CLINICAL GUIDELINE

# ANTIRETROVIRAL THERAPY IN CHILDREN

## *Southern African HIV Clinicians Society*

### INTRODUCTION: PAEDIATRIC ANTIRETROVIRAL THERAPY GUIDELINES – A STATE OF FLUX

The paediatric guidelines committee of the Southern African HIV Clinicians Society is proud to present the 2nd edition of our guidelines. This year we had the benefit of enlarging our committee to 6 members. I would like to thank our committee for all the effort they put into the guidelines and also to thank our overseas reviewers and Dr Lucille Blumberg for her assistance in the section on TB treatment and HAART.

One of our overseas reviewers was concerned that we did not have enough detail in our guidelines. When one looks at the American Guidelines[1] (± 50 pages) one can understand his concern. However these guidelines are a guide. They are not intended to turn a novice treater into an experienced clinician overnight. Instead we envisage that the clinician will use our guidelines as an addition to knowledge that they gain from continuing medical education and reading, supplemented if necessary with advice from the Southern African HIV Clinicians Society. Certainly when considering changing a regimen, we strongly recommend contacting the Society. Changing (or starting) antiretroviral therapy is never an emergency.

We were presented with an ever-increasing range of international ART guidelines on which to base our own – from the aggressive American Guidelines[1] through to the ultra-conservative World Health Organisation (WHO) guidelines,[2] with the European PENTA Guidelines[3] somewhere in between. We opted for a middle of the road approach with indications for initiating ART similar to the PENTA guidelines. In the light of the current trend of placing less significance on the viral load as an indication for starting therapy, we have dispensed with high viral load as an indication for starting ART. However, we still feel the viral load is important in following up response to therapy and for picking up problems of adherence or resistance early on.

Our first guidelines (November 2000) had a separate section on children under 3 months of age. These children, if treated aggressively, can develop a totally normal immunity. Our latest guidelines still have a separate recommendation on children under 3 months of age, but the pendulum has swung somewhat. Clinicians worldwide are questioning the merit of subjecting very young infants to lifelong treatment, sometimes years before they actually need the treatment. We therefore urge the clinician to exercise caution when deciding to place an asymptomatic young infant with normal CD4% onto long-term treatment.

The paediatric subcommittee of the Southern African HIV Clinicians Society has been quite active apart from drawing up Paediatric ART guidelines. We recently held a successful Paediatric ART workshop in Gauteng and we have our ongoing e-mail-based Paediatric Discussion Group (PDG) where we discuss interesting or difficult cases with paediatric HIV. We would encourage interested paediatricians to participate in our CME activities and to join our PDG by forwarding your e-mail address to the HIV Clinicians Society.

**Leon Levin**


REFERENCES

1. Centres for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in paediatric practice. *MMWR* 1998; 47: 1-43. Published and updated regularly on the **web www.hivatis.org**
2. Scaling up Antiretroviral Therapy in Resource -limited settings. Guidelines for a public Health Approach. Executive summary April 2002. **www.who.int**
3. Sharland M, Castelli G, Ramos JT, Blanche S, Gibb DM. On behalf of the PENTA Steering Committee Penta Guidelines for the use of Antiretroviral Therapy in Paediatric HIV Infection, **www.ctu.mrc.ac.uk/PENTA/**


Antiretroviral therapy (ART) is becoming an increasing option in paediatric practice. Promoting affordable ART for children is a priority for clinicians, health administrators and the pharmaceutical industry.

The use of ART in children is a highly specialised field. Initial and ongoing management of HIV-infected children by a paediatrician experienced in this field is strongly recommended. If this is impossible, we recommend consultation with such a paediatrician before initiation of ART so that the child may benefit from the most optimal regimen. Certainly a clinician who decides to change therapy should consult with an experienced treater in order to ensure maximum efficacy of the new regimen.

ART in children follows the same principles as in adults, but generally lags behind in terms of its application. The reasons for this are complex and include a reluctance to use new medication in children before efficacy and safety have been confirmed in adults, the need to develop liquid formulations, and the need for age-specific pharmacokinetic data. As a result, there are fewer therapeutic options available for children.

## VIRAL DYNAMICS: PERSPECTIVES IN CHILDREN

Viral loads in children are far higher in the first year of life than those in adults and only decline to adult values by 5 - 6 years of age. By 2 months of age most HIV-infected infants have viral loads above 100 000 RNA copies/ml plasma ranging from undetectable to 10 million copies/ml. The mean viral load in the first year of life is 185 000 copies/ml.[1] Generally, the higher the viral load, the more rapid disease progression, although in children there is considerable variability.

