PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 9: HUMAN IMMUNODEFICIENCY VIRUS
NEMLC 23 FEBRUARY 2023

General Comment

The Paediatric Hospital Level Human Immunodeficiency Virus (HIV) Chapter will be aligned with the recently finalised 2022 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates; and the 2022 Guideline for Maternal Care and Vertical Transmission Prevention of Communicable Infections (HIV, Syphilis, TB, Hepatitis, Listeriosis, and Malaria).

Sections Deleted

Cotrimoxazole: CPT for HIV-exposed infants to be deleted. Only HIV infected infants will receive CPT.

9.1 Human Immunodeficiency Virus Infection

Referral to the updated National Department ART Clinical Guidelines. Text inserted as follows:

Comprehensive guidelines are available for ART and the care of children with HIV infection in the 2022 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates

Purpose of ART guideline updated as follows:

» Children (< 10 years OR <30kgs): follow the Paediatric antiretroviral therapy (ART) Guidelines.
» Adolescents (10–19 years): follow the Adult and Adolescent ART Guidelines.

9.1.1 The HIV Exposed Infant

Information on vertical transmission prevention and management of HIV-exposed infants was updated in line with the National updated guidelines as follows:

DESCRIPTION

Infants and children born to mothers living with HIV until HIV infection in the infant or child is reliably excluded and the infant or child is no longer exposed through breastfeeding are defined as HIV-exposed.

Transmission of HIV infection may occur during pregnancy, during delivery, or via breastfeeding. Vertical transmission prevention (VTP) can be effectively carried out with a very high success rate by fully suppressing the mother's viral load with ART and giving prophylactic antiretroviral therapy to the infant. Maternal viral loads must be done, checked, recorded and acted upon during pregnancy and breastfeeding. The risk of breast milk transmission remains significant when the mother's viral load cannot be suppressed.

The VTP strategies include the initiation of ART in the mother (either pre- or post-conception) and the provision of HIV post-exposure prophylaxis to the infant. The mother's response to ART by the time of delivery is measured by the delivery VL. The delivery VL will determine the risk profile of the infant at birth. The risk profile of the infant (low risk or high risk) will determine the appropriate infant prophylaxis regimen that should be prescribed. All HIV-exposed infants will be

considered high-risk until the results of the delivery viral load are known. Therefore, if the delivery VL result is not available at the time of discharge, the HIV-exposed infant will be considered high risk until the result can be reviewed at the 3-6 day postnatal visit.

MANAGEMENT OF HIV-EXPOSED INFANTS

Maternal VL	Risk profile	Prophylaxis	Comment
Maternal delivery VL as yet unknown at discharge form labour ward (results pending)	High risk (until delivery VL results become available)	Provide dual prophylaxis: AZT twice daily for six weeks. daily for six weeks. NVP for a minimum of 12 weeks.	All HIV-exposed infants will be considered high risk until the final risk profile can be determined by the delivery VL. If delivery VL result not available at discharge from labour ward, review result at the 3-6 day PN visit and reclassify the infant accordingly. Dispense full 6 weeks supply of dual prophylaxis. Ask mother to return with all medication at 3-6 day PN visit.
Delivery VL $\geq$ 50 copies/mL in a breastfeeding mother	High risk	Continue dual prophylaxis: AZT twice daily for six weeks. NVP for a minimum of 12 weeks.	Do an ABCDE assessment and get the mother's VL re-suppressed as a matter of urgency Stop infant NVP only after confirmation of VL being less than 50 c/ml, or until four weeks after cessation of all breastfeeding. infant NVP only after confirmation of VL being less than 50 c/mL, or until four weeks after cessation of all breastfeeding.
Delivery VL$\geq$ 50 copies/mL in a mother who is exclusively formula-feeding her infant from birth	High risk	Continue dual prophylaxis: AZT twice daily for six weeks.AZT twice daily for six weeks. NVP at birth and then daily for six weeks.	Do an ABCDE assessment and get the mother's VL re-suppressed as a matter of urgency
Delivery V L< 50 copies/mL regardless of feeding choice	Re-classify as low risk	Change to low risk prophylaxis NVP at birth and then daily for six weeks.	Affirm and encourage good adherence Repeat maternal VL 6 monthly during breastfeeding
Maternal VL $\geq$ 50 c/mL during breastfeeding	High risk	Provide dual prophylaxis during breastfeeding: AZT twice daily for six weeks. NVP for a minimum of 12 weeks.	Do infant HIV PCR immediately; if infant tests HIV PCR positive, repeat the HIV PCR test and initiate ART immediately. Do infant HIV PCR immediately; if infant tests HIV PCR positive, repeat the HIV PCR test and initiate ART immediately Do an ABCDE assessment and get the mother's VL re-suppressed as a matter of urgency. Stop infant NVP only after confirmation of the mother's VL being less than 50 c/mL, or until four weeks after cessation of all breastfeeding.

- Unknown maternal status updated.
- Management of high maternal viral load after delivery added in line with updated National ARV Guidelines.
- Nevirapine/Zidovudine dosing chard updated:

	Birth–6 weeks		*6 weeks–6 months*	*6 – 9 months*	*9 – 24 months*
	2.0–2.49 kg	>2.5 kg			
NVP (Daily)	1 mL (10 mg) daily	1.5 mL (15 mg) daily	2 mL (20 mg) daily	3 mL (30 mg) daily	4 mL (40 mg) daily
AZT (Twice daily)	1 mL (10 mg) twice daily	1.5 mL (15 mg) twice daily	6 mL (60 mg) twice daily	Children >6 months of age requiring AZT prophylaxis should use treatment doses.	

