

Clinical Tract

Module on

Paediatric antiretroviral therapy

LEARNING OUTCOMES FOR DOCTORS AND NURSES

After completion of this module the learner should:

- Know the general principles of antiretroviral therapy (ARV) in children
- Know the goals of ARV in children
- Know when to initiate ARV on medical grounds
- Take psychosocial considerations into account when offering ARV to a patient
- Select a first-line ARV regimen for the different age categories
- Monitor a patient on ARV for safety and efficacy
- Understand Immune Reconstitution Disease in children
- Manage patients with TB and HIV
- Know the implications of failed mother-to-child transmission on the choice of ARV in the child
- Know the considerations that need to be taken into account when treating an adolescent
- Understand therapeutic failure and how to diagnose it
- Select a second-line regimen
- Know when to refer patients for specialist care

LEARNING OUTCOMES FOR COUNSELLORS, SOCIAL WORKERS, DIETICIANS, PHARMACISTS, LABORATORY TECHNICIANS AND DATA TYPISTS

After completion of this module the learner should:

- Know the general principles and goals of antiretroviral therapy (ARV) in children
- Know at what stage of the disease ARV is started in children
- Know the important psychosocial considerations that need to be taken into account when ARV is offered to a patient
- Have a basic knowledge regarding the first-line ARV regimen for the different age categories
- Know how children on ARV should be monitored regarding the safety and efficacy of the treatment
- Understand what Immune Reconstitution Disease in children is
- Know the potential problems that can be encountered when treating patients who suffer from both TB and HIV
- Know that children who become HIV infected despite the interventions of the mother-to-child transmission programme need special consideration when an ARV-regimen is chosen
- Know the important considerations when treating an adolescent with ARV
- Understand what therapeutic failure in a child on ARV is
- Know which regimens are used for second-line treatment
- Know when patients need to be referred for specialist care

1. INTRODUCTION:

Most paediatric HIV expertise is currently situated at academic hospitals. The antiretroviral treatment programmes will therefore start at these hospitals, where the doctor will initiate the treatment. The goal of the National Treatment Program is however to equip all levels of health care to deal with the burden of HIV in the communities. It is therefore foreseen that, as the programme expands, the provision of antiretroviral therapy (ARV) will be part of the comprehensive treatment package offered by doctors and nurses in the local clinics.

In the meantime, the doctors and nurses in the community have to be equipped to:

- Correctly diagnose HIV-infection
- Administer prophylactic treatment
- Treat common diseases of childhood and opportunistic infections in HIV-positive children
- Monitor and follow-up down referrals
- Appropriately refer children for antiretroviral therapy

2. GENERAL PRINCIPLES OF ANTIRETROVIRAL THERAPY (ARV) IN CHILDREN:

Although infected by a potentially lethal viral infection, not all children who are HIV-infected require ARV when they present to the health care services. Some children may even have long-term non-progressive disease, and might not require antiretroviral therapy until early in adult life. This is why criteria on when to start ARV have been developed, in order to guide the medical staff in the decision on when to initiate the therapy.

Similar as in adults, a combination of at least three antiretroviral drugs is considered the standard of care in children. This is due to the increased potency and decreased risk of viral resistance when these combinations are used. Children usually have higher viral loads than adults, especially in their first year of life, and this makes the goal of suppressing the viral load to under detection levels more difficult to achieve. Clinical improvement, though, is usually achievable even despite the incomplete viral suppression.

It is of utmost importance to see each child in the context of his or her social environment. This is due to the child's inability to take responsibility for his or her own health and medication. A holistic treatment programme should be offered, including social intervention, nutritional intervention, prophylactic management, attention to adherence, etc. Other underlying conditions, especially tuberculosis, must always be actively excluded and treated if needed.

Monitoring the response to therapy is done by clinical follow-up of patients, as well as by doing CD4+ counts and percentages and HIV viral load measurements.

3. GOALS OF ARV IN CHILDREN:

Although the clinical outcome following the introduction of ARV in children is excellent, the eradication of HIV from an infected person is not possible with the currently available drugs.

