

CHANGING ANTIRETROVIRAL THERAPY IN CHILDREN

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This article is an update of a similar article published in the November 2005 edition of this journal. The rapid pace of changes in this field necessitates this update. Alarming numbers of children are failing both first- and second-line antiretroviral therapy regimens in a very short space of time, underscoring the importance of adhering to the basic guiding principles of changing therapy outlined below.

An important maxim in treating patients with HIV is that the first regimen is your best chance for success. Get it right the first time. Recent data show that the response of children to antiretroviral therapy (ART) both overseas and locally has been phenomenal.¹⁻⁴ Nevertheless, inevitably, increasing numbers of children will require a second-line regimen. It is therefore important that we have an approach to changing therapy.

There are two main reasons for changing ART – toxicity or intolerance, and failure of the current regimen. Other reasons include poor adherence (often improved with alternative antiretrovirals (ARVs)) and emergence of more effective or safer regimens.

TOXICITY OR INTOLERANCE

See the Guidelines for Antiretroviral Therapy in Children, p. 32 of this issue. When a patient exhibits intolerance to or toxicity from a single drug, the offending drug can often be replaced, e.g. replacing zidovudine (AZT) with abacavir (ABC) for bone marrow toxicity caused by AZT. Rarely, a reduction in dosage may be considered as long as the reduced dose is still in the therapeutic range.

For severe toxicity such as lactic acidosis or ABC hypersensitivity reaction, all ART should be stopped until the patient recovers. Only then can one cautiously restart

Please note: The recommendations given in this article are only a guide. There is no substitute for expert advice when changing ART. Please consult the SA HIV Clinicians Society or the author for a list of local and overseas experts willing to assist you.

ART. The offending agent should be switched for one that does not cause the same reaction.

FAILURE OF CURRENT REGIMEN

Ideally one should not change therapy on the basis of a single viral load (VL) or CD4 count.

Before changing ART, a thorough assessment of adherence issues should be made. Adherence is the most important factor determining the success of an ART regimen.⁵⁻⁷ Adherence issues must be resolved before changing therapy.

The US Public Health Service Guidelines⁸ lists three types of failure of an antiretroviral regimen – virological, immunological and clinical failure (Fig. 1).

Unfortunately there are few paediatric data on when to change ART. PENPACT1, a study in Europe and the USA, is comparing changing ART at a VL of 1 000 versus 30 000 copies/ml. Their results will be presented at the World AIDS Congress in 2010. The South African guidelines recommend changing regimens when the VL is repeatedly above 1 000 copies/ml. Some paediatric experts would not change the therapy until the VL was repeatedly >5 000 - 10 000 copies/ml. Intervention does not necessarily mean a change of regimen. It may involve resolving adherence issues or changing to a holding strategy. With a persistently elevated VL, resistance mutations will accumulate⁹ and cross-resistance to drugs that the patient has not been exposed to will occur.

Isolated VL 'blips', e.g. single levels of 50 - 1 000 copies/ml, are not usually associated with subsequent virological failure.^{10,11} It is important to follow up a blip

Virological considerations:

Incomplete response to therapy:

- $<10 \times (1 \log_{10})$ decrease from baseline VL at 8 - 12 weeks
- HIV RNA >400 copies/ml after 6 months or above the level of detection using an ultrasensitive assay after 12 months of therapy (some would accept a VL $<5\ 000$ copies/ml in a stable patient)

Viral rebound:

Repeated detection of plasma HIV RNA on ultrasensitive PCR assays where viral load was previously undetectable. Infrequent episodes of low level viraemia ($<1\ 000$ copies/ml) are common and not generally reflective of virological failure, whereas repeated or persistent viraemia ($>1\ 000$ copies/ml) more probably represents viral rebound (some would accept a VL $<5\ 000$ copies/ml in a stable patient)

Immunological considerations:

Incomplete immunological response to therapy:

- <5 years of age: Failure to improve CD4% values by $\geq 5\%$ where CD4% was previously $<15\%$
- ≥ 5 years of age: Failure to improve CD4 values by ≥ 50 cells/ μl above baseline where CD4 was previously <200 cells/ μl within the first year of therapy

Immunological decline:

Sustained decline of 5% in CD4% below pre-therapy baseline at any age, or decline to below pre-therapy baseline in absolute CD4 cell count in children who are age 5 years and older

Clinical considerations:

Progressive neuro-developmental deterioration

Growth failure:

Persistent decline in weight-growth velocity despite adequate nutritional support and without other explanation

Severe or recurrent infection or illness:

Recurrence or persistence of AIDS-defining conditions or other serious infections

Fig. 1. Considerations for changing therapy in paediatric patients on antiretroviral therapy.⁸

with another VL after 3 months to exclude virological failure.

