Introduction

Every HIV-infected child has the right to comprehensive therapy, which includes ART. It can improve the morbidity and age-related mortality from HIV-infection and in addition improve the quality of life dramatically.

Antiretroviral drugs (ARVs) inhibit the process of replication at the level of the enzymes involved.

- Nucleoside reverse transcriptase inhibitors (NRTIs) attach to the RNA strand and shorten the transcription of DNA from RNA by the reverse transcriptase enzyme.
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) inhibit the reverse transcriptase enzyme directly.
- Protease inhibitors (PI) prevent the new formation of viral particles by inhibiting the protease enzyme.

These ARV drugs work best if used in combination of 3, e.g. 2 NRTIs and either an NNRTI or a PI.

Highly active ART (HAART) is an ARV combination regimen that can reasonably be expected to reduce the viral load to undetectable levels (i.e. <50 copies/ml) when treating patients with no prior use of ARVs. (Also referred to as ARV-naïve.) Absolute eradication of the virus is not achievable as it is also found in lymphoid tissue or the central nervous system, where the ARVs might not reach.

If the treatment is stopped or adherence to medication is poor, the virus will replicate to high levels again. Viral genetic material can readily change (mutate) during replication, particularly if the blood level of the ARV is too low to be effective. Consequently there is a strong possibility that the virus then becomes resistant to that drug.

N.B. **It is essential to ensure that adequate levels of the drugs are maintained in the body to prevent the development of resistant strains. It is extremely important that patients are adherent to their medication.**

Issues related to paediatric ART

- Children may need special formulation of the drugs, e.g. solutions.
- Very unpleasant taste can make administration problematic.
- A caregiver needs to be present constantly to administer the drug.
- Adherence thus becomes a serious issue.
- Adjustment of the dosage in relation to the child's growth and organ maturation.
- ART needs supportive health care, family and community environment.
- If ART is initiated without such support, it is likely that there will be failure and emergence of resistant viral strains.
- Guidelines for administering ART to children are different from those of adults.
- There are relatively few formulations of ARVs available for children.

Principles for ART

- Clinical indications may override 'normal' CD4 counts.
- Do not start too early (for example when the CD4 count is normal and the child is asymptomatic) or too late (when the immune system is irreversibly damaged).
- Choose drug regimens with proven efficacy.
- Choose drugs that are unlikely to have serious side effects.
- The simplest regimens possible should be chosen.
- Ensure constant availability of ARVs.
- Ongoing support of the patient and family to maintain adherence.
- It is important to be vigilant for drug interactions and resistance, which may reduce the potency of ARVs.
- Patients need to be monitored for adverse reactions.
- Creative solutions must be found to make sure that vulnerable children, e.g. orphans/children whose parents are ill, get access to ARVs if indicated, e.g. intervention by social worker, peer counsellor or school.

- For a good response at least 95% of the ARVs need to be taken. (Adherence is the key to successful therapy.)
- A minority of patients may not respond to ART and continue to deteriorate despite good adherence. (This may occur especially in those who are severely ill before starting ART. Underlying opportunistic infections should be sought.)

Continuity of care units

- In the initial provision of ART, children will be cared for in accredited units.
- These can be defined as units in primary, secondary or tertiary institutions, where expertise in managing children with ART exists and where ARV stocks are available.
- Such units will act as resources to train members of staff from other units, so that appropriate care through the health service is provided as quickly as possible.
- Initially ART delivery will occur at higher levels of health care and will be doctor-initiated as this is where expertise exists currently.
- As the program expands, provision of this treatment will occur at all levels by doctors and nurses.
- Stable patients will be referred to those primary care facilities where the necessary expertise, drug stocks and nutritional support are available.
- Training at all levels of care needs to be implemented immediately so that appropriate referral can occur. Eventually, tertiary care centres will become referral centres for complicated cases and/or ongoing research.

