Chapter 28

MANAGEMENT OF HIV INFECTION IN CHILDREN

The following guidelines are not intended to be a comprehensive overview of managing HIV-infected neonates, infants and children, but rather to give an overview of some of the key aspects of managing HIV in this age group. For more detailed information, a variety of guidelines are available – both local and international. Treating HIV infection in neonates, infants and children is a specialised field and should only be undertaken by those suitably trained and with sufficient experience.

For further reading we recommend the following detailed guidelines or publications

- SA National Department of Health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV and the management of HIV in children, adolescents and adults, 2015. Available at: www.sahivsoc.org
- World Health Organisation, 2016. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.
- Nuttall, J.J., 2015. Antiretroviral therapy during the neonatal period. *Southern African Journal of HIV Medicine*, 16(1): 1–8.

For up-to-date information on drug-drug interactions, please consult the University of Liverpool Drug Interactions Charts, available at: www.hiv-druginteractions.org.

DIAGNOSING HIV INFECTION IN INFANTS AND CHILDREN

All infants born to mothers who are known to be HIV-infected, as well as those with unknown or uncertain exposure need to be tested for HIV exposure and infection. Maternal HIV antibodies that cross the placenta will be detectable for up to 18 months in exposed infants, thus serological HIV tests (HIV rapid tests and ELISAs) in children and infants less than 18 months can only be used to screen for HIV exposure. HIV infection in this age group is determined by testing for HIV nucleic acid (DNA or RNA and DNA) by means of a qualitative HIV PCR. A positive HIV PCR in a neonate or infant indicates HIV infection and must be confirmed by means of a second HIV PCR. For children older than 18 months, standard HIV testing algorithms as used for adults can be followed (screen with a HIV ELISA followed by appropriate confirmatory tests).

There has been a shift from HIV PCR testing of exposed infants from six weeks to birth testing, so that neonates infected in-utero are detected and initiated on antiretroviral therapy (ART) as soon as possible as there is a high risk of disease progression in infants who acquired HIV infection during the pregnancy.

HIV PCR testing is advised in all HIV exposed infants less than 18 months of age at the following time points:

- At birth
- At 10 weeks of age
- At 18 weeks of age if the infant received 12 weeks of antiretroviral post exposure prophylaxis
- In breastfed infants: six weeks after all breastfeeding was stopped
- In any infant at any age where there is clinical suspicion of HIV infection

All infants with negative HIV PCR results should have a follow-up HIV ELISA at 18 months of age.

WHEN TO START ANTIRETROVIRAL THERAPY IN INFANTS AND CHILDREN

The "Children with HIV Early Antiretroviral Therapy" (CHER) study has shown a significant survival advantage for infants starting antiretroviral therapy (ART) as soon as possible after the diagnosis of HIV infection has been made. Without ART an estimated one-third of infected infants would have died by one year and about a half by two years of age. Universal treatment of all adolescents and adults is now recommended based on the START data. There is no randomised controlled trial data for younger children, however, with increasing evidence of the benefits of early ART, treatment is now recommended for all children.

THE FOLLOWING INFANTS AND CHILDREN ARE ELIGIBLE TO START ART

- Start ART in all children irrespective of CD4 count or WHO clinical stage.
- Prioritise treatment of the following infants and children
  - Children less than two years of age
  - Children younger than five years of age with WHO clinical stage 3 or 4 or CD4 count $\leq$ 750 cells/μL or $<$ 25%
  - Children five years and older with WHO clinical stage 3 or 4 or CD4 count $\leq$ 350 cells/μL
- Fast track the treatment for the following infants and children (ART to be started within seven days)
  - Children less than one year (start ART after initial positive PCR, while waiting for second confirmatory PCR)
  - WHO clinical stage 4
  - MDR or XDR-TB
  - CD4 count $\leq$ 200 cells/μL or $<$ 15%

WHAT ARE THE GOALS OF ART TREATMENT?

- Durable suppression of the HIV viral load (to undetectable levels).
- Restoring/preserving immunological function as monitored by the CD4 count.
- To keep infants and children symptom free.
- To reduce HIV-related morbidity and mortality.