In children with low CD4 counts, an opportunistic infection can occur before the immune system has recovered and is not an indication to change ART. Similarly, with bronchiectasis recurrent lower respiratory tract infections are to be expected. Immune reconstitution inflammatory syndrome (IRIS) is also not an indication to change ART.

CHANGING THERAPY

DIFFERENT SCENARIOS WHEN CHANGING ART

There are three main scenarios when changing ART for drug failure.

- Early failure of a first regimen – there is unlikely to be much cross-resistance. A simple choice of a different regimen is usually adequate.
- Intermediate failure of a first regimen – some cross-resistance may be present. Genotyping may be helpful in ascertaining the degree of cross-resistance.

- Extensive prior treatment – extensive drug resistance is likely.

INITIAL ASSESSMENT

This is important in determining the cause of failure, as frequently the same issues will be a barrier to the success of a subsequent regimen.

Assessing adherence

Adherence is the most important factor in determining the success of an ART regimen.⁵⁻⁷ Virological failure often follows poor adherence. Do not change therapy until the adherence issues have been resolved. Since the first regimen is often the best tolerated, subsequent regimens are often not as well tolerated and are likely to exacerbate adherence issues. Changing ART is never an emergency and is futile without addressing adherence. If adherence issues cannot be resolved quickly and you are worried about accumulating new resistance mutations, there may be a role for a 'holding strategy' until the family is ready to start the new regimen (see 'Holding strategies' below).

Exclude inadequate drug exposure

Possible causes include:

- Drug not being ingested, e.g. poor adherence, vomiting, or spitting up of an unpalatable drug such as ritonavir.
- Poor absorption, often in children with chronic diarrhoea or malabsorptive states.
- Increased drug metabolism – children beyond the neonatal age have markedly increased drug metabolism compared with adults. Post-marketing research often reveals package insert dosages to be inadequate. Consult an up-to-date paediatric ART guideline for correct dosages.
- Drug interactions – investigate all medications the patient is taking (including over-the-counter drugs and 'herbal' products) for possible drug interactions with ARV agents. Commonly implicated drugs include rifampicin, anti-epileptics, antimalarials and St John's wort.

Exclude other causes of a raised VL and/or a lower CD4 count

Intercurrent infections, opportunistic infections and immunisations may temporarily drop the CD4 count or raise the VL.

Ideally one should repeat the CD4 and VL 1 month later to ensure a return to baseline.

FACTORS TO CONSIDER WHEN CHANGING ANTIRETROVIRAL THERAPY

Expert advice

There is no substitute for expert advice when changing ART. The field is fraught with pitfalls for the unwary. Many patients' futures have been compromised by poor choices when changing therapy. There is always enough time to consult with an expert before changing therapy.

Resistance testing

Only genotypic assays are available in South Africa. Adult data reveal a short-term benefit of resistance testing in terms of virological response.^{12,13} Paediatric data are conflicting,¹⁴⁻¹⁷ but most experts believe that these assays have a role in changing ART in the face of resistance. Overseas guidelines recommend using resistance testing with every change of ART regimen caused by treatment failure.^{8,18} This is also the recommendation of the SA HIV Clinicians Society, but prohibitive cost (over R4 000) will probably mean that in the South African state sector genotyping will only be done (if at all) after failure of a second regimen. Apart from the cost, genotyping has other limitations, including the following:

- Genotyping will only give information about the current regimen. If a patient has failed a drug in a

previous regimen, genotyping may therefore falsely report susceptibility to that drug.

- Genotyping should be done while the patient is still taking their 'failing' regimen or within 4 weeks of stopping it.¹⁸
- Genotyping needs expert interpretation. It requires in-depth analysis by someone highly experienced in the field who also has all the details of the patient's treatment history. Knowledge of paediatric data and formulations are essential for correct advice.

At least 2 new drugs

Always try to include at least 2 (preferably 3) new or active agents.¹⁸ One needs to be aware of cross-resistance (see below), since what may look like a 'new agent' may be ineffective as the virus is already resistant to it. Genotyping may help to select which drugs in the present regimen could be re-used. This does not apply to drugs in a *previous* regimen, as resistance mutations may be below the level of detection.