Function of units

- Staging of children to assess eligibility for ART should occur where the child presents.
- Possible candidates for ART are then referred to the closest accredited unit.
- Patients are then re-evaluated for their eligibility for ART.
- If found not to be eligible, the patient may be referred back to PHC for ongoing management and re-evaluation at regular intervals.
- At PHC level every effort must be made to maintain the health and nutrition of the child including provision of co-trimoxazole prophylaxis for PCP.
- As soon as the disease has been found to have progressed, referral for ART must take place immediately.
- Patients on ART are followed up by the treatment unit for at least 6 months. After this the child may be referred back to the PHC facility for further care.
- Ongoing care for children on ART includes:
  - Monitoring treatment adherence
  - Providing the necessary ARVs on a monthly basis
  - Referral for laboratory investigations and re-assessment as required
  - Assessment for drug side effects or other complications
  - Routine care for immunisation and weight monitoring
  - Management of intercurrent infections
  - Provision of co-trimoxazole prophylaxis for PCP
  - Counselling and support of the parents/caregivers
  - Arranging for palliative care where appropriate with the support of NGOs
- The child's home is an important unit that must not be overlooked. Home visits together with a social worker must be encouraged.

Requirements before ART is implemented

Within the health-care system

- Supplies of drugs are assured.
- Staff have the training and skill to manage children on ART.
- Monitoring mechanisms exist.
- Supportive processes are in place and active.
- Effective and informative counselling services are in operation.
- Management, clinical staff and pharmacists at primary care level and at first referral level must receive adequate and appropriate training.

Within the child's family/environment

- Parents/caregivers/children understand:
  - That a responsible individual and a treatment supporter must be identified to administer the drugs every day on a long-term basis
  - That ART is life-long therapy
  - The prognosis of the condition
  - The side effects of the medicines and their mode of action

Information recording

The details of all patients undergoing ART will be captured in a database consistent with the patient information system (PIS) developed by the NDoH. Examples of forms can be obtained.

N.B. **Ensure that data forms are filled in correctly. Accurate information recording is essential for the programme.**

Goals of ART

The goal of ART for children is to increase survival and decrease HIV-related morbidity and mortality.

- The child's CD4 count should rise and remain above the baseline count.
- The child's viral load should become undetectable (<400 copies/ml or <25 copies/ml depending on the assay) and remain undetectable on ART.

Eligibility for ART

Patients must satisfy clinical and social criteria before being accepted for treatment.

Clinical criteria

- Confirmation of diagnosis of HIV-infection.
- Recurrent (>2 admissions per year) hospitalisations or prolonged hospitalisation (>4 weeks) for HIV-related illness **OR**
- The patient satisfies the provisional WHO Stage III/IV disease (see Appendix 1) **OR**
- For relatively asymptomatic patients, one can consider CD4 percentage <20% if under 18 months or <15% if over 18 months.

Social criteria

These criteria are extremely important for the success of the programme and need to be adhered to – the principle is that adherence to treatment must be at least probable.

- At least one identifiable caregiver who is able to supervise the child for administering medication. (All efforts should be made to ensure that the social circumstances of vulnerable children, e.g. orphans, are addressed so that they too can receive treatment.)
- Disclosure to another adult living in the same house is encouraged so that there is someone else who can help with the child's ART.

Treatment of mothers/caregivers/other family members

- Always ask about the caregiver's health, and the health of other members of the family.
- Ensure that mothers and other family members access medical care timeously, including ART if needed.
- Where possible HIV-positive mothers and caregivers requiring medical attention should be attended at the same time as the children to decrease the number of clinic visits, costs and absences from work.

ARV drug choices for children

Table 10: Drug choices for children

Regimen	6 months up to 3 years	Over 3 years and >10 kg
First-line	stavudine (d4T) lamivudine (3TC) Kaletra®	stavudine (d4T) lamivudine (3TC) efavirenz (EFV)
Second-line	zidovudine (AZT) didanosine (ddI) nevirapine/efavirenz*	zidovudine (AZT) didanosine (ddI) Kaletra®

*Efavirenz if age >3 years, nevirapine if <3 years

See Appendix 3 for details.

