PAEDIATRIC ANTIRETROVIRAL THERAPY FOR THE GENERAL PRACTITIONER

The care of HIV-infected children is somewhat different to that of adults, and although this poses some challenges, it should not impede paediatric access to life-saving medicines. This article attempts to simplify paediatric antiretroviral therapy for the general practitioner.

HEATHER B JASPAN

MD, PhD, FAAP

Senior Investigator, Paediatrician

Desmond Tutu HIV Centre
Institute of Infectious Disease and Molecular Medicine
University of Cape Town

Heather Jaspan's current interests are paediatric HIV infection and ART, paediatric and adolescent immunology and vaccinology, adolescent risk behaviour and risk reduction, and preventive HIV vaccines.

JAMES J C NUTTALL

MB ChB, Dip Obst SA, DCH SA, FCPaed (SA), DTM&H

Specialist

Infectious Diseases Clinic
Red Cross Children's Hospital and School of Child & Adolescent Health
University of Cape Town

James Nuttall's current interests are management of children on antiretroviral therapy, HIV and TB co-infection and immune reconstitution diseases.

BRIAN S ELEY

MB ChB, FCPaeds (SA)

Head

Clinical Infectious Diseases
Red Cross Children's Hospital
Cape Town

Brian Eley's current interests are HIV infection, HIV/TB coinfection and clinical services for HIV-infected children and adolescents, infectious diseases during childhood, childhood vaccination and vaccine adverse events. Research interests include effectiveness of antiretroviral therapy, HIV/TB coinfection, immunology of tuberculosis, immune reconstitution and the primary immunodeficiency diseases.

GOALS OF THERAPY

Antiretroviral therapy (ART) in children follows the same principles as in adults, the goals being suppression of viral load, preservation of immune function, reduction in morbidity and mortality, and optimisation of growth and development.

NATURAL HISTORY

The natural history of HIV in children is different from that in adults. Viral loads in children are far higher in the first year of life and only decline to adult values by 2 - 3 years of age. Generally, the higher the viral load, the more rapid the disease progression, and combination of viral load assay and CD4 percentage is most predictive of mortality.[6] Owing to the higher viral loads found in children, there is a poorer prognosis for children with HIV, and fewer children respond to highly active antiretroviral therapy (HAART) with completely suppressed viral loads (25 - 75% respond with VL < 400 copies/ml). Therefore, a suppressed yet detectable viral load in a clinically well child with a sustained, elevated CD4 percentage or count may be acceptable.

STAGING

As in adults, there are clinical and immunological staging systems for children. A number of different clinical staging systems exist (CDC, WHO).[1,8] In South Africa, paediatricians generally use a modified WHO staging system (Table I). There are only 3 stages of paediatric HIV infection in this system for children. The WHO is adapting its staging system which will include many of our modifications, but will also have 4 stages to be more consistent with adult staging.

CD4 cell numbers change drastically throughout childhood, and therefore we focus on CD4 percentage to measure immunological function until the age of 6 years, when cell numbers approach adult levels. Immunological staging can be found in Table II.

INITIATING HAART

Criteria for initiating HAART

Before initiating therapy, it is necessary to confirm HIV infection, especially where an ELISA in a child less than 18 months of age is the only result available. This includes confirming diagnosis with the use of DNA PCR in children less than 18 months or those who have breastfed in the prior 6 weeks. Even for children older than 18 months, an ELISA can remain positive in an HIV-uninfected exposed child for up to 3 months after cessation of breastfeeding. HAART should not be initiated on clinical suspicion and exposure alone.