HIV Testing

Section updated as follows:

HIV TESTING

Age appropriate testing

» < 18 months old – do an HIV PCR.
» ≥ 18 months old – do a rapid HIV antibody test
  - confirm HIV test in children between 18–24 months with an HIV PCR
  - confirm HIV test in children > 24 months with an HIV rapid test

Routine testing for HIV exposed children < 18 months:

» **Birth:** Do an HIV PCR at birth in all HIV-exposed infants.
» **10 Weeks:** Do an HIV PCR at ten weeks of age (chronological age) in all HIV-exposed infants.
» **6 Months:** Do an HIV PCR at six months of age in all HIV-exposed infants.
» The HIV status of all children not already known to be HIV-exposed should be established by offering the mother an HIV test at any time point.
» **Post cessation of breastfeeding:** If the child is breastfed and previous HIV PCRs were negative, repeat testing six weeks after complete cessation of breastfeeding. (If the child is 18 months or older, do an HIV ELISA or rapid test).

Routine testing for all children ≥ 18 months:

» **18 months:** Universal HIV testing at 18 months (HIV rapid test for ALL infants regardless of HIV exposure, except in those who previously tested HIV-positive and are on ART).
» If the first rapid test is positive, confirm the result with:
  > An HIV PCR test if the infant is between 18–24 months.
  > A second rapid test using a different manufacturer kit, preferably on a different blood specimen, if the infant is >24 months.

Testing for all children regardless of age or HIV exposure status:

» **Symptomatic child/infant:** If the child has evidence suggesting HIV infection at any time, even if the child has had a previous negative HIV PCR test, the child should be tested for HIV infection using an age-appropriate HIV test (HIV PCR or rapid test).
» If the HIV test is positive at any time point:
  > Confirm with a repeat age-appropriate HIV test.
  > Initiate treatment while awaiting the second HIV test result.

Note:

» Repeat HIV PCR testing at 10 weeks and 6 months should be done on all HIV- exposed infants with a prior negative or indeterminate HIV PCR.
» Any infant with a positive birth HIV PCR should be urgently initiated on ART as per section 9.1.2: The HIV- Infected Neonate.

» A child cannot be confirmed as HIV-negative until at least 4–6 weeks after other potential HIV exposure (including cessation of breastfeeding). Exposure to ART through prophylaxis (NVP/AZT) or maternal ART may affect the sensitivity of HIV PCR tests.
» 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 blood specimen to the laboratory for formal HIV ELISA testing. If test results are still equivocal, do an HIV PCR test.
» Patients already on ART should not have a repeat HIV antibody (rapid) test.

~~Recommended Intervals for Infant and Child Testing~~	
~~HIV PCR test~~	~~Rapid HIV Antibody test~~
~~At Birth~~ ~~» All HIV-exposed neonates.~~ ~~At 10 weeks~~ ~~» All HIV-exposed infants.~~ ~~At 6 months~~ ~~» All HIV-exposed infants.~~ ~~Repeat HIV PCR testing at 10 weeks and 6 months should be done on all HIV-exposed infants with a prior negative or indeterminate HIV PCR.~~ ~~Any infant with a positive birth HIV PCR should be urgently initiated on ART as per section 9.1.2: The HIV- Infected Neonate.~~	~~At 18 months~~ ~~» Universal HIV testing at 18 months (HIV rapid test for ALL infants regardless of HIV exposure, except in those who previously tested HIV-positive and are on ART).~~ ~~Note: Patients already on ART should not have a repeat HIV antibody test.~~ ~~Breastfed infants: (6 weeks post cessation of breastfeeding)~~ ~~» All HIV-exposed infants – age appropriate:~~ ~~<18 months old – do an HIV PCR.~~ ~~≥18 months old – do a rapid HIV antibody test (confirm HIV test in children between 18–24 months with an HIV PCR).~~ ~~HIV testing should be offered to all children and their families and caregivers.~~

If HIV PCR is indeterminate or discordant, refer to the National Department of Health Guidelines for Family-centered Transmission Prevention

All HIV PCR results need to be followed up as a matter of urgency.

Feeding advice

Updated as follows:

Feeding advice

» It ~~Exclusive breastfeeding~~ is strongly recommended that exclusive breastfeeding be initiated within 1 hour of birth and continued for the first six months of life, after which the child's nutritional requirements will require the introduction of complementary foods in addition to breastfeeding.
» Women living with HIV should be fully supported for ART adherence during the breastfeeding period and thereafter
» Women with a VL > 50 copies/mL on TLD1 should continue breastfeeding while every effort is made to regain viral suppression. Infants should receive high risk prophylaxis during breastfeeding
» The following may be indications to discontinue breastfeeding.
  > Infants of mothers who are failing TLD2 ~~except where a mother is shown to be failing ART, the advantages of breastfeeding exceed the risks of HIV transmission in a mother on ART, and the mother should be encouraged to breastfeed.~~
  > Infants of mothers who are failing third-line PI-based treatment
» Discuss appropriate feeding practices with the mother regarding the risks and benefits of continuing breastfeeding vs replacement feeding.

» The 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. For instance, it can be used as an interim measure during maternal mastitis

Text amended as follows:

Cotrimoxazole prophylaxis

Indications:

»~~Sub-classification for HIV-exposed uninfected infants at ten-week PCR test:~~According to the current guideline, only babies with a positive HIV PCR should be started or continued on cotrimoxazole prophylaxis as per section 9.1.2: The HIV-Infected Neonate, medicine treatment, cotrimoxazole prophylaxis below.

» ~~Babies born to mothers that are not virally suppressed (high-risk exposures) should be given cotrimoxazole from six weeks of age until the result of their ten-week PCR test is available. If 10-week PCR is negative and the mother remains not virally suppressed or engaging in mixed feeding, continue cotrimoxazole prophylaxis until HIV status is confirmed. However, if the mother is virally suppressed, discontinue the use of cotrimoxazole prophylaxis.~~

» ~~Babies born to mothers who are adherent to their ART regimen and are virally suppressed (low-risk setting) should not be given cotrimoxazole if Birth PCR is negative. Cotrimoxazole should only be initiated in the unlikely situation that such babies are subsequently confirmed to be HIV infected.~~

» ~~According to the current guideline, babies with a positive HIV PCR should be started or continued on cotrimoxazole prophylaxis.~~

~~as per section 9.1.2: The HIV-Infected Neonate, medicine treatment, cotrimoxazole prophylaxis below.~~

9.1.2 The HIV-Infected Neonate

Treatment Protocol updated in line with the National ARV Guideline

- » Protocol for ≥ 2kg and 35 weeks gestational age at birth added.
- » Protocol for < 2 kg and 35 weeks gestational age at birth added.