The goals of antiretroviral therapy in children are similar to those in adults:

- To achieve significant gains in the quality and quantity of life, and to promote the physical, social and intellectual development of the child in the context of his or her family.
- Preservation and/or reconstitution of the patient's immune system. This is usually measured by the CD4+ cell count and percentage.
- Maximal and sustainable suppression of the HI-viral load. In some children, though, a suppressed but still detectable viral load, with sustained elevation in CD4+count and absence of intercurrent and/or opportunistic infections, may be the best achievable goal.

4. CRITERIA FOR THE INITIATION OF ARV:

As antiretroviral therapy does not stand alone, but is part of a package of care for a child, medical and psychosocial considerations need to be taken into account when a child is evaluated for ARV. Children should meet both medical and psychosocial criteria before starting therapy.

The medical criteria include both clinical (WHO) and immunological criteria (CD4+ percentage). It should be noted that the child may require treatment because the CD4+ percentage is below a certain cut-off point for the child's age, even if the child has not had a clinical disease of stages 2 or 3.

If the psychosocial criteria are not met, the health care team should do their best to address these problems. The child needs to be re-evaluated frequently, until all the criteria are met and ARV can be initiated.

It should be mentioned again that ARV is not an emergency treatment and the child should only be started on the therapy once all members of the health care team are satisfied that the criteria are met.

Medical criteria:

- Recurrent hospitalizations (> 2 admissions per year) for HIV-related disease, or prolonged hospitalization (> 4 weeks), **OR**
- Modified WHO stage 2 or 3 disease, **OR**
- CD4+-percentage <20% in a child under 18 months old, irrespective of disease stage, **OR**
- CD4+-percentage <15% in a child over 18 months old, irrespective of disease stage

AND:

Psychosocial considerations:

- An identifiable adult, who has demonstrated reliability, and who is able to administer the medication. Disclosure of the caregiver to another adult in the household is strongly advised. This is of great benefit, because the other adult can support the caregiver both emotionally and also practically, like helping with the administration of the medication.

The caregiver must be able to bring the child to the ARV clinic as the visit schedule requires. The caregiver must also have demonstrated reliability by attending the visits to the clinic as per appointment. Previous compliance with chronic treatment such as TB treatment will also give an indication of adherence. An immunization record that is up to date also demonstrates reliability.

The caregiver does not need to be the mother. The sad fact of the matter is that a many of the children who are in need of ARV are orphaned. As a practicality, the possibility that the caregiver herself might get ill must be considered. That is why it is important (although this is not an exclusion criterion) that disclosure takes place and that another adult is able to continue administering the medication if needed.

The question of whether treatment will be continued when the child visits with family or goes on crèche-/school outings must also be discussed.

As the child grows older, he/she should be counselled over time and the HIV diagnosis has to be disclosed to every child at some stage. The decision on when and how to do this can be a very difficult one. There are no hard and fast rules regarding the disclosure, but counselling and involvement of the child in the treatment should happen according to the age and level of understanding of the child. It is much better if the disclosure takes place in the way the caregiver feels it is best for the child, rather than the child finding out the truth incidentally.

Treatment of mothers, caregivers and 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 in time, including ARV if needed. It is preferable not initiate ARV to the child and caregiver at the same time, as this will suddenly place a big burden on to the caregiver.

The screening visit has to cover all of the following:

