GUIDELINES FOR ANTIRETROVIRAL THERAPY IN CHILDREN – NOVEMBER 2009 VERSION

These guidelines are intended to provide paediatric HIV antiretroviral treatment (ART) recommendations for both the public and private sectors.

ART in children follows the same principles as in adults, and treaters should not be daunted by some of the differences, which include more frequent dose adjustments, liquid formulations occasionally being poorly palatable, and the dependence of children on adult caregivers for receiving medication. These should not be viewed as obstacles, and everything should be done to assist the process of treating children.

Since the last publication of these guidelines there have been pivotal paediatric studies that have necessitated the updating of paediatric guidelines in South Africa.

1. GOALS OF THERAPY

- Durable suppression of viral load (VL) (undetectable VL using an ultrasensitive assay)
- Restoration or preservation of immunological function (CD4+ count)
- Sustained improvement in clinical symptoms and quality of life
- Reduction in morbidity and mortality.

1.1 FAMILY TREATMENT

Since HIV is usually a disease occurring within families, the following are important:

- Always enquire about the health and HIV status of the caregivers and other family members.
- Encourage and assist caregivers to start ART if required; ideally families should receive treatment simultaneously in the same facility to avoid inconvenience and unnecessary expense for patients.
- HIV testing should be offered and recommended for other family members if their status is unknown.
- Ascertain and encourage HIV disclosure status of caregivers themselves, the child and other family members.

2. ADHERENCE

High levels of adherence to antiretroviral therapy (ART) are vital for treatment success. The goal is for the patient to receive 100% of scheduled doses. Factors that impact on adherence include:

- Parental/caregiver education: they must understand that poor adherence is the single most important factor for drug failure and resistance, leading to loss of future therapeutic options.
- A good health care provider-patient relationship underpins adherence.
- Motivation and commitment of caregiver/parent to the child's lifelong therapy.
- Address any social issues as appropriate.
- Although unpredictable events can acutely impact on adherence (e.g. severe illness or death of a parent), frequent visits and good communication may help to anticipate and pro-actively plan for such events

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TALKING ABOUT ADHERENCE

Working with the client

A short checklist of points should include:

- Checking caregiver's capacity to understand treatment plan/adherence (intellectual/developmental level, literacy)
- Checking the basic facts about ART
- Explaining adherence and why it is important
- Explaining common ART side-effects and likely course
- Explaining that symptoms associated with other illnesses (i.e. vomiting, diarrhoea, cough, fever, rash) overlap with drug toxicity and are not a reason to stop therapy. However, if an acute illness (acute gastro-enteritis) occurs and the child is unable to tolerate medications, it is permissible to stop all meds for a short period of time
- Exploring the caregiver's readiness to start the child on antiretroviral therapy
- Assessing the level of commitment to ART adherence
- Assessing the caregiver's perception of the advantages and disadvantages of being on ART.

Discussion should include an assessment of the caregiver's psychosocial situation. This covers:

- Exploration of the caregiver's lifestyle (e.g. work, daily routine, sleep, other responsibilities)
- Exploration of the caregiver's personality traits (e.g. sense of organisation, self-discipline and responsibility)
- Assessment of the caregiver's own HIV status and health and lifestyle choices (use of alcohol and drugs) (remember – HIV infection in adults not yet on ART can cause cognitive impairment)
- Possible use of alternative/complementary medicine
- Exploration of the caregiver's financial and material resources.

It is also necessary to explore possible barriers to adherence as well as sources of support, including:

- Discussion around disclosure (e.g. how much the child knows about own status/how much other household members know about child's status/reasons for not wanting to disclose to child/others if applicable). Disclosure is an evolving process requiring an active plan and involvement of the parent/caregiver
- Exploration of the current and potential sources of support
- Problem solving with regard to barriers
- Anticipation of events that might present an obstacle to adherence, e.g. school trips, visits to grandparents.

Finally, a specific adherence plan is developed in collaboration with the client (and child where appropriate). The plan should specify:

- The treatment regimen (specifics of medication, doses and the intervals at which the medication should be given). Remember that the same drug may have many names (formula, generic, trade, fixed-dose combinations), which may be confusing to patients and families
- Possible side-effects, what to do and who to contact in the case of serious side-effects
- Ways of integrating treatment into the daily routine of the caregiver/child, especially the specific times the medication will be given.

The plan should be individualised and the health care professional is encouraged to provide practical aids and supportive information sheets. Demonstration of dosage and method of administration by the counsellor as well as by the caregiver is important.

Social disruption or catastrophic events can happen at any time and could affect adherence. Events such as loss of a caregiver or severe illness in a caregiver should be mentioned, with possible solutions.

Tips

In the case of school-age children and adolescents, it is important that adult caregivers are available to supervise. Routine is reassuring: caregivers should try to give medication in the same way, at the same time and in the same place every day. Caregivers should be encouraged to:

- Remind the child that medicines are important and will help to keep him or her from getting sick.
- Be positive and consistent when it comes to giving the child medicine.
- Always say something positive when the child has taken his/her medication.
- Reward the child with a sticker or a star on a record chart or calendar or other age-appropriate token.
- Allow the child to earn a special treat for sticking to his/her schedule (e.g. a small weekly treat and a bigger monthly treat. Avoid monetary rewards; a story or a favourite meal is more than adequate).
- Get other people who care about the child to encourage and reward him/her for taking medication.
- Anticipate and talk about possible problems before they arise.
- Be flexible with the treatment plan. Accommodate change (e.g. in the scheduled time of doses) if this would result in better adherence.
- Think of possible simplification of the regimen.
- Ask about any side-effects. Suggest ways to manage less serious side-effects and indicate the likelihood of relatively short duration.
- Ask about other medication that the child may be taking in order to avoid possible drug interactions and better co-ordinate dosing of all medications.
- Anticipate possible adherence fall-off during times of increased stress. Make time to discuss and deal with problems and feelings.
- Vomiting after taking medication: make sure that the caregiver knows that if a child vomits within 30 minutes of taking a medication the dose should be repeated.

Some tools and strategies

- Setting an alarm on an alarm clock
- Setting a cell phone alarm or reminder
- Using a pillbox
- Using a diary card
- Using a wall calendar
- Keeping a treatment diary
- Sending SMS reminders to the caregiver
- Using daily TV or radio programmes as cues
- Using mealtime (breakfast and supper) as a cue
- Having a treatment supporter
- Having a treatment buddy (another child, also on treatment)
- Keeping medication in a familiar place and not hidden or locked up
- Using directly observed treatment support (DOTS) as for TB if needed.

Additional factors enhancing adherence include:

- Children should be taught to swallow pills/capsules as early as possible (from about 4 years). This can be done using appropriately sized sweets. Liquid formulations may have an unpleasant taste or involve administering large volumes of liquids.
- Ideally the caregiver should identify and disclose to one other person in the home who can help with treatment (treatment buddy) as a back-up and enhance treatment support.
- Dosages of liquid formulations should be rounded up to a convenient volume.
- Syringes for liquid formulations should be marked at the correct dosage with a blade or permanent marker. Show the caregiver how to draw up the correct volume and expel excess air. Make sure that the syringes are appropriately cleaned.
- Each liquid medicine and its syringe should be colour-coded to prevent confusing medicines and dosages.
- Ensure that the caregiver's eyesight is adequate to administer medication accurately.
- Teach caregivers to open childproof containers.
- Medications should fit into the patient's lifestyle. For example, twice-daily medication does not have to be given strictly 12-hourly, rather at a convenient time. It is far better to give a dose later than usual than not to give the medication at all.
- Too many caregivers involved in administering medicines can be an obstacle to good adherence. A different caregiver accompanying the child to

each appointment is a warning sign, requiring exploration.

