitation.

11.10 ANAEMIA

See Section 3.1: Anaemia

HIV PREVENTION

11.11 PRE-EXPOSURE PROPHYLAXIS (PREP)

Z29.2

Consult the most recent National Department of Health Guideline for PrEP eligibility criteria.

DESCRIPTION

Pre-exposure prophylaxis (PrEP) is the use of antiretroviral medicines by HIV-negative individuals before potential exposure to HIV to prevent them from acquiring HIV infection. PrEP only protects against HIV infection; it does not offer protection against other STIs or pregnancy.

PrEP should be used as part of a package including condoms, lubricants for anal sex, STI management, screening and management of intimate partner violence, sexual and reproductive health services, medical male circumcision and HIV services, including counseling and testing, HIV management, ART, PEP, and PrEP.

All individuals requesting PrEP should be assessed and initiated if elgible.

Individuals initiated on PrEP must be:

» HIV-negative.
» At substantial risk of HIV infection.
» Willing and able to adhere to PrEP.
» Prepared to come for repeat HIV testing every 3 months.
» No contra-indications to tenofovir or emtricitabine.
» No suspicion of acute HIV-infection (see clinical features, below).

Clinical features of acute HIV infection

Symptoms	Signs
Malaise, anorexia, myalgia, headache, sore throat, sore glands, rash	Fever, sweating, viral meningitis, generalised lymphadenopathy, hepatosplenomegaly, pharyngitis, truncal rash, orogenital herpetiform ulceration, oral/oesophageal candidiasis, cervical adenopathy

CONTRA-INDICATIONS TO PREP

» Pre-existing HIV infection.
» Estimated creatinine clearance or eGFR < 60 mL/min.
» Use of nephrotoxic medicines e.g. aminoglycosides.
» Young women/men < 35 kg or < 15 years of age who are not Tanner stage 3 (sexual maturity) or greater.
» Unwilling or unable to adhere to daily PrEP.

ORAL PREP REGIMEN

A fixed dose combination formulation of:

- Tenofovir, oral, 300 mg daily.

AND

- Emtricitabine, oral, 200 mg daily. *LoE:Ia*[66]

Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required.

Screening investigations before starting PrEP *LoE:IIIb*[67]

Investigation	Purpose	Action
HIV test (using algorithm in the HTS guidelines)	Assessment of HIV status.	If HIV-negative, consider PrEP If HIV-positive. Link to treatment and care services.
Estimated creatinine clearance/ eGFR	To identify pre-existing renal disease.	Do not initiate PrEP if creatinine clearance/eGFR < 60 mL/min. Repeat creatinine clearance after two weeks. If renal function returns to normal and other PrEP criteria are met, PrEP may be initiated. Refer for further investigation if renal function remains abnormal.
Hepatitis B surface antigen (HBsAg)	To diagnose chronic hepatitis B infection. To identify those eligible for vaccination against hepatitis B.	Consider vaccination if available for HBsAg-negative. If HBsAg-positive, do ALT prior to PrEP initiation.
ALT if HBsAg-positive		If ALT persistently elevated or other abnormal liver function tests, refer for assessment.
Urine pregnancy test	To identify if pregnant.	Provide counselling covering risk of HIV infection during pregnancy and benefits of taking PrEP.
RPR	To diagnose syphilis infection for treatment.	Manage according to STI guidelines.
Syndromic STI screening	To diagnose and treat STI.	Manage according to STI guidelines.

Table 11.14: Screening investigations before starting PrEP

Note:

» If symptoms or signs of acute HIV infection are present, PrEP should be postponed until symptoms subside and a repeat rapid HIV test after 4 weeks remains negative.

» TDF + FTC is active against hepatitis B (HBV) infection. HBV infection is not a contra-indication to PrEP, but will require LFT monitoring. Discontinuation of TDF + FTC in patients with HBV requires referral to a specialist because of a risk of a hepatitis flare.

Hepatitis B immune status and PrEP eligibility

Hepatitis B surface antigen (HBsAg)	Hepatitis B surface antibody (HBsAb)	Action
Negative (-)	Negative (-)	Start PrEP. Vaccinate concurrently if available
Negative (-)	Positive (+)	Start PrEP. No vaccine needed
Positive (+)	N/A	Refer for evaluation, if ALT > 2 times upper limit of normal.

Table 11.15: PrEP eligibility determined by hepatitis B immune status

Note:

» PrEP users with chronic hepatitis B infection who develop abnormal liver function tests should be referred for assessment.

PrEP follow up and monitoring

Activity	Frequency
Confirmation of HIV-negative status	At 1 month, then every 3 months
Address side effects	Every visit
Adherence counseling	Every visit
Estimated creatinine clearance	Frequency dependant on pregnancy status, age and co-morbidity: *LoE:IVb*[68]

Age/ pregnant	Co-morbidity	Creatinine
< 30 years	None	n/a
30–49 years	None	Baseline
< 49 years	Diabetes/ hypertension	Baseline, annually
≥ 50 years	None	Baseline
≥ 50 years	Diabetes/ hypertension	Baseline, annually
Pregnant	n/a	Baseline, 3 & 6 months

STI screening and treatment	Every visit
PrEP dispensing	1 month supply, then 3 monthly supply
Behavioural sexual risk reduction counseling	Every visit

Table 11.16: Monitoring of person(s) on PrEP

PREP SAFETY

Relevant medicine interaction information

Medicine	Interaction information	Advise
Standard TB medicines	No interaction	No need for dose adjustments
MDR-TB medicines	Increase risk of renal side effects	Avoid PrEP. Advise other prevention methods
Hormonal contraception	No interaction	Hormonal contraception does not affect PrEP effectiveness, nor does PrEP affect hormonal contraceptive effectiveness
Nephrotoxic medicines	Increase risk of renal side effects	Avoid PrEP. Advise other prevention methods

Table 11.17: Oral PrEP drug interactions

Side effects of TDF + FTC combination

Major	Renal toxicity, decreased bone mineral density, extremely small risk of lactic acidosis and hepatic steatosis or steatohepatitis
Minor	Gastrointestinal symptoms (diarrhoea, nausea, vomiting and flatulence), unintentional weight loss

Table 11.18: Side effects of oral PrEP

Note:

» Minor side effects are relatively common (approximately 1 in 10 individuals in the first 1-2 months).
» Mild and self-limiting; do not require discontinuation.
» Renal toxicity and decreased bone mineral density usually reversible upon stopping PrEP.

STOPPING PREP

PrEP should be stopped if:
» Tests HIV-positive.
» Renal disease develops.
» Non-adherent to PrEP.
» Does not need or want PrEP.
» No longer meets eligibility criteria.
» There are safety concerns where the risks of PrEP use outweigh potential benefit.

Continue PrEP for 7 days after the last potential HIV exposure. *LoE:IVb*[69]

Note: Patients with chronic HBV may experience a hepatitis flare on discontinuation of PrEP.

REFERRAL

» HBsAg-positive, with abnormal ALT.
» Discontinuation of TDF + FTC in patients with HBV.