- Taking a complete medical history
- Doing a complete clinical evaluation, including weight and height.
- Updating the growth chart.
- Calculating the body surface area of the child: $BSA = \sqrt{\frac{Hgt(cm) \times Wgt(kg)}{3600}}$ m²
The dosages of some of the paediatric antiretroviral drugs depend on the weight of the child and others on the body surface area (BSA)
- Ensuring that TB is adequately excluded:
 - History of TB contact
 - Chest radiograph (CXR)
 - Gastric aspirates or induced sputum if the CXR is abnormal or if there is a clinical suspicion of TB
 - TB skin test, like a Mantoux test
 - Abdominal ultrasound (if clinically indicated & possible) for abdominal lymphadenopathy
- Naming the caregiver responsible for administering the medication and making sure that this person is present and involved during all discussions regarding the antiretroviral therapy.
- Explaining the importance of adherence as well as tools to help improve adherence including the use of pillboxes, syringes, diary cards as well as the bringing back of all empty containers and unused drugs for all follow up visits.
- Explaining the side effects of ARV, with the emphasis on problems associated with the chosen drug regimen.
- Explaining the exact drug schedule to the caregiver.
- Doing the following baseline investigations (if no recent result is available):
 - Full blood count with differential count
 - CD4+ count
 - Viral load
 - ALT/AST, glucose, cholesterol and triglycerides if indicated

5. DRUGS USED FOR ARV IN CHILDREN

Drug classes and examples:

The drugs and drug classes used in paediatric ARV are the same as those that are being used in the adult guidelines. The drug combinations in children of the different age groups differ though, due to licensing requirements of the drugs, and due to the fact that young children are started on more potent regimens due to their generally higher viral loads.

Drug classes that are used are, with examples: (Refer back to the module on drugs used for ARV)

- Reverse transcriptase inhibitors (RTI):
 - NRTI (nucleoside RTI):
 - AZT (zidovudine), 3TC (lamivudine), d4T (stavudine), ddI (didanosine), etc.
 - NNRTI (non-nucleoside RTI):
 - NVP (nevirapine), efavirenz
- Protease inhibitors (PI):

- Lopinavir/ritonavir combination (Kaletra®), ritonavir

First line treatment guidelines:

- In children > 3 years: 2 NRTI + 1 NNRTI

- d4T (stavudine)
- 3TC (lamivudine)
- Efavirenz

- In children 6 months to age 3 years: 2 NRTI + 1 PI (or 1 NNRTI)

- d4T (stavudine)
- 3TC (lamivudine)
- Lopinavir/ ritonavir (Kaletra®)
Or
- Nevirapine (if not used for prevention of mother to child transmission)
Or
- Ritonavir (if also on TB treatment)

- In children under 6 months of age

- Expert opinion should be sought in these children.
- ARV in small infants can be complex. Both the drug absorption and metabolism are very different in this age group, and very high dosages, especially of the protease inhibitors, may be needed to achieve adequate drug levels.
- Maternal antiretroviral therapy and the possibility of the transmission of a potentially drug resistant virus must also be kept in mind.
- Options:
 - o d4T or AZT, 3TC and Ritonavir or Nevirapine (if not exposed to NVP in infancy)