Viral load assays are of value in monitoring ART in order to assess the efficacy of the regimen. A combination of viral load assay and CD4+% is most predictive of mortality, as indicated in Table I.[2]

**TABLE I. BASELINE CD4+% AND HIV COPY NUMBER: RISK OF DEATH**

| HIV RNA (copies/ml) | Baseline CD4+% | Patients (*N*) | Deaths (%) |
|---|---|---|---|
| < 100 000 | >15 | 103 | 15 |
| | <15 | 24 | 63 |
| > 100 000 | >15 | 89 | 36 |
| | <15 | 36 | 81 |

Mean age 3.4 years, mean follow-up 5.1 years.[2]

## GOALS OF THERAPY[3]

As in adults, the goals of paediatric ART are:.

- restoration or preservation of immunological function (usually measured with CD4+ lymphocyte cell count)
- improvement in clinical symptoms
- reduction in morbidity and mortality
- maximal and durable suppression of viral load.

The overall objective of therapy is to enhance the quality and quantity of life and to promote physical, social and intellectual development of the child in the context of a functional family. A practical goal is to avoid hospitalisation by minimising the impact of intercurrent disease, thus keeping the child with his/her family. Finally, the wellbeing of a child impacts positively on the parents' well being and a healthy parent is vital to the child.

Even in the absence of antiretrovirals (ARVs)

- good supportive care
- aggressive treatment of intercurrent infections
- provision of nutritional support, and
- prevention of opportunistic infections promote significant improvement in quality of life and survival.

## IS THERE A ROLE FOR MONOTHERAPY?

Monotherapy is not recommended because of lack of sustained benefit and the superior efficacy of combination therapy.

## COMBINATION THERAPY

As in adults, a combination of at least three drugs is considered optimal therapy. The higher viral loads in children may make suppression of plasma HIV RNA to below the limits of detection more difficult to achieve than in adults.

While triple therapy is the most common regimen, quadruple therapy in children under 1 year of age with high viral loads may have a role.

The rationale for combination therapy is to increase the likelihood of achieving undetectable plasma HIV RNA, thereby minimising the possibility of viral breakthrough and resistance. However, even partial viral suppression is usually accompanied by an improved clinical outcome.

Where cost or adherence is an issue, there may be a role for dual nucleoside therapy, especially in children with less advanced disease. However, the durability of such a regimen is likely to be limited.

## ADHERENCE

Adherence to ART is vital for a successful outcome. The factors that impact on adherence are:

- Affordability of ART. Before initiating therapy, treaters should ascertain whether the parents/caregiver can afford a proposed regimen over a prolonged period of time.
- Motivation and commitment of caregiver/parent to the child's lifelong therapy. Adherence involves administering every dose of medication 1 - 3 times daily, every day of every year. Weekends away, schooling and other parental obligations need to be anticipated and planned for.
- Parental/caregiver understanding that poor adherence is the single most important factor associated with drug failure and resistance, and implies loss of future therapeutic options.

*NOTE:*

- Good adherence should be emphasised at each visit. It is useful to compare ART with therapy for diabetes and hypertension, both of which may require lifelong therapy and where poor adherence is associated with disease progression.
- In addition, the treater should be aware that the doses will probably need to be modified at each visit as the child gains weight and grows.
- It is useful to dispense the antiretroviral drugs yourself or else to have them delivered to your rooms in order to keep track of those patients who are not collecting their medications on time. This could alert you to a potential adherence problem.

## CLASSIFICATION OF HIV IN CHILDREN

**The Centers for Disease Control have utilised both clinical and immunological parameters for paediatric practice (Tables II and III).[4]**

## INDICATIONS FOR STARTING ART

Highly active antiretroviral therapy (HAART) should be used whenever possible for the best clinical results and to prevent resistance.

There are two distinct clinical settings in infants:

- Where HIV infection has been confirmed in an infant < 3 months of age whose mother is HIV-positive, by one qualitative polymerase chain reaction (PCR) test followed by a quantitative viral load test.
- Where HIV is identified later, either because of symptomatic disease in the infant or child, or because of a positive diagnosis in the mother.