PREP INITIATION ALGORITHM

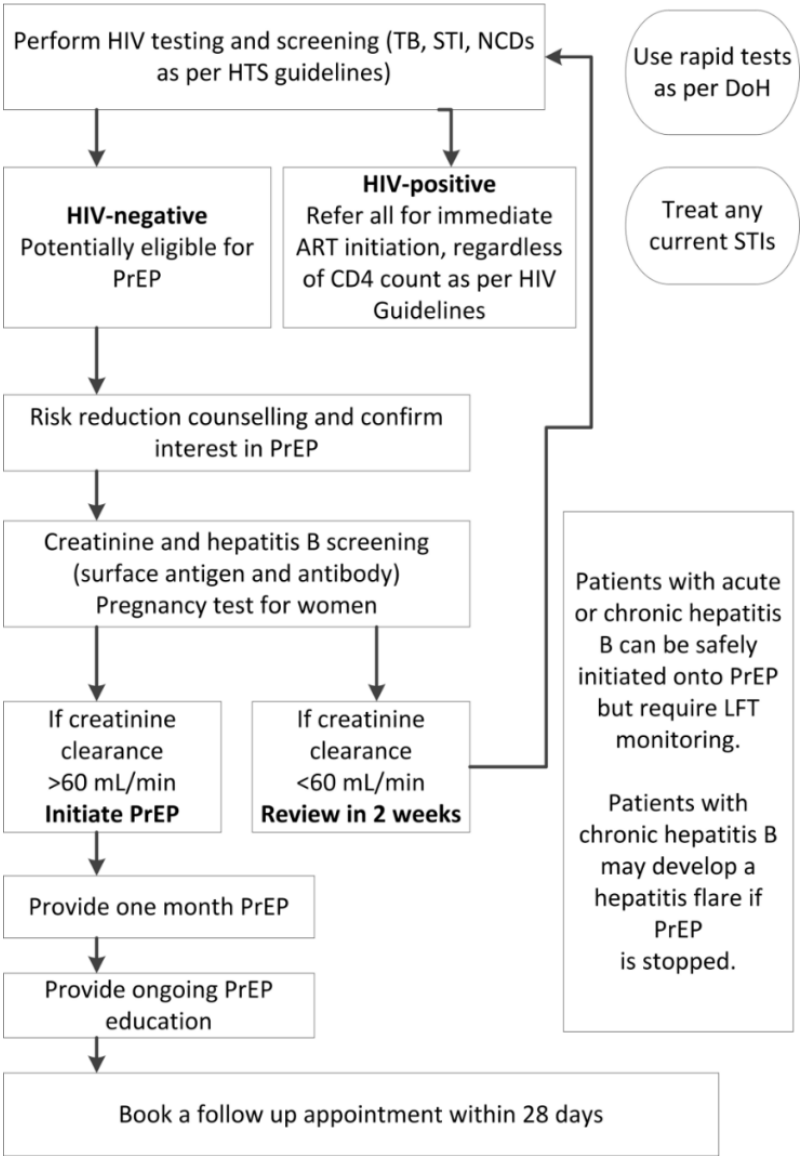

Figure 11.8: PrEP initiation algorithm

11.12 POST EXPOSURE PROPHYLAXIS

See Section 21.3.6: Post exposure Prophylaxis (PEP).

11.13 SIDE EFFECTS AND COMPLICATIONS OF ART

Refer to the Adult Hospital Level STGs and EML: Section 10.1.1 Management of selected antiretroviral adverse drug reactions, and consult with an infectious disease specialist as required.

11.13.1 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME (IRIS)

D89.3 + (Y41.5 + B24)

DESCRIPTION

Clinical deterioration can occur after starting ART due an improvement in the immune system response to organisms already causing infection, e.g.

» M.Bovis (BCG)
» M. tuberculosis (MTB)

There are 2 types of IRIS:

1. Unmasking: when a previously unsuspected condition becomes manifest.
2. Paradoxical: known condition on appropriate treatment becomes worse.

DIAGNOSTIC CRITERIA

» Exclude other active or inadequately treated diseases (including DR-TB).
» Presentation:
  - Usually during the first 6 weeks after starting ART.
  - Depends on the causative organism and the organ system involved, e.g. TB presents with fever, lymphadenopathy, worsening of the original tuberculous lesion, and/or deteriorating chest radiographic manifestations such as miliary pattern or pleural effusion.

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All.

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Chapter 12

SOUTH AFRICAN PRIMARY HEALTHCARE ESSENTIAL MEDICINES LIST
CHAPTER 11: HIV AND AIDS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -2023 REVIEW CYCLE)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).
Medicine reviews may be accessed at: https://www.knowledgehub.org.za/elibrary/primary-healthcare-phc-medicine-reviews-2020-2023
Costing reports may be accessed at: https://www.knowledgehub.org.za/elibrary/primary-healthcare-phc-costing-reports-2020-2023

MEDICINE AMENDMENTS:

SECTION	MEDICINE	ADDED/DELETED/AMENDED/NOT ADDED/RETAINED
A: HIV INFECTION IN ADULTS		
11.1 Antiretroviral therapy, adults and adolescents - *Clinical indications for deferring ART initiation*		
- TB co-infection	ART	Directions amended
- TB meningitis co-infection	ART	Directions amended
- Cryptococcal meningitis co-infection	ART	Directions amended
- Asymptomatic cryptococcal infection	ART	Directions amended
11.1 Antiretroviral therapy, adults (1st line) *- Treatment-naïve patients without TB*	TDF +3TC + DTG	Indication expanded from ≥6 weeks gestation to ALL women
11.1 Antiretroviral therapy, adults (1st line) *- Treatment-naïve patients without TB*	TAF	Not added
11.1 Antiretroviral therapy, adults (1st line) *- Treatment-naïve patients with TB*	Double-dosed DTG	Indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy
	TDF +EFV+FTC	Retain
11.1 Antiretroviral therapy, adults (1st line) *- Contraindication to TDF*	ABC + 3TC	Amended as preferred treatment
11.1 Antiretroviral therapy, adults (2nd line) *- Recycling TDF in 2nd-line regimens*	TDF	Added
	AZT	Deleted
11.1 Antiretroviral therapy, adults (2nd line)	ATV/r	Expanded to include all patients - preferred 2nd line PI
	LPV/r	Retain
	DRV/r	Not added to the STG, but proposed for inclusion in therapeutic interchange database for patients not on TB-rifampicin therapy
11.1 Antiretroviral therapy, adults (2nd line) *- Failing a NNRTI-based 1st line regimen + HbsAg positive*	AZT + 3TC + DTG plus TDF	Deleted
11.1 Antiretroviral therapy, adults (2nd line) *- DTG contraindicated/not tolerated, not on rifampicin*	TDF + 3TC/FTC + ATV/r	Added
11.1 Antiretroviral therapy, adults (2nd line) *- TDF contraindicated/not tolerated, not on rifampicin*	AZT + 3TC + DTG	Added
11.1 Antiretroviral therapy, adults (2nd line) *- AZT and TDF contraindicated/not tolerated, not on rifampicin*	ABC + 3TC + DTG	Added
11.1 Antiretroviral therapy, adults (2nd line) *- Failing a DTG- based 1st line regimen for >2 years (TDF+3TC+DTG)*	AZT + 3TC/FTC + ATV/r	Deleted
	TDF + 3TC/FTC +ATV/r	Added
11.1 Antiretroviral therapy, adults (2nd line) *- Rifampicin-based TB treatment (on DTG-regimen)*	DTG	Added
11.1 Antiretroviral therapy, adults (3rd line ART regimens)	Resistance testing	Retained, and emphasised
11.1 Antiretroviral therapy, adults *- Currently available ARV FDC preparations on contract*	ATV/r	Added
	ABC + 3TC + DTG	Added
Defaulting ART	Guidance (VL & ART regimen)	Added
Monitoring on ART *- At HIV diagnosis: CrAg screening*	CrAg screening	Not amended
ART: Dosing and important adverse effects	TDF, ABC, 3TC, FTC	Amended - very low risk, "Hyperlactataemia/ steatohepatitis" was deleted
	Dolutegravir, oral	Amended - weight-gain deleted

