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Editorial: HIV care beyond garlic, beetroot and olive oil

This edition's SAFP *updAIDS* column features the third article in a series of four articles on paediatric HIV/AIDS care focusing on best strategies to maintain children and adolescents on antiretroviral therapy. In the week prior to the Toronto AIDS Conference, which has unfortunately been in the news as a result of culinary and nutritional issues rather than life saving scientific breakthroughs, the World Health Organization published detailed guidelines for the treatment of infants and children in resource-limited settings. The guidelines highlight the difficulties in determining drug doses for children, and urge pharmaceutical companies to work towards producing fixed dose combinations that can be used to treat children. They also urge national governments to invest in better methods for diagnosing HIV infection in children below 18 months, where diagnosis with HIV antibody tests is complicated by the presence of maternal antibodies in the infant's bloodstream. WHO wants national governments to strengthen laboratory capacity so that they can use real-time PCR testing to detect genetic material from the virus itself (HIV RNA or DNA), rather than having to wait until a child is 18 months old. Where virological testing is not available clinical signs of HIV disease will continue to be the main means of diagnosis in children under the age of 18 months, but the WHO guidelines warn that clinical algorithms are rarely more than 70% sensitive and are least reliable in children below the age of 12 months, underscoring the need for diagnostic alternatives that can be used in children below the age of 18 months where laboratory facilities are limited or non-existent.

The guidelines note that large volumes of AZT liquid formula are poorly tolerated, and that although d4T is better tolerated, it carries a long-term risk of lipoatrophy in children. Tenofovir, now recommended for first-line treatment in adults, is not available in a paediatric formulation and dosing studies of the tablet formulation have not been carried out in children. Fixed dose triple combinations for children containing nevirapine are being developed by several Indian companies and are expected to be approved within the next year. Detailed dosing tables for all drugs according to weight are available within the guidelines document.

WHO points out that children and infants who have symptomatic HIV disease or who are recovering from an acute infection need to consume 20-30% more calories than HIV-negative children if they are not suffer poor growth and poor recovery from illness. Since severe wasting is a common clinical presentation in children with HIV infection, the guidelines advise that severe malnutrition needs to be stabilised before antiretroviral therapy is begun. Although this phase shouldn't take longer than ten days in HIV-negative children, the guidelines warn that the response to malnutrition treatment may be limited and slow in HIV-positive children. If after six to eight weeks a child has not achieved a weight for height of 85% as a result of special feeding, antiretroviral therapy should probably be initiated. Once a child begins to gain weight on antiretroviral treatment, drug doses need to be reviewed regularly to ensure that the child is still receiving an adequate dose, WHO warns. The full guidelines document can be downloaded from the WHO website at http://www.who.int/hiv/pub/guidelines/art/en/index.html

Maintaining infants and children on highly active antiretroviral therapy

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Introduction

It needs to be emphasized that human immuno-deficiency virus (HIV) infection is not a curable disease and therefore highly active antiretroviral therapy (HAART) requires a life long commitment. This is why it is of paramount importance to ensure adequate preparation before HAART is initiated and to continue supporting the child and the caregiver/family throughout. Strict

and non-wavering adherence is more important in the treatment of HIV than in any other infectious or chronic disease. This is clearly demonstrated by the fact that at least 95% adherence is required to ensure an optimal virologic response in the majority of children. (Table 1) Achieving an optimal virologic response (undetectable viral load) is vital, as the development of drug resistance is far more rapid if this is not attained. Due to the rapidity with which resistance may develop, treatment failure is always a concern and careful follow-up is required to ensure treatment success.

Table 1: Association between treatment adherence and virologic response[1]

Adherence to HAART (percentage of doses taken)	Virologic Failure
> 95%	22%
80%-94%	61%
<80%	80%

In addition, regular follow-up is required because children are dynamic beings; drug dosages require adjustment, treatment adherence must be monitored and the complex psychosocial needs of children with a highly stigmatized chronic life threatening illness needs to be managed. Small children are highly dependant and the success of treatment is closely linked to the caregiver's ability to adhere to the HAART regimen. Therefore, the needs of the caregiver and the child's home circumstances in general should be taken into consideration and assistance provided wherever possible.