WHAT TO START: RECOMMENDED FIRST-LINE REGIMENS

ANTIRETROVIRAL THERAPY FOR NEONATES

Safety and efficacy data on neonatal ART is limited and there are currently no published trial data comparing ART regimens during the neonatal period. Abacavir is not recommended for infants less than three months and there is a lack of studies to guide dosing in this age group. Lopinavir/

ritonavir is not recommended in neonates < 14 days and < 42 weeks corrected gestational age due to toxicity concerns. Lamivudine, although not approved for use in infants less than three months, has been used and studied in neonates.

ART REGIMENS FOR NEONATES

PREMATURE NEONATE < 35 WEEKS GESTATION

Obtain expert advice

NEONATE ≤ 14 DAYS AND ≥ 35 WEEKS GESTATIONAL AGE

Zidovudine **AND** lamivudine **AND** nevirapine.

When these neonates are ≥ 15 days switch to zidovudine **AND** lamivudine **AND** lopinavir/ritonavir

NEONATE ≥ 15 DAYS AND ≥ 42 WEEKS CORRECTED GESTATIONAL AGE

Zidovudine **AND** lamivudine **AND** lopinavir/ritonavir

ART DOSING FOR NEONATES*

ANTIRETROVIRAL	DOSING
Zidovudine 10 mg/mL	Birth – < 4 weeks of age (≥ 35 weeks gestational age): 4 mg/kg/dose twice daily ≥ 4 weeks of age: • If < 3 kg body weight: 12 mg/kg/dose twice daily OR 240 mg/m²/dose twice daily • If ≥ 3 kg body weight: may be dosed according to SA ARV dosing chart
Lamivudine 10 mg/mL	Birth – 4 weeks of age: 2 mg/kg/dose twice daily ≥ 4 weeks of age: • If < 3 kg body weight: 4 mg/kg/dose twice daily • If ≥ 3 kg body weight: may be dosed according to SA ARV dosing chart
Nevirapine 10 mg/mL	≤ 14 days of age: treatment dose is undetermined Investigational dose is 6 mg/kg/dose twice daily ≥ 15 days of age: • If < 3 kg body weight: 200 mg/m²/dose twice daily • If ≥ 3 kg body weight: may be dosed according to SA ARV dosing chart
Lopinavir/ritonavir 80 mg/20 mg per 1 mL	300 mg/m²/dose twice daily

NOTE: Body surface area (m^2) = (0.05 x Weight [kg]) + 0.05.

*Taken from: Nuttall JJ, 2015. Antiretroviral therapy during the neonatal period. *Southern African Journal of HIV Medicine*,16(1):1-8

ANTIRETROVIRAL THERAPY FOR INFANTS AND CHILDREN

Standard national ART regimens should be followed. Doses are based on the child's weight (refer to dosing chart for children). Always check the child's weight to ensure that they are receiving the correct dose and do not exceed the maximum recommended dose.

Traditionally ARV dosing in children is determined by body surface area or body weight. For practical reasons simple weight band dosing tables were established whereby a fixed dose of drug is assigned for a particular weight band. Refer to the ARV drug dosing chart for children at the end of this chapter compiled by the DOH and the SA HIV Clinicians Society for further information on drug dosing.

FIRST-LINE ART REGIMENS FOR INFANTS AND CHILDREN (EXCLUDING NEONATES)

INFANTS AND CHILDREN < 3 YEARS (OR < 10 KG)

Abacavir **AND** lamivudine **AND** lopinavir/ritonavir.

CHILDREN ≥ 3 YEARS (OR ≥ 10 KG)

Abacavir **AND** lamivudine **AND** efavirenz.

CHILDREN ≥ 3 YEARS WHO RECEIVED NEVIRAPINE FOR 6 WEEKS AND LONGER AS PART OF PREVENTION OF MOTHER TO CHILD TRANSMISSION (PMTCT)

Abacavir **AND** lamivudine **AND** lopinavir/ritonavir.