DOSAGE AND FREQUENCY OF ARV USED IN CHILDREN					
DRUG	FORMULATIONS	DOSAGE (PER DOSE)	FRE- QUENCY	STOR AGE	COMMENTS
NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NRTI)					
Zidovudine (ZDV) Retrovir®	Susp: 10 mg/ml Caps: 100mg, 250mg	90-180mg/m ² 180 mg/m ²	3 2	Room temperature	
Didanosine (ddl) Videx®	Susp: 10 mg/ml Tabs: 25mg, 50mg, 100mg, 150mg	90-120mg/m ²	2 Can give total daily dosage x 1 in older children	Refrigerate suspension	Half hr pre-meals or 1 hr after meal Use single daily dose if necessary for adherence
Stavudine (d4T) Zerit®	Susp: 1 mg/ml Caps: 20mg, 30mg, 40mg	1 mg / kg	2	Refrigerate suspension	Capsules stable in water suspension for 24 hours in refrigerator
Abacavir Ziagen®	Susp: 20mg/ml Tabs: 300mg	8 mg/kg	2	Room temperature	WATCH FOR HYPERSENSITIVITY REACTION. DO NOT RECHALLENGE AFTER HYPERSENSITIVITY REACTION.
Lamivudine (3TC®)	Susp: 10mg/ml Tabs: 150mg	4 mg/kg	2	Room temperature	
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTI)					
Nevirapine Viramune®	Susp: 10mg/ml Tabs: 200 mg	120-200mg/m ² Start at 120mg/m ² daily for 14 days and increase to bd dosage if no rash or severe side-effects	2	Room temperature	Skin rash usually occurs in 1 st 6 weeks; do not increase dosage until rash resolves. WATCH FOR LIVER TOXICITY
Efavirenz Stocrin®	Caps: 50 and 200mg (Suspension available for manufacturer)	13-<15kg: 200mg 15-<20kg: 250mg 20-<25kg: 300mg 25-<32.5kg: 350mg 32.5-<40kg: 400mg >40kg: 600mg	1	Room temperature	No data <3 yrs and <13Kg. Give at night to avoid CNS side-effects
PROTEASE INHIBITORS					
Ritonavir Norvir®	Susp: 80mg/ml	Start at 250 mg/m ² /dose and increase by 50 mg / m ² every 2-3 days up to 400 mg/m ² If <2 years of age 450 mg/m ²	2		Take with food. Bitter; coat mouth with peanut butter or give with chocolate milk. Take 2 hours apart from Didanosine
Lopinavir/ Ritonavir Kaletra®	Oral solution 80mg Lopinavir (LPV) & 20mg ritonavir (RTV) per ml. Capsules 133mg LPV/33mg RTV	Patients not taking NVP or EFV -230mg LPV component /m ² (max 400mg LPV =Adolescent dose) Patients taking NVP or EFV or ARV experienced- 300mg LPV component /m ² (max 533mg LPV =Adolescent dose)	2	Oral solution and capsules should be refrigerated. Can be kept at room temperature up to 25°C if used within two months.	Administer with food. High fat meal increases absorption, especially of the liquid preparation. If co administered with ddl, ddl should be given one hour before or two hours after Lopinavir/ritonavir.

Adapted from: Levin L. Antiretroviral therapy in children. Clinical guidelines of the Southern African HIV Clinicians Society. *The Southern African Journal of HIV medicine*, Oct. 2002, p23– 33.

6. POTENTIAL PROBLEMS WITH ARV

- The potential toxic side effects of drugs: This includes both the short-term and the long-term side effects. These side effects should be actively sought, and actively managed.
- Need for combination therapy: Caregivers need to understand the reason for the combination therapy, and the fact that all antiretroviral drugs must always be available and administered according to schedule.
- Complex dosing regimens: This has fortunately become less of an issue with the currently used first line therapy, where all drugs are given either once or twice daily, and are not so dependant on the food intake.
- Lack of adherence as a major risk factor for treatment failure: The caregiver needs to understand that adherence, and therefore the potential for the ARV to have a positive long-term effect, is one of their greatest responsibilities.
- Emergence of viral resistance: This is closely linked to adherence, and is the reason why an ARV regimen that has been successful in a certain patient, ceases to be effective. Future treatment options are diminished when drugs are not given according to schedule, or if drug regimens are changed without a good reason.
- Lack of understanding of the need for life-long treatment.

Adherence to therapy is vital for a successful outcome. It has been shown that adherence decreases over time, due to the fact that as the patient improves, the reality of the lethal nature of the HIV-disease retreats from the minds of the patient and the family. Ongoing support and monitoring is therefore an absolute necessity, and every interaction with the patient should be seen as an opportunity to reinforce the importance of adherence. The treatment counsellor plays a vital role in this regard, although all members of the team should be reinforcing the same message in this regard.

Adherence needs special attention in teenagers, as this phase of their lives can interfere with adequate adherence to treatment.

In addition, the caregiver should be aware of the fact that the doses are likely to be modified at each visit as the child grows and gains weight.

Most drugs used in children are available in the form of tablets and in suspensions. Suspensions should be changed to tablets as soon as possible, as large volumes of suspension can be difficult to administer. Tablets and capsules are also less vulnerable to environmental factors like heat, and are also more cost effective. Doing pill counts to assess adherence is also much easier, than assessing the volumes of drugs that were given.