Apart from wonderful leash of life that HAART provides, it must be acknowledged that HAART also poses a significant toxicity risk, especially with prolonged drug use. The management of these short and long term toxicities is an important aspect of clinical follow-up. Aspects of follow-up that will be discussed in more detail include regular clinical assessment including toxicities, intermittent laboratory investigations, constant support of adherence and addressing difficult psychosocial issues including disclosure. All these issues need to be borne in mind, while also trying to ensure that the most basic things, such as food security, are in place.

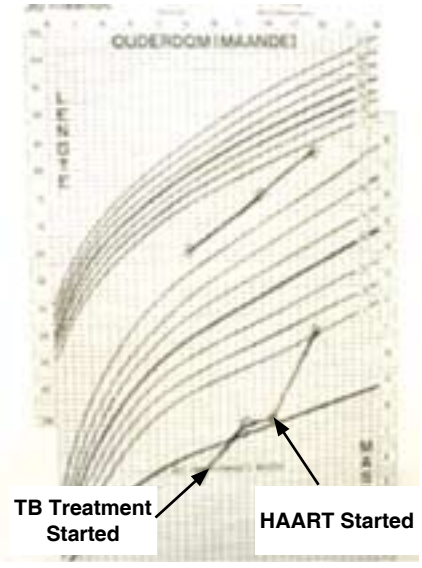
Clinical assessment

Regular clinical assessment should follow the usual sequence, take a relevant medical history, perform routine measurements and complete a thorough physical examination.

History

- Adherence and problems with taking drugs
- Home circumstances
- Health of the caretaker
- Routine vaccinations
- New or worsening complaints , inter-current illnesses should be carefully documented as it is an important marker of treatment response
- Possible contact with infectious illness, particularly tuberculosis
- Symptoms suggestive of drug toxicity
- Monitor developmental milestones and school performance
- Psychosocial issues / Disclosure

Figure 1: Growth chart illustrating a good treatment response



Measurements

- Document the weight and height on the growth chart. In children <3 years the head circumference should also be measured and plotted. These simple measurements are extremely useful to monitor both disease progression and/or treatment response (Figure 1)
- Document basic vital signs including temperature and respiratory rate.
- Consider urine dipstix at regular intervals to detect occult urinary tract infections and/or undiagnosed proteinuria

Physical examination

- This should include a normal tho-rough physical examination, inclu-ding regular neuro-developmental evaluation
- Always asses for possible drug toxicity eg. skin rash, jaundice, enlarged liver, tender abdomen, signs of peripheral neuropathy and lypodystrophy.

Once the physical examination has been completed it is important to review the progress of the child with the caretaker and to discuss potential problems openly and honestly. Adjust drug dosages as required and reinforce the need for good adherence. Explain the new dosing regimen to the caretaker and ensure that the dates for future drug collection and follow-up is clearly communicated.

Potential toxicities

HAART-related toxicity can be divided into short and long term complications. Caretakers should be well informed regarding possible signs and symptoms of drug toxicity and should know how to contact the clinic to seek medical advice. They should be encouraged to seek help immediately and not wait for the next appointment. Clinicians should be careful not to lower the drug dosage below the recommended dose if a specific drug is thought to be the cause of toxicity, as sub-optimal blood levels increase the risk for developing drug resistance.

Short term (<6 months after treatment initiation)

Rashes

There should be a low threshold to review any patient with a rash,

particularly if the child is on drugs where this may indicate a potentially serious side effect i.e. nevirapine (Stevens Johnson Syndrome) or abacavir (hypersensitivity).

Gastro-intestinal symptoms

Diarrhoea is common soon after treatment initiation, particularly when the regimen contains a protease inhibitor (PI). This usually improves when the drug is taken with food. Nausea is also common, but can be expected to settle down after a few weeks. If nausea is a very prominent complaint it is important to consider other causes and to exclude hepatic and/or pancreatic involvement, especially when drugs with potential hepato-toxicity are used.