- Children less than two years of age who have been exposed to any form of ART taken by the mother or infant require a baseline drug resistance test. Many of these children harbour drug-resistance mutations as a result of the PMTCT antiretrovirals and, although they are started on a PI-based regimen, it is important to document these mutations as it will influence the choice of a second-line regimen.
- Children aged more than two years who have stopped taking prophylactic nevirapine for more than two years do not need baseline drug-resistance testing.
- Efavirenz is not recommended in children younger than three years or less than 10 kg due to efficacy and toxicity concerns.
- Any child older than three years who has been exposed to nevirapine for six weeks or longer as part of their PMTCT regimen should be initiated on abacavir + lamivudine + lopinavir/ritonavir. The reason for this is that NNRTI mutations are likely to be present and will be selected for if the child is placed on an NNRTI-based regimen. Children started on this regimen before the age of three should continue the same regimen after they turn three years.
- Any child who is on a stavudine-containing regimen should have the stavudine changed to abacavir if the viral load is fully suppressed. If the viral load is > 1000 c/mL then manage as a treatment failure.
- Fixed dose combinations of drugs are preferred where available and children should be switched to tablets or capsules from syrups or solutions as soon as they are tolerated.
- Keep lopinavir/ritonavir cool (< 25°C). It can be kept out of the fridge for up to 42 days once dispensed.

HIV-INFECTED CHILDREN WITH TUBERCULOSIS

In children with TB, rifampicin increases the breakdown of PIs and NNRTIs and there are overlapping toxicities between TB drugs and ARVs. For children on standard anti-TB drugs use the following ART regimen:

- ≥ 3 years: abacavir **AND** lamivudine **AND** efavirenz (standard dose)
- < 3 years: abacavir **AND** lamivudine **AND** superboosted lopinavir/ritonavir 300 mg/m^2/dose 12 hourly plus extra ritonavir dosed at 0.75 x volume of lopinavir/ritonavir.

An alternative to superboosted lopinavir/ritonavir in children less than three years with TB may be lamivudine **AND** abacavir **AND** nevirapine at 200 mg/m^2 or a triple NTRI regimen. These cases need to be discussed with a paediatric infectious diseases expert prior to being used.

CLINICAL AND LABORATORY MONITORING

At the first visit a full clinical examination including weight, height and head circumference should be performed. Counselling and clinical monitoring should cover:

- Social support, caregivers, disclosure of HIV diagnosis
- WHO clinical staging and screening for TB symptoms
- HIV prognosis
- Treatment options
- Adherence – this is crucial for virological suppression and for successful HIV treatment
- Drug formulations and how ARVs are administered
- Need for dose adjusting based on weight
- The taste of the medication
- Side effects of ART
- Nutritional advice
- Immunisations
- Opportunistic infections and prophylaxis

An HIV viral load and CD4 count must be done on the first visit. A baseline viral load is useful to monitor subsequent responses to ART and serves as an additional confirmatory test in addition to the PCR. The frequency of subsequent visits varies depending on the guideline followed, and for certain ARVs such as AZT and NVP additional safety bloods are required. As a guideline the following tests are recommended at the following time points by the SA HIV Clinicians' Society:

RECOMMENDED ROUTINE LABORATORY MONITORING

		MONTHS				
LABORATORY TESTS	**BASELINE**	**2WKS**	**1***	**3***	**6**	**THEN**
HIV viral load	X+			X	X	Every 3–6 months*
CD4 cell count	X			X	X	Every 3–6 months*
FBC with differential	X		X	X	X	Every 3–6 months*
ALT	X	X	X	X	X	Every 3–6 months*
Glucose (fasting)	X					Every 12 months
Lipid profile (cholesterol/TG)	X					Every 12 months
Urine dipstick	X					Every 12 months

*NDOH guidelines recommend 6-monthly monitoring.

+NDOH guidelines recommend not to do a baseline HIV viral load as a cost-saving practice. It is imperative that a baseline

VL is done in all infants diagnosed on PCR as this doubles as a confirmatory test. Do not delay initiation of HAART while awaiting the confirmatory test result.

FBC = full blood count; ALT = alanine transaminase

Taken from: 'Guidelines for Antiretroviral Therapy in Children – November 2009 Version. *The Southern African Journal of HIV Medicine*. December 2009.