General comments

- All infants under 6 months of age who require ART should be started on treatment under specialist supervision.
- Stavudine solution requires refrigeration. If no fridge is available, stavudine capsules may be opened and dissolved, and the required amount administered to the child. The rest can be discarded. If the caregiver experiences difficulty with stavudine capsules, zidovudine suspension may be used instead.

- Switch to tablets or capsules from syrups or solutions as soon as possible.
- Children may occasionally need to change a drug from the first-line regimen to one from the second-line regimen, because of intolerance or a serious adverse reaction. Swapping limits the patient's second-line treatment options. The decision to swap must be made by a doctor with antiretroviral experience. Swapping of a single drug should only be done if there is full viral suppression, failing which the whole regimen may need to be changed.
- If intolerance develops to ritonavir or lopinavir/ritonavir (Kaletra®), switch to nelfinavir.
- Lopinavir/ritonavir needs to be kept cool (<25ºC).
- Didanosine (ddl) must be taken alone, on an empty stomach, at least an hour before (or 2 hours after) a meal. Tablets should be dissolved in at least 30 ml of water. It is important to use 2 tablets of didanosine to obtain sufficient antacid buffering, e.g. if child needs 100 mg, prescribe 2 x 50 mg tablets.
- Abacavir may be used if adverse events occur with other NRTIs.
- Drugs not listed in the first- and second-line regimens but mentioned above, e.g. ritonavir, nelfinivir, saquinavir, abacavir, nevirapine, should be available at all tertiary-care centres.
- See Table 11 for reasons for moving from first- to second-line ART.

For dosage and frequency information on ARVs see Appendix 3.

Move from first- to second-line therapy

Consider a move to second-line therapy under the conditions listed in Table 11. For practical purposes, at first and second level it is primarily the clinical features that are of importance.

Table 11: Reasons to move to second-line ART in children

Clinical	Immunological	Virological
■ Lack of growth or decline of growth in a child showing initial response to treatment despite adequate intake ■ Loss of neurodevelopmental milestones or development of HIV encephalopathy ■ New evidence of Stage III/IV disease (not IRIS: see page 93) ■ Recurrence of prior opportunistic infections e.g. oral candidiasis that is refractory to treatment	■ No improvement in CD4 value despite therapy (at least 24 weeks) ■ Confirmed return of CD4 percentage (repeated within one month) to baseline or below before starting therapy in the absence of concurrent illness to explain CD4 decline ■ More than 50% decline in CD4 percentage from peak (confirmed within one month) in the absence of concurrent illness to explain CD4 decline	■ Rebound of viral load to baseline (a detectable viral load may be tolerated in children, providing that growth and elevated CD4 count are sustained)

- Short episodes of pneumonia, lower respiratory tract infection and gastroenteritis should not be regarded as clinical failure.
- Presentation with TB while on first-line therapy is NOT an indication to switch to second-line therapy even though it can present as progression to Stage III/IV disease.

- Immune reconstitution disease may present as a new Stage III/IV event. However, this will usually be associated with a CD4 count and/or percentage, which have improved over time. This is NOT an indication to switch to second-line therapy.

N.B.

- **Changing from first- to second-line ART is a decision that is undertaken only after careful consideration. It should not be rushed into before considering possible improvements in managing therapy at home.**

- First check adherence: if it is not possible to improve adherence, attempt directly observed therapy (DOT) with a health-care worker or the trusted 'other' family member or friend identified under 'social criteria' on page 81.
- Ensure that second-line therapy does not include any drugs used in first-line therapy.
- It is essential that switching ARV regimens is done in consultation with a paediatrician with ARV experience.

Concomitant tuberculosis (TB)

TB occurs commonly with HIV. There are two scenarios to consider:

1. Child presents with TB before starting ART

- Complete TB therapy if possible before starting ART or delay ART for at least 2 months. (In severe cases it may be necessary to start ART even sooner.)
- If the child has failed the nevirapine vertical transmission programme or is less than 3 years old or weighs less than 10 kg, use ritonavir as the third drug.
- If the child was not on the nevirapine vertical transmission programme and is more than 3 years old and weighs more than 10 kg, use efavirenz as the third drug.
- Monitor ALT monthly if ARV and TB treatment given concurrently.