**TABLE II. CLINICAL CATEGORIES FOR CHILDREN WITH HIV INFECTION**

| Category | Characteristics |
|---|---|
| N | No signs or symptoms considered to be the result of HIV infection, or only 1 condition listed in A |
| A (mild) | Two or more conditions listed below but none from B or C:<br>• Lymphadenopathy (≥ 0.5 cm at more than 2 sites; bilateral = 1 site)<br>• Hepatomegaly<br>• Splenomegaly<br>• Parotitis<br>• Dermatitis<br>• Recurrent or persistent upper respiratory tract infections, sinusitis, or otitis media |
| B (moderate) | Symptomatic conditions other than from A or C and attributed to HIV infection, including but not limited to:<br>• Anaemia (< 8 g/dl), neutropenia (< 1 000/µl), thrombocytopenia (< 100 000/µl) - persisting ≥ 30 days<br>• Bacterial meningitis, pneumonia or sepsis (single episode)<br>• Candidiasis, persisting > 2 months in children > 6 months of age<br>• Cardiomyopathy<br>• Cytomegalovirus (CMV) infection, onset < 1 month of age<br>• Diarrhoea, recurrent or chronic<br>• Hepatitis<br>• Herpes simplex virus (HSV) stomatitis > 2 episodes within a year<br>• HSV bronchitis, pneumonitis or oesophagitis with onset < 1 year of age<br>• Herpes zoster (shingles) ≥ 2 episodes or > 1 dermatome<br>• Leiomyosarcoma<br>• Lymphoid interstitial pneumonitis (LIP) or pulmonary lymphoid hyperplasia complex<br>• Nephropathy<br>• Nocardiosis<br>• Persistent fever (> 1 month)<br>• Toxoplasmosis, onset < 1 month of age<br>• Varicella, disseminated |
| C (severe) | Any condition listed below:<br>• Serious bacterial infections, multiple or recurrent (at least 2 culture-confirmed episodes within a 3-year period): septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity<br>• Candidiasis (oesophageal or pulmonary)<br>• Coccidioidomycosis (disseminated)<br>• Cryptococcosis (disseminated)<br>• CMV disease with onset at age > 1 month (at site other than lymph nodes, spleen, liver)<br>• Encephalopathy<br>• HSV causing mucocutaneous ulcer persisting > 1 month, or bronchitis, oesophagitis, pneumonitis, oesophagitis in a child > 1 month<br>• Histoplasmosis (disseminated)<br>• Kaposi's sarcoma<br>• Lymphoma: primary in brain, Burkitt's, immunoblastic, large cell, B cell or unknown<br>• *Mycobacterium tuberculosis* (disseminated or extrapulmonary)<br>• *M. avium* complex or *M. kansasii* (disseminated)<br>• *Pneumocystis carinii* pneumonia<br>• Progressive multifocal leucoencephalopathy<br>• Salmonella septicaemia (recurrent)<br>• Cerebral toxoplasmosis with onset > 1 month of age<br>• Wasting syndrome in the absence of illness other than HIV that could explain the following: persistent weight loss > 10% of baseline, or downward crossing of at least 2 of the following percentiles on a weight-for-age chart (95th, 50th, 25th, 5th) in a child ≥ 1 year of age; or < 5th centile weight for height on 2 consecutive measurements ≥ 30 days apart plus (1) chronic diarrhoea (≥ 2 loose stools per day ≥ 30 days); or (2) documented fever ≥ 30 days, intermittent or constant |

## INDICATIONS FOR ART IN CHILDREN

- Clinical category B (except for single episode of bacterial sepsis or single episode of herpes zoster) or C

*or*

- CD4% < 20%.

In any child, it may be beneficial to wait until adherence can be assured and the family has been adequately counselled and are ready for the rigors of ART.

## INITIATION OF THERAPY

### FIRST 1 - 2 VISITS

Blood samples should be taken for HIV viral load and CD4+ count. Counselling and information – topics to be covered include:

- HIV prognosis
- treatment
- adherence
- drug formulations
- taste issues (including taste test where appropriate).

### NEXT VISIT

Graphically illustrate the drugs and how and when to take them, preferably with actual drugs or samples.

### 1 - 2 WEEKS LATER

A phone call to the caregiver/parent is recommended to discuss tolerance and adherence issues.

### ONE MONTH AFTER STARTING TREATMENT

A general examination should be conducted by the clinician and blood tests carried out to monitor drug toxicity. Tolerance and adherence issues should be discussed.

### THREE MONTHS AFTER STARTING TREATMENT

A general examination should be conducted by the clinician and blood tests carried out to monitor drug toxicity. Blood samples should be taken for HIV viral load and CD4+ count.

Adverse effects, tolerance and adherence issues should be discussed with the caregiver.

### THREE-MONTHLY THEREAFTER

A general examination should be conducted and blood tests carried out to monitor drug toxicity, the HIV viral load and CD4+ count. If the patient's results remain stable, clinical examinations and blood tests can be carried out 6- monthly.

Discuss adverse effects, tolerance and adherence issues with caregiver.