IMPORTANT POINTS REGARDING HIV VIRAL LOAD TESTING

- Repeat the HIV viral load should you get an unexpected result.
- Intercurrent infections or vaccinations may temporarily increase the HIV viral load.
- Changes in viral load more than five-fold (0.7 log) in children aged younger than two years or more than three-fold (0.5 log) in children older than two years should be considered significant.
- Two HIV viral loads performed one month apart should be taken before instituting any changes to the ART regimen.

IMPORTANT POINTS REGARDING CD4 COUNT TESTING

- Infants and children have higher normal CD4 counts than adults that decline to adult levels at around six years of age.
- CD4 cell percentage is a better marker for HIV disease progression than CD4 cell count, but both measures should be used for monitoring response to ART.
- Viral load changes precede any change in CD4 count.
- Intercurrent infection and vaccination may drop the CD4 count, taking up to a month or longer to recover.
- Lymphopenia or lymphocytosis may under- or over-estimate the CD4 percentages and count.

FAILURE OF FIRST-LINE ARV THERAPY IN CHILDREN

Children initiated on ARVs should suppress their HIV viral load to undetectable levels within three to six months of starting treatment. Subsequent detection of plasma viremia requires immediate intervention. In addition, any child that fails to drop their HIV viral load > 2 log from the baseline viral load between three to six months requires intervention and possibly a change to their ARV regimen.

When viraemia is detected it requires urgent adherence counselling and investigation of 'technical' problems such as drug dosages or spitting or vomiting of medication. If the plasma viral load remains above 1000 c/mL, as measured one to three months apart, then a drug-resistance test needs to be performed for all children failing either an NNRTI or a PI-based first-line regimen. The drug-resistance test should be performed while the patient is on the failing regimen or within four weeks of discontinuation.

Based on the results of the drug-resistance test, a new regimen needs to be chosen and must include at least two new active drugs. Consultation with a paediatric infectious diseases expert is recommended when deciding on an appropriate second-line regimen.

FAILURE OF SECOND-LINE AND SUBSEQUENT REGIMENS IN CHILDREN

Choice of subsequent regimens should always be based on results of a drug-resistance test. When interpreting these results, it is important to take into account results from previous drug-resistance tests, as these mutations will not necessarily be found on the latest drug-resistance test report, but will be selected for if a new drug is chosen to which resistance was previously detected. Consultation with a paediatric infectious diseases expert is essential when deciding on an appropriate salvage regimen.

ISONIAZID PREVENTIVE THERAPY FOR HIV-INFECTED CHILDREN

At every visit HIV-infected children need to be assessed for TB exposure or active disease. Isoniazid preventive therapy (IPT) should be provided after each documented TB exposure (someone with TB who resides with the child) unless already receiving TB treatment or INH prophylaxis. It is crucial to first exclude active TB before starting IPT.

IPT may also be given to children who were diagnosed or initiated on ART after three months of age and who have no documented TB exposure (pre-exposure IPT). This is likely to be most beneficial for those who are tuberculin skin test (TST) positive.

The dose of INH is 10 mg/kg/day (max 300 mg/day) and should be given for six months for both pre- and post-exposure IPT. Vitamin B6 25 mg daily in children more than five years or 12.5 mg daily in children less than five years should also be given for the duration of the IPT.

COTRIMOXAZOLE PROPHYLAXIS FOR PCP IN HIV-EXPOSED AND HIV-INFECTED CHILDREN

All HIV-exposed infants should receive cotrimoxazole (CTX) from four to six weeks of age until infants are confirmed HIV-uninfected and no longer exposed to HIV through breastfeeding. CTX should be continued until HIV infection is excluded by ELISA testing at 18 months or by virological (PCR) testing before 18 months.

In HIV-infected children under one year of age, CTX is indicated regardless of CD4 cell count or clinical status. CTX prophylaxis should be continued in all HIV-infected children when not on ART. For those on ART, stop the CTX only when there is evidence of immune reconstitution, i.e. when they are 18 months or older with a CD4 count of > 15% on two occasions taken three months apart.