- Emphasise good adherence at each visit. It is useful to compare ART with therapy for diabetes and hypertension, both conditions requiring lifelong therapy and in which poor adherence is associated with disease progression. HIV is a chronic, manageable condition, with minimal morbidity, if the correct approach is taken.
- It is useful to monitor whether treatment is being collected.

3. INDICATIONS FOR STARTING ART IN CHILDREN

First assess the child clinically and stage the child according to the World Health Organization (WHO) Staging System (Table I) to determine whether the child needs ART or not (*note:* all infants diagnosed <12 months of age should be started on ART regardless of clinical or immunological staging). If the child is clinically well, CD4 testing will further ascertain whether the child needs ART.

TABLE I. WHO CLINICAL STAGING OF HIV/AIDS FOR CHILDREN WITH CONFIRMED HIV INFECTION

CLINICAL STAGE 1
Asymptomatic
Persistent generalised lymphadenopathy

CLINICAL STAGE 2
Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Extensive wart virus infection
Extensive molluscum contagiosum
Fungal nail infections
Recurrent oral ulcerations
Unexplained persistent parotid enlargement
Lineal gingival erythema
Herpes zoster
Recurrent or chronic upper respiratory tract infections
(otitis media, otorrhoea, sinusitis or tonsillitis)

CLINICAL STAGE 3
Unexplained moderate malnutrition not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.5°C intermittent or constant for longer than one month)
Persistent oral candidiasis (after first 6 - 8 weeks of life)
Oral hairy leukoplakia
Acute necrotising ulcerative gingivitis or periodontitis
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8 g/dl), neutropenia ($<0.5\times10^9$/l) and/or chronic thrombocytopenia ($<50\times10^9$/l)

CLINICAL STAGE 4i
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (such as empyema, pyomyositis, bone or joint infection or meningitis but excluding pneumonia)
Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site)
Extrapulmonary tuberculosis
Kaposi's sarcoma
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after 1 month of life)
HIV encephalopathy
Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than 1 month
Extrapulmonary cryptococcosis (including meningitis)
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis)
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated non-tuberculous mycobacterial infection
Cerebral or B-cell non-Hodgkin's lymphoma
Progressive multifocal leuco-encephalopathy
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy
HIV-associated rectovaginal fistula

The CHER Study[1] demonstrated that:

- By 6 weeks of age 20% of infants already had severe immunosuppression.
- In relatively asymptomatic infants, starting ART before 3 months of age reduced the mortality rate by 76%.

As a result of this research, all international ART guidelines now recommend immediate ART for all HIV-positive infants <12 months of age, irrespective of the clinical or immunological status (Table II). In the infant, ART should be started as soon as possible after diagnosis, preferably within 2 weeks.

4. INITIATION OF THERAPY

Note: **For young infants initiation of treatment should be rapid, with ongoing counselling while on ARVs.**

4.1 FIRST 1 – 2 VISITS

Full clinical examination, including accurate baseline weight, height, and for children <2 years, head circumference measurement. Bloods should be taken for HIV VL and CD4+ count.

Counselling and information – topics to be covered include:

- HIV prognosis
- Treatment options
- Adherence
- Drug formulations
- Taste issues (including taste test where appropriate)
- Initiate prophylaxis as indicated
- Ensure family/caregivers have contact details for staff in case of any questions/adverse events.

4.2 NEXT VISIT

If therapy is indicated and if the family is adequately counselled and able to continue to maintain adherence, dispense drugs. Graphically illustrate the drugs and how and when to take them, preferably with actual drugs or samples. Consider observing initial administration of the drugs.

TABLE II. CRITERIA FOR ART INITIATION

Age	Clinical stage	CD4 criteria
<1year	All infants	Any CD4
1 - 5 years	WHO stage III, IV	CD4 ≤25% Absolute CD4 <750 cells/µl
>5 years	WHO stage III, IV	CD4 <350 cells/µl

4.3 DAY 2 OF TREATMENT

If possible, a quick phone call to make sure that everything is in order is a good idea.

4.4 1 – 2 WEEKS LATER

A phone call to the caregiver/parent is recommended to discuss tolerance and adherence issues. The government roll-out programme recommends a 2-week visit where adherence is discussed and medication technique is checked.

4.5 ONE MONTH AFTER STARTING TREATMENT

The clinician should conduct a general examination and draw blood to monitor drug toxicity (in national Department of Health (NDoH) guidelines, only if on tuberculosis (TB) treatment or on zidovudine (AZT)).

Tolerance and adherence issues should be discussed. It may be useful to ask how many doses have been missed in the last 3 days, and how many in the last month.

In young children weight gain can be surprisingly rapid. Check whether doses need to be increased.

4.6 THREE MONTHS AFTER STARTING TREATMENT

The clinician should conduct a general examination and draw blood to monitor drug toxicity. Check weight and alter doses accordingly.

Bloods should also be taken for HIV VL and CD4+ count. In the NDoH guidelines, bloods would only be drawn if clinically indicated for suspected toxicity, if on AZT or if co-treated for TB.

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

4.7 THREE-MONTHLY THEREAFTER

The clinician should conduct a general examination and draw blood for drug toxicity, HIV VL and CD4+ count. NDoH guidelines recommend 6-monthly bloods with 3-monthly clinical checks. Check weight and alter doses accordingly. If the patient's results remain stable, clinical examinations and blood tests can be carried out 6-monthly, but children aged less than 2 years need to be seen at least 3-monthly to adjust drug doses according to growth.

Discuss adverse effects, tolerance and adherence issues with the caregiver at every visit.

5. MONITORING: SPECIAL CONSIDERATIONS FOR CHILDREN (TABLE III)

5.1 VIRAL LOAD

Recent reports on outcomes on ART of children from resource-poor centres demonstrate that undetectable VLs are initially achieved in over 80% of treatment-naïve children.[2]

VLs should be measured at baseline and then 3 - 6-monthly. In the NDoH guidelines VL testing is recommended at 6-monthly intervals unless there is a clinical indication to do it earlier. A recent meta-analysis suggests that VL monitoring at intervals of ≥3 months was associated with a significantly lower risk of resistance mutations at the time of failure.[3]

Therapeutic options for children are currently limited. The decision to switch therapy because of suboptimal response should therefore be carefully considered and balanced against the risk of accumulating additional resistance in a non-suppressive regimen.

Although there is no consensus, a growing number of international experts advise aggressively achieving and maintaining viral suppression.

Note:

- A repeat test is recommended whenever a routine measurement yields an unexpected result. It is usually not worth doing routine plasma HIV RNA levels during an intercurrent infection. Additional non-routine testing may be indicated if the clinical condition changes.
- Two measurements should be performed 1 month apart before instituting changes.
- VLs can be temporarily raised for up to a month after intercurrent infection or vaccination.
- Patients should be sequentially tested using the same method and the same laboratory.
- The NDoH has decided to omit the baseline VL in order to save costs. Since the baseline VL doubles as a confirmatory test for infants diagnosed by PCR, it is strongly recommended that the baseline VL still be done in infants diagnosed by PCR.

5.2 CD4+ LYMPHOCYTE COUNTS AND PERCENTAGES

The CD4+ count should be measured with the VL, except when the VL is repeated for an unexpected result. Absolute CD4+ lymphocyte counts are much higher in infancy than adulthood, but the CD4+ percentage is more constant, although also higher in children <2 years. CD4+ percentages may be easier to work with, but CD4+ counts should also be used. Over the age of 5 years, adult cut-offs using CD4 counts can be used for therapeutic decision making. Lymphopenia and lymphocytosis may over- or understate CD4 percentages or counts.