	Nevirapine, oral	Adverse effects and dosing information deleted
	Raltegravir, oral	Adverse effects and dosing information deleted
ART interactions with rifampicin and recommendations for administration	Rifabutin, oral	Not added
11.2.2 Tuberculosis preventive therapy (TPT)	TPT	Added as a therapeutic group
-Adult PLHIV initiated on ARVs	Isoniazid (12H)	Retained as an example of class in the STG
	Rifapentine + isoniazid (3HP)	Added as a therapeutic alternative in the therapeutic interchange database
11.3.4 Cryptococcosis	CrAg screening	Not amended
	Fluconazole, oral	Directions for use amended
- CSF CrAg positive	Flucytosine, oral	Not added
11.4 HIV and kidney disease	Routine screening for renal disease	Retained
B: HIV INFECTION IN CHILDREN		
11.5 The HIV exposed infant	Nevirapine	Dosing expanded to 3-years of age
	Cotrimoxazole, oral	Prophylaxis treatment for HIV-exposed infants was amended
11.6 Management of HIV-infected children (<10 years)	DTG	Not added
11.7 Opportunistic infections, prophylaxis in children	Cotrimoxazole, oral	Directions for use amended
C: HIV PREVENTION		
11.11 Pre-exposure prophylaxis (PrEP)		
- Initiating oral PrEP	TDF + FTC	Duration of therapy amended
- Oral PrEP follow up and monitoring	Estimated creatinine clearance	Monitoring updated
- Stopping oral PrEP	TDF + FTC	Duration of therapy amended
- Other PrEP agents	Dapivirine vaginal ring	Not added
	Cabotegravir	Not added
D: SIDE EFFECTS AND COMPLICATIONS OF ART		
11.13.1 Lactic acidosis	STG	Deleted

ABC= Abacavir, ATV/r=Atazanavir/ritonavir, AZT=Zidovudine, 3TC= Lamivudine, DRV/r=Darunavir/ritonavir, DTG= Dolutegravir, EFV= Efavirenz FTC = Emtricitabine, LPV/r=Lopinavir/ritonavir, PrEP=Pre-exposure prophylaxis;TAF=tenofovir alafenamide, TDF = Tenofovir disoproxil fumarate

A. HIV INFECTION IN ADULTS & ADOLESCENTS

11.1 ANTIRETROVIRAL THERAPY, ADULTS & ADOLESCENTS

- ***CLINICAL INDICATIONS FOR DEFERRING ART INITIATION:***

TB co-infection

STG text was aligned to the Adult Hospital Level STG.

» In TB co-infection, start with TB treatment first, followed by ART initiation according to CD4 count (except TB meningitis – see below):
- CD4 counts < 50 cells/mm^3: start ART within 2 weeks of starting TB treatment.
- CD4 count ≥ 50 cells/mm^3: defer ART until 8 weeks after starting TB treatment, which does not increase the risk of mortality and reduces the risk of deterioration due to the immune reconstitution inflammatory syndrome (IRIS).

TB meningitis

STG text was aligned to the Adult Hospital Level STG.

» In patients with TB meningitis (irrespective of CD4 count), defer ART until 8 weeks after starting TB treatment.

Cryptococcal meningitis

STG text was aligned to the Adult Hospital Level STG.

» Defer ART until 4–6 weeks after starting antifungal treatment (earlier initiation has been shown to increase the risk of death).

Asymptomatic cryptococcal infection

ART: *directions added*

In patients with positive cryptococcal antigen and no evidence for meningitis on LP, guidance provided in the STG to defer ART until 2 weeks after initiating fluconazole. Immediate ART initiation is not recommended among PLHIV who have cryptococcal meningitis because of the risk of increased mortality presumed to be caused by immune

reconstitution inflammatory syndrome in the central nervous system.[1] Thus, the STG recommends that ART be deferred 4–6 weeks from the initiation of antifungal treatment. The South African HIV Clinicians Society guideline[2] recommends that asymptomatic CrAg-positive patients who decline consent for a lumbar puncture or where lumbar punctures are contra-indicated to initiate ART after at least 2 weeks of antifungal treatment. For pragmatic purposes, deferral of ART for 2 weeks was retained for asymptomatic CrAg-positive patients with no evidence of meningitis on lumbar puncture.

The STG text was amended as follows:

Positive cryptococcal antigen and no evidence for meningitis on LP:
» Defer ART until 2 weeks after initiating fluconazole

Level of Evidence: Very low certainty, conditional recommendation

11.1 ANTIRETROVIRAL THERAPY, ADULTS (1ST LINE ART REGIMENS)

- ***TREATMENT-NAÏVE PATIENTS WITHOUT TB***

Tenofovir + lamivudine + dolutegravir, oral: *amended indication to include all women*
Indication expanded from "≥6 weeks gestation" to "ALL women".
Refer to the medicine review: Dolutegravir in pregnancy, 17 June 2021 v2:

DTG in pregnancy_PHC-Adult

Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG *(strong recommendation)*

Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.

Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance.

Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.

A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide.

Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP (Women of Child Bearing Potential), as well as potential short-term benefits to their infants, outweigh the risks.

Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

[1] Eshun-Wilson I, Okwen MP, Richardson M, Bicanic T. Early versus delayed antiretroviral treatment in HIV-positive people with cryptococcal meningitis. Cochrane Database Syst Rev. 2018 Jul 24;7(7):CD009012.
[2] Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, Rabie H, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. South Afr J HIV Med. 2019 Nov 8;20(1):1030.

Tenofovir alafenamide (TAF): *not added*

Refer to the updated medicine review, May 2022 (update of initial February 2020 review), noting that no new evidence was identified:

Tenofovir alafenamide for HIV_A

Recommendation: TAF not be considered for inclusion in the national Adult Hospital Level EML, currently *(strong recommendation).*

Note:

- Based on the best available evidence, TAF is no better in efficacy than TDF and may have small safety benefits whose clinical relevance is still uncertain. TAF can be considered in first line regimens in the future should the TAF/FTC co-formulation or FDCs be licensed in RSA (FTC/TAF/DTG) – for patients with contraindications to TDF i.e., advanced renal disease.
- There is very limited clinical experience of TAF in pregnancy and we therefore do not recommend TAF use in pregnancy.
- The potential for the interaction of TAF with rifampicin exists and concurrent therapy still needs further evaluation.