## MONITORING: SPECIAL CONSIDERATIONS FOR CHILDREN

### VIRAL LOAD

The percentage of children on triple therapy who achieve and maintain a plasma viral load of below 400 copies/ml varies from approximately 25% to 75%.[5-8]

Therapeutic options for children are limited. Because ART is currently a lifelong commitment, it may be preferable not to switch ARVs until the CD4% or count consistently drops or

**TABLE III. IMMUNOLOGICAL CATEGORIES FOR CHILDREN WITH HIV INFECTION**

| | Age of child | | | | | |
|---|---|---|---|---|---|---|
| | < 12 months | | 1 – 5 years | | 6 – 12 years | |
| Immunological category | CD4+/ml | CD4+% | CD4+/ml | CD4+% | CD4+/ml | CD4+% |
| 1. No immunosuppression | > 1 500 | ≥ 25 | ≥ 1 000 | ≥ 25 | ≥ 500 | ≥ 25 |
| 2. Moderate immunosuppression | 750 - 1 499 | 15 - 24 | 500 - 999 | 15 - 24 | 200 - 499 | 15 -24 |
| 3. Severe immunosuppression | < 750 | < 15 | < 500 | < 15 | < 200 | < 15 |

definite evidence of clinical failure has occurred. Such evidence includes:

- failure to thrive
- reappearance of 'refractory' oral candidiasis
- other intercurrent disease such as cryptosporidial diarrhoea, invasive bacterial sepsis or neuro-developmental deterioration.

*NOTE:*

- *For children on triple therapy, viral suppression of < 10-fold (1 log) and dual NRTI therapy < 5-fold (0.7 log) may not be adequate.*
- *In children who have responded with durable but not absolute viral suppression, a reproducible increase > 3-fold (0.5 log) in children ≥ 2 years and 5-fold (0.7 log) in infants < 2 years may be an indication to change ARVs.*
- *A repeat test is recommended whenever a routine measurement yields an unexpected result.*
- *Additional non-routine testing may be indicated if the clinical condition changes.*
- *Two measurements one month apart should be performed before instituting changes.*
- *Viral loads can be temporarily raised for up to a month after intercurrent infections or vaccinations.*
- *Patients should be sequentially tested using the same method and the same laboratory.*

### CD4+ LYMPHOCYTE COUNTS AND PERCENTAGES

The CD4+ count should be measured whenever the viral load is determined, except when the viral load is repeated to verify an unexpected result. CD4+ lymphocyte counts are much higher in infancy than adulthood but the CD4+ percentage remains relatively constant. CD4%s may be easier to work with, but CD4+ counts should also be used and knowledge of normal values for age is a prerequisite. A CD4% below 15% should be viewed in the same light as a CD4+ count < 200/µl in adults (see Table III).

In South Africa, some laboratories use a non-standardised method of determining CD4% (CD4 count/CD3 count) and some do not provide a CD4%. In these cases, the CD4 count must be divided by the total lymphocyte count (from the full blood count) to obtain the CD4%. Please contact your pathologist in this regard.

CD4+ counts are useful for monitoring response to ARVs. A falling CD4 count or CD4% may be a more important reason to change therapy than a rising viral load. CD4+ counts can be temporarily lowered due to intercurrent infections or vaccinations and can take up to a month to recover.

Although there is a strong association between CD4+% and the risk of opportunistic diseases, *Pneumocystis carinii* pneumonia in the first year of life may occur despite 'normal' counts for age.

It is important that all HIV-infected or HIV-exposed children under 1 year of age should receive co-trimoxazole prophylaxis from 6 weeks of age. This can be stopped at 1 year if the CD4+% is >20%, or when HIV infection has been reasonably excluded.

### HEIGHT AND WEIGHT

The 'Road to Health' chart is a valuable tool for monitoring the well-being of children. Failure to maintain growth is suggestive of progressive HIV disease or superimposed infection such as tuberculosis.

## RECOMMENDED ARV REGIMENS

### CHILDREN UNDER 3 MONTHS OF AGE (TABLE IV)

Recent data suggest that if treated aggressively these children can achieve viral suppression and normal immunity in a high percentage of cases.[9] This is presumably because we are dealing with primary HIV infection in these infants. However, there are other issues that need to be considered before subjecting an infant < 3 months of age to lifelong therapy. The following implications should be considered:

- there is a lack of HIV-specific immune response
- long-term toxicity
- resistance to antiretroviral drugs
- increased cost of treatment
- need for four-drug regimens to achieve virological control with accompanying increased toxicity, cost and resistance.

The decision to initiate ART must therefore only be taken after counselling and consultation with caregivers and, where applicable, health care funders. Generally speaking, most babies < 3 months of age should not be on treatment unless they fulfil the indications for starting ART detailed above.

**TABLE IV. RECOMMENDED ARV REGIMENS IN CHILDREN UNDER 3 MONTHS OF AGE**

| | |
|---|---|
| Category I (NRTI - thymidine base) | Stavudine (d4T)<br>Zidovudine (ZDV) |
| Category II (NRTI - other) | Didanosine (ddI)<br>Lamivudine (3TC) |
| Category III (NRTI) | Nevirapine (NVP) |
| Category IV (PI) | Ritonavir (RTV)<br>Nelfinavir (NFV) |
| Category V (NRTI – new) | Abacavir (ABC) |

### Suggested drug regimens

- **3 NRTIs** (one from category I, one from category II, ABC (category V))
  **plus**
  **1 PI** (one from category IV).[9]
- **3 NRTIs** (one from category I and one from category II, ABC (category V))
  **plus**
  **NVP.**[9,10]
- **2 NRTIs**
  **plus**
  **1 PI**
  **plus**
  **1 NNRTI**
  (one each from categories I - IV).[9]

*NOTE:* Although very potent, this last regimen leaves few alternatives available for future use and should only be considered in special circumstances.