7. FOLLOW-UP OF CHILDREN ON ARV

Clinical follow-up:

- 2 Weeks after initiation of ARV
 - This visit is aimed at dealing with problems and side effects, as well as lending support and counselling to the child and the caregiver
 - A full medical examination is done

- 4 Weeks after initiation of ARV
 - Again the focus lies on side effects and adherence
- Monthly visits
 - The visits are scheduled monthly until the child is stabilised on the treatment
 - A full medical examination, including weight, height and body surface area, is done at each visit. The 'Road to Health'-chart is a valuable tool for monitoring the wellbeing of children. Failure to maintain growth is suggestive of progressive HIV disease or a superimposed infection such as tuberculosis, and signals the need for further diagnostic tests and intervention.
 - Remember to increase the dosages of the drugs as the weight and BSA of the child increases
 - Side effects and toxicities are actively screened for
- Three monthly visits:
 - Once the child is stabilised on the treatment, the visits can be scheduled on a 3-monthly basis
 - A prerequisite for this would be, that the caregiver understands the importance of coming and collecting the medication on a monthly basis, and that the caregiver knows the danger signs of when to come and seek medical help.
 - PCP prophylaxis (co-trimoxazole) can be discontinued when the CD4+% is >20% for >6 months

Blood tests done for monitoring:

Blood tests done for monitoring children on ARV are either to monitor the response to therapy (e.g. CD4+count and HIV viral load), or to monitor for toxicity of the drugs (full blood count, liver enzymes, serum glucose and lipids)

The CD4+ count and viral load are done at baseline (i.e. before start of therapy), and then on a six-monthly basis. The tests can also be done if clinically indicated, i.e. if there is a concern regarding the efficacy of the treatment and the decision whether or not to move to a second line treatment regimen needs to be taken.

A fall in the CD4+ count and/or percentage may be more important than a rising viral load in considering the need for the change of the therapy. It should however always be remembered that the CD4+ cells can be temporarily lowered due to intercurrent infections or immunizations, and that the CD4+count should therefore ideally only be done after a month of recovery.

The bloods done to monitor for toxicity vary according to the drug regimen that the patient is on. Regimen containing protease inhibitors for instance (Kaletra®, ritonavir) need 6-monthly monitoring of the fasting serum glucose and lipids (cholesterol, triglyceride), due to the known long term metabolic side effects of these drugs. Children on nevirapine-containing regimen need their liver functions checked due to the known liver toxicity, and children on AZT need their full blood counts done regularly to assess the drug's potential for bone marrow suppression. Refer to the table below for more information.

Routine laboratory monitoring of paediatric ARV regimens:

Regimen	Test	Frequency
d4T / 3 TC / Lopinavir & ritonavir	CD4 Viral load Fasting glucose Fasting cholesterol and triglycerides	Staging, 6-monthly Baseline, 6-monthly Baseline, 6-monthly Baseline, 6-monthly Baseline, 6-monthly
d4T / 3TC / efavirenz	CD4 Viral load	Staging, 6-monthly Baseline, 6-monthly
ddl / AZT / nevirapine	CD4 Viral load FBC ALT	Staging, 6-monthly Baseline, 6-monthly Baseline, monthly for 3 months, then 6-monthly Baseline, week 2, 4, 8, then 6-monthly
ddl / AZT / efavirenz	CD4 Viral load FBC	Staging, 6-monthly Baseline, 6-monthly Baseline, monthly for 3 months, then 6-monthly
ddl / ABC / efavirenz	CD4 Viral load	Staging, 6-monthly Baseline, 6-monthly
AZT / ddl / Lopinavir & ritonavir	CD4 Viral load FBC Fasting glucose Fasting cholesterol and triglycerides	Staging, 6-monthly Baseline, 6-monthly Baseline, monthly for 3 months, then 6-monthly Baseline, 6-monthly Baseline, 6-monthly Baseline, 6-monthly

8. SIDE EFFECTS OF ARV:

Most side effects in children on ARV are predictable and mild. They should however always be actively sought and managed, as some side effects are potentially life threatening, and others may be mild, but may still impact negatively on the quality of life of the child. Side effects of the drugs can also interfere with adherence to treatment, and should therefore never be ignored. For side effects known to specific drugs, please refer to the table below.