Anemia

Zidovudine is the drug most likely to cause severe anemia; this is usually macrocytic with a low reticulocyte count. However, it is always important to consider causes other than drug toxicity as well, and iron deficiency anaemia and anemia of chronic illness remains the most common. Regular deworming and routine iron and/or folate supplementation are advised. A haemoglobin level of <7-8g/dl warrants further investigation.

Long term (>6 months after treatment initiation)

Hyperlactatemia

Lactic acidosis and hyperlactatemia are potentially life-threatening complications that arise due to mitochondrial dysfunction; mainly caused by nucleoside reverse transcriptase inhibitors (NRTI), particularly stavudine. Remember to collect either an arterial or a free flowing veneus blood sample, as using a tourniquet may lead to falsely elevated lactate levels. It is important to note that lactate levels are slightly raised in many asymptomatic patients and therefore the routine monitoring of lactate levels in asymptomatic patients is not advised. However, caregivers and clinicians should maintain a high index of suspicion and should request serum lactate levels whenever suggestive symptoms are present. Initial symptoms are vague and include fatigue, abdominal discomfort, loss of appetite and weight loss. More

Table 2: Suggested management of hyperlactataemia*

Suspect Hyperlactataemia – do lactate level • Unexplained anorexia / weight loss / persistent abdominal discomfort or pain / • persistent nausea and vomiting • Unexplained tachycardia / dyspnoea or tachypnoea • Unexplained persistent raised hepatic enzymes			
Interpreting the lactate level#			
Excluded	**Mild**	**Moderate**	**Severe**
Lactate level < 2.5 mmol/ml	Lactate level 2,5-5 mmol/l and Bicarbonate level >20 mmol/l and Minimal symptoms	Lactate level 5-10 mmol/l And/or Bicarbonate level <20 mmol/l	Lactate level >10 mmol/l and/or Bicarbonate level <15 mmol/l
Consider other causes	1) If on stavudine switch to zidovudine or abacavir 2) Repeat lactate after 3 days then weekly 3) STOP HAART IF: -Lactate cannot be monitored -Severe symptoms -Patient not on stavudine -Lactate increasing or symptoms worsening	1) STOP HAART 2) ADMIT TO HOSPITAL 3) Supportive therapy and maintain hydration 4) Investigate for sepsis, opportunistic infections and pancreatitis. Start broad spectrum antibiotic if acutely ill	

* Adapted from HIV Clinicians society guidelines
\# If in any doubt contact an experienced clinician

Table 3: Suggested frequency of routine laboratory investigations in children on HAART*

Regimen	Investigation	Frequency
Basic schedule for all regimens	CD4 Percent	▲Staging & 6 monthly
	Viral load	Baseline and 6 monthly
	Whole blood count	Baseline and 6 monthly
	Alanine transaminase (ALT)	Baseline and 6 monthly
	Urine dipsticks	Baseline and 6 monthly
For protease inhibitor containing regimens	*Fasting cholesterol and triglycerides	Baseline and 6 monthly
	*Fasting glucose	Baseline and 6 monthly
For zidovudine containing regimens	Whole blood count	Baseline & monthly for the first 3 months
For nevirapine containing regimens	Alanine transaminase (ALT)	Baseline 2,4 and 8 weeks

* Adapted from the National Department of Health Guideline
* It may be more practical to take random samples and to follow with fasting samples if required. In addition it may be helpful to do these tests at baseline in all cases if funding permits
▲ If the CD4 count was performed >2-3 months before HAART initiation, then it is justified to repeat it at the time of treatment initiation, for reference purposes

Table 4: Understanding and monitoring adherence, and tools to improve adherence to HAART