CD4+ counts/percentages are useful for monitoring response to ARVs. VL changes will typically precede changes in CD4 counts. CD4+ counts can be temporarily lowered by intercurrent infections or vaccinations, taking up to a month to recover.

Although there is a strong association between CD4+ depletion and opportunistic diseases, *Pneumocystis jirovecii* pneumonia (PCP) may occur in the first year of life despite 'normal' counts for age.

5.3 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 TB.

TABLE III. ROUTINE MONITORING

Test	Baseline	2 weeks (NVP)	1 month*	3 months*	6 months	3 – 6–monthly thereafter*	Additional annual tests
Viral load	X†			X	X	X	
CD4	X			X	X	X	
FBC with differential	X		X	X	X	X	
ALT	X	X	X	X	X	X	
Cholesterol							X
Triglycerides							X
Glucose							X
Urine dipstix	X						X

*NDoH guidelines recommend 6-monthly monitoring.
†NDoH guidelines recommend **not** to do a baseline VL as a cost-saving practice. It is imperative that a baseline VL be 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.

6. RECOMMENDED ARV REGIMENS

ART drugs are listed in Table IV, and dosages in Table V. Simplified weight-based dosing is set out in Fig. 1.

6.1 PREFERRED REGIMENS

First line

<3 years: 3TC + abacavir + lopinavir/ritonavir.

>3 years *and* >10 kg: 3TC + abacavir + efavirenz.

Alternate first line

<3 years: 3TC + stavudine + lopinavir/ritonavir.

>3 years *and* >10 kg: 3TC + stavudine + efavirenz.

This is the regimen currently recommended by the NDoH. There are major concerns about d4T toxicity, especially lipodystrophy. Stavudine should be changed to ABC at the first sign of lipodystrophy. In addition, zidovudine as part of second-line therapy will be compromised by resistance to stavudine.

Consider a boosted PI as the third drug in a child over 3 years exposed to SD-NVP or where there are concerns about adherence.

TABLE IV. ART DRUGS

Category I NRTI – thymidine base	Stavudine (d4T)* Zidovudine (ZDV)*
Category II NRTI – other	Didanosine (ddI)*† Lamivudine (3TC)* Emtricitabine (FTC) Abacavir (ABC)*
NtRTI	Tenofovir (TDF)†
Category III NNRTI	Nevirapine (NVP)* Efavirenz (EFV)¶ Etravirine (ETR)§
Category IV PI	Ritonavir (RTV)* Lopinavir/ritonavir (LPV/RTV)* Saquinavir (SQV) Indinavir (IDV)‡ Darunavir (DRV)§ Atazanavir (ATV)‡ Fosamprenavir (FPV)
Category V Integrase inhibitors	Raltegravir§
Category VI CCR5 inhibitors	Maraviroc§

*Available in paediatric formulations.
†Enteric-coated formulation for adults can be used (especially when given once instead of twice daily).
‡Not available in paediatric formulation.
¶EFV is only available in capsule form and tablet form. There are no data for children under 3 years of age or <10 kg.
§Paediatric dosage still uncertain. Requires Section 21 authorisation from the Medicines Control Council.
NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

Rationale for choice of regimen

3TC and ABC backbone:

- Very good long-term data from PENTA 5.[4]
- Spares thymidine analogue for next regimen.
- Both drugs select for the same resistance pathway (M184V).
- ABC should only be used for first line (without genotyping) since >3 TAMS + M184V confers high level cross-resistance to ABC.
- Hypersensitivity is linked to HLA B*5701, which is extremely uncommon in the black population. The ARROW study of >1 200 HIV-infected children in Uganda and Zimbabwe had a hypersensitivity reaction rate of 0.2%.
- Tenofovir should not be used in children because of potential toxicity issues.

Lopinavir/ritonavir in children <3 years

Data show that young children have far better viral suppression on a boosted PI regimen than on an NNRTI regimen[5] (irrespective of single-dose NVP). In addition the IMPAACT P1060 study indicates that in SD-NVP-exposed infants, those starting NVP-based regimens have poorer virological outcomes than those starting a boosted PI regimen.[6]

7. DRUG INTERACTIONS

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

- Rifampicin reduces levels of lopinavir, indinavir, saquinavir, atazanavir, fosamprenavir (PIs) and nevirapine and should not be used with any of these drugs.
- Efavirenz causes reduced levels of clarithromycin, but not azithromycin.
- Ritonavir should not be given with numerous drugs.
- Of the anti-epileptic drugs, sodium valproate is the safest to use with antiretrovirals.
- Ritonavir inhibits cytochrome P450 3A4, preventing metabolism of inhaled steroids, thereby facilitating systemic absorption and Cushing's syndrome. Rather use an NNRTI if the patient is on inhaled or nasal steroids, or consult the HIV Clinicians Society if this is not feasible.
- Oral contraceptives. There are limited data available on potential drug interactions between many ARVs (particularly some NNRTIs and RTV-boosted PIs) and hormonal contraceptives, which may modify their safety and effectiveness. RTV-boosted PIs are not recommended with combined or

TABLE V. DOSAGE AND FREQUENCY OF ARVs IN CHILDREN

Drug	Formulations	Dosage (per dose)	Frequency	Storage	Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)					
Zidovudine (AZT, ZDV) Retrovir® generics	Susp: 10 mg/ml Caps: 100 mg, 250 mg, tabs 300 mg	Neonates 4 mg/kg/dose until 29 d, then 240 mg/m^2	2 2	Room temperature	May be taken with or without food
Didanosine (ddI) Videx® generics	Susp: 10 mg/ml Tabs: 25 mg, 50 mg, 100 mg, 150 mg Enteric-coated didanosine (EC) 250 mg, 400 mg	2 wks - 3 mo. of age: 50 - 100 mg/m^2/dose >3 mo. of age: 90 - 120 mg/m^2/dose	2 2 Can give total daily dosage × 1	Refrigerate suspension	Half hour before or 1 hour after meal Use single daily dose if necessary for adherence. Give at least 2 tabs of buffered formulation. Needs to be separated from PI by 1 - 2 hours. EC ddI still needs to be taken on empty stomach but can be given together with PI EC ddI capsules can be opened and sprinkled on food
Stavudine (d4T) Zerit® generics	Susp: 1 mg/ml Caps: 15 mg, 20 mg, 30 mg, 40 mg	Neonates <2 wks of age: 0.5 mg/kg/dose thereafter 1 mg/kg/dose (max 30 mg/dose)	2 2	Refrigerate suspension	May be taken with or without food. Capsules stable in water suspension for 24 hours at room temperature
Abacavir (ABC) Ziagen® generics	Susp: 20 mg/ml Tabs: 300 mg Kivexa® tabs = 600 mg ABC & 300 mg 3TC	All ages: 8 mg/kg/dose ≥25 kg: 1 tab or 2 tabs Kivexa® If ≥25 kg – 1 tab	2 2 1 1	Room temperature	May be taken with or without food **Watch for hypersensitivity reaction (HSR). Do not rechallenge if HSR occurs** If being given as suspension with 3TC, the two volumes should always be equal
Lamivudine 3TC (3TC®) generics	Susp: 10 mg/ml Tabs: 150 mg, 300 mg Kivexa® tabs = 600 mg ABC & 300 mg 3TC	Neonates: 2 mg/kg Paediatric (>1 month): 5 - 6 mg/kg ≥25 kg: 1 × 150 mg tab or 2 × 150 mg tab or 1 × 300 mg tab	2 2 2 1 1	Room temperature	May be taken with or without Can food use tablets from 25 kg
Nucleotide reverse transcriptase inhibitors (NtRTIs)					
Tenofovir (TDF) Viread®	Tablets 300 mg Truvada® = 300 mg TDF + 200 mg FTC Atripla®* = 300 mg TDF + 200 mg FTC + 600 mg EFV*	8 mg/kg/dose 8 mg/kg/dose of TDF component	1 1	Room temperature	**Should not be routinely used in children <18 years –** concerns about osteopenia and renal toxicity. May have a place in salvage in older children. Consult with a paediatric HIV expert. Viread tablets irregular shape – difficult to halve. May be taken with or without food. Dose adjustment required with renal impairment
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Nevirapine (NVP) Viramune® generics	Susp: 10 mg/ml Tabs: 200 mg	Infants (>14 days) and children: 150 - 200 mg/m^2/dose Give dose once daily for first 14 days and increase to bd if no rash or severe side-effects occur	2	Room temperature	May be taken with or without food Skin rash usually occurs in 1st 6 weeks; do not increase dosage until rash resolves **Watch for liver toxicity** Try to maintain dosage >150 mg/m^2/dose bd