9.1.3 The HIV infected Infant/child (< 10 years)

Cotrimoxazole prophylaxis updated as follows:

Cotrimoxazole prophylaxis

Indications:

~~• Sub-classification for HIV-exposed uninfected infants at ten-week PCR test:~~

» ~~Babies born to mothers that are not virally suppressed (high-risk exposures) should be given cotrimoxazole from six weeks of age until the result of their 10-week PCR test is available. If ten-week PCR is negative and the mother remains not virally suppressed or engaging in mixed feeding, continue cotrimoxazole prophylaxis until confirmation of HIV status. However, if the mother is virally suppressed, discontinue the use of cotrimoxazole prophylaxis.~~

» ~~Babies born to mothers who are adherent to their ART regimen and are virally suppressed (low-risk setting) should not be given cotrimoxazole if Birth PCR is negative. Cotrimoxazole should only be initiated in the unlikely situation that such babies are subsequently confirmed to be HIV infected.~~

»According to the current guideline, babies with a positive HIV PCR should be started and ~~or~~ continued on cotrimoxazole prophylaxis until criteria for discontinuation met.

ART regimen

- » Regimen updated in line with National ARV Guideline (and DTG review)

» Management of virological failure on TLD
» ART regmen for children with confirmed virological failure
» Dosing chart updated in line with National ARV Guideline and SAHIV

Specific information on ARVs:

» Dolutegravir – adverse effects updated as follows:

	Storage	Adverse effects
Nucleoside reverse transcriptase inhibitors (NRTIs)		
Dolutegravir (DTG)	Room temperature	» Insomnia-rare » ~~Weight gain~~ » ~~Potential teratogenic – neural tube defects~~

Criteria for changing therapy

Text amended as follows:

Note: A single drug substitution **can only be made** if the viral load is < 50 c/ml /undetectable or if the change is made in the first six months of starting a regimen. The decision to swap must be made by a doctor with antiretroviral experience (this can be by telephonic consultation), as inappropriate choices of antiretrovirals may be ineffective or dangerous.

9.5 HIV in Adolescence

Text aligned with first line regimen changes:

Dosage of ARVs

In children over the age of ten years and over ~~35~~ 30 kg, use adult dosage regimens – consult ART guidelines**.**

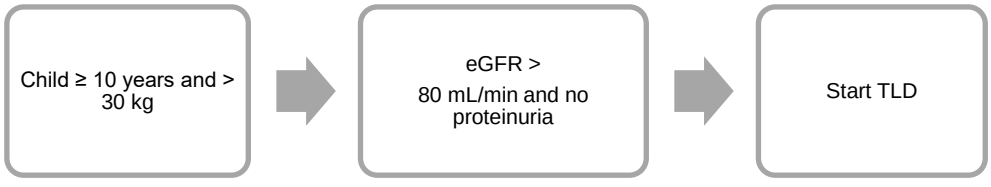
The transition from paediatric ART regimens to adolescent/adult regimens:

» Adolescents with an undetectable VL (< 50 copies/mL) and no side effects on ABC + 3TC + ~~EFV/~~DTG can remain on the same regimen until the patient becomes eligible for the TDF + 3TC + DTG (TLD FDC) at ten years of age and weighing ≥ 30 ~~35~~ kg.

» When an adolescent ~~with an undetectable viral load (taken within the last 8 weeks)~~ reaches ten years of age and is ≥ 30 ~~35~~ kg, a creatinine level, calculation of the estimated glomerular filtration rate (eGFR) using a standard formula, and urine strip test should be performed.

- ~~>~~ If the eGFR is >80 mL/min and there is no proteinuria on a urine strip test, the patient can be switched to the TDF + 3TC ~~FTC +~~ DTG ~~EFV~~ (TLD FDC)
- > If the eGFR is < 80 mL/min or there is >1+ proteinuria on a urine strip test, then refer to an expert for advice before switching.

Transition from child to adolescent regimen



~~If the HIV VL is between 50 – 1000 copies/mL, consult an expert for advice.~~

~~If the HIV VL is > 1000 copies/mL, exclude non-adherence, then treat it as a virological failure.~~

PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 9: HUMAN IMMUNODEFICIENCY VIRUS
NEMLC 20 OCTOBER 2022

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
9.1.1 The HIV exposed infant	Zidovudine	The definition of "high-risk" amended which increases the number of infants classified as high-risk and therefore affects quantities of zidovudine syrup to be procured.
	Cotrimoxazole	Cotrimoxazole Preventive Therapy (CPT) is no longer to be provided to HIV exposed and uninfected infants, regardless of the mother's VL and ongoing breastfeeding status.

General Comment

The Paediatric Hospital Level Human Immunodeficiency Virus (HIV) Chapter will be aligned with the recently finalised 2022 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates; and the 2022 Guideline for Maternal Care and Vertical Transmission Prevention of Communicable Infections (HIV, Syphilis, TB, Hepatitis, Listeriosis, and Malaria).

Sections Deleted

Cotrimoxazole: CPT for HIV-exposed infants to be deleted. Only HIV infected infants will receive CPT.