There are many different guidelines for the use of HAART in children, including the Centers for Disease Control (CDC)[1] guidelines and the Paediatric European Network for Treatment of AIDS (PENTA)[5] guidelines. This is due to the lack of randomised, controlled trials in paediatrics. The South African National Treatment Guidelines (SANTG)[4] eligibility criteria for initiating HAART in children are based on WHO guidelines,[8] which are more suited to sub-Saharan Africa and are as follows:

- **Clinical criteria** – recurrent hospitalisations (> 2 per year) for HIV-related disease, or prolonged hospitalisation (> 4 weeks), or modified WHO stage 2 or 3 disease.
- **Immunological criteria** – CD4% < 20% in a child < 18 months, or CD4% < 15% in a child over 18 months of age.
- **Social criteria** – a knowledgeable caregiver who has demonstrated adherence to clinic visits and other medications (co-trimoxazole and vitamins).

Process of initiating HAART

Treatment should never be initiated at the first visit. Prior to HAART initiation, the family or primary caregiver must receive counselling that covers the need for lifelong treatment and discussion of prognosis, importance of adherence, and procedures if medication runs out. More than one session is often necessary. In addition,

Table I. **Modified WHO staging system for paediatric HIV infection**

Stage 1

Asymptomatic
Generalised lymphadenopathy
Hepatomegaly
Splenomegaly
Parotomegaly
Chronic suppurative otitis media
Eczema/seborrhoeic dermatitis

Stage 2

Unexplained chronic diarrhoea (≥ 2 weeks)
Failure to thrive 60 - 80% EBW, non-responsive to nutritional or TB treatment
Recurrent or severe bacterial infection (≥ 2 episodes pneumonia or 1 episode of meningitis)
Oral candidiasis, non-neonatal, severe, persistent, or recurrent
TCP (plt < 40 000 x 10^9/l) non-responsive to prednisone
Neutropenia (neutrophils < 500 x 10^9/l) despite switching co-trimoxazole to dapsone
Severe LIP
- persistent hypoxia < 90% or tachypnoea in absence of acute infection
- SOB on exertion
- evidence of bronchiectasis (clubbing plus persistent nocturnal cough)
- cor pulmonale

≥ 2 episodes of severe herpetic disease including zoster
A single episode of probable or proven PTB*
Otorrhoea > 6 weeks*

Stage 3

Severe FTT < 60% EBW, non-responsive to nutritional or TB treatment
Progressive encephalopathy
Recurrent septicaemia (≥ 2 episodes)
Bronchiectasis
Cardiomyopathy
Progressive nephropathy
Candidiasis (oesophageal or pulmonary)
Disseminated fungal infection (coccidio, crypto, or histoplasmosis)
Disseminated mycobacterial infection (MTB, BCG, MAI, *M. kansasii*)
Recurrent, culture-positive TB
Cytomegaloviral disease with onset at age > 1 month (at site other than lymph node, liver or spleen)
Herpes simplex virus mucocutaneous ulcer persisting > 1 month, HSV bronchitis, oesophagitis, pneumonitis, at age > 1 month
Pneumocystis jiroveci pneumonia (PCP)
Progressive multifocal leukoencephalopathy
Recurrent (non-typhoid) salmonella (recurrent)
HIV-related malignancy
Cerebral toxoplasmosis onset at age > 1 month

EBW = expected body weight; FTT = failure to thrive; SOB = shortness of breath; TCP = thrombocytopenia; PTB = pulmonary tuberculosis; MTB = *Mycobacterium tuberculosis*; MAI = *Mycobacterium avium intracellulare;* LIP = lymphoid interstitial pneumonitis.
*Criteria used by Western Cape paediatricians.

Table II. **Immunological categories for children with HIV infection**

	Age of child					
	<12 Months		1-5 Years		6 -12 Years	
Immunological category	CD4+/µl	CD4+%	CD4+/µl	CD4+%	CD4+/µl	CD4+%
No immunosuppression	>1 500	≥ 25	≥ 1 000	≥ 25	≥ 500	≥ 25
Moderate immunosuppression	750 - 1 499	15 - 24	500 - 999	15 - 24	200 - 499	15 - 24
Severe immunosuppression	< 750	< 15	< 500	< 15	< 200	< 15

Table III. **First-line regimens for paediatric HIV in South Africa[4]**

Age 6 months - 3 years	> 3 years and > 10 kg
d4T	d4T
3TC	3TC
Lopinovir/ritonavir (Kaletra)	Efavirenz (EFV)