**TABLE V. DOSAGE OF ARVs IN INFANTS UNDER 3 MONTHS OF AGE (SEE TABLE VII FOR STORAGE AND COMMENTS)**

| Drug | Formulation | Dosage |
|---|---|---|
| NRTI | | |
| Zidovudine (ZDV) Retrovir® | Susp. 10 mg/ml | 4 mg/kg/dose tds until 29 days, then 160 mg/m²/dose tds |
| Didanosine (ddI) Videx® | Susp.10 mg/ml Tabs 25 mg | 50 mg/m²/dose bd |
| Stavudine (D4T) Zerit® | Susp. 1 mg/ml | < 29 days: 0.5 mg/kg/dose bd<br>> 30 days: 1 mg/kg/dose bd |
| Abacavir (ABC) Ziagen® | Susp. 20 mg/ml | 8 mg/kg/dose bd |
| Lamivudine (3TC®) | Susp. 10 mg/ml | < 1 month: 2 mg/kg/ dose bd<br>> 1 month: 4 mg/kg/ dose bd |
| NNRTI | | |
| Nevirapine Viramune® | Susp. 10 mg/ml | 5 mg/kg/day x 14 days then 120 mg/m²/dose bd x 14 days then 200 mg/m²/dose bd |
| PI | | |
| Ritonavir (RTV) Norvir® | Susp. 80 mg/ml | > 1 month 450 mg/m²/dose bd |
| Nelfinavir (NFV) Vira-cept® | Powder 50 mg/g Tabs 250 mg | 55 - 65 mg/kg/dose bd |

A four-drug regimen may be more effective than the standard three-drug regimen because of extremely high viral loads in young infants, but should only be contemplated if parental commitment is obtained. This regimen will have long-term financial impact, as costs will increase dramatically as the child grows. The efficacy of downscaling to a three-drug regimen awaits further studies. If cost constraints make the above regimens impractical, refer to regimens for children over 3 months of age (next section).

Dosages for infants under 3 months of age are set out in Table V (once the infant reaches 3 months of age, follow the dosages in Table VII).

## CHILDREN OVER 3 MONTHS OF AGE (TABLE VI)

**TABLE VI. CHILDREN OVER 3 MONTHS OF AGE**

| | |
|---|---|
| Category I (NRTI - thymidine base) | Stavudine (d4T)*<br>Zidovudine (ZDV)* |
| Category II (NRTI – other) | Didanosine (ddI)*<br>Lamivudine (3TC)*†<br>Abacavir (ABC)* |
| Category III (NNRTI‡) | Nevirapine (NVP)*†<br>Efavirenz (EFV)†‡ |
| Category IV (PI) | Ritonavir (RTV)*<br>Nelfinavir (NFV)*<br>Lopinavir/ritonavir (LPV/RTV)*<br>Saquinavir (SQV) soft gel<br>Indinavir (IDV) |

*Available in paediatric formulations.
†Require single mutation for development of resistance and therefore some experts only use them in regimens with a good chance of attaining undetectable viral loads.
‡(Efavirenz (EFV) is only available in capsule form. There are no data for children under 3 years of age.

### Preferred regimens

- **2 NRTIs** (1 each from categories I and II [or 3TC + ABC]) **+ 1 PI** (category IV)
- **2 NRTIs + EFV or NVP** (1 each from categories I, II and III) (or 3TC + ABC + EFV or NVP)

*NOTE:* EFV and NVP develop resistance rapidly if undetectable viral loads are not achieved; they should only be used for viral loads < 150 000 copies/ml.

### Alternative regimens

- **1 NRTI + EFV or NVP + 1 PI** (1 each from categories I or II, + III + IV)

*NOTE:* Although very potent, this regimen leaves few alternatives available for future use and should only be considered in special circumstances.

- **ABC + ZDV + 3TC** – for children with low viral loads.

### DUAL NRTI: REGIMEN WHERE THERE ARE COST CONSTRAINTS

These regimens are more affordable but are sub-optimal therapy; however, they may be of benefit in children with less severe disease:

**d4T + ddI**
**ZDV + ddI**
**ZDV + 3TC***
**d4T + 3TC***

*Some experts only use 3TC where there is a good chance of attaining undetectable plasma HIV RNA.

## DRUG INTERACTIONS OF NOTE

There are multiple opportunities for serious drug interactions. Treaters are advised to scrutinise package information and seek advice if uncertain.

- Efavirenz causes reduced levels of clarithromycin, but not azithromycin.
- Ritonavir should not be given with cisapride, midazolam and numerous other drugs.