SIDE-EFFECTS OF ARV IN CHILDREN:		
Class	Drug	Side-effects
NRTI	AZT	Bone marrow suppression, gastro-intestinal symptoms Myopathy, cardiomyopathy, lactic acidosis
	ddl	Common: abdominal pain, nausea and vomiting Uncommon: pancreatitis, peripheral neuropathy, lactic acidosis
	d4T	Common: headache, rash, gastro-intestinal symptoms Uncommon: pancreatitis, peripheral neuropathy, lactic acidosis
	Abacavir	Hypersensitivity reaction (with or without a rash) - may be fatal. Lymphopenia, lactic acidosis
3TC		Common: headache, fatigue and abdominal pain Uncommon: pancreatitis, peripheral neuropathy, lactic acidosis
NNRTI	Nevirapine	Skin rash, nausea, vomiting and diarrhoea. LIVER TOXICITY
	Efavirenz	Skin rash, gastro-intestinal symptoms CNS – Sleep disturbances, vivid dreams, confusion, dizziness. Teratogenicity in primates
PI	Lopinavir/Ritonavir (Kaletra®)	Gastro-intestinal symptoms, lipodystrophy Hypercholesterolaemia and hypertriglyceridaemia
	Ritonavir	Nausea, vomiting, diarrhoea Hypercholesterolaemia and hypertriglyceridaemia

Table adapted from: Levin L. Antiretroviral therapy in children. Clinical guidelines of the Southern African HIV Clinicians Society. *The Southern African Journal of HIV medicine*, Oct. 2002, p23– 33.

Side effects in children are graded with a grading system similar to the one used in adults (see module on adult ARV). With grade 1 and 2 side effects the treatment is continued and the patient is reassessed after 2 weeks. With a grade 3 side effect, the treatment is continued, but the blood test is repeated after 1 week. If the grading then remains grade 3, then expert advice is sought regarding the stopping of all the antiretroviral drugs. With grade 4 side effects an expert is consulted immediately regarding the stopping of all the antiretroviral drugs. All side effects should be recorded and reported to the National HIV/AIDS Cluster. Serious adverse events should be reported urgently to the MCC as well.

If there is a need to stop the antiretroviral therapy due to the severity of the side effects, it is advisable to stop all of the drugs, rather than continuing with only one or two. It may be possible to recommence therapy with a different regimen after the recovery of the patient from the adverse event. The decision to recommence therapy should be done in consultation with an expert.

A rash in a child on nevirapine with mucosal involvement OR associated with fever / systemic symptoms / derangement of the liver functions should be treated as a Grade 4 toxicity. All antiretrovirals should be stopped immediately. Patients at primary care level should urgently be referred to a specialist for advice regarding the restarting of antiretroviral therapy. The patient should never be given nevirapine or efavirenz again.

The potential hepatotoxicity of nevirapine should also be kept in mind, especially during the first 2 months of treatment. The patient may present with nausea, vomiting, right upper quadrant tenderness or jaundice. In such cases liver function tests should be done, and the antiretroviral therapy should be stopped if the toxicity is severe (grade 3 or 4).

Lactic acidosis has been associated with all nucleoside analogues. However, it is usually associated with the use of the combination of d4T and ddI. This is a rare but potentially life-threatening metabolic complication of the treatment. The aetiology is believed to be direct drug-induced damage to the mitochondria. The clinical picture can be variable, and very vague, with generalized fatigue, weakness, gastrointestinal symptoms like nausea, vomiting, diarrhoea, abdominal pain or unexplained weight loss, respiratory symptoms like tachypnoea and dyspnoea and neurologic symptoms like motor weakness.