9.1.1 The HIV Exposed Infant

Zidovudine: *Projected quantities to be amended*

The rationale for the guideline change

Current guidelines

2019 (Current) PMTCT Guideline defines a high-risk HIV-exposed infant as an infant born to a mother living with HIV who meets one of the following criteria:

- A delivery viral load (VL) result of more than 1000 c/ml (the delivery VL will determine the final risk status of the infant)
- In the absence of a delivery VL result at discharge from labour ward, the results of the most recent VL taken in the last 12 weeks of pregnancy should be assessed. The infant will be high-risk if either:
    - The VL in the last 12 weeks of pregnancy was more than 1000 c/ml, or
    - There was no VL result in the last 12 weeks of pregnancy
- Where an assessment was made using the antenatal VL result (in the absence of the delivery VL result), the delivery VL should be reviewed at the 3-6 day postnatal visit and the infant's risk profile reclassified accordingly:

- Delivery VL ≥ 1000 c/ml = high-risk (AZT twice daily x 6/52 and NVP once daily for a minimum of 12 weeks)
- Delivery VL < 1000 c/ml = low-risk (NVP once daily for 6 weeks)

Proposed Updates

The proposed changes to the 2022 MCVTP (Maternal Care and Prevention of Vertical Transmission) guideline are as follows:

1. **Tighten the definition of a high-risk HIV-exposed infant (HEI)**
   a. **Lower the maternal VL criteria from VL ≥ 1000 c/ml to VL ≥ 50 c/ml** to determine the final risk status at the 3–6-day postnatal visit.
   Rationale: Based on a 1,7% postnatal vertical transmission rate (from 6 weeks to 18 months)[1], and 82% of cumulative MTCT occurring by 6 months post-delivery[1], providing dual prophylaxis to an additional 40 650 HEIs (exposed to VLs between 50 and 999 c/ml) could potentially prevent 566 new HIV infections in children.
   b. **In the absence of a VL result at discharge from labour ward, all infants should be considered as "high-risk" until the delivery VL result can be reviewed at the 3 to 6-day postnatal visit** (aligned with Western Cape PMTCT Guideline).

   Rationale:
   - By current guidelines, 84% of all infants born to pregnant women living with HIV (PWLHIV) will qualify for dual prophylaxis based on the scenario of "no VL in the last 12 weeks of pregnancy". An additional proportion will qualify for dual prophylaxis if the results of the VL result in the last 12 weeks of pregnancy was > 1000 c/ml.
   - The WHO currently uses the criteria of "no VL in the last 4 weeks of pregnancy, or not on ART for > 4 weeks prior to delivery for high-risk of transmission
   - By the WHO definition, given that 70% of women book before 20 weeks gestation, and 75% are already on ART at entry into ANC, the 4-week criteria will result in 94% of all infants born to PWLHIV qualifying for dual prophylaxis based on the scenario of "no VL in the last 4 weeks of pregnancy".
   - Moving to a universal dual prophylaxis approach at birth for all HEIs (pending delivery VL result review at 3-6 day postnatal visit) will significantly simplify the decision-making process for prescribing infant prophylaxis at delivery while adding only an additional 6% (94% to 100%) compared to if the WHO criteria were used.

   c. The term "universal dual prophylaxis" should replace the term "high-risk prophylaxis" under these circumstances where, at discharge from labour ward, the final risk profile of the infant is as yet unknown.

2. **Cotrimoxazole prophylaxis**
   a. Early studies of CPT benefits were in the context of no maternal ART, no infant prophylaxis

[1] Impact of breastfeeding, maternal antiretroviral treatment and health service factors on 18-month vertical transmission of HIV and HIV-free survival: results from a nationally representative HIV-exposed infant cohort, South Africa. Ameena Ebrahim Goga, Carl Lombard, Debra Jackson, Vundli Ramokolo, Nobubelo Kwanele Ngandu, Gayle Sherman, Adrian Puren, Witness Chirinda, Sanjana Bhardwaj, Nobuntu Makhari, Trisha Ramraj, Vuyolwethu Magasana, Yagespari Singh, Yogan Pillay, Thu-Ha Dinh. J Epidemiol Community Health 2020;0:1–9. doi:10.1136/jech-2019-213453

b. RCT by Lockman et al[2] in Botswana (2017) (n= 2348) and Daniels et al[3] in South Africa (2019) (n = 1220) found that prophylactic CTX did not improve 18-month survival among HEU children in a non-malarial area. The studies concluded that, in non-malarial settings with very low risk for MTCT, CTX for HIV-exposed children did not improve morbidity and mortality.
c. Without ART, PJP incidence of 9.5 cases per 100 child years in the first year of life[4]
d. In SA with high birth PCR coverage and ART initiation, this incidence may be less
e. Public health policy must be good for at least 80% of the population. Therefore, treating 32 400 high-risk HEIs to benefit 552 HIV-positive children (of whom 55 or less may be at risk of PJP) is against policy norms and even ethics[5]
f. Potential harm to 32 400 children i.t.o.
    i. Microbiome dysbiosis[6,7]
    ii. Antimicrobial resistance (incl. amoxicillin)[8,9]

9.1.2 The HIV-Infected Neonate

» Removal of option of ABC/3TC/LPV/r in neonates between 2weeks and 4 weeks: For simplification of the neonatal treatment guideline as after 4 weeks, will transition to ABC/3TC/DTG as compared to LPV/rtv. The advantage of having ABC/3TC/LPV/r in neonates between 2-4 weeks are therefore now lost. Regimen simplified to AZT/3TC/NVP for the first 4 weeks.
» Aligning Near-term dosing chart with the WHO Guideline: Dosage to start from 2kgs as included in the WHO guideline compared to 2.5kg

9.1.3 The HIV infected Infant/child (< 10 years)

» Aligning the transition to TLD in adolescents to be in line with the WHO Guideline: From 10years and 35 kgs to 10 years and 30 kgs.
» Streamlining of algorithm for transition of patients to DTG based regimens