TABLE V. DOSAGE AND FREQUENCY OF ARVs IN CHILDREN (CONTINUED)

Drug	Formulations	Dosage (per dose)	Frequency	Storage	Comments
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)					
Efavirenz (EFV) Stocrin® generics	Tabs: 50 mg, 200 mg, 600 mg Caps: 50 mg, 200 mg	10 - <15 kg: 200 mg 15 - < 20 kg: 250 mg 20 - <25 kg: 300 mg 25 - <32.5 kg: 350 mg 32.5 - <40 kg: 400 mg >40 kg: 600 mg	1	Room temperature	No data <3 yrs and <10 kg Tablets cannot be crushed. Use generic capsules in children unable to swallow tablets. Capsules can be opened & given with food Give at night to avoid CNS side-effects **Anticipate** mild transient rash and CNS side-effects
Protease inhibitors (PIs)					
Atazanavir (ATV) Reyataz®	Capsules:150 mg, 200 mg	From 6 years of age: 205 mg/m^2 6 - 18 years: 15 - <25 kg: ATV 150 mg + RTV 80 mg 25 - <32 kg: ATV 200 mg + RTV 100 mg 32 - <35 kg: ATV 300 mg + RTV 100 mg >35 kg: ATV 300 mg + RTV 100 mg, both given once daily with food	1		**Ideally** should always be used with RTV boosting (unboosted ATV requires a higher dose and gives unpredictable plasma levels) Give with food Unconjugated hyperbilirubinaemia may occur and as long as the patient is comfortable with it, is not a reason to discontinue the drug
Fosamprenavir (fAPV) Telzir®	Tablets 700 mg Oral suspension, 50 mg/ml	2 - 5 years: 20 mg/kg/dose (max. dose 700 mg) + RTV 3 mg/kg/dose (max. dose 100 mg) 6-18 years: 18 mg/kg/dose (max. dose 700 mg) + RTV 3 mg/kg/dose (max. dose 100 mg)	2 2 2 2	Room temperature	**Ideally** should always be used with RTV boosting (unboosted fAPV requires a higher dose) Give suspension with food and tablets with or without food
Lopinavir/ritonavir (LPV/r) Kaletra® Aluvia®	Oral solution (Kaletra®) 80 mg Lopinavir (LPV) & 20 mg ritonavir (RTV) per ml Kaletra® capsules 133 mg LPV/33 mg RTV Aluvia® tablets 200 mg LPV/50 mg RTV Aluvia® half-dose (HD) tablets* 100 mg LPV/25 mg RTV	300 mg/m^2/dose LPV component (max. 400 mg LPV = adolescent dose)	2	Capsules should be refrigerated Oral solution should be refrigerated until dispensed Can be kept at room temperature up to 25°C if used within 6 weeks Aluvia tabs can be stored at room temperature	Aluvia® tabs can be given with or without food. Aluvia tabs **must** be swallowed whole Crushing the tabs reduces the absorption of the drugs Kaletra Solution and Capsules: administer with food. High-fat meal increases absorption, especially of the liquid preparation If co-administered with buffered ddI, ddI should be given 1 hour before or 2 hours after lopinavir/ritonavir Aluvia® can be taken with EC didanosine on an empty stomach Dose adjustments required if LPV/r used in combination with NNRTIs Kaletra® Capsules are being discontinued

progesterone-only oral contraceptives, while NNRTIs can be used. A combined oral contraceptive containing at least 30 µg of ethinyl oestradiol should be used. Progesterone-only injectables can be used with all ARVs. Concomitant consistent condom use is recommended for preventing HIV transmission

TABLE V. DOSAGE AND FREQUENCY OF ARVs IN CHILDREN (CONTINUED)

Drug	Formulations	Dosage (per dose)	Frequency	Storage	Comments
		Protease inhibitors (PIs)			
Ritonavir (RTV) Norvir®	Susp: 80 mg/ml Capsules: 100 mg	**No longer recommended for use as full-dose single PI** >1 mo.: 350 - 450 mg/m²/dose For pharmacological boosting of other PIs: see individual PI concerned **Boosting dose of RTV when used with rifampicin and LPV/r:** same dose in mg as LPV. Alternatively ¾ (volume) of Kaletra dose	2 2 2		Take with food Bitter: coat mouth with peanut butter or give with chocolate milk. Take 2 hours apart from didanosine Can be taken together with EC didanosine
Saquinavir (SQV) Invirase® – hard gel capsule	Hard gel capsules (HGC) 200 mg (only use together with RTV)	SQV 50 mg/kg RTV 100 mg/m² Adolescent /adult SQV 1 000 mg RTV 100 mg	2 2 2 2		Should always be used with RTV boosting Administer within 2 hours of a full meal to increase absorption Sun exposure can cause photosensitivity reactions; sunscreen or protective clothing recommended

*Awaiting MCC approval. Available with Section 21 authorisation.
Body surface area (m^2) = $\sqrt{(\text{height (cm)} \times \text{weight (kg)} \div 3\,600)}$.

and to compensate for any possible reduction in the effectiveness of the hormonal contraceptive.

- LPV/r co-administration can increase tenofovir levels by 30%, and may result in increased renal and bone toxicity.

The following website may be of assistance in assessing potential interactions:

http://www.hiv-druginteractions.org/frames.asp?drug/drg_main.asp

8. ADDITIONAL PRACTICAL POINTS

8.1 PRACTICAL DOSING

Although paediatric dosages are calculated using the child's weight or surface area, one must consider the practicalities of the dose. For example, 1.75 ml is very difficult to measure accurately, so a more practical dose is 2 ml (generally round upwards). Certain ARV solutions, e.g. LPV/RTV (Kaletra) or RTV (Norvir) are highly concentrated, so dosages do need to be calculated to the nearest 1/10th of a ml (but it is not necessary to calculate to the nearest 1/100th of a ml). Others, e.g AZT, 3TC, NVP (Viramune) or ABC (Ziagen) solutions, can quite safely be rounded up to the nearest ml. The volume of 3TC and ABC should always be the same, which makes dosing easier for caregivers. When using d4T capsules dissolved in water, dosages can be rounded up to the nearest 5 mg. Every effort should be made to switch to tablets or capsules as soon as possible. Certain drugs should still rather be dosed according to surface area, but where this is difficult the weight-based chart (Fig. 1) can be used.

Kivexa

Kivexa is a fixed-dose combination tablet containing 300 mg 3TC and 600 mg ABC. It is dosed as 1 tablet once a day and can be given to children >25 kg who can swallow this large tablet. It is particularly useful in older children to facilitate adherence.