Rationale:

- The efficacy and safety of TAF-containing regimens vs. TDF-containing regimens have been mostly evaluated in the context of the coformulation of elvitegravir, cobicistat, emtricitabine and darunavir. There is insufficient data where it has been evaluated in standard formulations used in low-middle income countries (LMICs).
- The synthesis shows that TAF is no more effective than TDF. TAF overall, shows slightly lower toxicity in these studies especially with regard to renal and bone health markers – the clinical significance of these differences in markers is not clear. However, these findings should be interpreted cautiously as in most studies TAF was co-formulated with cobicistat, where the TAF dose is reduced from 25mg to 10mg. There is a need for trials comparing or evaluating efficacy and especially safety of TAF head for head in standard coformulations used in low middle-income countries.
- Emerging observational data suggests switching from TDF to TAF and may cause a statistically significant worsening of the lipid profile that may have clinical relevance. This is likely seen in patients with cardiovascular risk factors such as older age and high body mass index (BMI). The lower concentrations of TDF in plasma from TAF as compared with TDF, and the lipid-lowering effect of TDF may explain the increases in total cholesterol in the TAF group compared with the TDF group. It may be important to weigh the possible benefit of lipid changes associated with TDF against the possible benefit of TAF for bone and kidney.

Level of Evidence: Systematic Reviews and Meta-Analysis of Randomized Clinical Trials

Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC MEETING OF 19 MARCH 2019:

NEMLC accepted this evidence review and the proposal as recommended by the Adult Hospital Level Expert Review Committee, above. NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered and thus not currently available on the South African market. The current antiretroviral recommendations, as recommended in the Standard Treatment Guidelines (Adult Hospital Level, 2019 edition) and National HIV Guidelines, 2019 edition are sufficient.

NEMLC MEETING OF 23 JUNE 2022:

NEMLC Discussion

- *Renal impairment:* It was noted that patients with renal impairment are generally referred to the tertiary level of care and TAF may be potentially advantageous for this cohort so there may be some consideration to limit access to tertiary centres
- *SAHPRA registration:* TAF is currently not registered locally.

NEMLC Recommendation: The NEMLC upheld the previous decision from 2019 which was not to recommend TAF for the inclusion on the national EML. However, TAF could be accessed by Provinces for individual patients on a named-patient basis. NEMLC also acknowledged that TAF-containing fixed-dose combination formulations are currently not SAHPRA registered.

- ***ART- TREATMENT-NAÏVE PATIENTS WITH TB***

Double-dosed dolutegravir (TLD + DTG 50 mg): *indication expanded to DTG-naïve patients initiating ART with concomitant rifampicin-containing TB therapy*
Tenofovir + Efavirenz + Emtricitabine (TEE): *retained*

Refer to the updated DTG in HIV-infected patients review with addendum, 21 July 2021 (second update of initial 26 January 2017 review):

DTG for HIV-infected patients commencing

Recommendation: Based on this evidence summary, the PHC/Adult Hospital Level Committee recommends that dolutegravir 50mg 12 hourly be included as an option in the standard treatment guidelines for adult patients initiating antiretroviral therapy while taking rifampicin-containing TB treatment, as an alternative to using efavirenz for the duration of TB treatment *(conditional recommendation).*
Rationale: Randomised open-label INSPIRING study[3] [4] showed that initiation of DTG-containing ART with DTG double dosing is well tolerated; and that virological suppression for efavirenz-containing ART regimen and double-dosed DTG-containing ART regimen were similar amongst ART-naive adults initiating ART, whilst on rifampicin-based tuberculosis treatment.
Level of evidence: Low certainty evidence

NEMLC MEETING OF 21 JULY 2021:
NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee.

- ***CONTRAINDICATION TO TDF***

Abacavir + lamivudine, oral: *amended as preferred treatment*
Abacavir preferable zidovudine, as kidney disease is often progressive, resulting in anaemia.

Aminoglycoside nephrotoxicity caution: *deleted*
The following STG text was deleted:

~~Use of additional nephrotoxic drug e.g., aminoglycoside.~~

Aminoglycosides are no longer recommended for management of drug-resistant TB. However, available evidence did not show a significant increased risk of nephrotoxicity with TDF in DR-TB patients on kanamycin.[5] [6]

11.1 ANTIRETROVIRAL THERAPY, ADULTS (2nd LINE ART REGIMENS)

- ***RECYCLING TDF IN 2ND-LINE REGIMENS***

Tenofovir: *added*
Zidovudine: *deleted*

As the 96-weeks follow up data of the NADIA RCT[7] has been published in peer-review format, and the initial evidence summary was updated (TDF-backbone as 2nd line in HIV, Adult review, 19 May 2022, update of the initial review of 30 November 2021):

[3] Dooley KE, Sayre P, Borland J, Purdy E, Chen S, Song I, et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):21-7.
[4] Dooley KE, Kaplan R, Mwelase N, Grinsztejn B, Ticona E, Lacerda M, et al; International Study of Patients with HIV on Rifampicin ING study group. Dolutegravir-based Antiretroviral Therapy for Patients Coinfected With Tuberculosis and Human Immunodeficiency Virus: A Multicenter, Noncomparative, Open-label, Randomized Trial. Clin Infect Dis. 2020 Feb 3;70(4):549-556.
[5] Perumal R, Abdelghani N, Naidu N, Yende-Zuma N, Dawood H, Naidoo K, et al. Risk of nephrotoxicity in patients with drug-resistant tuberculosis treated With kanamycin/capreomycin with or without concomitant use of tenofovir-containing antiretroviral therapy. J Acquir Immune Defic Syndr. 2018;78: 536–542. https://pubmed.ncbi.nlm.nih.gov/29683992/
[6] Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Mengistu A, Mekonen TT, et al.. Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with antiretroviral agents. Int J Tuberc Lung Dis. 2017;21: 1245–1250. https://pubmed.ncbi.nlm.nih.gov/29297444/
[7] Paton NI, Musaazi J, Kityo C, Walimbwa S, Hoppe A, Balyegisawa A, 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. 2022. https://pubmed.ncbi.nlm.nih.gov/35460601/

TDF-backbone as 2nd line in HIV_Adults

Recommendation: Based on this evidence review, the PHC/Adult Hospital Level Committee suggest that tenofovir should be recycled in 2nd line dolutegravir-based antiretroviral therapy *(conditional recommendation).*
Rationale: For patients in whom neither agent is contraindicated, recycled TDF is non-inferior to AZT in 2nd line therapy (assuming TDF use in 1st line), and adverse events rates are similar. In addition, compared to AZT, it is cheaper, can be given once daily, is available as a single fixed dose combination tablet (TLD), and requires less intense initial monitoring.
Level of Evidence: RCTs of moderate certainty evidence
Review indicator: Evidence of harm or inferior viral suppression rates

NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022):
NEMLC accepted the proposed recommendation, as mentioned above.