[2] 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. The Lancet Global Health. 2017;5(5):e491-e500.
[3] 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. The Lancet Global Health. 2019;7(12):e1717-e27.
[4] Morris A, Lundgren JD, Masur H, Walzer PD, Hanson DL, Frederick T, Huang L, Beard CB, Kaplan JE. Current epidemiology of Pneumocystis pneumonia. Emerg Infect Dis. 2004 Oct;10(10):1713-20. doi: 10.3201/eid1010.030985. PMID: 15504255; PMCID: PMC3323247.
[5] Daniels B, Kuhn L, Spooner E, Mulol H, Goga A, Feucht U, et al. Cotrimoxazole guidelines for infants who are HIV-exposed-uninfected: A call for a public health and ethics approach to the evidence. Lancet Global Health, . 2022;In Press.
[6] Gasparrini AJ, Wang B, Sun X, Kennedy EA, Hernandez-Leyva A, Ndao IM, et al. Persistent metagenomic signatures of early-life hospitalization and antibiotic treatment in the infant gut microbiota and resistome. Nature microbiology. 2019;4(12):2285-97.
[7] Schwartz DJ, Langdon AE, Dantas G. Understanding the impact of antibiotic perturbation on the human microbiome. Genome medicine. 2020;12(1):1-12.
[8] 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. Journal of the International AIDS Society. 2017;20(3):e25021.
[9] D'Souza AW, Moodley-Govender E, Berla B, Kelkar T, Wang B, Sun X, et al. Cotrimoxazole Prophylaxis Increases Resistance Gene Prevalence and --Diversity but Decreases --Diversity in the Gut Microbiome of Human Immunodeficiency Virus Exposed, Uninfected Infants. Clinical Infectious Diseases. 2020;71(11):2858-68.

PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 9: HUMAN IMMUNODEFICIENCY VIRUS
NEMLC 25 AUGUST 2022

Additional amendments

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
9.1.3 The HIV infected infant/child	Dolutegravir	Added for weight band 3-20kg
	ABC/3TC/LPV/r 4-in-1 tablet	Dosing table updated to include formulation

9.1.3. The HIV infected infant/child (< 10 years)

Dolutegravir: Dosing table amended for band 3-20kg

Dolutegravir accepted as part of regimen for addition for weight band 3-20kg, at NEMLC meeting of 23 June 2022. See Dolutegravir Review.

Paeds Medicine Review_Dolutegravi

Chapter, associated algorithms and dosing table updated to reflect accepted change.

Dosing table updated to include formulation: ABC/3TC/LPV/r 4-in-1 tablet

This formulation has been recently registered with SAHPRA, and although with current regimen recommendations its use is expected to be small, it has been added as a formulation option to the dosing table.

PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 9: HUMAN IMMUNODEFICIENCY VIRUS
NEMLC 17 SEPTEMBER 2020

Additional amendments

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
9.1.3 The HIV infected infant/child	Lopinavir/ritonavir	Dosing amended

9.1.3. The HIV infected infant/child (< 10 years)

Lopinavir/ritonavir: *Dosing table amended for band 30-35kg*

A dosing chart for lopinavir/ritonavir in children was developed in conjunction with the South African HIV Clinicians' Society and the National HIV and TB Health Care worker hot line and medicine information centre, and it was proposed that the Paediatric Standard Treatment Guideline (STGs) and Essential Medicines List (EML) align with these dosing recommendations.

This chart largely mirrored that of the Paediatric STGs and EML dosing chart, with the exception of the 30 to 35 kg group. In the Paediatric STGs and EML, there was a separate 30-34.9kg group, and a ≥ 35k group; however there proposed new dosing chart only included a ≥ 30 kg group (see below).

Paeds STG and EML

Weight (kg)	Lopinavir/ritonavir (LPV/r)
Target dose	300/75 mg/m^2/dose LPV/r **TWICE daily**
Available formulations	Sol. 80/20 mg/ml Pellets 40/10mg Adult Tabs 200/50 mg, Paeds Tabs 100/25 mg
30-34.9	5 ml 12 hourly **OR** 8 capsules (pellets) 12 hourly **OR** 4 x 100/25 mg paed tabs 12 hourly **OR** 2 x 200/50 mg adult tabs 12 hourly
35 – 39.9	5 ml 12 hourly **OR** 10 capsules (pellets) 12 hourly **OR** 4 x 100/25 mg paed tabs 12 hourly **OR** 2 x 200/50 mg adult tabs 12 hourly
≥ 40	

Proposed updated dosing chart

Weight (kg)	Lopinavir/ritonavir (LPV/r)
Target dose	300/75 mg/m^2/dose LPV/r **TWICE daily**
Available formulations	Sol. 80/20 mg/ml Pellets 40/10mg Adult Tabs 200/50 mg, Paeds Tabs 100/25 mg
≥ 30 kg	5 ml 12 hourly **OR** 10 capsules (pellets) 12 hourly **OR** 4 x 100/25 mg paed tabs 12 hourly **OR** 2 x 200/50 mg adult tabs 12 hourly

The only real difference is the dosage of pellets.

Combining the 30-34.9kg and ≥ 35 kg would will only have slight over dosing in the lower weights, but will allow for aligned recommendations and dosing.