2. Child develops TB while on ART

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

* Discuss all cases with a paediatrician with ARV experience, before interrupting therapy.

Dosage of ART

Provide ARV dosages according to dosing table in Appendix 3. In older children or adolescents ensure that maximum doses for adults are not exceeded.

Monitoring for efficacy and safety

This will have to be carried out at the first referral level, where feasible, in preparation for review of the child at the ARV treatment unit.

Table 12: Paediatric ARV regimens and routine monitoring during treatment

Regimen	Test	Frequency
d4T/3TC/lopinavir + ritonavir (Kaletra®)	■ CD4 ■ VL* ■ Fasting cholesterol ■ Fasting glucose ■ Fasting triglycerides** ■ ALT*** and FBC	■ Staging, 6-monthly ■ Baseline, 6-monthly ■ Baseline, 6-monthly ■ Baseline, 6-monthly ■ Baseline, 6-monthly ■ Baseline, 6-monthly
d4T/3TC/EFV	■ CD4 ■ VL ■ ALT and FBC	■ Staging, 6-monthly ■ Baseline, 6-monthly ■ Baseline, 6-monthly
ddI/AZT/NVP	■ CD4 ■ VL ■ FBC ■ ALT	■ Staging, 6-monthly ■ Baseline, 6-monthly ■ Baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load) thereafter ■ Baseline, week 2, 4 and 8, thereafter 6 monthly

(continues on following page.)

Regimen	Test	Frequency
ddI/AZT/EFV	■ CD4 ■ FBC ■ ALT	■ 6-monthly ■ Baseline, then monthly for 3 months, then 6 monthly (with CD4 and viral load) thereafter ■ 6-monthly
ddI/ABC/EFV	■ CD4 ■ ALT ■ FBC	■ 6-monthly ■ 6-monthly ■ 6-monthly

Staging = initial testing (screening) for all patients when being referred for antiretroviral therapy.

Baseline = testing for ART eligible patients, at initiation of ART.

* VL = viral load

**For practical purposes it is more convenient to take random samples, and fasting samples if the random sample is abnormal.

*** ALT = liver function test

It is at the discretion of the initiator of ART to decide whether monitoring for efficacy or toxicity be done outside of the routine schedule.

N.B. **For all regimens a baseline serum lipase will be useful. This may be repeated if there is clinical indication to do so.**

Adverse reactions

Also see Appendix 4.

ARVs commonly have side effects and occasionally serious adverse events (SAEs) can occur. Side effects are thought to be less common amongst children than amongst adults.

Side effects are those reactions to drugs that are known to occur and would be listed in the package insert, e.g. nausea, abdominal pain and vomiting. Life-threatening episodes should be referred to as serious adverse events.

Mild side effects include:

- Mild nausea, vomiting, diarrhoea
- Dizziness (efavirenz)
- General malaise
- Peripheral neuropathy
- Nail discolouration

Generally it is recommended that patients continue with the medication if the side effects are mild.

Table 13: Grading the severity of paediatric adverse reactions (PACTG)

Laboratory test abnormalities				
Item	**Grade 1 toxicity**	**Grade 2 toxicity**	**Grade 3 toxicity**	**Grade 4 toxicity**
Haemoglobin 3 months up to 2 yrs	9.0–9.9 g/dL	7.0–8.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Haemoglobin 2 years and over	10–10.9 g/dL	7.0–9.9 g/dL	<7.0 g/dL	Cardiac failure secondary to anaemia
Absolute neutrophil count	0.75–1.2 x10^9/L	0.4–0.749 x 10^9/L	0.25–0.399 x 10^9/L	<0.25 x 10^9/L
ALT (SGPT)	1.1–4.9 x upper normal limit	5.0–9.9 x upper normal limit	10.0–15.0 x upper normal limit	>15 x upper normal limit
Triglycerides	–	1.54–8.46 mmol/L	8.47–13.55 mmol/L	>13.56 mmol//L
Cholesterol	–	4.43–12.92 mmol/L	12.93–19.4 mmol/L	>19.4 mmol/L