Table IV. **Routine monitoring for children on ARVs**

Test	Drug	Frequency
CD4 count and percentage	All	Baseline, then q 6 monthly
Viral load	All	Baseline, then q 6 monthly
FBC with platelets	AZT	Baseline, 1, 2, 3, 6 months, then q 6 monthly
ALT	NVP*	Baseline, 1, 2, 3 and 6 months, then q 6 monthly
Fasting glucose, cholesterol and triglycerides†	Protease inhibitors	Baseline, then 6 monthly

* SANTG only require ALT to be followed for patients on nevirapine; however, most classes of ARVs can cause hepatotoxicity, and therefore we recommend checking ALTs on all. Consider this for FBC also.
† SANTG recommended q 6 monthly monitoring of these parameters, but in practice is done annually in resource-limited settings.

clinical history and physical exam, neurodevelopmental assessment, growth parameters, alanine aminotransferase (ALT), full blood count (FBC), viral load and CD4 count/percentage prior to treatment should be recorded. TB should be ruled out, but work-up should not delay therapy initiation indefinitely.

DRUG REGIMENS

The available regimens for children include a double nucleoside reverse transcriptase inhibitor back-bone, with either a non-nucleoside (nNRTI) or a protease inhibitor as the third drug.[3,9] Regimens chosen for first-line therapy are shown in Table III. Dosages can be found in Table VII. Body surface area (BSA) can be calculated as follows:

$$\text{Body surface area } (m^2) = \frac{\text{square root of [height (cm) x weight (kg)]}}{60}$$

When treating children, the following drug facts are important to remember:

- Efavirenz is not approved for use in children < 3 years old and weighing < 10 kg.
- ddI and d4T syrups should be refrigerated; however capsules can be dissolved in water and kept in solution at room temperature for 24 hours.
- ddI must be taken alone, on an empty stomach, and tablets must be dissolved in at least 30 ml of water.
- Ritonavir syrup is very bitter and is often vomited for the first few weeks. It is therefore best to dose this drug first so as to prevent the need to redose all drugs after vomiting. It helps to coat the mouth with something sweet.
- Resistance to non-nucleoside RT inhibitors may be present after failed PMTCT with nevirapine. Therefore, use of either nNRTI (NVP or EFV) after PMTCT should be avoided if possible, since cross-resistance occurs.

FOLLOW-UP AND MONITORING

It is recommended that the child is seen or contacted during the first month after HAART initiation, for 2 reasons:

- to check that the dosing is correct, since it is quite a task to administer all the syrups at the correct dosage
- to assess for adverse events, since these often occur in the first 6 weeks.

Thereafter, clinic visits should occur monthly, until the child is stable and compliance with medications is demonstrated. At clinic visits, weight, height, and a physical exam should be performed. A head circumference should be followed for children less than 2 years. Dosage needs to be recalculated AT EVERY VISIT. The caregiver should bring in the medication and demonstrate each dose in the clinic. In addition to monitoring via history of intercurrent illnesses, and physical examination, the recommended laboratory monitoring for children on HAART is shown in Table IV. Clinical judgement should be used in making decisions about monitoring, as for treatment. Immune reconstitution syndrome is

Table V. **Criteria for changing to second-line therapy in children**

Virological	Clinical	Immunological
Rebound of VL to baseline	Persistent oral thrush refractory to treatment	A persistent decline in CD4 count or percentage†
Detectable VL after initial responding with undetectable VL	New evidence of stage 3 disease*	A return of CD4 count or percentage to baseline†, ‡
Less than 1 log decrease in VL after 24 weeks of treatment‡	Progressive cognitive or developmental deterioration or development of encephalopathy‡	50% decline from peak level while on therapy†, ‡
Persistent increase in VL after beginning treatment‡	Crossing of weight-for-age centiles over 2 months, despite nutritional support & exclusion of TB	

VL = viral load.
*Immune reconstitution can manifest as a new stage II disease, this does not count as failure. Be sure that the stage 3 illness is clearly NEW.
† In the absence of intercurrent infections.
‡ Criteria used by Western Cape paediatricians.