Reasons for non-adherence relating to drugs	Poor Palatability and unpleasant avour
	Amount of pills/solution volume
	Frequency of dosing
	Nausea
	Fear of adverse effects (particularly if prior bad experience)
Reasons for non-adherence relating to the family	Lack of disclosure in the family and to the child
	Strangers of visitors in the house
	Parental/ care taker illness
	Lack of believe in the value of the treatment
	Responsibility for giving the medication not residing with a specific member of the family
	Poor understanding
	Denial
	Lack of food security and funding to return to the clinic
	Child refusal
Tools for the parent	Colour coded bottles and syringes
	Pillboxes
	Diary cards to use as aid memoir
	Encourage use of alarms (ie in cellular phones)
	Link medication specific times eg meals or television programs
	Make use of treatment supporters in the community
	Regular visits to therapeutic counsellors
	Early switch to pills
	Treatment buddies
Tools to measure adherence	Calculate adherence by measuring the drugs returned [(Drugs dispensed – drugs returned)/(prescribed)]x100
	Check for late returns to both the clinic and the pharmacy
	Ask regarding missed doses over the preceding week
	Ask about problems with specific drugs
	Looking at diary cards
The clinic should	Stress adherence at every visit
	Assist with disclosure with in the family and to the child
	Help explain do children why they must take these drugs
	Assist with financial and food security through grants and referral to appropriate NGO's
	Support groups

serious symptoms include vomiting, abdominal pain and hyperventilation. In all cases with a raised lactate level, blood gas analysis, hepatic enzymes and amylase or lipase should also be performed. Table 2 include current recommendations to guide the decision making process. The treatment of severe hyperlactataemia with lactic acidosis consists of stopping HAART and providing supportive care, including hospital admission and supplementing B-complex vitamins, especially thiamine.

Lipid disturbances

Hyperlipidemia is particularly associated with the use of PI's but stavudine and efavirenz have also been implicated. Lipid disturbances are linked to increased cardiovascular risk in adults and in children the long-term outcome remains unclear. Cholesterol lowering drugs (eg. statins) have proven benefit to reduce the cardio-vascular risk in adults, but the huge cost and potentially serious interactions between these drugs and HAART limit their use in the public sector; an expert should be consulted. A healthy diet and sufficient exercise remains the mainstay of prevention and should be actively encouraged in all children on HAART.

Lypodystrophy and lypoatropy is represented by specific fat redistribution patterns; PI's are associated with the accumulation of fat in the abdomen, dorsocervical area and breasts. Stavudine has been implicated in the loss of subcutaneous fat in the buttocks, face and extremities. Managing these complications is problematic as the changes are irreversible, although switching the offending drug should prevent further deterioration. Offering cosmetic surgery is not feasible in the public sector, but patients should be prepared psychologically for these potential long term complications

Laboratory investigations

Laboratory investigations have two main functions; 1) to monitor treatment response (CD4 percent/count and viral load tests), and 2) to screen for HAART-related toxicities. The National Department of Health (NDoH) published guidelines to indicate the frequency with which specific tests should be performed. (Table 3) Note that monitoring the lactate level is not part of routine screening and this test should only be performed in patients with suspicious symptoms.

Remember that abnormal laboratory findings are not necessarily related to HAART, the possibility of other clinical conditions and drugs should always be taken into consideration. Severity grading systems with appropriate actions to be taken for specific drug related toxicities are included in current HAART treatment guidelines provided by the NDoH.

Adherence

Adherence is a complex issue that is influenced by multiple interactions between the child and the caregiver, the medical staff and the medication. The crucial importance of good adherence and the strong association between adherence and viral suppression has been emphasized already. (Table 1) Therefore, adequate preparation before initiation of treatment is imperative together with ongoing support and the need to act pre-emptively if things start to go wrong to avoid treatment failure. Every opportunity should be used to enforce the importance of adherence. Medical staff cannot reliably predict adherence and therefore a structured program for monitoring and support should be in place. Caregivers should be provided with tools such as pillboxes and diary cards as well as a structured treat-