Atazanavir (Reyataz)

ATV is a useful PI. It has the advantage of minimal lipid disturbances (although RTV boosting will cause some elevations of cholesterol and triglycerides). It should generally always be given with RTV boosting. Its advantages include once-daily dosing, a low pill burden and a good safety and tolerability profile. For this reason ATV may be a preferable alternative to Aluvia in PI-naïve older children in the private sector with adherence issues. It is best not to use ATV in PI-experienced patients unless one knows that no or limited PI mutations are present.

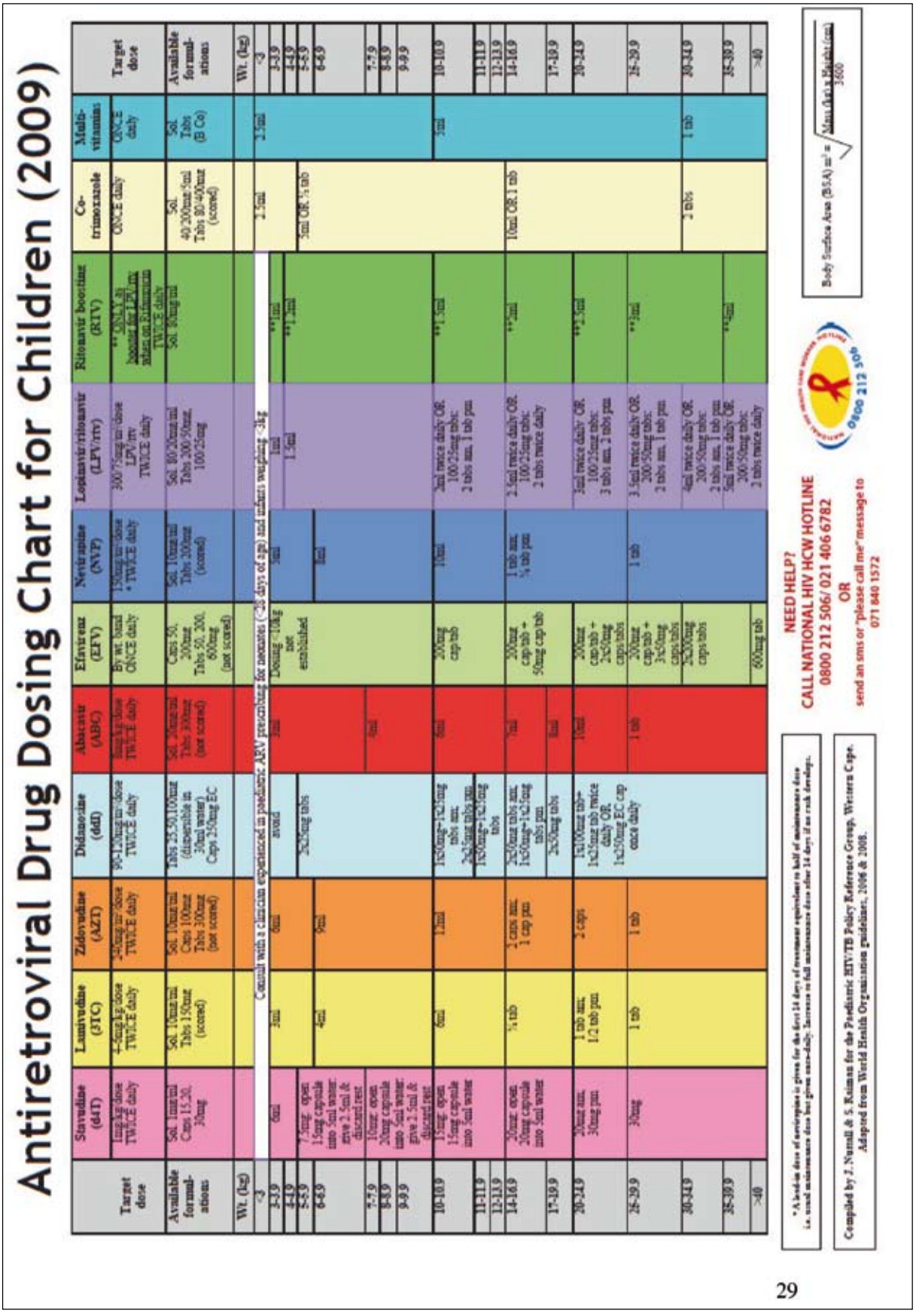

Fig. 1. Weight-based dosing chart.

8.2 TIMING OF DOSING

There is a common misconception that ARVs need to be given exactly 12 hours or 24 hours apart. This is because older drugs with very short half-lives needed to be dosed exactly on time. However, there is much more flexibility with the drugs in current use. Drugs with twice-daily doses can generally be given between 10 and 14 hours apart. For drugs that are dosed with meals, the best approach is to give them strictly twice daily with breakfast and supper. It is clearly much more important to fit the drugs into our patients' lifestyles than vice versa.

8.3 HAART AFTER FAILED MTCT PROPHYLAXIS

- **Where nevirapine was used as a single dose in prevention of mother-to-child (PMTCT) prophylaxis.** In the HIVNET 012 study, up to 45% of HIV-infected infants had NNRTI-associated resistance mutations after 1 dose of NVP to the mother and the infant. There are good data in adults and infants suggesting reduced efficacy of future NNRTI-containing highly active antiretroviral therapy (HAART) regimens. Results from P1060 also indicate that in children who have been exposed to NNRTIs for PMTCT, there is an increased risk of virological failure when NVP is used subsequently for treatment.[6] It is therefore advisable to avoid nevirapine and efavirenz as part of first-line therapy in this situation.
- **If AZT monotherapy was used in MTCT prophylaxis.** Data support its use in combination therapy for infected infants. Resistance has, however, been described.
- **If the mother was on triple combination therapy.** In this situation, do genotyping on the baby and design a regimen accordingly. If unable to do genotyping, avoid the drugs the mother was taking, especially if she had a detectable VL. If the mother had an undetectable VL, it is probably acceptable to use the same agents in her HIV-infected baby.

8.4 TUBERCULOSIS TREATMENT AND HAART IN CO-INFECTED CHILDREN

Rifampicin increases the breakdown of PIs and NNRTIs. Also, there are overlapping toxicities between TB drugs and ARVs. The immune reconstitution inflammatory syndrome (IRIS) causes morbidity and higher risk of mortality. IRIS can be misinterpreted as progression of TB or medication side-effects. In addition, the increased pill burden can impact on adherence.

Options

When to start ARVs:

- Since TB is a clinical stage 3 disease, most children will need to be started on ART. ART should be initiated 2 - 4 weeks after starting TB treatment. This may reduce the likelihood of immune reconstitution disease and will allow time to identify early adverse events from anti-TB drugs.
- If the CD4 count is normal and the child is >12 months old, initiation of ART may be delayed until completion of TB treatment. (Allow 2 weeks for the effects of rifampicin on the liver to 'wash out'.)
- If the child is already on ART when TB is diagnosed, continue ART with TB treatment. Monitor for IRIS and adapt ARVs as required.

What regimen to use:

- Try to make a bacteriological diagnosis. Submit all sputa and gastric washings for mycobacterial culture. All isolates require speciation into *Mycobacterium tuberculosis* and *M. bovis*-BCG and drug susceptibility testing. Make every effort to exclude multidrug-resistant (MDR) TB in the patient and in the source case.
- Use standard TB treatment (i.e. a rifampicin-based regimen).
- ARV regimens:

  >3 years: 2 NRTIs + efavirenz (standard dose)

  <3 years: 2 NRTIs + superboosted LPV/RTV 300 mg/m^2/dose bd + extra ritonavir (dosed at 0.75 × volume of LPV/r) bd to achieve per mg equivalence for LPV and RTV).