## TABLE VII. DOSAGE AND FREQUENCY OF ARVs IN CHILDREN

| Drug | Formulations | Dosage (per dose) | Frequency | Storage | Comments |
|---|---|---|---|---|---|
| **Nucleoside reverse transcriptase inhibitors (NRTIs)** | | | | | |
| Zidovudine (ZDV) Retrovir® | Susp. 10 mg/ml<br>Caps 100 mg, 250 mg<br>Tabs 300 mg | 90 - 180 mg/m²<br>180 mg/m² | 3<br>2 | Room temperature | |
| Didanosine (ddI) Videx® | Susp. 10 mg/ml<br>Tabs 25 mg, 50 mg, 100 mg, 150 mg | 90 - 120 mg/m² | 2<br>Can give total daily dosage x 1 in older children | Refrigerate suspension | Half h before meals or 1 h after meal<br>Use single daily dose if necessary for adherence |
| Stavudine (d4T) Zerit® | Susp. 1 mg/ml<br>Caps 20 mg, 30 mg, 40 mg | 1 mg/kg | 2 | Refrigerate suspension | Capsules stable in water suspension for 24 h in refrigerator |
| Abacavir Ziagen® | Susp. 20 mg/ml<br>Tabs 300 mg | 8 mg/kg | 2 | Room temperature | WATCH FOR HYPERSENSITIVITY REACTION. DO NOT RECHALLENGE AFTER HYPERSENSITIVITY REACTION |
| Lamivudine (3TC®) | Susp. 10 mg/ml<br>Tabs 150 mg | 4 mg/kg | 2 | Room temperature | |
| **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** | | | | | |
| Nevirapine Viramune® | Susp. 10mg/ml<br>Tabs 200 mg | 120 - 200 mg/m²<br>Start at 120 mg/m² daily for 14 days and increase to bd dosage 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<br>WATCH FOR LIVER TOXICITY |
| Efavirenz Stocrin® | Caps 50 and 200 mg (susp. available from manufacturer) | 13 - < 15 kg: 200 mg<br>15 - < 20 kg: 250 mg<br>20 - < 25 kg: 300 mg<br>25 - < 32.5 kg: 350 mg<br>32.5 - <40 kg: 400 mg<br>> 40 kg: 600 mg | 1 | Room temperature | Na data < 3 yrs and < 13 kg. Give at night to avoid CNS side-effects |
| **Protease inhibitors** | | | | | |
| Ritonavir Norvir® | Susp. 80 mg/ml | Start at 250 mg/m²/dose and increase by 50 mg/m² every 2 - 3 days up to 400 mg/m². If < 2 years of age 450 mg/m² | 2 | | Take with food. Bitter; coat mouth with peanut butter or give with chocolate milk. Take 2 h apart from didanosine |
| Nelfinavir Vira-cept® | Susp. 50 mg/1 g spoon and 200 mg per teaspoon<br>Tabs 250 mg | Paediatric: 55 mg/kg (adolescent: 750 mg tds or 1 250 bd)<br>Some experts use 35 - 45 mg/kg/ dose tds > 2 yrs of age<br>45 - 55 mg/kg/dose tds < 2 yrs of age | 2 | | Give 2 h before or 1 h after ddI. Best with light meal. Do not use with rifampicin. Powder is 5% active drug and the rest is carrier powder. Most experts prefer to crush the tablets and suspend in milk or water or sprinkle on pudding |
| Lopinavir/ ritonavir Kaletra® | Oral solution 80 mg Lopinavir (LPV) & 20 mg ritonavir (RTV) per ml<br>Caps 133 mg LPV/33 mg RTV | Patients not taking NVP or EFV – 230 mg LPV component/m² (max. 400 mg LPV = adolescent dose)<br>Patients taking NVP or EFV or ART experienced – 300 mg LPV component /m² (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 2 months | Administer with food. High-fat meal increases absorption, especially of the liquid preparation.<br>If co-administered with ddI, ddI should be given 1 h before or 2 h after lopinavir/ritonavir |
| Saquinavir<br>Invirase® – hard gel capsule<br>Fortovase® – soft gel capsule | Hard gel caps (HGC) 200 mg (only use together with RTV)<br>Soft gel caps (SGC) 200 mg | Single PI (SGC only) – 50 mg/kg<br>Dual PIs<br>SQV 50 mg/kg<br>RTV 100 mg/m²<br>Adolescent 1 200 mg *or* 1 600 mg | 3<br><br>2<br>2<br>3<br>2 | | Administer within 2 h of a full meal to increase absorption. Sun exposure can cause photosensitivity reactions; therefore, sunscreen or protective clothing is recommended |

Body surface area (m²) = $\sqrt{\text{height (cm) x weight (kg)}} \div 60$

- Rifampicin reduces levels of indinavir, nelfinavir and saquinavir (protease inhibitors) and nevirapine and should not be used together with any of these drugs.