Table 5: Talking about HIV to HIV-infected children*

TALKING TO CHILDREN <6 YEARS OF AGE
General considerations
Most children will not understand the concept of HIV infection or be able to keep it private
Suggestions for explaining HIV
You have a germ in your blood that is hurting the healthy parts of your body
That is why you get sick with coughing or diarrhoea or other things that make you feel bad
The medicine will kill these germs so that your blood can become healthy again
If you take your medicine every day you can stay healthy and stop the germ from making you sick
You can always talk to (indicate which family members) or to the doctors and nurses if you have questions
Some possible questions (Q) and answers (A).
Q-How did I get this germ? **A**-You were born with it; you have had it since you where a baby
Q-Can you get rid of this germ? **A**-The medicine can get rid of most of it so you can stay healthy, but we cannot get rid of all of it.
Q-When can I stop taking my medicine? **A**-You have to take your medicine every day so that you can stay healthy. May be one day doctors will be able to get rid of all of the germs, but for now you have to take your medicine every day.
TALKING TO CHILDREN 6-12 YEARS OF AGE
General considerations
Not all children seek the same amount of information. Take your lead from the child as to how much information to provide. You can and should explain infection, immune depletion and the reasons for taking drugs without mentioning HIV in children where the child or the family is not ready for full disclosure (although it should be encouraged at this age).
Keep information simple if the child asks no questions
Suggestions for explaining HIV
You have come to the doctor because you have a germ (virus) that lives in your blood. Ask if child wants to know about germs and illness and correct misinformation.
If the child is ready to hear about HIV give the name of the virus and ask the child what they know about HIV so that you can correct misinformation.
The virus (HIV) kills the cells in your blood that helps you to stay healthy
The name of these cells are T-cells – The virus (HIV) kills T cells
Without T-cells your body struggles to stay well and you get sick with coughing or other things that make you feel bad
The medicine kills the virus (HIV) so that your T-cells can grow back and they can help you stay healthy.
If you stop taking you medicine the virus (HIV) will get stronger again and kill you T-cells then you will get sick again
If you don't take your medicine every day the virus (HIV) can get stronger and the medicine may stop working. The doctors call this a "resistant virus". We do not want this to happen, but if it happens the doctor will change your medicine.
We take blood so that we can measure the T cells and the virus is in your blood. When you are doing well we see lots of T-cells and very little virus
Explaining transmission
You got this virus when you where born. Your mother has the same virus. You got this virus from your mother
You can not get this virus by being friends or hugging or touching. It is OK to play and go to school. If you hurt yourself you must not let other people touch your blood
Regarding privacy
We are explaining all this to you so that you can take better care of yourself
This is private information. Indicate the persons the child can discuss this with
Some possible questions (Q) and answers (A)
Q-Can you get rid of this virus?
A-The medicine can get rid of most of it so you can stay healthy, but can not get rid of all of it. Currently there is no cure.
Q-When can a stop taking medicine?
A-You have to take your medicine every day so that you can stay healthy. Maybe one day doctors will be able to cure HIV, but for now you have to take your medicine every day.
Q-Am I going to die?
A-If you take medicines every day you can stay healthy for a long time.
Q-How did my mom get HIV?
A-Defer to the mother.

* Adapted from Francois-Xavier Bagnoud Center Pocket Guide for Clinicians,2005

ment plan. (Table 4) Once problems with adherence are detected (ie missed appointments, late attendance and returned medication/ missed doses) there should be an increase in counselling and adherence support. It is important that medical staff maintain a supportive non-judgemental attitude that will allow caregivers to discuss their problems freely.

Disclosure

Disclosure and discussion of the child's illness forms an essential part of regular follow-up. Disclosure is a process and not a single event and clinicians should guide and advise caregivers appropriately, taking into consideration the developmental age of the child, the family and their wishes as well as home circumstances. Caregivers are often reluctant to discuss illness and to disclose the child's HIV-status to them, but it is an important process, as sensitive disclosure helps children to adjust faster. It allows them to become a full partner in the management of their disease, are able to assert their autonomy and ultimately it facilitates the transfer of the responsibility to the child.