Table VI. **Second-line regimens for paediatric HIV in South Africa[4]**

Age 6 months - 3 years	> 3 years and > 10 kg
AZT	AZT
ddI	ddI
Nevirapine	Lopinavir/ritonavir (Kaletra)

commonly seen after therapy initiation, and generally, one should treat symptomatically rather than stopping therapy. However, a full discussion of this syndrome is beyond the scope of this paper.

TREATMENT FAILURE

The decision to change from first- to second-line therapy (found in Table VI) should not be taken lightly.[2] The main reason for treatment failure is lack of adherence. No decision should be based on a single viral load or CD4 result. Intercurrent illnesses including upper respiratory tract infections can elevate viral loads and depress CD4 counts and percentages for up to a month. A detectable viral load is often tolerated in children, as long as a sustained increase in CD4 count/percentage and clinical response is evident. The criteria for switching are found in Table V.

DRUG SIDE-EFFECTS

In general, antiretroviral side-effects in children are similar to those in adults, although children may have fewer adverse reactions. If the side-effect is due to a specific drug, a single drug substitution can be made. If drugs need to be stopped, all 3 should be stopped simultaneously.

TB TREATMENT AND HAART IN CHILDREN

Tuberculosis is a common co-infection with HIV. Significant pharmacokinetic interactions occur between rifampicin and the protease inhibitors and the nNRTIs. This may require modification of the HAART regimen.

Two main clinical scenarios exist:

1. *Child presents with TB before commencing ART.*

- Many children who present with TB and HIV infection and who have not yet started HAART, are severely immunocompromised. In these children, HAART should be started after completing 3 - 6 weeks of TB treatment, provided TB treatment is well tolerated and liver function tests (LFTs) are not markedly abnormal.
- If the child has failed the nevirapine vertical transmission programme, is less than 3 years old or weighs less than 10 kg, use ritonavir as the third drug.
- If the child was not on the nevirapine vertical transmission programme and is more than 3 years old and weighs more than 10 kg, use efavirenz as the third drug.
- Monitor ALT, and full LFTs if abnormal, monthly, for the first 3 months of TB treatment and HAART.
- In children who are not severely immunocompromised (CD4 count > 15%), HAART may be delayed until after completion of TB treatment, allowing 2 weeks for the effect of rifampicin on the liver to resolve. It is recommended that the clinical and immunological status be closely monitored during the course of TB treatment.

2. *Child develops TB while on ART therapy.*

- If the child is on:
  - lopinavir/ritonavir or nelfinavir, then switch to ritonavir
  - nevirapine, and is less than 3 years old or weighs less than 10 kg, switch to ritonavir
  - nevirapine and is more than 3 years old and weighs more than 10 kg, switch to efavirenz.
- If the child is unable to tolerate the large number of drugs, ART may have to be interrupted until TB therapy has been completed.