The following drugs are metabolised by cytochrome P450 (CYP3A4), hence there is the possibility of multiple interactions:

Protease inhibitors (PIs)
- Saquinavir
- Ritonavir
- Nelfinavir
- Indinavir

NNRTIs

- Nevirapine
- Efavirenz

*NOTE*: However, NVP + IDV decrease individual drug levels.

## ADDITIONAL PRACTICE POINTS

### HYDROXYUREA IN CHILDREN

As a result of increased toxicity (pancreatitis, peripheral neuropathy and bone marrow suppression) in adults, there is no current role for hydroxyurea (HU) in the routine management of HIV-infected children. Although limited data suggest that HU may be better tolerated in children, HU should not be used until more data are available.

### NUCLEOSIDE ANALOGUES

Resistance to nucleoside analogues is slow to develop, with the exception of 3TC. Resistance to 3TC arises within weeks when the drug is used in a regimen that fails to suppress viral replication fully. For this reason many experts recommend the use of 3TC only in 3-drug combinations. 3TC resistance may, however, sensitise HIV to the antiviral activity of ZDV, but the durability of this effect is uncertain.

All nucleoside analogues have been associated with lactic acidosis, a rare but potentially life-threatening metabolic complication of treatment. The pathogenesis is believed to involve drug-induced mitochondrial damage.

A recent study showed that the combination of abacavir and 3TC together with a PI, yielded a very potent antiretroviral regimen with favourable implications for future options.[11] However, this combination is very costly indeed.

### HAART AFTER FAILED MTCT PROPHYLAXIS

- **Where nevirapine was used as a single dose in MTCT prophylaxis.** In the HIVNET 012 study, up to 45% of HIV-infected infants had resistance mutations against NVP after 1 dose of NVP to mother and the infant.[12] There are no data on the significance of these resistance mutations. Until such data become available it may be prudent to avoid nevirapine and efavirenz as part of combination therapy in this situation.
- **If AZT monotherapy was used in MTCT prophylaxis,** data support the use of AZT as part of combination therapy in infected infants.[13-15]
- **If AZT and 3TC were used as dual therapy for MTCT prophylaxis,** avoid 3TC only if the mother had a prolonged course of treatment without adequate viral suppression. In a study by Mandelbrot *et al.* it was associated with M184V resistance mutation in 2 of 5 infants.[16] However, in the usual short courses used for MTCT (< 4 weeks), it would be acceptable to use 3TC in the HIV-infected infant.
- **If the mother was on triple combination therapy,** where possible avoid the drugs the mother was taking, especially if the mother had a detectable viral load. If unavoidable, it is advisable to get resistance testing done on the mother first and only use those drugs to which her virus is sensitive. If the mother had a undetectable viral load, then it is probably acceptable to use the same agents in her HIV-infected baby.

### TB TREATMENT AND HAART IN CHILDREN

As a result of the interaction between rifampicin and the PIs and the NNRTIs, one needs to modify the TB treatment or the ART or both. It is important to diagnose TB accurately to avoid unnecessarily jeopardising the success of the ART.

*Options:*

- Ideally delay initiation of ART until after course of TB treatment. (Allow 2 weeks for the effects of rifampicin on the liver to 'wash out'.)[17]
- If not possible, then delay ART for at least 1 month of TB treatment to prevent immune reconstitution disease.[17]
- Use standard TB treatment together with ARVs compatible with rifampicin, i.e. 2 NRTIs + either ritonavir or efavirenz (children > 3 years).[17,18] The efavirenz dose should be increased by 30% (personal communication – Prof Courtney Fletcher).
- Use standard TB treatment with a triple NRTI regimen,[17] e.g. ZDV/3TC/ABC (this combination is only effective with low viral loads).

