CHANGING ANTIRETROVIRAL THERAPY IN PAEDIATRIC PATIENTS

Leon J Levin, *MB BCh, FCPaed (SA), DTM&H*
Paediatrician in Private Practice, Benoni, Gauteng

An important principle in treating patients with HIV is that the first regimen is your best chance for success. So get it right the first time. Historically children have always lagged behind adults in their (virological) response to antiretrovirals (ARVs).[1-3] However, with improvements in knowledge about pharmacokinetics, adherence and newer more potent and tolerable drugs in children, response to therapy in children is now approximating that in adults.[4-6] Nevertheless, it is inevitable that over time, for a variety of reasons, a significant number of patients will need to move to a second-line regimen. For this reason, it is important that we have an approach to changing therapy.

There are two main reasons for changing antiretroviral therapy (ART) – firstly toxicity or intolerance, and secondly failure of the current regimen. Other reasons include poor adherence that may be improved with another regimen and new data becoming available suggesting that a new drug or regimen is superior to the existing regimen.

TOXICITY OR INTOLERANCE

Readers are referred to the SA HIV Clinicians Guidelines for Paediatric ART (p. 18, this issue).

When a patient exhibits intolerance to or toxicity from a single drug it may be acceptable to just replace the offending drug with another that does not have the same toxicity, e.g. replacing AZT with d4T in the case of bone marrow toxicity caused by AZT. In rare instances a reduction in dosage may be considered, but only where the new reduced dose will still provide the necessary therapeutic range.

Where a severe toxic reaction such as lactic acidosis or abacavir hypersensitivity reaction occurs, all ART should be stopped until the patient recovers. Only then can one cautiously restart ART. The offending agent should be switched for one that does not have the same toxicity profile.

FAILURE OF CURRENT REGIMEN

Ideally one should not change therapy based on a single viral load (VL) estimation or CD4 count. VL and CD4 may be falsely affected by intercurrent infections or recent vaccinations. Ideally, therefore, these investigations should be repeated after 1 month before considering changing therapy.

Please note: The recommendations given in this article are merely 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 who would be willing to assist you.

Before any consideration is given to changing ART, a thorough assessment of adherence issues should be made. As discussed below, adherence is the most important factor in determining the success of an ART regimen.[7-9] Adherence issues should first be resolved before changing therapy.

The US Public Health Service Guidelines[10] lists three types of failure of an antiretroviral regimen – virological, immunological or clinical failure (Table I). Children differ from adults in their response to therapy. As mentioned above, this may be changing with the advent of newer more potent drugs. In addition, children may have a very good immunological and clinical response to ART despite not having an undetectable viral load. This leads to the following dilemma:

- if they are changed too soon, there is a risk of using up all available agents in a short space of time
- if they are kept on the 'failing' regimen, there is a risk of accumulating resistance mutations.

Most paediatric experts would not change the therapy if the viral load is < 10 000 copies/ml and the CD4 count is normal or increasing and the child is doing well clinically. This approach, however, does lead to the accumulation of resistance mutations,[11] which means that when one eventually changes regimens it is no longer a simple case of moving from the prescribed first-line to the second-line regimen. Therefore it is imperative that a paediatric ART expert be consulted whenever a change in therapy is contemplated.

Isolated viral load 'blips', e.g. single levels of 50 - 1 000 copies/ml, are not usually associated with subsequent virological failure.[12,13] In children with low CD4 counts an opportunistic infection may still occur before the immune system has recovered and is not an indication to change ART.

TABLE I. CONSIDERATIONS FOR CHANGING THERAPY IN PAEDIATRIC PATIENTS ON ANTIRETROVIRAL THERAPY

Virological considerations
- < 10 × (1 $\log_{10}$) decrease from baseline VL at 8 - 12 weeks
- HIV RNA not undetectable at 4 - 6 months (where initial VLs are high, an immediate change in therapy may not be warranted if there is a sustained 1.5 - 2.0 $\log_{10}$ decrease in HIV RNA copy number, even if RNA remains detectable at low levels)
- Repeated detection of HIV RNA where previously undetectable
- Reproducible increase in VL where previously a good response but low HIV RNA levels:
  < 2 yrs - > 5 × (0.7 $\log_{10}$) increase
  > 2 yrs - > 3 × (0.5 $\log_{10}$) increase

Immunological considerations
- Change in immunological classification (e.g. 2 to 3)
- For children with CD4+ T-cell percentages of < 15% (i.e. those in immune category 3), a persistent decline of 5 percentiles or more in CD4+ T-cell percentage (i.e. from 15% to 10%)
- Rapid and substantial decrease in absolute CD4+ T-cell count (i.e. > 30% decline in < 6 months)

Clinical considerations
- Progressive neuro-developmental deterioration
- Growth failure
- Disease progression, e.g. from clinical category A to B

Adapted from reference 10.
VL = viral load.