If RTV is not available, one can consider giving LPV/r 600 mg/m^2/dose bd. However, one should revert to superboosted LPV/RTV when RTV becomes available. The efficacy and toxic side-effects of this approach are unknown. Recent pharmacokinetic data show that super-boosted LPV/r yields good levels of LPV whereas simply doubling the dose yields suboptimal levels.[7]

8.5 SPECIFIC ISSUES FOR ADOLESCENTS

These issues apply to both vertically and sexually transmitted HIV.

- Non-adherence is often a problem, and strategies should be introduced to promote adherence, including more frequent visits and intensive counselling.
- Adult supervision of treatment should continue throughout adolescence and includes verification that the medicine has been swallowed.
- Disclosure of HIV status must have occurred before onset of sexual activity.
- Adolescent-friendly services include:
  - A specific convenient day set aside for adolescent clinics
  - Adolescent groups and peer support groups
  - Access to family planning, sexually transmitted infection (STI) treatment, cervical cancer prevention and screening and gynaecological services
  - Human papillomavirus vaccination.

8.6 CHANGING THERAPY

For toxicity or intolerance, a simple substitution can be made, being mindful of previous therapies that may have failed. Do not reduce dosage unless the reduced dose is still in the therapeutic range.

For failure of a regimen, proceed as outlined below.

Failure of first-line therapy

If viraemia occurs, even at a low level, check and encourage adherence. Also check dosages or other 'technical problems'. These include vomiting or spitting out medications and not receiving meds on time.

If the VL is persistently >5 000 copies/ml on two or three occasions despite good adherence and technical problems having been resolved, consider changing regimens. Be sure to resolve the adherence problems before changing therapy, otherwise the second regimen will fail. On the other hand, continuing with a failing regimen results in ongoing viral replication with the development of new mutations and cross-resistance, thus limiting future options.

Resolving adherence issues is paramount for any child failing ART. In children on a PI-based first-line regimen, adherence interventions may be sufficient. On the other hand, failing an NNRTI-based regimen invariably requires a regimen change after resolving adherence issues. See below for choice of second-line regimen.

Since virological failure usually precedes immunological and clinical failure, by changing on virological criteria, one can hopefully prevent clinical and immunological deterioration.

When failure is due to viral resistance, at least two new active drugs should be used. Previous drug history and genotyping (see below) are helpful in deciding on a new regimen.

In the case of NNRTI resistance

- There is no place for maintaining patients failing an NNRTI regimen on the same regimen; the longer it is maintained, the more resistance mutations are likely to occur.
- The regimen should be changed to a boosted PI with 2 active NRTIs (based on genotyping if possible).

In the case of PI resistance

- Patients on a boosted PI regimen not suppressing may have no PI and minimal NRTI mutations, in which case the original regimen may be resumed after addressing the adherence issues.
- In NNRTI-naïve patients with no NNRTI and at least 2 fully active NRTIs on genotyping, a simple switch to 2 NRTIs + NNRTI may be appropriate.
- Patients with multiple PI mutations may achieve viral control when some of the newer agents not yet registered in South Africa are used. Consult an expert.

Failure of second-line or subsequent regimens

In this situation, consult an expert.

8.7 RESISTANCE

Nucleoside analogues

Resistance is slow to develop, except for 3TC. Resistance to 3TC occurs within weeks on a non-suppressive regimen. Useful benefits of 3TC resistance are the partial reversal of AZT, d4T and TDF resistance and rendering HIV less pathogenic (M184V mutation).

Non-nucleoside reverse transcriptase inhibitors

There is complete cross-resistance between the currently available NNRTIs. A patient resistant to NVP will also have resistance to efavirenz (despite what the genotyping indicates). This does not apply to the new second-generation NNRTI (not yet available in South Africa) etravirine, which needs a few NNRTI mutations for high-level resistance. For this reason, a patient failing an NNRTI should change regimens soon to prevent compromising this future option.

Protease inhibitors

The boosted PIs are very slow to develop resistance and need several mutations before high-level resistance occurs. In a PI-naïve patient who fails a boosted PI, it is generally accepted that resistance mutations do not occur over a short period of time. However, if a patient has PI mutations from previous PI failure, new mutations can occur even with a boosted PI.

Resistance testing

At present only genotypic resistance testing is available in South Africa. Genotyping is still expensive (±R4 400). Genotyping will only provide information about resistance to the current regimen, and not necessarily about previous ART the child may have been exposed to. For this reason genotyping needs to be interpreted in conjunction with a detailed ART history. The interpretation is complicated and should be done in conjunction with an expert. Ideally genotyping should be done in any child whose VL is persistently above 5 000 copies/ml despite good adherence. Genotyping is also indicated for infants infected despite maternal HAART, before starting ART. Contact the South African HIV Clinicians Society for further information on when to perform and interpreting genotyping.

8.8 CHOICE OF SECOND-LINE REGIMEN

Patient failing ABC/3TC/EFV or d4T/3TC/EFV

Second-line choice: AZT + ddI + LPV/r. Genotyping, if available, may suggest an easier alternative regimen. Discuss with an expert.

Patient failing ABC/3TC/LPV/r or d4T/3TC/LPV/r

Current NDoH guidelines recommend AZT + ddI + NVP (<3 years) or EFV (>3 years). Some experts feel that this regimen is prone to failure. It is advisable to do resistance testing and /or discuss with an expert to devise a suitable second-line regimen.

After changing regimens, there should be frequent adherence and toxicity checks.

8.9 SWITCHING FROM A PI- TO AN NNRTI-CONTAINING REGIMEN

Numerous adult studies and one paediatric study have demonstrated the feasibility of switching from a PI to an NNRTI once VLs are <50 copies/ml. This approach will avoid some long-term adverse effects of the PIs. Only consider if VLs are consistently <50 copies/ml and adherence is excellent. Where the mother and/or baby were given a single dose of NVP for PMTCT, switching should be avoided until further data are available.

8.10 INTERRUPTING THERAPY

Generally ART should not be stopped except on the advice of an expert. When it is necessary to stop or interrupt a regimen containing an NNRTI, be aware that the long half-life of the NNRTI will cause sub-therapeutic levels to persist for up to several weeks. Either continue the NRTIs for a week after stopping the NNRTI if feasible (for example if NNRTI-associated rash is suspected) or use a boosted PI for a week to avoid developing resistance to the NNRTI.

8.11 IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

IRIS is characterised by a paradoxical clinical deterioration after starting HAART. This results from rapid restoration of pathogen-specific immunity to opportunistic infections (OIs) and causes deterioration of an existing infection (paradoxical IRIS) or new clinical manifestations of a previously unrecognised subclinical infection (unmasking IRIS) during the early stages of ART. IRIS is usually associated with improvements in surrogate markers of HIV infection (virological, immunological, clinical). It may have distinct clinical presentations with pronounced inflammatory response. IRIS usually occurs within 6 months of starting HAART and in patients with a low starting CD4 count. The most common presentations in South African children include BCG adenitis, TB and herpes zoster.

Causes include *M. tuberculosis,* BCG, *M. avium* complex (MAC), *M. leprae*, *Cryptococcus neoformans, Aspergillus, Candida albicans, P. jirovecii*, cytomegalovirus (CMV), JC virus, human herpesviruses, herpes simplex virus, varicella zoster virus, human papillomavirus and hepatitis B and C viruses (HBV, HCV).

9. SELECTED ADVERSE EFFECTS OF ANTIRETROVIRAL DRUGS IN CHILDREN (TABLE VI)

ARVs are generally well tolerated in children. A few more serious adverse effects are mentioned here.