The lopinavir/ritonavir dosing table was updated as follows:

Weight (kg)	Lopinavir/ritonavir (LPV/r)	Lopinavir/ritonavir when on rifampicin (and for 2 weeks after stopping rifampicin) *Choose one of the 2 options below as appropriate*	
Target dose	300/75 mg/m^2/dose LPV/r **TWICE daily**	LPV/r std dose + super-boosting with ritonavir (RTV) powder **TWICE daily** (≥ 0,75 x LPV dose 12 hourly)	Double-dose LPV/r tabs ONLY if able to swallow whole LPV/r tabs **TWICE daily**
Available formulations	Sol. 80/20 mg/ml Pellets 40/10mg Adult Tabs 200/50 mg, Paeds Tabs 100/25 mg	Oral powder 100 mg/packet	Adult tabs 200/50 mg, Paed tabs 100/25 mg
3–4.9	*1 ml 12 hourly **OR** 2 capsules (pellets) 12 hourly	100 mg (1 packets) 12 hourly	Do not use double-dose LPV/r tabs
5–5.9	*1.5 ml 12 hourly **OR** 2 capsules (pellets) 12 hourly		
6–6.9	*1.5 ml 12 hourly **OR** 3 capsules (pellets) 12 hourly		
7–7.9			
8–9.9			
10–10.9	2 ml 12 hourly **OR** 4 capsules (pellets) 12 hourly		3 x 100/25 mg tabs 12 hourly
11–13.9			
14–14.9	2.5 ml 12 hourly **OR** 5 capsules (pellets) 12 hourly **OR** 2 x 100/25 mg paed tabs 12 hourly **OR** 1 x 200/50 mg adult tab 12 hourly	200 mg (2 packets) 12 hourly	4 x 100/25 mg tabs 12 hourly OR 2 x 200/50 mg tabs 12 hourly
15-16.9			
17-19.9			
20–24.9	3 ml 12 hourly **OR** 6 capsules (pellets) 12 hourly **OR** 2 x 100/25 mg paed tabs 12 hourly **OR** 1 x 200/50 mg adult tab 12 hourly		
25–29.9	3.5 ml 12 hourly **OR** 7 capsules (pellets) 12 hourly **OR** 3 x 100/25 mg paed tabs 12 hourly	300 mg (3 packets) 12 hourly	6 x 100/25 mg tabs 12 hourly OR 3 x 200/50 mg tabs 12 hourly
30-34.9	5 ml 12 hourly **OR** 10 capsules (pellets) 12 hourly **OR** 4 x 100/25 mg paed tabs 12 hourly **OR** 2 x 200/50 mg adult tabs 12 hourly	400 mg (4 packets) 12 hourly	4 x 200/50 mg tabs 12 hourly OR 8 x 100/25 mg Tabs 12 hourly
35 – 39.9			
≥ 40			

PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 9: HUMAN IMMUNODEFICIENCY VIRUS
NEMLC 5 DECEMBER 2019

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
9.1.1 The HIV exposed infant	Zidovudine	Duration amended
9.1.2 The HIV infected neonate, ≥ 2.5 kg at birth	Lamivudine	Weight bands amended
	Zidovudine	
	Nevirapine	
9.1.2 The HIV infected neonate, < 2.5 kg at birth	Lamivudine	Dosing recommendations added
	Zidovudine	
	Nevirapine	
9.1.3 The HIV infected infant/child (<10 years)	Cotrimoxazole	CD4 cut-off for discontinuing amended
First-line	Dolutegravir	Added
	Efavirenz	Removed from first-line
	Abacavir	Weight/age bands amended
	Lamivudine	
	Lopinavir-ritonavir	
	Tenofovir	Weight band amended
Second-line	PI-based regimen	Resistance testing
	InSTI-based regimen	Resistance testing
9.2 Tuberculosis and HIV	Dolutegravir plus rifampicin	Dosing recommendations added

General Comment

The Paediatric Hospital Level Human Immunodeficiency Virus (HIV) Chapter was aligned with the recently finalised 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates; and the 2018 Guideline for the Prevention of Mother to Child Transmission of Communicable Infections (HIV, Hepatitis, Listeriosis, Malaria, Syphilis and TB).

Sections Deleted

Specific adverse events and complications: Lipodystrophy and Wasting Syndrome removed.

Lipodystrophy: removed as not a common adverse effect since stavudine not part of regimens.
Wasting Syndrome: removed as guidance not different to recommendation around malnutrition in Alimentary chapter.

9.1.1 The HIV Exposed Infant

Zidovudine: *Duration amended*

The duration of zidovudine was amended from 12 weeks to 6 weeks

Other changes

HIV testing

The Paediatric STGs and EML was updated in terms of the National PMTCT guideline. The testing timelines were updated as follows:

- Birth for all HIV expose infants;
- 10 weeks for all HIV exposed infants;
- Post-cessation of breastfeeding if HIV PCR is negative at 10-weeks and;
- 6 months – repeat testing 6 weeks after cessation of breastfeeding.

WHO clinical staging

The Paediatric Committee proposed that the WHO clinical staging text be removed. A link to this information on the WHO website was added.

Unknown maternal status

The algorithm from the updated PMTCT guidelines (abandoned babies) was added.

9.1.2 The HIV Infected Neonate

NEONATES ≥ 2.5 KG

Lamivudine, Zidovudine, Nevirapine: *Weight bands amended*

_The dosing weight bands for neonates ≥ 2.5 kg were amended in line with the World Health Organisation updated recommendations on first-line and second-line antiretroviral regimens.[10]

[10] World Health Organisation. Annex 3: Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. July 2018. https://www.who.int/hiv/pub/guidelines/ARV_Guidelines-2018-Annex3.pdf?ua=1

The updated doses reflect as follows:

	Lamivudine (3TC)		Zidovudine (AZT)		Nevirapine (NVP)	
Target dose	2 mg/kg/dose TWICE daily		4 mg/kg/dose TWICE daily		6 mg/kg/dose TWICE daily	
Available formulation	10 mg/ml		10 mg/ml		10 mg/ml	
Weight (kg)	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**
≥2.5-<3.0	0.5ml 12 hourly	5 mg 12 hourly	1 ml 12 hourly	10 mg 12 hourly	1.5 ml 12 hourly	15 mg 12 hourly
≥3.0-<4.0	0.8 ml 12 hourly	8 mg 12 hourly	1.5 ml 12 hourly	15 mg 12 hourly	2 ml 12 hourly	20 mg 12 hourly
≥4.0-<5.0	1 ml 12 hourly	10 mg 12 hourly	2 ml 12 hourly	20 mg 12 hourly	3 ml 12 hourly	30 mg 12 hourly

NEONATES < 2.5 KG

Lamivudine, Zidovudine, Nevirapine: *Dosing recommendations added.*

The Paediatric STGs and EML previously did not include dosing guidance for neonates < 2.5 kg. The Committee however recommended that it would be important to outline the recommendations in this cohort.