Clinical adverse events				
Item	**Grade 1 toxicity**	**Grade 2 toxicity**	**Grade 3 toxicity**	**Grade 4 toxicity**
Peripheral neuropathy	Diagnosis of peripheral neuropathy is difficult in children. Screen motor function against milestones and refer to specialist if peripheral neuropathy is suspected.			
Skin rash/ dermatitis*		Diffuse maculo-papular rash OR dry desquamation	Vesiculation OR ulcers	Exfoliative dermatitis OR Stevens-Johnson syndrome OR erythema multiforme OR moist desquamation

* See box below for rash due to nevirapine.
Adverse reactions will be graded according to the Paediatric AIDS Clinical Trial Group (PACTG) grading.

Action on grading

Also see Appendix 5.

- Grades 1 and 2 – client remains on therapy. Repeat the test. Reassess clinically within 2 weeks.
- Grade 3 – test should be repeated within 1 week and if still Grade 3, stop ALL ARV drugs and seek expert medical advice.
- Grade 4 – Stop all drugs immediately and seek specialist advice. If the patient restarts therapy after the event has resolved, and the same Grade 4 event recurs, appropriate changes or withdrawal of ART may need to be made.

A rash in a child on nevirapine with mucosal involvement **OR** associated with fever/systemic symptoms/derangement in liver functions should be treated as a Grade 4 toxicity. All ARVs should be stopped immediately. Patients at primary care should be referred to a specialist for advice regarding restarting ARVs. The patient should never be rechallenged with nevirapine.

Lactic acidosis

All nucleoside analogues have been associated with lactic acidosis. It is a rare but potentially life-threatening metabolic complication of treatment. The pathogenesis is believed to involve drug-induced (NRTI) mitochondrial damage. Initial symptoms are variable; cases have occurred as early as 1 month and as late as 20 months after starting therapy.

It is usually associated with combination ddI and d4T.

N.B. **There are no good screening tests to detect lactic acidosis and a high index of clinical suspicion should be maintained.**

Clinical features:

- Generalised fatigue, weakness
- Gastro-intestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly, anorexia, and/or sudden unexplained weight loss)
- Respiratory symptoms (tachypnea and dyspnoea)
- Neurologic symptoms (including motor weakness)

Laboratory abnormalities:

- Hyperlactataemia (>2mmol/L)
- Increased anion gap [(Na + K) - (Cl + HCO_3); normal <15]
- Elevated aminotransferases, CPK, LDH, lipase, and amylase
- Microvesicular steatosis is seen on histology of the liver

N.B. **Discuss management of the patient with a treatment expert. ART should be discontinued in patients with clinical features.**

Management:

- Therapy is primarily supportive (fluid, bicarbonate administration and respiratory support).
- Administration of riboflavin, thiamine and/or L-carnitine has been reported by some to have benefit in uncontrolled case reports.
- Symptoms associated with lactic acidosis may continue or worsen following discontinuation of ART.

Hepatotoxicity due to nevirapine

Hepatotoxicity may occur mainly in the first 8 weeks after starting therapy. In the initial phases of therapy ALT should be done frequently (see Table 12). The patient may present with nausea, vomiting, right upper quadrant tenderness and jaundice if severe.

Management

Grade the level of toxicity as on Table 13. ARVs should be stopped if the toxicity is Grade 3 or 4.

N.B. **Skin rash associated with nevirapine toxicity may occur in association with liver dysfunction. Always check liver function tests if skin rash occurs (see above).**

Lipodystrophy syndrome

HIV-associated lypodystrophy includes fat loss and/or fat accumulation in distinct regions of the body: increased fat around abdomen, buffalo hump, breast hypertrophy, and fat loss from limbs, buttocks and face.