CTX for use in children is available as both as a suspension (200 mg/40 mg per 5 mL) or single strength tablets (400 mg/80 mg).

WEIGHT (KG)	3–4.9	5–9.9	10–13.9	14–29.9	≥ 30
Cotrimoxazole Dose	2.5 mL OD	5 mL OD	5 mL OD	10 mL OR 1 tablet OD	2 tablets OD

ANTIRETROVIRAL DRUG-DOSING CHART FOR CHILDREN 2013

Compiled by the Child and Adolescent Committee of the SA HIV Clinicians' Society in collaboration with the Department of Health

	ABACAVIR (ABC)	LAMIVUDINE (3TC)	EFAVIRENZ (EFV)
Target dose	8 mg/kg BD OR ≥ 10 kg: 16 mg/kg OD	4 mg/kg BD OR ≥ 10 kg: 8 mg/kg OD	By weight band OD
Formulations	Sol: 20 mg/mL Tabs (scored): 60 mg Tabs (not scored): 300 mg ABC/3TC: 600 mg /300 mg	Sol: 10 mg/mL Tabs (scored): 150 mg Tabs (not scored): 300 mg ABC/3TC: 600 mg/300 mg	Caps: 50, 200 mg Tabs (not scored): 50, 200, 600 mg

Weight (kg)	Currently available tablet formulations of abacavir (except 60 mg) and efavirenz must be swallowed whole and NOT chewed, divided or crushed			
< 3	Consult with a clinician experienced in paediatric ARV prescribing for neonates (< 28 days of age) and infants weighing < 3 kg			
3–3.9 4–4.9	2 mL BD		2 mL BD	Avoid using when < 10 kg or < 3 years dosing not established
5–5.9 6–6.9	3 mL BD		3 mL BD	
7–7.9 8–8.9 9–9.9	4 mL BD		4 mL BD	
10–10.9 11–13.9	6 mL BD OR 12 mL OD OR 2 x 60 mg tabs BD OR 4 x 60 mg tabs OD		6 mL BD OR 12 mL OD	200 mg nocte (1 x 200 mg cap/tab)
14–16.9 17–19.9	8 mL BD OR 15 mL OD OR 2.5 x 60 mg tabs BD OR 5 x 60 mg tabs OD OR 1 x 300 mg tab OD		8mL BD OR 15 mL OD OR ½ x 150 mg tab BD OR 1 x 150 mg tab OD	300 mg nocte (200 mg cap/tab + 2 x 50 mg cap/tab)
20–22.9	**Choose one option only**		15 mL BD OR 30 ml OD OR 1 x 150 mg tab BD OR 2 x 150 mg tab OD OR 1 x 300 mg tab OD	300 mg nocte (200 mg cap/tab + 2 x 50 mg cap/tab)
	10 mL BD	1 x 300 mg tab **AND** 1 x 60 mg tab OD		
23–24.9	OR 3 x 60 mg tabs BD	1 x 300 mg tab **AND** 2 x 60 mg tabs OD		

25–29.9	1 x 300 mg tab BD OR 2 x 300 mg tabs OD OR 1 x ABC/3TC 600/300 mg tab OD	1 x 150 mg tab BD OR 2 x 150 mg tabs OD OR 1 x 300 mg tab OD OR 1 x ABC/3TC 600/300 mg tab OD 600 mg nocte	400 mg nocte (2 x 200 mg caps/tabs)
30–34.9			
35–39.9			
> 40			
OD = once daily, BD = twice daily			

	LOPINAVIR/RITONAVIR (LPV/RTV)	**RITONAVIR BOOSTING (RTV)**	**STAVUDINE (D4T)**
Target dose	300/75 mg/m^2/dose LPV/RTV BD	ONLY as booster for LPV/RTV when on rifampicin BD (0.75 x LPV dose BD)	1 mg/kg/dose BD
Formulations	Sol: 80/20 mg/mL Paeds tabs: 100/25 mg Adult tabs: 200/50 mg	Sol: 80 mg/mL	Sol: 1 mg/mL Caps: 15, 20, 30 mg
Weight (kg)	Currently available tablet formulations LPV/RTV must be swallowed whole and NOT chewed, divided or crushed		
< 3	Consult with a clinician experienced in paediatric ARV prescribing for neonates (< 28 days of age) and infants weighing < 3 kg*		
3–3.9	*1 mL BD	1 mL BD	6 mL
4–4.9			
5–5.9	*1.5 mL BD	1.5 mL BD	7.5 mg BD: open 15 mg capsule into 5 mL water: give 2.5 mL
6–6.9			
7–7.9			10 mg BD: open 20 mg capsule into 5 mL of water and give 2.5 mL
8–8.9			
9–9.9			
10–10.9	2 mL BD	1.5 mL BD	15 mg BD: open 15 mg capsule into 5 mL water
11–13.9			