**TABLE VIII. SIDE-EFFECTS OF ARVs IN CHILDREN**

| Class | Drug | Side-effects |
|---|---|---|
| NRTI | ZDV (Retrovir®) | Anaemia, granulocytopenia<br>Myopathy, lactic acidosis |
| | ddI (Videx®) | Common: abdominal pain, nausea and vomiting<br>Uncommon: pancreatitis, peripheral neuropathy, lactic acidosis |
| | Stavudine (Zerit®) | Common: headache, rash, gastrointestinal<br>Uncommon: pancreatitis and peripheral neuropathy, lactic acidosis |
| | Abacavir (Ziagen®) | Hypersensitivity reaction (with or without rash) – may be fatal in adults and children, fever, rash, fatigue, nausea, vomiting, diarrhoea, pharyngitis, dyspnoea and cough, elevated ALT, creatinine or CPK, lymphopenia<br>Lactic acidosis |
| | Lamivudine (3TC®) | Common: headache, fatigue and abdominal pain<br>Uncommon: pancreatitis and peripheral neuropathy, lactic acidosis |
| NNRTI | Nevirapine (Viramune®) | Skin rash, sedative effect and diarrhoea. LIVER TOXICITY |
| | Efavirenz (Stocrin®) | Skin rash<br>CNS – sleep disturbance, confusion, abnormal thinking. Teratogenic in primates |
| PI | Ritonavir (Norvir®) | Nausea, vomiting, diarrhoea<br>Hypercholesterolaemia and hypertriglyceridaemia |
| | Nelfinavir (Vira-cept®) | Diarrhoea<br>Can exacerbate chronic liver disease. Hypercholesterolaemia and hypertriglyceridaemia |
| Ribo-nucleotide reductase inhibitor | Hydroxyurea (Hydrea®) | Granulocytopenia, anaemia<br>Withdrawn from ARV studies because of reports of fatal pancreatitis in patients on combination therapy<br>Side-effects more common in patients with advanced disease |

**TABLE IX. TANNER STAGING FOR BOYS**

| Stage | Pubic hair | Penis | Testes |
|---|---|---|---|
| 1 | None | Pre-adolescent | Pre-adolescent |
| 2 | Scanty, long, slight pigmented | Slight enlargement | Enlarged scrotum, pink texture altered |
| 3 | Darker, starts to curl, small amount | Longer | Larger |
| 4 | Resembles adult, less than adult | Larger, glans and breadth increase size | Larger, scrotum dark |
| 5 | Adult distribution spread to medial surface of thighs | Adult | Adult |

**TABLE X. TANNER STAGING FOR GIRLS**

| Stage | Pubic hair | Breasts |
|---|---|---|
| 1 | Pre-adolescent | Pre-adolescent |
| 2 | Sparse, lightly pigmented, straight, medial border labia | Breast and papilla elevated as small mound; areola diameter increased |
| 3 | Darker, beginning to curl, increased amount | Breast and areola enlarged, no contour separation |
| 4 | Coarse, curly, abundant but less than adult | Areola and papilla form 2° mound |
| 5 | Adult feminine triangle, spread to medial surface of thighs | Mature; nipple projects, areola part of general breast contour |

- Use rifabutin instead of rifampicin (difficult to obtain and very expensive); ritonavir should not be used with rifabutin.[17,18]

## REDUCING THE COST OF HAART IN CHILDREN IN SOUTH AFRICA

- Cheapest NRTIs are d4T, ddI.
- Cheapest PIs are RTV, LPV/RTV, IDV, SQV.
- NNRTIs (EFV and NVP tablets) are relatively cheap.
- Suspensions are more expensive than tablets/capsules.
- ddI can be given once daily – aiding adherence and reducing cost.
- d4T capsules are stable in suspension for 24 hours and can very often be used in place of the more expensive d4T solution.

## SPECIFIC ISSUES FOR ADOLESCENTS

- Adult guidelines are appropriate for post-pubertal adolescents (Tanner stage V) (Tables IX and X).
- For adolescents in early puberty (Tanner stage I and II) use paediatric guidelines.
- For intermediate puberty, monitor closely and choose either adult or paediatric guidelines.
- Non-compliance is problematic and strategies should be introduced to promote adherence, including more frequent visits and intensive counselling.

### Changing therapy

- In case of toxicity or intolerance, a simple substitution can be made.
- When failure is due to viral resistance, at least two drugs should be charged.
- Since future options are limited, whether to change and choice of new regimen should only be made by an experienced clinician.
- Consult the HIV Clinicians Society.


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RECOMMENDED READING

Centres for Disease Control and Prevention. Guidelines for the use of antiretroviral agents in paediatric practice. *MMWR* 1998; **47:** 1-43. Published and updated regularly on the web **www.hivatis.org**

Sharland M, Castelli G, Ramos JT, Blanche S, Gibb DM. On behalf of the PENTA Steering Committee Penta Guidelines for the use of Antiretroviral Therapy in Paediatric HIV Infection, **www.ctu.mrc.ac.uk/PENTA/**


DISCLAIMER: Specific recommendations provided in this document are intended only as a guide to clinical therapy, based on expert consensus and best current evidence.
Recommended drugs and dosages are based on current available data and may differ from dosages recommended by manufacturers. Treatment decisions for patients should be made by their responsible clinicians with due consideration for individual circumstances. The most current version of this document should always be consulted.


GUIDELINES FOR ANTIRETROVIRAL THERAPY IN CHILDREN – October 2002 VERSION
Chairman – Dr Leon Levin; Expert Panel Members – Drs Razia Bobat, Mark Cotton, Glenda Gray, Leon Levin, Tammy Meyers, Avye Violari; International Reviewers – Prof Mark Kline, Drs Elaine Abrams, Diana Gibb, Ann Melvin
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