- ***DTG CONTRAINDICATED/ NOT TOLERATED/FAILING***

Atazanavir/ritonavir: *expanded to include all patients - preferred 2nd line PI*
Lopinavir/ritonavir: *retained*
Refer to the medicine review (Atazanavir/ritonavir vs lopinavir/ritonavir as 2nd line adult HIV therapy, 18 November 2021), below:

Atazanavir-ritonavir vs lopinavir-ritonavir a

Recommendation: The PHC/Adult Hospital Level Committee suggests that ritonavir-boosted atazanavir be the preferred protease inhibitor for second-line therapy in all adult patients without concomitant TB. Ritonavir-boosted lopinavir must still be available for use with rifampicin-containing TB therapy *(conditional recommendation).*
Rationale: Ritonavir-boosted atazanavir is at least non-inferior to ritonavir-boosted lopinavir in terms of viral suppression, is associated with fewer gastrointestinal side-effects and lipid profile abnormalities than ritonavir-boosted lopinavir and is dosed once-daily.
Level of Evidence: Low to moderate certainty evidence

NEMLC MEETING 9 DECEMBER 2021:
NEMLC Recommendation: The NEMLC accepted the proposed recommendation. It was furthermore noted that the global market is shifting from LPV/r to other protease inhibitors (i.e., DRV/r and ATV/r) and competition will likely push down the price of other protease inhibitors.

Darunavir/ritonavir: *not added to the STG, but proposed for inclusion in therapeutic interchange database for patients not on TB-rifampicin therapy*
Refer to the medicine review (Darunavir-ritonavir vs lopinavir-ritonavir as 2nd line adult HIV therapy review, 27 July 2021):

Darunavir-ritonavir vs lopinavir-ritonavir_2nd

Recommendation: The Committee suggests that DRV/r not be used in preference to LPV/r *(conditional recommendation).*
Rationale: Despite DRV/r-containing ART regimens being associated with higher viral suppression rates and being better tolerated than LPV/r, at the current cost it is considered unaffordable, and there are concerns regarding the supply. It would also not be suitable for the minority of patients on a PI-based regimen who require rifampicin-based tuberculosis treatment. DRV/r is recommended for inclusion on the therapeutic interchange database as an alternative to LPV/r and ATV/r, for patients not on TB-rifampicin therapy.
Level of Evidence: Moderate certainty evidence
Review indicators: Reduction in DRV/r price

NEMLC MEETING 9 DECEMBER 2021:
NEMLC Recommendation: The NEMLC accepted the proposed recommendation made by the PHC/Adult Hospital Level Committee above.

The therapeutic interchange database update as follows:

Indication	Medicine (INN)	Daily dosing	Therapeutic class	Therapeutic ATC
Adult 2nd line HIV management (patients not on rifampicin TB therapy)	Darunavir and ritonavir	800/100 mg	Protease inhibitors for HIV (combinations)	J05AR
	Lopinavir and ritonavir	800/200 mg	Protease inhibitors for HIV (combinations)	J05AR

As the proposed second line ART regimen is now a TDF-containing regimen, the following was updated, accordingly – aligned with guideline recommendations:

a. Failing a NNRTI-based 1st line regimen + HbsAg positive
AZT + 3TC + DTG plus TDF: *deleted*

b. DTG contraindicated/not tolerated, not on rifampicin
TDF + 3TC/FTC + ATV/r: *added*

c. TDF contraindicated/not tolerated, not on rifampicin
AZT + 3TC + DTG: *added*

d. Failing a DTG- based 1st line regimen for >2 years (TDF+3TC+DTG)
AZT + 3TC/FTC + ATV/r: *deleted*
TDF + 3TC/FTC +ATV/r: *added*

Rifampicin-based TB treatment (on DTG-regimen)
DTG: *added*
STG text was amended to align with the previously reviewed addendum to the DTG review (see details above):

If on DTG: DTG needs to be given at a dose of 50 mg 12-hourly (add DTG 50mg)

11.1 ANTIRETROVIRAL THERAPY, ADULTS (3rd LINE ART REGIMENS)

Resistance testing: *emphasised*
The PHC/Adult Hospital Level Committee raised concerns regarding the emergence of DTG resistance in 4 NADIA participants, especially as DTG is used in second-line antiretroviral therapy in South Africa. Therefore, the statement in the STG, prompting consideration of resistance testing for patients failing DTG-containing 2nd line antiretroviral therapy, was emphasised.

- ***CURRENTLY AVAILABLE ARV FDC PREPARATIONS ON CONTRACT***

ATV/r: *added*
ABC + 3TC + DTG: *added*
STG text was updated to reflect currently available fixed-dose combination antiretrovirals that are accessible on the current public sector tender.[8]

- ***DEFAULTING ART***

Re-initiating ART in patients who have interrupted treatment
The following note was added,

» Recommence previous regimen. » Do VL, recommence ART regimen, repeat at 3- or 6-month VL test. » If VL does not to decrease to <1000 copies per mL at 6 months, manage virological failure according to the specific regiment (refer to ART regimens table).

Level of Evidence: Low certainty evidence[9]

- ***MONITORING ON ART: CRAG SCREENING AT HIV DIAGNOSIS***

CrAg screening*: not amended (threshold not amended to CD4<200 cells/mm^3, but maintained at CD4<100 cells/mm^3)*

[8] Contract circular HP13-2022ARV http://www.health.gov.za/

[9] WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021.

Reflex screening of Cryptococcal Antigen (CrAg) in PLHIV was maintained at CD4<100 cells/mm^3. This is aligned with the WHO guidelines that recommends "Screening for cryptococcal antigen followed by pre-emptive antifungal therapy among cryptococcal antigen–positive people to prevent the development of invasive cryptococcal disease are recommended before initiating or reinitiating ART for PLHIV who have a CD4 count <100 cells/mm^3 (*strong recommendation, moderate certainty evidence*).[10] The cost per disability-adjusted life year saved was estimated as $21 (95% CI, $15-$32) for CrAg screening of PLHIV at CD4<100 cells/mm^3 with pre-emptive fluconazole treatment.[11] Ford et al's systematic review showed that Africa had the highest prevalence of CD4<100 cells/mm^3 and the authors suggest that "cconsideration should be given to screening at a higher CD4 count of ≤200 cells/mm^3 in settings where there are sufficient resources to implement such an approach, or where a simplified package of care for advanced disease is required based on a unified CD4 threshold" (*conditional recommendation, moderate certainty evidence*). [12] However, the NDoH HIV Programme recommends the lower threshold of CD4<100 cells/mm^3,[13] and have not recommended a higher CD4 threshold as it is currently unaffordable. It is noted that NHLS recommends reflex monitoring of CrAg at a CD4 ≤200 cells/mm^3, aligned with the South African HIV Clinician Society Guidelines[14], which probably needs to be addressed.

- ***ART: DOSING AND IMPORTANT ADVERSE EFFECTS***

Tenofovir, abacavir, lamivudine, emtricitabine, oral: *amended - very low risk, "Hyperlactataemia/ steatohepatitis" deleted*
Dolutegravir, oral: *amended - weight-gain deleted*
Nevirapine, oral: *adverse effects and dosing information deleted*
Raltegravir, oral: *adverse effects and dosing information deleted*

Dolutegravir (weight gain):
Refer to the NEMLC-approved medicine review: Dolutegravir in pregnancy, June 2021 – see page 2:
"Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is unlikely to be clinically relevant".

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

Nevirapine, oral: The Information on the dosing and adverse effects of nevirapine was removed as long-term use of has been removed from the National Guidelines.

Raltegravir, oral: Dosing and adverse effects information was deleted, as raltegravir has been removed from the 3rd line National ARV protocols.