Preferably a new drug class

Studies have shown that the success of a subsequent regimen is increased if it contains an antiretroviral class to which the patient has not previously been exposed.^{19,20} Two new drug classes, integrase and CCR5 inhibitors, should be available locally soon. They will be useful in highly experienced patients.

Do not add one drug to a failing regimen

Adding one drug to a failing regimen will predispose to the rapid development of resistance. This is the equivalent of monotherapy, which should generally be avoided at all costs. A variant of this is combining an active drug with a low genetic threshold for resistance, such as a non-nucleoside reverse transcriptase inhibitor (NNRTI) or raltegravir (integrase inhibitor), with 2 partially active drugs – in this situation the active drug will fail quickly.

Consider cross-resistance

Cross-resistance can be defined as phenotypic resistance to one drug resulting from mutations (genotypic) selected by another drug.²¹ There is no cross-resistance between the different ARV classes. In the nucleoside reverse transcriptase inhibitor (NRTI) class, AZT and stavudine (d4T) are both thymidine analogues that select for the same resistance mutations, and there is cross-resistance between them. Generally, however, there is unlikely to be much NRTI cross-resistance after failing a first regimen.²¹ With the currently available NNRTIs, on the other hand, there is a high level of cross-resistance. If a patient fails nevirapine (NVP), there will be high-level resistance to efavirenz (EFV). The new second-generation NNRTI etravirine (ETR), which will soon be available in South Africa, needs a few NNRTI mutations before there is high-level resistance against it. Unfortunately,

genotyping is necessary to ascertain whether ETR will be active after failing an NNRTI.

Cross-resistance in the protease inhibitors (PIs) depends on the PI concerned. Some PIs, e.g. atazanavir, amprenavir and nelfinavir, develop specific primary mutations first without conferring cross-resistance to other PIs. Secondary mutations conferring cross-resistance to other PIs will only occur after prolonged non-suppressive therapy.

Genotyping may help to clarify whether cross-resistance is present. Expert advice can be invaluable in this situation.

Consider drugs used for prevention of mother-to-child transmission (PMTCT)

Numerous studies have demonstrated resistance to NVP where mothers and their babies each receive one dose of NVP. There are emerging data in adults and infants suggesting reduced efficacy of future first-generation NNRTI-containing regimens.²²⁻²⁴ It is therefore advisable to avoid NVP and EFV as part of first-line therapy in this situation. Consult the Guidelines for Antiretroviral Therapy in Children (p. 32 of this issue) when other ARVs have been used for prophylaxis.

Consider adding 3TC where M184V mutation present to maintain M184V mutation

Resistant HIV-1 with the hallmark 3TC resistance mutation, M184V, has reduced viral fitness, i.e. it replicates at a reduced rate and may reverse resistance to AZT, d4T and tenofovir (TDF). Therefore there may be value in adding in 3TC for salvage despite documented resistance.

However, the data are conflicting.^{25,26} ABC will also maintain the M184V mutation without adding in 3TC (personal communication, Professor Mark Wainberg).

Pharmacokinetic enhancement

Where a single PI has been used previously, there may be a place for using a 'boosted PI', i.e. adding a small dose of ritonavir to the PI to inhibit the enzyme cytochrome P450 3A4, thus resulting in much higher levels of the PI. This may overcome minor degrees of PI resistance. Generally, however, it is advisable to only use boosted PI regimens.

Therapeutic drug monitoring (TDM)

TDM is still largely experimental in ART. However, there may be a place for TDM in salvage therapy with multiple drugs and multiple possible interactions. Contact the SA HIV Clinicians Society.

Dual PIs

This used to be quite 'fashionable' as a salvage therapy a few years ago. Invariably these children will have ex-

tremely high cholesterol and triglyceride levels. With the advent of newer agents and with data suggesting that dual PIs are no more efficacious than one boosted PI, this approach has become less popular.^{27,28}

Mega- or giga-HAART

There are some adult data on empiric multidrug regimens,^{29,30} but these are complex and poorly tolerated, and often with unfavourable drug interactions. With the advent of newer ARVs these regimens are no longer used much. A feeding gastrostomy tube may be used to simplify the administration of multiple medications.³¹

New ARVs

Several new agents are already available overseas with activity against resistant virus. TDF is available in South Africa, but it is not used routinely in children because of osteopenia and nephrotoxicity. However, if properly monitored TDF has some merit as a salvage drug in older patients. New PIs such as darunavir³² and tipranavir³³ have revolutionised the management of highly resistant patients overseas. Raltegravir will be the first integrase inhibitor to be launched in South Africa. This potent and well-tolerated agent has shown phenomenal results in both naïve and ART-experienced adults.^{34,35} Paediatric studies are ongoing.³⁶