The reasons for parents/caregivers reluctance to disclose are complex and include:

- Fear of the impact that disclosure may have on the child's psychological and emotional health
- Fear of inadvertent disclosure to others by child
- Protecting the child from social rejection and stigma
- Guilt and a reluctance to discuss how the child became infected
- Difficulty coping with their own illness or illness of other loved ones
- Dysfunctional coping strategies within families e.g. denial
- A belief that the child will not understand
- A reluctance to discuss disease and death

However, children frequently ask what is wrong and want to know why they have to take medications that other children don't take. Older children frequently suspect the di-

agnosis and may develop fantasies about their illness or discover their HIV status at an inopportune moment. It has been shown that children with chronic / fatal illness have higher levels of self esteem and lower rates of depression if they are fully informed about their illness.

Parents, caregivers and medical staff should be truthful at all times; it is possible to provide simple honest explanations to a child regarding their illness without using the words HIV or AIDS. It should always be emphasized that it is not their fault that they or their parents are sick. Always let the family answer sensitive questions about how parents became infected. If parents/caregivers are not present the discussion should be deferred. Table 5 provides some simple guidelines on how to approach these discussions. In cases where parents/caregivers ask medical staff to assist with breaking the news it is better to attend to the feelings of family members before disclosure. Schedule a separate appointment for disclosure and keep the medical facts to a minimum; be respectful of the child's response and accept silence. The child should be followed 1-2 weeks after disclosure to check on their emotional wellbeing.

Assessing treatment success

The indications that a HAART regimen is failing can be divided into clinical, immunological and virological categories. If treatment failure occurs, the underlying reasons should be addressed before switching to a new regimen i.e. if failure is a consequence of poor adherence then it is imperative that this must be addressed before changing to a second line regimen. The decision to change treatment should never be taken lightly; at the same time persisting with a failing regimen will accumulate more resistance mutations, which may compromise future treatment options. It is recommended that clinicians with little experience discuss the case with more experienced providers before switching to a new regimen. Resistance testing is expensive, has limitations and is currently not included in the guidelines of the NDoH, although if may have value under certain circumstances.

Clinical failure

Before diagnosing clinical failure one should ensure that the infant/child has been on an effective regimen for at least 6 months.

- Occurrence of new or recurrence of previous opportunistic infections or malignancy
- Persistent neuro-developmental regression
- Unexplained failure to thrive, not responding to deworming and food supplementation, in children that showed a good initial response to treatment

Note that initial deterioration may occur due to immune reconstitution inflammatory syndrome (IRIS). This phenomenon is well documented during the first few months after treatment initiation and is more likely to occur in children with severe immune suppression.

Deterioration due to IRIS is not regarded as clinical failure, in fact it is a sign of treatment response. A new episode of uncomplicated tuberculosis is also not regarded as indicative of clinical failure, particularly in high-burden areas where the risk of re-infection is high.

Immunological failure

It is important to remember that CD4 counts are variable (natural range of variability 10-20%) and are influenced by intercurrent infections. Therefore, a persistent and significant decline in CD4 count should be present on at least two occasions.

- Change in immune classification
- For children with <15% CD4 Cells - Persistent decline of 5 percentiles or more
- Rapid and persistent decrease in CD4+ count

Virological failure

Viral loads are also highly variable, and as with the CD4 count a persistent and significant trend should be demonstrated, by measuring the viral load on at least two occasions.

- Less than 1.0 log decrease in viral load from baseline after 8–12 weeks
- Persistent rise in HIV RNA levels after an initial decrease or achieving undetectable levels

It is unclear when to switch regimens if virological failure occurs in the absence of clinical and/or immunological failure. Currently NDoH suggest a watch and wait approach, but persisting with failing regimen may lead to the development of more extensive drug resistance that may compromise the performance of second line regimens. This is true for all classes, but has important implications for NRTI's that usually act as the backbone of first and second line HAART regimens, in particular zidovudine and stavudine that share resistance mutations.

Conclusion

Maintaining a child on HAART remains a major challenge due to the need for excellent adherence, the dynamic development of the child both physically and psychologically, and the long and short term toxicity related to HAART. However, with the necessary commitment from the health care team as well as the child and family, HAART provides the opportunity for desperately ill children to flourish and live a healthy fulfilled life, even if the very long-term outcome remains guarded.

Final topic to be covered in this series of articles

- Common opportunistic infections in HIV-infected infants and children

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