Rx	14–16.9	2.5 mL BD OR 100/25 mg paeds tabs: 2 BD OR 200/50 mg adult tabs: 1 BD	2 mL BD	20 mg BD: open 20 mg capsule into 5 mL water (if the child cannot swallow a capsule)
	17–19.9			
	20–22.9	3 mL BD OR 100/25 mg paeds tabs: 2 BD OR 200/50 mg adult tabs: 1 BD	2.5 mL BD	
	23–24.9			
	25–29.9	3.5 mL BD OR 100/25 mg paeds tabs: 3 BD OR #200/50 mg adult tabs: 1 BD **AND** 100/25 mg paeds tabs: 1 BD	3 mL BD	30 mg BD
	30–34.9	4 mL BD OR 100/25 mg paeds tabs: 3 BD OR #200/50 mg adult tabs: 1 BD **AND** 100/25 mg paeds tabs: 1 BD		
	35–39.9	5 mL BD OR 200/50 mg adult tabs: 2 BD	4 mL BD	
	> 40			

OD = once daily, BD = twice daily

*Avoid LPV/RTV in full-term infants < 14 days of age, or premature infants < 14 days after the due date of delivery (40 weeks post conception)

Children 25–34.9 kg may also be dosed with LPV/RTV 200/50 mg adult tabs: 2 tabs am; 1 tab pm

	DIDANOSINE (DDI)	NEVIRAPINE (NVP)	ZIDOVUDINE (AZT)
Target Dose	180–240 mg/m^2/dose OD	160–200 mg/m^2/dose BD (after once daily lead-in x 2 weeks)	180–240 mg/m^2/dose BD
Formulations	Tabs: 25, 50, 100 mg (dispersible in 30 mL water) Caps: 250 mg EC	Sol: 10 mg/mL Tabs: 200 mg (scored)	Sol: 10 mg/mL Caps: 100 mg Tabs: 300 mg (not scored) AZT/3TC: 300/150 mg
Weight (kg)	Currently available tablet formulations of AZT must be swallowed whole and NOT chewed, divided or crushed		
< 3	Consult with a clinician experienced in paediatric ARV prescribing for neonates (<28 days of age) and infants weighing < 3 kg		
3–3.9	Avoid	5 mL BD	6 mL BD
4–4.9			
5–5.9	100 mg OD (2 x 50 mg tabs)		
6–6.9	125 mg OD (1 x 100 mg **AND** 1 x 25 mg tabs)	8 mL BD	9 mL BD
7–7.9			
8–8.9			12 mL BD OR 1 cap BD
9–9.9			
10–10.9	150 mg OD (1 x 100 mg **AND** 1 x 50 mg tabs)	10 mL BD	
11–13.9			
14–16.9	175 mg OD (1 x 100 mg **AND** 1 x 50mg **AND** 1 x 25 mg)	15 mL BD OR 1 tab AM **AND** ½ tab PM	15 mL BD OR 2 caps am **AND** 1 cap pm
17–19.9			
20–22.9	200 mg OD (2 x 100 mg tabs)		20 mL BD OR 2 caps BD
23–24.9			
25–29.9	250 mg OD (2 x 100 mg **AND** 1 x 50 mg tab) OR 1 x 250 mg EC cap OD	1 tab BD	1 x 300 mg tab BD OR 1 x AZT/3TC 300/150 mg tab BD
30–34.9			
35–39.9			
> 40			

OD = once daily, BD = twice daily