Etravirine, the second-generation NNRTI, may still be active in the face of resistance to first-line NNRTIs.^{37,38} The CCR5 inhibitor maraviroc will probably have limited use in South Africa since it is only effective in patients who are CCR5-tropic and requires an expensive tropism assay prior to initiation.³⁹

These new agents have achieved undetectable VLs in heavily ARV-experienced adults in contrast to earlier salvage regimens. Paediatric dosages and formulations are in development. Nevertheless, one can obtain Section 21 authorisation from the Medicines Control Council. Consult an expert.

Holding strategies

Not uncommonly one encounters a situation where a child needs to change ART but for various reasons is unable to. Common situations are unresolved adherence issues, inability to swallow tablets, or needing a new ARV that lacks paediatric dosing data or formulations. If the CD4 count is not too low, there may be place for a 'holding strategy'. These are only temporary solutions and do not replace a **suppressive regimen**. Holding strategies include **structured treatment interruptions, 3TC monotherapy and holding regimens**. These approaches should only be used on the advice of an expert.

■ *Structured treatment interruptions (STIs)*

There are three scenarios where one might consider stopping therapy:

Infants. Since paediatric HIV infection occurs with an immature immune system, treating with ARVs may allow the immune system to mature. Thus, a baby who has had several months of ART and is now over 1 year of age may cope without ART for several years because the immune system is now mature enough to cope with the baby's own HIV virus. The CHER study is currently looking at this phenomenon. Until the results of this study are published, this is not recommended as a routine practice.

Infants and children with immune reconstitution. This is a situation where the patient's CD4 count has recovered but the child is now virologically failing the current regimen. In this situation, there may be a place for taking the child off all therapy and watching the CD4 count carefully. Once the CD4 count drops below the criteria for starting ART, a new regimen can be started. The SMART study, in adults, showed a worse outcome in patients who stopped their ART compared with those who remained on ART,⁴⁰ but there are few paediatric data. PENTA11, a pilot interruption study in children, showed no deaths or serious clinical events on interruption for up to 48 weeks.⁴¹

Multidrug-experienced children with low CD4 counts. Adult data reveal that there is no place for STIs in a salvage situation.⁴²⁻⁴⁴ The CD4 count drops rapidly and the patients are at risk for opportunistic infection.

■ 3TC monotherapy

Although there are comparatively few adult data on this approach, 3TC monotherapy has gained popularity. There are data to suggest that giving 3TC monotherapy in patients failing multiple drugs results in slower disease progression than no therapy at all⁴⁵ because of reduced viral fitness in virus with the M184V mutation. This can be attempted. The approach may have merit in patients failing 3TC but with good CD4 counts and unable to start a definitive suppressive regimen. 3TC monotherapy should be avoided in patients who have ever had a very low CD4 count (low CD4 nadir). When the CD4 drops or symptoms develop, the child should be placed on a fully suppressive regimen.

■ Holding or bridging regimens

These are simplified regimens, usually consisting of 3 or 4 NRTIs with the purpose of maintaining resistance mutations so that the virus has a reduced replicative ability. The aim once again is to 'buy time' for the child who is unable to start a definitive suppressive regimen. A suitable child would be one with extensive NRTI resistance but in whom you would not want to develop more PI or NNRTI resistance. Therefore future options are preserved. Since there is already extensive NRTI resistance, there is no worry that the child will develop more resistance to the NRTIs. In adults, AZT/3TC/ABC/TDF has been used.⁴⁶ In younger children, TDF can be omitted. Once again this

approach is inappropriate for patients with a very low CD4 count. Once the CD4 count drops or symptoms develop the child should be placed on a fully suppressive regimen.

Quality of life in end-stage disease

In patients without further ARV options and who are failing or not tolerating mega-HAART, there may be a place for reducing the number of drugs to make life more tolerable. The disease will still progress more slowly than if off ARVs. Consult an expert to reduce the number of agents to a more tolerable regimen. 3TC should always be included in such a regimen. As more new drugs become available, this scenario is becoming less common.

CONCLUSION

Changing ART is a highly complex field, which can have major impact on a child's future if done incorrectly. It is therefore strongly recommended that an expert be consulted before changing any child's ART. This would apply equally to a child failing their first regimen. However, the future is rosy with wonderful new antiretroviral options and certainly something worth looking forward to.

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