Table VII. **Dosages and frequency of ARVs in children**

Drug	Formulation	Dosage (per dose)	Frequency	Storage	Comments
Nucleoside reverse transcriptase inhibitors (NRTI)					
Zidovudine (ZDV) Retrovir	Susp: 10 mg/ml Caps: 100 mg, 250 mg	180 mg/m^2	2	Room temperature	
Didanosine (ddI) Videx	Susp: 10 mg/ml Tabs: 25 mg, 50 mg, 100 mg, 150 mg	90 - 120 mg/m^2	2 Daily dosing not recommended	Refrigerate suspension	30 min pre-meals or 1 h after meal
Stavudine (d4T) Zerit	Susp: 1 mg/ml Caps: 20 mg, 30 mg, 40 mg	1 mg/kg	2	Refrigerate suspension	Capsules stable in water suspension for 24 h in refrigerator
Lamivudine (3TC)	Susp: 10 mg/ml Tabs: 150 mg	4 mg/kg	2	Room temperature	
Abacavir Ziagen	Susp: 20 mg/ml Tabs: 300 mg	8 mg/kg	2	Room temperature	Watch for hypersensitivity Do not rechallenge after hypersensitivity reaction
Non-nucleoside reverse transcriptase inhibitors (nNRTI)					
Nevirapine Viramune	Susp: 10 mg/ml Tabs: 200 mg	120 - 200 mg/m^2 Start at 120 mg/m^2 daily for 14 days and then increase to 180 - 200 mg/m^2 BD if no rash or severe side-effects	2	Room temperature	Skin rash usually occurs in 1st 6 weeks – do not increase dosage until rash resolves WATCH FOR LIVER TOXICITY
Efavirenz Stocrin	Caps: 50 and 200 mg	10 - 14.9 kg: 200 mg 15 - 19.9 kg: 250 mg 20 - 24.9 kg: 300 mg 25 - 32.4 kg: 350 mg 32.5 - 39.9 kg: 400 mg > 40 kg: 600 mg	1	Room temperature	No data < 3 yrs and < 10 kg. Give at night to avoid CNS side-effects
Protease inhibitors					
Ritonavir Norvir	Susp: 80 mg/ml	Start at 250 mg/m^2/dose and increase by 50 mg/m^2 every 2 - 3 days up to 400 mg/m^2 If < 2 years of age 450 mg/m^2	2		Take with food Bitter; coat mouth with peanut butter or give with chocolate milk Take 2 hours apart from didanosine

Table VII. **Dosages and frequency of ARVs in children (continued)**

Drug	Formulation	Dosage (per dose)	Frequency	Storage	Comments
Protease inhibitors					
Lopinavir/ ritonavir Kaletra	Oral solution 80 mg lopinavir (LPV) & 20 mg ritonavir (RTV) per ml Capsules 133 mg LPV/33 mg RTV	Patients not taking NVP or EFV – 230 mg LPV component/m^2 (max 400 mg LPV = adolescent dose) Patients taking NVP or EFV or ART experienced – 300 mg LPV component/m^2 (max 533 mg LPV = adolescent dose)	2	Oral solution and capsules should be refrigerated. Can be kept at room temperature up to 25°C if used within two months	Administer with food; high-fat meal increases absorption, especially of the liquid preparation If co-administered with ddI, ddI should be given 1 h before or 2 h after lopinavir/ ritonavir

Adapted from South African HIV Clinicians Society.[7]

Discuss all cases with a paediatrician with antiretroviral experience.

- Monitor ALT, and full LFTs if abnormal, monthly for the first 3 months of TB treatment and HAART.

SPECIFIC ISSUES FOR ADOLESCENTS

- Adult guidelines are appropriate for post-pubertal adolescents (Tanner stage 4 and 5).
- For adolescents in early puberty (Tanner stage I and 2) use paediatric guidelines.
- For intermediate puberty, monitor closely and choose either adult or paediatric guidelines.
- The Tanner staging system can be found in the *National Antiretroviral Treatment Guidelines* (SANTG).[4]
- Non-compliance is problematic and strategies should be introduced to promote adherence, including more frequent visits and intensive counselling.

References available on request.

IN A NUTSHELL

The natural history of perinatal HIV infection is somewhat different to that of adults. Children have much higher viral loads.

Children's clinical staging follows a modified WHO 3 staging system.

Their immunological monitoring is according to CD4 percentage rather than absolute count until about 6 years of age.

Children often cannot swallow pills, syrups can be unpalatable and some require refrigeration.

Many drugs have not undergone safety testing in young children, therefore options for therapy are limited.

Due to high viral loads to start with, children are harder to treat and we sometimes tolerate detectable levels of vireamia if clinical and immunological improvement is sustained.

Drug metabolism changes quite rapidly in the first years of life, therefore drug dosing requires careful calculations.

Drug dosing goes according to body weight and surface area, and therefore necessitates dose adjustments at almost every visit.