The laboratory abnormalities consist of the following:

- Increased serum lactate levels (>2mmol/L)
- Increased anion gap [(Na + K) - (Cl + HCO₃); normal being < 15]
- Elevated liver enzymes (AST and ALT), CPK, LDH, lipase and amylase
- Liver biopsy: microvesicular steatosis

The management of these patients should always be discussed with an expert. The antiretroviral drugs should be discontinued. The treatment of the lactic acidosis is supportive, with the administering bicarbonate and fluid therapy, respiratory support if needed, etc.

Lipodystrophy syndrome includes both fat loss and/or fat accumulation in distinct body regions. The fat loss is mainly from the limbs, the buttocks and the face, whereby the fat accumulation occurs mostly on the abdomen, the shoulders and the breasts. It is associated with high serum glucose levels, insulin resistance and diabetes mellitus as well as increased triglycerides and cholesterol in the blood. The patients are at increased risk of coronary artery disease. The syndrome is mostly seen in patients who have been on long-term antiretroviral therapy, especially regimes including NRTI's and PI's.

Management of the condition is difficult, and consists of:

- Exercise
- Switching therapy from a PI to a NNTRI can improve the condition in some patients
- Atrophy of the fat tissue improves by switching d4T or AZT to Abacavir
- Administration of drugs that lower the cholesterol and triglyceride levels in the blood should be done with care in children, and expert advice should be obtained
- Insulin resistance can improve on anti-diabetic agents

9. IMMUNE RECONSTITUTION DISEASE (IRD) IN CHILDREN

As in adults, children can experience a paradoxical deterioration in their clinical condition after the initiation of ARV. Drug toxicity must always be kept in mind in these patients, although immune reconstitution disease should also be considered. This syndrome is due to the fact that the recovering immune system interacts with organisms that have colonized the patient's body before the start of treatment. Organisms that are implicated in this process are multiple, and include typical and atypical mycobacteria, PCP, candida and other fungal infections, viral infections like cytomegalovirus, herpes simplex virus, papilloma virus, etc.

In our context tuberculosis is the most important reason for the immune reconstitution disease, and this emphasizes the fact that tuberculosis must be actively excluded in all children before the start of ARV. Treatment of IRD consists of treating the underlying infectious cause (if possible). ARV should be continued if at all possible.

10. DRUG INTERACTIONS WITH ARV

There are multiple opportunities for serious drug interaction in patients on ARV. Most antiretroviral drugs are metabolised in the liver, and this is the most common reason for drug interactions. If a patient is on any other concomitant therapy, the package insert of the drugs should be read carefully, and expert advice should be sought if uncertainty persists.

11. CONCOMITANT TB-TREATMENT AND ARV

Problems that arise when a patient needs both TB treatment and ARV are mostly due to drug interactions (especially with rifampicin and protease inhibitors or NNRTIs) and due to shared toxicities, like hepatic toxicity and peripheral neuropathy.

Options:

- If ARV not started yet:
 - Delay ARV until TB-treatment has been completed, or at least until the first two months of TB-treatment has been completed (to prevent immune reconstitution disease). In exceptional cases only, ARV is initiated as soon as two weeks after the start of the TB-treatment.
- If already on ARV, and then requiring TB-treatment:
 - Use standard TB treatment together with ARV that is compatible with rifampicin
 - Nevirapine is contraindicated due to the shared liver toxicity. Change to efavirenz if possible (if > 3 years and > 10 kg), or otherwise use ritonavir or lopinavir/ritonavir with added ritonavir.
 - Change Kaletra® to ritonavir, or use lopinavir/ritonavir with added ritonavir.
 - Monitor liver functions (ALT) monthly
 - Pay special attention to adherence in these patients, considering the fact that the amount of tablets that the patient needs to be given increases.

12. ARV IN CHILDREN AFTER FAILURE OF MOTHER-TO-CHILD-TRANSMISSION

It is known that there is a considerable risk of resistance mutations in the HIV-strains of infected infants, after the use of single dose, single drug nevirapine for MTCT. The significance of these resistance mutations is unclear though. Until more information becomes available, it is safer to avoid both nevirapine and efavirenz as first line treatment options in these children.