9.1 LACTIC ACIDOSIS

Lactic acidosis is a rare but serious, life-threatening complication of NRTI therapy, especially when ddI and d4T are used together. Symptoms include nausea and vomiting, abdominal pain, tachypnoea and dyspnoea, weight loss and fatigue. It may also cause neurological symptoms including a Guillain-Barré-like picture. There is no value in screening for lactic acidosis in asymptomatic children. Clinicians should be aware of the symptoms and diagnose the condition timeously. Diagnosis is confirmed with a serum lactate level >5 mmol/l, metabolic acidosis and a raised anion gap. Liver enzymes may be increased.

In patients with a lactate level >10 mmol/l or >5 mmol/l with metabolic acidosis, ART should be discontinued and supportive therapy instituted. Treatment (usually in an ICU) consists of intravenous fluids and ensuring oxygenation. Some reports suggest that alkalinising the blood with bicarbonate might improve prognosis, but this remains controversial. Other controversial treatments include thiamine (vitamin B_1), riboflavin (vitamin B_2) and L-carnitine (no data to show efficacy).

Following an episode of lactic acidosis, it may take several months for lactate levels and liver enzymes to normalise. Contact the HIV Clinicians Society for assistance in designing a new regimen after lactic acidosis.

9.2 HAEMATOLOGICAL TOXICITY

The two major agents are AZT and co-trimoxazole (usually only high-dose co-trimoxazole for treating PCP, but occasionally with prophylactic doses, and this is reversible with folinic acid – not folic acid).

Patients on AZT should have full blood counts (FBCs) monitored monthly for the first 3 months and 3-monthly thereafter. The main bone marrow toxicities from AZT are anaemia and neutropenia.

Anaemia may be due to HIV infection itself, or to AIDS-related conditions such as disseminated MAC, CMV or lymphoma. It may also be nutritional (e.g. iron or folate deficiency) or drug-related. Management depends on the underlying cause of anaemia, available options and the extent of the problem. It is reasonable to switch to a drug that causes fewer haematological side-effects,

TABLE VI. ADVERSE EFFECTS OF ARVs IN CHILDREN*

Class	Drug	Adverse effects
NRTIs	AZT (Retrovir®)	Anaemia, granulocytopenia, myopathy, lactic acidosis
	ddI (Videx®)	Common: abdominal pain, nausea and vomiting Uncommon: diarrhoea, pancreatitis, peripheral neuropathy, lactic acidosis
	Stavudine (Zerit®)	Common: headache, rash, gastro-intestinal, lipo-atrophy Uncommon: pancreatitis, peripheral neuropathy (adults), lactic acidosis
	Abacavir (Ziagen®)	Hypersensitivity reaction (with or without rash) – fever, rash, fatigue, nausea, vomiting, diarrhoea, pharyngitis, dyspnoea, cough Elevated ALT, creatinine or CK. Lymphopenia Lactic acidosis
	Lamivudine (3TC®)	Well tolerated. Common: headache, fatigue and abdominal pain Uncommon: lactic acidosis
NtRTIs	Tenofovir (Viread®)	More common: nausea, diarrhoea, vomiting, flatulence Less common: osteomalacia, renal toxicity, lactic acidosis
NNRTIs	Nevirapine (Viramune®)	Skin rash, sedative effect and diarrhoea. Liver toxicity
	Efavirenz (Stocrin®)	Skin rash. CNS – sleep disturbance, confusion, abnormal thinking Teratogenic in primates, but prospective data in humans are reassuring (no higher than background fetal malformation rate). May be implicated in breast enlargement (lipomastia)
PIs	Ritonavir (Norvir®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy
	Atazanavir (Reyataz®)	Common: unconjugated hyperbilirubinaemia – usually mild and does not warrant discontinuing drug. Has less effect on lipids than other PIs but RTV boosting may affect lipids
	Lopinavir/ritonavir (Kaletra®)(Aluvia®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy
	Fosamprenavir (Telzir®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy. Less common (more severe): life-threatening rash, including Stevens-Johnson syndrome, in <1% of patients, neutropenia, elevated serum creatinine kinase levels
	Saquinavir (Invirase®)	Nausea, vomiting, diarrhoea. Hypercholesterolaemia and hypertriglyceridaemia, lipodystrophy

ALT = alanine transaminase; CK = creatine kinase.
*See section 9.

e.g. switch from ZDV to d4T or ABC. A haemoglobin level below 7 – 8 g/dl warrants investigation and treatment. Nutritional deficiencies, especially iron, should be addressed.

Neutropenia is quite common before or on HAART. Unless severe, $<0.25\times10^9$/l, neutropenia often resolves spontaneously (providing there are no associated signs such as persistent fever or localised infection) and a repeat FBC should be done a week later. If neutropenia is severe, $<0.25\times10^9$/l, the offending agent should be replaced if feasible.

9.3 RASHES

Most rashes following ARVs are mild to moderate and resolve spontaneously with drug continuation. Most rashes are either maculopapular or urticarial. The most severe rashes include Stevens-Johnson syndrome, toxic epidermal necrolysis, ABC hypersensitivity, and the drug rash with eosinophilia and systemic symptoms (DRESS) reported with NNRTIs.

The highest prevalence of drug rashes occurs with the NNRTIs (more severe and more frequent with NVP). Rash usually occurs in the first 2 - 4 weeks of treatment. The rash is usually maculopapular and erythematous.

NVP is given daily for the first 2 weeks and only increased to twice daily once the rash has resolved. Mild to moderate rashes will often resolve spontaneously but must be closely monitored. Oral antihistamines can be used in mild to moderate cases.

In children who develop severe rash, cutaneous bullae or target lesions, mucosal lesions or systemic symptoms, NVP

should be permanently discontinued and hospitalisation is required.

If NVP is discontinued for mild or moderate rash, restarting NVP after the rash has resolved may be considered with close monitoring.

Cross-reactivity among NNRTIs may occur. Therefore avoid EFV after a severe rash. However, in children with mild or moderate rash without mucosal involvement or systemic symptoms, EFV may be substituted with caution.

Rashes may occur in children receiving EFV. These rashes are usually less severe than those with NVP, and resolution during treatment continuation is common. However, if EFV-associated rash is severe, or is accompanied by mucosal or systemic symptoms, EFV should be permanently discontinued.

9.4 HYPERSENSITIVITY SYNDROME

ABC and NVP are most commonly implicated.

ABC hypersensitivity reaction occurs in 4 - 8% of patients but is less common in black Africans. There is a 100% correlation between skin patch test-positive reactions and HLA B*5701. HLA B*5701 is rare in black Africans. Hypersensitivity reaction *usually* occurs in the first 6 weeks of ABC. ABC hypersensitivity is multisystemic. Fever and rash occur commonly and may be associated with nausea, vomiting, diarrhoea, fatigue, myalgia and arthralgia. Respiratory symptoms, such as pharyngitis, cough or dyspnoea, may also be present.

The skin rash, usually maculopapular or urticarial, occurs in about 70% of cases. Symptoms worsen with each dose. ABC hypersensitivity reaction is fully reversible on discontinuing ABC, and fatalities have not been reported on first exposure to the drug. Patients must however *never* be rechallenged with ABC after a hypersensitivity reaction, as deaths have occurred due to hypotension. Parents need specific counselling to recognise the hypersensitivity reaction; they also require a letter to alert any health care worker who may be consulted and need the contact number of the prescribing doctor.

A hypersensitivity reaction has been described for NVP. Systemic symptoms such as fever, myalgia, arthralgia, hepatitis, and eosinophilia may occur. It usually occurs in the first 8 weeks of treatment. NVP should then be permanently discontinued and EFV should be avoided as well.