- ***ART INTERACTIONS WITH RIFAMPICIN AND RECOMMENDATIONS FOR ADMINISTRATION***

Rifabutin, oral: *not added*
Rifabutin, oral was not added as an essential medicine for primary level of care, as the medicine which has a sole supplier with intermittent supply constraints, and is already included on the Adult Hospital Level EML. However, a cross-reference to the respective Adult Hospital STG was added, as follows:

Patients on atazanavir or darunavir, or if double dose LPV/r is not tolerated, replace rifampicin with rifabutin (doctor prescribed) – see Adult Hospital Level STGs and EML. section 10.1: Antiretroviral therapy.

[10] WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021.
[11] Meya DB, Manabe YC, Castelnuovo B, Cook BA, Elbireer AM, Kambugu A, Kamya MR, Bohjanen PR, Boulware DR. Cost-effectiveness of serum cryptococcal antigen screening to prevent deaths among HIV-infected persons with a CD4+ cell count < or = 100 cells/microL who start HIV therapy in resource-limited settings. Clin Infect Dis. 2010 Aug 15;51(4):448-55.
[12] Ford N, Shubber Z, Jarvis JN, Chiller T, Greene G, Migone C, Vitoria M, Doherty M, Meintjes G. CD4 Cell Count Threshold for Cryptococcal Antigen Screening of HIV-Infected Individuals: A Systematic Review and Meta-analysis. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S152-S159.
[13] National Department of Health: National Consolidated Guidelines for the Management of HIV in Adults, Adolescents, Children and Infants and Prevention of Mother-to-Child Transmission, June 2020.
[14] Govender NP, Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, et al. Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update. S Afr J HIV Med 2019;20(1):a1030.

11.2.2 TUBERCULOSIS PREVENTIVE THERAPY (TPT)

Adult PLHIV initiated on ARVs

TB preventive therapy: *added as a therapeutic group*
Isoniazid (12H): *retained as an example of class in the STG*
Rifapentine + isoniazid (3HP): *added as a therapeutic alternative in the therapeutic interchange database*

Background: During the previous review cycles, the NEMLC approved 12 months of daily isoniazid (12H) for PLHIV and not 3HP. Non-inferiority trials suggested that 3HP prophylaxis was not inferior to 12H in PLHIV. However, 3HP is more expensive than 12H. Refer to the previous NEMLC-approved reviews for rifapentine in PLHIV (14 November 2019) and rifapentine in PLHIV on DTG-containing antiretroviral therapy (11 November 2019), and the historic NEMLC minutes (meeting of 21 February 2019):


Rifapentine (3HP) as TPT in PLHIV -Adult re


TPT in PLHIV on DTG-

BACKGROUND

NEMLC MEETING OF 21 FEBRUARY 2019:

Available evidence for IPT in PLHIV: *Most of the evidence for isoniazid prevention therapy (IPT) in people living with HIV (PLHIV) was from the pre-ART era. Two RCTs done in PLHIV: i) RCT in Khayelitsha by Rangaka et al, 20146 of PLHIV either starting or established on ART comparing 12 months of isoniazid vs placebo; ii) Temprano RCT by Danel et al, 20157, where IPT; ART and IPT+ART were evaluated either starting early or late.*

Previous NEMLC recommendation: *In the PHC STGs and EML, 2018 IPT was simplified to 12 months, from the previous complex algorithm requiring TST, based on the Khayelitsha RCT.*

Evidence for 6 months IPT: *The Adult Hospital Level Committee's recommendation to change duration of IPT to 6 months based on a mortality benefit from the Temprano RCT, raised a concern. The Temprano RCT was done in West Africa, where the incidence of TB is lower compared to South Africa. It was stated that greater mortality benefit of 6 months IPT compared to 12 months IPT was biologically implausible, unless IPT is very toxic, however this is not the case.*

Network meta-analysis *of individual patient data (including South African data) is currently underway in the USA which should further inform decision-making on duration of IPT in PLHIV.*

WHO recommendation *of 36 months was discussed, noting that the evidence base was from the pre-ART era. IPT with ART was reported to be more durable than IPT without ART.*

Recommendation: *Previous NEMLC recommendation of IPT in PLHIV be retained as 12 months duration, until further evidence is forthcoming.*

Rationale: Biologically plausible that 12 months rather than six months IPT would have greater benefit.
Despite the lack of data comparing duration of IPT therapy, available evidence in the local South African setting suggests that 12 months IPT would be reasonable.

Level of Evidence: I RCT

Current 2020-3 review cycle: In the current review cycle, 3HP was recommended for inclusion to the therapeutic interchange database:

- 12H: Isoniazid, oral, 300 mg daily for 12 months
- 3HP: Isoniazid, oral 900 mg + Rifapentine, oral 900 mg weekly for 3 months (preferably as an FDC).

NEMLC MEETING OF 23 JUNE 2022:

NEMLC recommended that 3HP be included as a therapeutic alternative to 12H in PLHIV initiated on ART – however, for DTG-containing regimens patients to be virally suppressed (this would promote competitive pricing).

However, as there is currently no available RCT evidence for concomitant use of rifapentine with viraemic patients on DTG, the following text was added to the STG:

Ideally start TPT together with ARVs. However, if a rifapentine-containing TPT regimen is available, it should only be initiated together with an EFV-based ART regimen. A rifapentine-containing TPT regimen can be used with a DTG-based ART regimen in patients who are already virally suppressed. Do not use in patients on protease inhibitor-based ART, or in women on oral or hormonal contraceptives. *[See the therapeutic interchange database for details regarding the rifapentine-containing TPT regimen].*

The therapeutic interchange database update as follows:

Indication	Criteria	Medicine (INN)	Treatment course	Therapeutic class	Therapeutic ATC
TPT for ART-naïve HIV adult patients	n/a	Isoniazid	300 mg daily x 12 months	TPT	J04A
	• Initiated on TEE • Initiated on TLD BUT virally suppressed • NOT on a PI • Not on oral hormonal contraceptives	Isoniazid and rifapentine (FDC)	900/900 mg weekly x 3 months	TPT	J04A

FDC=fixed dose combination; TEE= TDF+EFV+FTC; TLD= TDF+3TC+DTG; TPT=TB preventive therapy; PI=protease inhibitor

11.3.4 CRYPTOCOCCOSIS

CrAg screening*: not amended*
Refer to discussion above - **Monitoring on ART: CrAg screening at HIV diagnosis.**

Fluconazole, oral: *caution updated*
The fluconazole caution box was updated to align with the amended Adult Hospital Level STG and EML, with the inclusion of the following text:

» Fluconazole is potentially teratogenic when used during the 1st trimester, but pregnant women should be counselled that the benefits of fluconazole likely outweigh the risks in the management of cryptococcosis.

CSF CrAg positive
Flucytosine, oral: *not added*
External comment received regarding flucytosine, oral as induction therapy in this clinical setting was noted. Though, flucytosine, oral is included in the respective Adult Hospital Level STG.

11.4 HIV AND KIDNEY DISEASE

Routine screening for renal disease: *retained*
An external comment was received regarding annual screening of renal disease, despite use of ARVs that did not include tenofovir. However, HIV was considered a risk factor for chronic kidney disease.[15]

B. HIV INFECTION IN CHILDREN

11.5 THE HIV-EXPOSED INFANT

Nevirapine: *dosing expanded to infants 3 years of age*
Nevirapine doing for infants from birth to 6 months on PMTCT is 4mg/kg/daily. For children older than 6 months to 3 years requiring prophylaxis should use treatment doses. The STG cross-refers to the Paediatric Hospital STGs and EML, section 9.1.3 The HIV Infected Infant/Child. On receipt of an external query the PHC/Adult Hospital Level Committee recommended that dosing for the older infant to be included in the appendix of paediatric weight-band dosing tables for various medicines.