The following recommendations from KZN protocol were added:

Drugs	**Lamivudine (3TC)**		**Zidovudine (AZT)**		**Nevirapine (NVP)**	
< 30 weeks	2 mg/kg twice daily		2 mg/kg twice daily		2 mg/kg twice daily	
30 – 35 weeks	2 mg/kg twice daily		Day 0-14	2 mg/kg twice daily	2 mg/kg twice daily	
			Day 14 >	3 mg/kg twice daily		
> 35 weeks	2 to < 3kg	0.6 ml twice daily	2-< 3kg	1 ml twice daily	Day 0-14	4 mg/kg twice daily
	3 to < 4kg	0.8 ml twice daily	3- <4kg	1.5 ml twice daily	Day 14 >	6 mg/kg twice daily

9.1.3 The HIV infected Infant/child (< 10 years)

Cotrimoxazole prophylaxis: *CD4 cut-off for discontinuing amended*

The previous recommendations for cotrimoxazole prophylaxis discontinuation was for patients with CD4 counts of >350 cells/mm^3. However there is a move to making the CD4 cutoff > 200 cells/mm^3. The US ARV guideline uses 200, supported good evidence base.[11, 12, 13, 14, 15, 16, 17] The cut-off was thus changed to 200 cells/mm^3 .

Dolutegravir: *Added*
Efavirenz: *Removed from first-line*
Abacavir/lamivudine/lopinavir ritornavir: *Weight/age bands amended*
Tenofovir: *Weight band amended*

The Paediatric STGs and EML has aligned with the National 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates; and the 2018 Guideline for the Prevention of Mother to Child Transmission of Communicable Infections (HIV, Hepatitis, Listeriosis, Malaria, Syphilis and TB). The algorithms from this guideline were amended to be incorporated into this chapter.

First-line

The first-line regimen as been amended as follows:

Age/weight	First-line regimen
0-<1 month	AZT/3TC/NVP
≥ 4 weeks and ≥ 42 weeks gestational age (3kg – 20kg)	ABC/3TC/LPV/r
< 10 years of age (20kg – 35kg)	ABC/3TC/DTG
≥10 years (≥35Kg)	FDC (TDF/3TC/DTG)

[11] Nachman S, Gona P, Dankner W, et al. The rate of serious bacterial infections among HIV-infected children with immune reconstitution who have discontinued opportunistic infection prophylaxis. *Pediatrics*. Apr 2005;115(4):e488-494. Available at http://www.ncbi.nlm.nih.gov/pubmed/15772172.

[12] Furrer H, Egger M, Opravil M, et al. Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. *N Engl J Med*. Apr 29 1999;340(17):1301-1306. Available at http://www.ncbi.nlm.nih.gov/pubmed/10219064.

[13] Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for Pneumocystis carinii pneumonia in HIV-1-infected patients treated with highly active antiretroviral therapy. Lancet.Jan 16 1999;353(9148):201-203. Available at http://www.ncbi.nlm.nih.gov/pubmed/9923876.

[14] Dworkin MS, Hanson DL, Kaplan JE, Jones JL, Ward JW. Risk for preventable opportunistic infections in persons with AIDS after antiretroviral therapy increases CD4+ T lymphocyte counts above prophylaxis thresholds. *J Infect Dis*. Aug 2000;182(2):611-615. Available at http://www.ncbi.nlm.nih.gov/pubmed/10915098.

[15] Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against Pneumocystis carinii pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med*. Jan 18 2001;344(3):168-174. Available at http://www.ncbi.nlm.nih.gov/pubmed/11188837.

[16] Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. *N Engl J Med*. Jan 18 2001;344(3):159-167. Available at http://www.ncbi.nlm.nih.gov/pubmed/11172138.

[17] Urschel S, Ramos J, Mellado M, et al. Withdrawal of Pneumocystis jirovecii prophylaxis in HIV-infected children under highly active antiretroviral therapy. *AIDS*. Dec 2 2005;19(18):2103-2108. Available at http://www.ncbi.nlm.nih.gov/pubmed/16284459.

Dolutegravir plus an optimised regimen has been shown to be safe, well tolerated and efficacious in a children aged 12 - < 18 years treatment experienced HIV-1 infected adolescents.[18] Dolutegravir is currently only available as a 50 mg tablet (no paediatric formulations). The WHO recommends the use of 50mg dolutegravir from ≥ 20 kg.

Data presented at the Conference on Retroviruses and Opportunistic Infections (CROI) May 2019 found that the adult dose of a 50mg tablet daily can be used in children from 20kg.[19]

Second-line

Second-line regimen was amended to include resistance testing for both failing on PI-based and InSTI-based regimens.

Regimens/algorithms

It was proposed that the algorithms for the switching of therapy, and the first and second line regimens be included in the guideline.

9.2 Tuberculosis and HIV

Dolutegravir plus rifampicin-containing treatment: *dosing recommendations added.*

The recommendations on dolutegravir dosing with rifampicin are extrapolated from Adult data, recommending double dolutegravir dosing. There is no data on the use of concomitant rifampicin and dolutegravir in children between 25 – 35 kg, and it is thus recommended that an expert be consulted in these situations. In patients >35 kg and >10 years, tenofovir/lamivudine/dolutegravir can be used with rifampicin, however dolutegravir 50mg must be added at night to ensure 12 hourly dosing.

18 Viani RM, et.al. Long-term safety and efficacy of dolutegravir in treatment-experienced adolescents with human immunodeficiency virus infection: Results of the IMPAACT P1093 Study. J Pediatric Infec Dis Soc. 2019.