9.5 HEPATOTOXICITY

All three classes of ARV drugs currently in use in South Africa have been implicated. Liver dysfunction in HIV infection may be caused by HIV, co-infection with hepatitis B or C viruses, OIs, malignancies, drug interactions or drug-induced hepatotoxicity. NRTI-associated hepatotoxicity is primarily caused by mitochondrial toxicity. NNRTIs are associated with asymptomatic elevations in liver enzymes and hypersensitivity with hepatitis. NVP is associated with more hepatotoxicity than EFV. PI-associated elevations in liver enzymes can occur at any time during therapy. Patients with chronic hepatitis B or C may experience an increase in liver enzymes after starting HAART as part of IRIS. There may also be an increase in liver enzymes after discontinuing drugs such as 3TC or TDF (which are used to treat hepatitis B). Children do seem to get less hepatic dysfunction on HAART than adults.

Patients on NVP should have liver function tests (LFTs) done 2-weekly for the first 2 months, then 3-monthly thereafter. LFTs should be monitored routinely 3 - 4-monthly in patients on other HAART regimens.

If transaminases are elevated <10 times the upper limit of normal (ULN) there is no need to interrupt HAART. Patients with clinical hepatitis or severe hepatotoxicity (>10 × ULN) should have a work-up for other causes of hepatitis, e.g. hepatitis A, B or C, and interruption of HAART. Patients on NVP with clinical hepatitis should discontinue NVP and have their HAART regimen changed. Rechallenge with NVP or ABC after acute hepatitis is not recommended. Patients with hepatitis B co-infection may need to continue with 3TC if their HAART regimen is changed to prevent a flare-up in hepatitis B.

9.6 LIPODYSTROPHY (LIPO-HYPERTROPHY/LIPO-ATROPHY)

Lipodystrophy typically involves accumulation of visceral fat in the abdomen (central obesity), dorso-cervical area (buffalo hump) and breasts (visceral fat accumulation) and/or loss of subcutaneous fat in the face, extremities and buttocks (lipo-atrophy (LA)). PIs have been implicated in fat accumulation, whereas the NRTIs, especially stavudine, have been implicated in LA. EFV may be implicated in breast enlargement. There are no data in children, but adult data suggest that switching from d4T or ZDV to ABC will at least arrest and may partially reverse LA but not the visceral fat accumulation. Switching early, when the LA is mild, is advisable as LA may be irreversible. There are also limited data indicating that switching to a regimen containing a PI and an NNRTI only will also reverse LA.

9.7 HYPERLIPIDAEMIA

PIs (especially RTV and LPV/r) are implicated in hyperlipidaemia. However, both d4T and EFV have also been implicated. While PI therapy in adults is associated with an increased risk of cardiovascular disease, there is currently no evidence of an association between elevated cholesterol levels in children and an increased risk of premature death. As a result, there is no consensus

or experience in lipid-lowering agents in children. Cholesterol and triglycerides should be measured 12-monthly in children on PIs. A random cholesterol and triglyceride is probably adequate, but if these are raised, a fasting level should be done. Referral to a dietician and encouraging exercise are the first interventions. If these are unsuccessful, consult the HIV Clinicians Society. Options available include observation, ARV agent switching (e.g. from a PI to an NNRTI or to ATV), or lipid-lowering agents. Statins are metabolised by cytochrome P450 resulting in either toxicity or diminished effect with RTV, so use with caution and only on the advice of an expert.

10. PROPHYLAXIS

10.1 *PNEUMOCYSTIS JIROVECII* PNEUMONIA

Indications for co-trimoxazole prophylaxis and when to start and stop it are set out in Table VII.

Re-institute co-trimoxazole prophylaxis if the CD4 count or percentage subsequently drops and the criteria in Table VII for starting prophylaxis are reached.

10.2 INH PROPHYLAXIS

The following children should receive INH prophylaxis:

- HIV-infected infants and children with a positive PPD test (>5 mm)
- HIV-infected infants and children exposed to a person who has contagious TB.

Active TB disease first needs to be excluded. The dosage of INH is 10 - 15 mg/kg/day and it should be continued for 6 months. Where the source case has INH-resistant TB, give rifampicin 15 mg/kg/d for 4 - 6 months. For MDR and extensively drug-resistant (XDR) contacts an expert should be consulted.

TABLE VII. CO-TRIMOXAZOLE PROPHYLAXIS

Indications for co-trimoxazole	When to start	When to stop
All HIV-exposed newborns	Start from 4 - 6 weeks after birth	Stop when PCR negative ≥6 weeks after full weaning AND infant is clinically HIV negative
All HIV-exposed exclusive formula-feeding children (EFF)	Start from 4 - 6 weeks after birth	Stop when PCR negative AND infant is clinically HIV negative AND EFF is expected to continue
All HIV-exposed breastfeeding children	Start from 4 - 6 weeks after birth	Stop when PCR negative ≥6 weeks after full weaning AND infant is clinically HIV negative
HIV-infected infants <12 months old	Start from 4 - 6 weeks after birth or as soon as possible after HIV diagnosis even if on HAART *Note:* all HIV-positive infants <1 year should be started on HAART regard-less of clinical stage or CD4 count or percentage	All infants <12 months should remain on prophylaxis
HIV-infected children 1 - 5 years with or without ART	All symptomatic children (WHO clinical stage 2, 3 or 4) or CD4 <15% or <500 cells/µl*	Stop once ART-associated immune recon-stitution has occurred for ≥6 months, i.e. CD4+ percentage ≥15% or CD4 count ≥500 cells/µl on ≥2 occasions, 3 - 6 months apart
HIV-infected children ≥6 years of age with or without HAART	Start if CD4 count <200 cells/µl or <15% OR WHO clinical stage 3 or 4 disease (including TB)	Stop once ART-associated immune recon-stitution has occurred for ≥6 months: CD4 ≥15% or ≥200 cells/µl on ≥2 occasions, 3 - 6 months apart
Any HIV-infected child with high risk for bacterial infections, e.g. severe malnutrition, on oncological drugs or corticosteroids or at risk of malaria	Start co-trimoxazole prophylaxis even with ART immune reconstitution	Do not stop until risk has been eliminated and all CD4 cell percentage or CD4 cell count criteria listed above have been met
HIV-infected child with previous PCP infection	Start as soon as first PCP episode has been treated	Stop once ART-associated immune recon-stitution has occurred for ≥6 months in children over 1 year of age: CD4 ≥15% or ≥500 cells/µl (1 - 5 years) or ≥200 cells/µl (>6 years) on ≥2 occasions, 3 - 6 months apart

Note: any one of the criteria could be used for starting therapy.

10.3 *MYCOBACTERIUM AVIUM* COMPLEX

MAC is a true OI. Disseminated MAC only occurs in patients with extremely low CD4 counts, although it is unusual in very young children. The best prophylaxis against MAC is ART and immune recovery. Where resources allow, there is a role for azithromycin prophylaxis against disseminated MAC in patients with extremely low CD4 counts. Before prophylaxis is instituted a mycobacterial blood culture should be done to exclude disseminated MAC. Children aged 2 - 5 years with a CD4 count <75 cells/µl and >6 years with a CD4 count <50 should be offered azithromycin prophylaxis. The dosage of azithromycin is 20 mg/kg body weight (max. 1 200 mg) orally once weekly. Discontinue once the CD4 count has been >200 cells/µl for children aged 2 - 5 years and >100 cells/µl for children aged ≥6 years for >6 months in children on stable ART.

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.

RECOMMENDED READING

Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. February 23, 2009; pp 1-139. http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf

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/

WHO guidelines: www.who.int

NDoH guidelines: www.doh.gov.za/

Centers for Disease Control and Prevention. Guidelines for the Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected. *MMWR Morb Mortal Wkly Rep* 2009; 58 (No. RR-11): 1-166.

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