Cotrimoxazole prophylaxis treatment (CPT), oral: *directions for use amended*
Aligned with the proposed amended draft Paediatric Hospital Level HIV chapter (2021) based on the benefit:risk assessment of CPT in HIV exposed, uninfected (HEU) infants at low- and high-risk of HIV infection through vertical mother-to-child transmission (MTCT).

Evidence: There is strong evidence that CPT significantly reduces mortality and infectious morbidity amongst HIV-infected adults and children;[16] and CPT has been shown to be beneficial in HEU infants living in malaria endemic

[15] Wyatt CM. Kidney Disease and HIV Infection. Top Antivir Med. 2017 Feb/Mar;25(1):13-16. https://pubmed.ncbi.nlm.nih.gov/28402929/
[16] Church JA, Fitzgerald F, Walker AS, Gibb DM, Prendergast AJ. The expanding role of co-trimoxazole in developing countries. Lancet Infect Dis. 2015 Mar;15(3):327-39. https://pubmed.ncbi.nlm.nih.gov/25618179/

areas.[17] However, a recent appraisal of the evidence by the World Health Organization included two Sub-Saharan studies[18] [19] (n= 2848 and n=1219, respectively), which showed that CPT did not improve survival amongst HEUs with low risk for MTCT, in areas unaffected by malaria. CPT also was shown not to have an effect on hospitalisation, or the incidence of grade 3 or 4 common childhood illnesses (pneumonia or diarrhoea) compared to no CPT. However, harms such as more grade 3/4 neutropaenia as well as cotrimoxazole resistance was more prominent amongst HEUs on CPT. Broad-spectrum CPT has also been shown to select for antimicrobial resistance of other non-sulfonamide antimicrobials,[20] [21] by decreasing gut microbiome diversity and increasing antibiotic resistance. Powis et al. showed that HEUs on CPT had commensal gastrointestinal bacteria that were more resistant to cotrimoxazole and amoxicillin compared to the placebo group.[9]
Therefore, targeted CPT rather than global CPT for HEU infants has been proposed in order to minimise unnecessary selection of antimicrobial resistance and unnecessary adverse effects, especially amongst HEUs who are at low risk of MTCT of HIV.

Recommendations:
Initiate CPT:
- HIV-infected infants - initiate CPT from 6 weeks of age.
- Low-risk HIV-exposed infants with a negative PCR at birth – CPT not required.
- High-risk HIV-exposed infants with a negative PCR at birth – initiate CPT.

Discontinue CPT:
- High-risk HIV-exposed infants with a negative PCR at 10 weeks AND mother is virally suppressed – stop CPT.
- High-risk HIV-exposed infants with a negative PCR at 10 weeks AND mother is not virally suppressed or engaged in mixed feeding – continue CPT until mother is virally suppressed or mixed feeding stopped.
- HIV-infected infants – as per routine management of HIV-infected children (<10 years of age).

The STG was updated as follows:

Initiation:
» High-risk HIV-exposed or infected infants, starting from 6 weeks of age.
Note: Low-risk HIV-exposed infants with a negative birth PCR do not need CPT (unless subsequently confirmed HIV-infected).

Discontinuation:
» If 10-week PCR is negative and;
- mother is virally suppressed – discontinue CPT.
- mother is not virally suppressed or engaged in mixed feeding – continue CPT until mother is virally suppressed or mixed feeding has stopped.

» *If HIV-infected:* See Section: 11.6 Management of HIV-infected children (<10 years).

Level of Evidence: Moderate certainty evidence [6,7,8,9]

11.6 MANAGEMENT OF HIV-INFECTED CHILDREN (<10 YEARS)

ART regimens
Dolutegravir: *not added*
The WHO July 2021 guidelines now recommends DTG in combination with an NRTI backbone as the preferred first-line regimen for HIV-positive infants and children older than four weeks and weighing at least 3 kg (conditional

[17] Ewing AC, King CC, Wiener JB, Chasela CS, Hudgens MG, Kamwendo D, et al. Effects of concurrent exposure to antiretrovirals and cotrimoxazole prophylaxis among HIV-exposed, uninfected infants. AIDS. 2017 Nov 28;31(18):2455-2463. https://pubmed.ncbi.nlm.nih.gov/28926409/
[18] Lockman S, Hughes M, Powis K, Ajibola G, Bennett K, Moyo S, et al. Effect of co-trimoxazole on mortality in HIV-exposed but uninfected children in Botswana (the Mpepu Study): a double-blind, randomised, placebo-controlled trial. Lancet Glob Health. 2017 May;5(5):e491-e500. https://pubmed.ncbi.nlm.nih.gov/28395844/
[19] Daniels B, Coutsoudis A, Moodley-Govender E, Mulol H, Spooner E, Kiepiela P, et al. Effect of co-trimoxazole prophylaxis on morbidity and mortality of HIV-exposed, HIV-uninfected infants in South Africa: a randomised controlled, non-inferiority trial. Lancet Glob Health. 2019 Dec;7(12):e1717-e1727. https://pubmed.ncbi.nlm.nih.gov/31832638/
[20] D'Souza AW, Moodley-Govender E, Berla B, Kelkar T, Wang B, Sun X, Daniels B, Coutsoudis A, Trehan I, Dantas G. Cotrimoxazole Prophylaxis Increases Resistance Gene Prevalence and α-Diversity but Decreases β-Diversity in the Gut Microbiome of Human Immunodeficiency Virus-Exposed, Uninfected Infants. Clin Infect Dis. 2020 Dec 31;71(11):2858-2868. https://pubmed.ncbi.nlm.nih.gov/31832638/
[21] Powis KM, Souda S, Lockman S, Ajibola G, Bennett K, Leidner J, et al. Cotrimoxazole prophylaxis was associated with enteric commensal bacterial resistance among HIV-exposed infants in a randomized controlled trial, Botswana. J Int AIDS Soc. 2017 Nov;20(3):e25021. https://pubmed.ncbi.nlm.nih.gov/29119726/

recommendation, low-certainty evidence).[22]
However, SAHPRA registration for the various dispersible formulations for use in the young child is pending. The PHC HIV chapter will therefore be aligned with the updated Paediatric Hospital Level HIV chapter.

11.7 OPPORTUNISTIC INFECTIONS, PROPHYLAXIS IN CHILDREN

Cotrimoxazole prophylaxis treatment (CPT), oral: *directions for use amended*
STG text for CPT was aligned to section 11.5 The HIV exposed infant, with amendments:

Initiation
» All HIV-infected infants (< 1 year), starting from 6 weeks of age.
» Any child 1–5 years of age with CD4% < 25%.
» Any child > 5 years of age with CD4 count < 200 cells/mm^3.
- Cotrimoxazole, oral, once daily (everyday). See dosing table, pg. 23.4.