Other manifestations: insulin resistance, hyperglycaemia, hypertriglyceridaemia, hypercholesterolaemia and low HDL levels. These individuals are at risk of type 1 diabetes mellitus and coronary artery disease.

Association with ARVs: Usually occurs in patients who have been on long-term therapy. Lipodystrophy is more common in individuals taking stavudine or protease inhibitors.

Management

There are no established methods for treating lypodystrophy. Encourage exercise to reduce fat accumulation. Some patients improve if switched from a protease inhibitor to an NNRTI. Insulin resistance can be improved with anti-diabetic agents. Lipoatrophy may improve if d4T or AZT is replaced with abacavir. Statins and/or fibrates are effective at lowering cholesterol and triglyceride levels. However drug interactions between statins and ARVs may occur.

N.B.

- **If there is a need to discontinue ART, it is advisable to discontinue all ARVs rather than continuing with one or two agents alone. When a patient discontinues an NNRTI-containing regime, attempt to continue the NRTI component for 2 days after stopping the NNRTI. (For example, if NNRTI-related hepatotoxicity is suspected.)**
- **Adverse events should be recorded and reported regularly to the National HIV and AIDS Cluster. Serious adverse events (SAEs) should be reported within 48–72 hours (Grade 4 or death) to the Medicines Control Council. Adverse event forms on yellow paper will be made available at all centres. (Appendix 7)**
- **After the patient has recovered from the adverse event it may be possible to recommence therapy with a different regimen. Decision to recommence therapy should be done in consultation with a treatment expert.**

Important drug interactions

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

Immune reconstitution inflammatory syndrome (IRIS)

This is a paradoxical clinical deterioration after starting ART. It is due to the improving immune system interacting with organisms that have colonised the body during the early stages of HIV-infection.

Causes

A wide range of pathogens may induce IRIS including *Mycobacterium tuberculosis* (MTB), BCG, *Mycobacterium avium complex, Mycobacterium leprae, Cryptococcus neoformans, Aspergillus fumigatus, Aspergillus terreus, Candida albicans, Pneumocystis jerovici*, CMV, JC virus, human herpes viruses, human papilloma virus and hepatitis B and C viruses (HBV, HCV).

Presentation

IRIS usually presents during the first 6 weeks after starting ART. Clinical presentations vary and depend on the causative organism and the organ-system that is colonised. For example IRIS caused by MTB may present with high fever, lymphadenopathy, worsening of the original tuberculous lesion, and/or deteriorating chest X-ray features including the development of a miliary pattern or pleural effusion.

Management

Includes specific antimicrobial therapy e.g. TB treatment for IRIS caused by MTB. In severe reactions glucocorticosteroids and/or temporary discontinuation of HAART may help.

BCG adverse events

Adverse events related to BCG immunisation have also been reported during immune reconstitution. These include:

- Abscess at the site of injection 10–15mm
- Lymphadenitis (>1.5cm) (lymphadenopathy may also occur at other sites e.g. supraclavicular and cervical)
- Suppurative lymphadenopathy in association with BCG injection
- Disseminated BCG disease (indicated by failure to thrive, fever, hepatosplenomegaly)
- Osteitis
- Skin and eye reactions including erythema nodosum, lupus vulgaris and iritis

If these reactions are noted, it is important to notify the authorities on a vaccine adverse event form. If an abscess is present, this should be drained to avoid sinus formation. Pus may be sent for TB culture with reference to the fact that a suspected BCG reaction has occurred.

In all HIV-infected children with BCG reaction, treatment with INH (20 mg/kg/day), rifampicin and ethionamide (25 mg/kg) should be commenced for a period of 6 months. BCG is PZA resistant, hence the choice of drug regimen. Single anti-TB drugs are usually only available at hospital level, and the patient should be referred appropriately.

Adherence

See Section 11 for details.

Adherence greater than 95% will ensure a good virological response and prevent the emergence of viral resistance. Good adherence can be achieved with regular education and support. Adherence may be monitored using diary cards, medication check and other measures. All efforts should be made to encourage this level of adherence.