[19] Bollen P, et.al. Adult dolutegravir 50mg tablets in children living with HIV weighing 20 – 25 kg. CROI. March 2019, Abstract number: 830. https://www.croiconference.org/sessions/adult-dolutegravir-50mg-tablets-children-living-hiv-weighing-20

PAEDIATRIC HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 9: HUMAN IMMUNODEFICIENCY VIRUS
NEMLC 11 JUNE 2019

Additional amendments

MEDICINE AMENDMENTS

SECTION	MEDICINE	ADDED/DELETED/NOT ADDED
9.1.2 The HIV infected neonate, > 14 days and ≥ 3kg	Lamivudine	Added
	Abacavir	
	Lopinavir/ritonavir	

9.1.2. The HIV infected neonate (< 1 month of age)

Key change: Addition of option to start the standard infant first line ART regimen

(Abacavir/Lamivudine/Lopinavir/ritonavir) in infants over 14 days of age and over 3 kg: *Added*

Rationale:
The intention of performing an HIV DNA PCR at birth is to start ART within the first few days of live. However in practice, this rapid ART initiation is often not possible due to delays in getting the test result back and to bring the infant/caregiver back into care. Often these infant only start ART in the second week of life. Based on the current protocol this would require that the infant will start AZT/3TC/NVP and change to ABC/3TC/LPV/ritonavir 2 weeks later.

Additionally AZT related anaemia is a common in neonates starting ART and may require modification of antiretroviral regimen. [20] Primary HIV Drug Resistance to NVP is high (up to 65%) in HIV-infected infants and limiting exposure to a potentially ineffective regimen would be advisable.[21]

Evidence: To support the use of ABC and LPV/rtv in infants from 14 days of age and over 3 kgs:
LPV/ritonavir:
FDA approved for use in neonates from 42 weeks gestational age and over 14 days of age – therefore current FDA approval will support the proposed change to the protocol.[22]

[20] HIV Paediatric Workshop 2017. Asymptomatic Hematologic Toxicity with Very Early Combination Antiretroviral Therapy in In Utero HIV-infected Infants EG Chadwick, C Tierney, A Coletti, MF Cotton, TD Ruel, CA Reding, B Zimmer, M Qin, P Jean-Philippe, R Hazra, C Jackson, SA Spector, EV Capparelli, M Mirochnick, LT Purdue, D Costello, C Jennings, K Luzuriaga, C Perlowski, M Bwakura-Dangarembizi, KL Naidoo, D Persaud, Y Bryson for the IMPAACT P1115 Team

[21] Boerma RS, Sigaloff KC, Akanmu AS, Inzaule S, Boele van Hensbroek M, Rinke de Wit TF, Calis JC.J Alarming increase in pretreatment HIV drug resistance in children living in sub-Saharan Africa: a systematic review and meta-analysis. Antimicrob Chemother. 2017 Feb;72(2):365-371. doi: 10.1093/jac/dkw463. Epub 2016 Dec 20.PMID: 27999070.

[22] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021251s052_021906s046lbl.pdf

ABC:
There is currently limited pharmacokinetic data in infants less than 3 months of age even though the current South African National guidelines recommend the use of ABC from 1 month of age. Two studies were recently presented at CROI 2020 to address the issues of safety and pharmacokinetics of ABC in infants less than 3 months particularly less than 1 month of age and support the use of 8mg/kg/day.[23,24]

3TC:
Dose of 3TC in infants less than 1 month of age has already established.

The flow diagram was updated, and the dosing charts were updated as follows:

ARV drug dosing chart:
If < 14 days of age and weighing ≥ 2.5 kg at birth

	Lamivudine (3TC)		Zidovudine (AZT)		Nevirapine (NVP)	
Target dose	2 mg/kg/dose TWICE daily		4 mg/kg/dose TWICE daily		6 mg/kg/dose TWICE daily	
Available formulation	10 mg/ml		10 mg/ml		10 mg/ml	
Weight (kg)	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**
≥2.5-<3.0	0.5ml 12 hourly	5 mg 12 hourly	1 ml 12 hourly	10 mg 12 hourly	1.5 ml 12 hourly	15 mg 12 hourly
≥3.0-<4.0	0.8 ml 12 hourly	8 mg 12 hourly	1.5 ml 12 hourly	15 mg 12 hourly	2 ml 12 hourly	20 mg 12 hourly
≥4.0-<5.0	1 ml 12 hourly	10 mg 12 hourly	2 ml 12 hourly	20 mg 12 hourly	3 ml 12 hourly	30 mg 12 hourly

If > 14 days of age and weighing ≥ 3 kg

	Lamivudine (3TC)		Abacavir (ABC)		Lopinavir/ritonavir (LPV/rtv)	
Target dose	2 mg/kg/dose TWICE daily		8 mg/kg/dose TWICE daily		300/75 mg/m^2/dose TWICE daily	
Available formulation	10 mg/ml		20 mg/ml		80/20 mg/ml	
Weight (kg)	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**	**Dose in ml**	**Dose in mg**
≥3.0-<4.0	0.8 ml 12 hourly	8 mg 12 hourly	2 ml 12 hourly	40 mg 12 hourly	1 ml 12 hourly	80/20 mg 12 hourly
≥4.0-<5.0	1 ml 12 hourly	10 mg 12 hourly	2.5 ml 12 hourly	50 mg 12 hourly	1.5 ml 12 hourly	120/30 mg 12 hourly

[23] Cressey TR, Bekker A, Cababasay M, Wang J, Nakwa F, Smith E. Abacavir Safety and Pharmacokinetics in Normal and Low Birth Weight Infants with HIV. Abstract 842. CROI 3 August to 3 November 2020, Boston, Massachusetts.

[24] De Waal R, Rabie H, Technau K, Eley B, Sipambo N, Cotton M, et al. Abacavir Safety and Efficacy in Young Infants in South African Observational Cohorts. Abstract 845. CROI 3 August to 3 November 2020, Boston, Massachusetts.