Discontinuation
» HIV-infected child > 1 year of age whose immune system is fully reconstituted on ART (i.e., 1–5 year: CD4% > 25% or > 5 years: CD4 count > 200 cells/mm^3 on two tests at least 3–6 months apart).
» Child is HIV-infected with PJP infection: after treatment, continue cotrimoxazole prophylaxis until 5 years of age.

C. HIV PREVENTION

11.11 PRE-EXPOSURE PROPHYLAXIS (PREP)

Note: PrEP is now available at all primary level facilities in the public sector.

Contraindications to PrEP
The following was amended for clarity purposes:

» Estimated creatinine clearance or eGFR < 60 mL/min.

Initiating oral PrEP
Tenofovir + emtricitabine: *duration of therapy amended*
To reach adequate protective levels in tissue, guidance is provided to continue oral PrEP for 7 days for all sexual practices, aligned with the 2021 updated National Department of Health PrEP guidelines.[23]
STG text was amended as follows:

Note: To reach adequate protective levels in tissues, 7 days of daily dosing are required ~~for anal sex and 20 days for vaginal sex.~~

Level of Evidence: III Guidelines[24]

Oral PrEP follow up and monitoring
Estimated creatinine clearance: *monitoring updated*
Aligned with 2021 updated National Department of Health PrEP guidelines,[25] and STG text was updated as follows:

Activity	Frequency		
Estimated creatinine clearance	**Frequency dependant on pregnancy status, age and co-morbidity:**		
	Age/ pregnant	**Co-morbidity**	**Creatinine**
	< 30 years	None	n/a
	30–49 years	None	Baseline
	< 49 years	Diabetes/ hypertension	Baseline, annually
	≥ 50 years	None	Baseline
	≥ 50 years	Diabetes/ hypertension	Baseline, annually
	Pregnant	n/a	Baseline, 3 & 6 months

[22] WHO. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, July 2021.
[23] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[24] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.
[25] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.

Stopping oral PrEP

Tenofovir + emtricitabine**:** *duration of therapy amended*

The following was amended, aligned with 2021 updated National Department of Health PrEP guidelines.[26]

Continue oral PrEP for ~~28~~ 7 days after the last potential HIV exposure.

Other PrEP agents:

Dapivirine vaginal ring: *not added*

Refer to the medicine review (Dapivirine ring for HIV PrEP, 9 June 2022 and economic analysis, 23 May 2022):

DapvirineRingForPrEP _CEA and costing rep

Recommendation: Based on this evidence review, the PHC/Adult hospital level committee suggests not to use the dapivirine ring as an additional option for prevention of HIV acquisition in women (conditional recommendation).

Rationale: Available evidence for the dapivirine ring is restricted to placebo-controlled data, with no studies comparing dapivirine to oral tenofovir plus emtricitabine, the current standard of care in South Africa. There is currently no data for efficacy in adolescents. The dapivirine ring cannot be used in pregnancy. There is a sub-group of women who cannot use tenofovir plus emtricitabine for whom the dapivirine ring may be an option. However, at the current proposed price, dapivirine is unaffordable. The estimated threshold price for reviewing this recommendation is R52.00 per ring.

Level of Evidence: Moderate quality of evidence

Review indicator: Reduction in price, Uptake of all PrEP; Social harms of all PrEP

NEMLC MEETING OF 23 JUNE 2022: The NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation with amendments to the review indicator (added, uptake and social harms), as follows: **Review indicator:** Reduction in price; Uptake of all PrEP; Social harms of all PrEP

Cabotegravir: *not added*

Refer to the medicine review (carbotegravir as PrEP for HIV in adults, 15 May 2022):

Cabotegravir as PrEP for adults _EvidenceSu

Recommendation: Although the efficacy of CAB is high, and the safety profile acceptable, the PHC/Adult Hospital Level Committee suggests not to use CAB as PrEP for HIV, until such time as (1) the medicine is SAHPRA-registered, (2) a budgetary impact assessment is completed once the price becomes known, and (3) evidence of efficacy for regimens that do not include an oral lead-in phase are available (conditional recommendation).

Rationale: Two phase 3 RCTs both found that PrEP with long-acting injectable CAB had greater efficacy than oral tenofovir plus emtricitabine. However, the drug is not yet registered with SAHPRA, and is likely to cost significantly more than TDF-FTC, necessitating a budgetary impact and cost-effectiveness analysis.

Level of Evidence: High certainty evidence

Review indicator: SAHPRA registration, evidence of efficacy in regimens that do not require oral lead-in doses, information on cost.

NEMLC RECOMMENDATION (MEETING OF 23 JUNE 2022): The NEMLC accepted the proposal not to recommend CAB-LA injection as PrEP in the PHC STGs and EML (conditional recommendation; high certainty evidence), with review indicators - SAHPRA registration; Evidence of efficacy in regimens that do not require oral lead-in doses, information on cost. Furthermore, NEMLC recommended that CAB-LA and rilpivirine for treatment of HIV be prioritized for review in the next review cycle.

[26] National Department of Health. 2021 Updated guidelines for the provision of oral pre-exposure prophylaxis (prep) to persons at substantial risk of HIV infection.

D: SIDE EFFECTS AND COMPLICATIONS OF ART

11.13 SIDE EFFECTS AND COMPLICATIONS OF ART

Lactic acidosis STG: *deleted*

An external comment was received querying why guidance was provided for lactic acidosis only and why not other adverse effects. Therefore, section 11.13.1: Lactic acidosis was deleted and a cross-reference was made to the Adult Hospital Level STGs and EML for detailed information on adverse effects associated with ARVs.

The following was added to the STG text:

Refer to the Adult Hospital Level STGs and EML: Section 10.1.1Management of selected antiretroviral adverse drug reactions, and consult with an infectious disease specialist as required.

And the following was deleted:

~~**11.14 LACTIC ACIDOSIS**~~

~~E87.2 + (Y41.5 + B24)~~

~~**Description**~~

~~All nucleoside analogues have been associated with lactic acidosis, which is rare but life-threatening. Initial symptoms vary and occur between 1-20 months (median 4 months) after starting therapy. The risk is highest with stavudine, followed by didanosine and then zidovudine.~~

~~**Diagnostic criteria**~~

~~*Clinical*~~

~~Clinical prodromal syndrome:~~

~~» Generalised fatigue~~

~~» Weakness and myalgia~~

~~» Gastrointestinal symptoms:~~

- ~~nausea~~
- ~~vomiting~~
- ~~diarrhoea~~
- ~~unexplained weight loss~~
- ~~vague abdominal pain~~
- ~~hepatomegaly~~
- ~~anorexia~~

~~» Respiratory symptoms: tachypnoea and dyspnoea.~~

~~» Neurologic symptoms, including motor weakness.~~

~~*Investigations*~~

~~» Laboratory abnormalities:~~

- ~~Hyperlactataemia~~
  - ~~Raised: 2.1-5 mmol/L~~
  - ~~Severely raised : > 5 mmol/L~~
- ~~Lactic acidosis, defined by:~~
  - ~~Lactate: > 5 mmol/L~~
  - ~~Bicarbonate: < 20 mmol/L~~
  - ~~Severe acidosis i.e. pH < 7.3~~
  - ~~Increased anion gap i.e. > 15 mEq/L~~

~~**Referral**~~

~~All urgently.~~