If AZT monotherapy was used to prevent MTCT, AZT can still be used as combination therapy in the infected infant. If both AZT and 3TC were used, 3TC should be avoided if the mother had received a prolonged course of treatment without reaching adequate viral suppression. Usually, though, only a short course of 3TC is used for MTCT, and then it would be acceptable to use 3TC as part of the therapy for the infected infant.

For an infant of a mother who was on triple therapy, it is better to avoid the drugs that the mother was taking, if the mother's viral load was still detectable. If the mother did have an undetectable viral load, it is probably acceptable to use the same ARV drugs in her HIV-infected infant.

There is currently inadequate information regarding whether or not a mother on ARV can safely breastfeed her infant. Further studies are awaited in this regard.

13. ARV IN ADOLESCENTS

It is important to look at the stage of pubertal development when deciding whether to use the adult or the children's guidelines for ARV. The staging of puberty is done using the Tanner system. For children who are pre-pubertal or in early puberty (Tanner stages I and II) the paediatric guidelines are used. Adult guidelines are used for adolescents in intermediate and late puberty (Tanner stages III and IV), as well as post-pubertal adolescents. (Tanner stage V)

Non-compliance can be problematical in this age group and strategies should be introduced to promote adherence, including more frequent visits and intensive counselling.

14. NEED FOR SECOND-LINE ARV

There are different reasons to change the first-line therapy of a patient on ARV. If drug therapy needs to be changed due to the severity of side effects, the offending drug alone can be changed. This should be done with care, due to the fact that any changing of drugs limits the patient's future second-line treatment options.

Reasons to move on to second-line therapy can be clinical, immunological or virological. The decision should, though, never be a rush. Clinical reasons include oral thrush that is persistent despite the treatment thereof, or any new evidence of onset of a WHO stage 3 disease. Clinical events not necessitating change of treatment include

intercurrent infections, new-onset of tuberculosis or diseases that form part of the spectrum of the immune reconstitution disease.

Immunological reasons to change treatment include the persistent decline in the CD4+ percentage over 2 months, in the absence of acute infections or tuberculosis. If the decline in CD4+ percentage is modest (less than 5%), and it is not associated with clinical signs and symptoms, the patient should be continued on his/her treatment and monitored closely.

Virological reasons to change treatment include a rebound of the viral load to baseline levels. In some children it is impossible to achieve an undetectable viral load. This is not an indication to change the therapy, providing that the child shows clinical improvement and the elevated CD4+ percentage is sustained.

Standardized second-line treatment for infants in the age group 6 months to 3 years consists of AZT, ddI and nevirapine and for children older than 3 years it consists of AZT, ddI and lopinavir/ritonavir.

Second line therapy should not include any of the drugs used in the first-line therapy. The whole treatment of the child should be reviewed thoroughly by a doctor trained in antiretroviral therapy, before any changes are made. Counselling regarding adherence should be stepped up during the process of evaluating the need to change the therapy, as the patient and the caregiver should understand clearly that moving to second-line treatment means that future treatment options in the case of recurrence of the treatment failure will be limited.

15. INDICATIONS FOR EXPERT OPINION

- Previous exposure to antiretroviral drugs
- Infants younger than 6 months
- Concomitant drug therapy with potential drug interactions
- Concomitant diseases: Especially in liver and kidney diseases, the metabolism and excretion of ARV may be changed dramatically, and this needs to be evaluated to ensure that the patient will have adequate blood levels of the antiretroviral drugs to achieve adequate viral suppression.
- Serious side effects

16. FURTHER READING

- National Department of Health, South Africa, 2004: National Antiretroviral Treatment Guideline.
- Levin L. Antiretroviral therapy in children. Clinical guidelines of the Southern African HIV Clinicians Society. *The Southern African Journal of HIV medicine*, Oct. 2002, p23 – 33.
- Kruger M. HIV-infected children: Anti-retroviral therapy. *MIMS Disease Review* 2003: 522-532