Similarly, immune reconstitution inflammatory syndrome (IRIS) is not an indication to change ART.

CHANGING THERAPY

DIFFERENT SCENARIOS WHEN CHANGING ART

There are three main scenarios encountered when changing ART for drug failure.
- **Early failure** of a first regimen – there is unlikely to be much cross-resistance, and 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

Initial assessment 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.[7-9] Virological failure often follows poor adherence. It is therefore logical that if poor adherence is the reason for failure of a regimen, one should not change therapy until the adherence issues have been resolved. Since the first regimen is often the best tolerated regimen, subsequent regimens that are not as well tolerated are likely to compound any adherence issue. Just as starting ART is never an emergency, so changing ART is never an emergency. Changing ART before adherence issues have been resolved is futile. If it is going to take a while before the adherence issues are resolved and one is concerned about accumulating new resistance mutations, there may be justification for stopping all ART until the family is ready to start the new regimen (see 'Structured treatment interruptions' below).

Exclude inadequate drug exposure

Another cause of treatment failure is inadequate drug exposure due to a number of possible factors:
- **Drug not being ingested**, e.g. poor adherence, vomiting, spitting out of a drug such as ritonavir, which is very unpalatable.
- **Poor absorption**. Children with chronic diarrhoea or malabsorptive states may not be absorbing their ARV drugs adequately.
- **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 updated paediatric ART guidelines for correct dosages.
- **Drug interactions**. It is imperative to investigate all medications the patient is taking (including over-the-counter drugs and 'herbal' products) for the possibility of drug interactions with ARV agents. Commonly implicated drugs include rifampicin, anti-epileptic agents, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and St John's wort.

FACTORS TO CONSIDER WHEN CHANGING ANTIRETROVIRAL THERAPY

Expert advice

As mentioned above, there is no substitute for expert advice when changing ART. It is a field full of pitfalls for the unwary. Many patients' futures have been compromised by poor choices made when changing therapy. Since there is no emergency in changing ART, there is certainly enough time to consult with an expert.

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.[14,15] Paediatric data are conflicting[16-18] and adequate trials are not available, but most experts would see themselves as having a role in changing ART in the face of resistance. Overseas guidelines seem to be recommending resistance testing with every change of ART regimen due to treatment failure.[10,19] However, its prohibitive cost (over R3 000) will probably mean that genotyping will only be used after failure of a second regimen in South Africa. Apart from the cost, genotyping has other limitations:
- Genotyping will only give information about the patient's current regimen, i.e. it will not give information about viral resistance to a previous regimen. Therefore a genotyping

report suggesting that a virus is sensitive to a certain drug may not be correct if the patient has previously failed this drug or a drug in the same class in a previous regimen.

- Genotyping should be done while the patient is still taking his/her 'failing' regimen or within 4 weeks of stopping it.[19]
- Genotyping needs expert interpretation. It cannot simply be interpreted as one would a microbiology culture and sensitivity report, but needs an in-depth analysis by someone highly experienced in the field who also has all the details of the patient's previous treatment history.

At least 2 new drugs

Always try to include at least 2 (preferably 3) new agents.[19] The issue of cross-resistance needs to be borne in mind. Genotyping may help in selecting which drugs in the present regimen could be used again. As mentioned, this does not apply to drugs in a previous regimen, as resistance mutations to previously taken drugs may not be detected by genotyping.

Preferably a new drug class

Studies have shown that the success of a subsequent regimen is increased if it contains an ARV drug class to which the patient has not previously been exposed.[20,21] For this reason it is not a good idea to start with a regimen containing all three drug classes, as this will mean that there is no new drug class available for the next regimen. Enfuvirtide is the first of a new class of drugs, the HIV entry-inhibitors, which is now available overseas. It is useful in that it allows one to use a new class of ARV drugs in highly drug-experienced patients. However, its prohibitive cost and the fact that it must be given by subcutaneous injection twice daily means that it will probably have restricted use in South Africa.

Don't add one drug to a failing regimen

Adding one drug to a failing regimen is likely to result in rapid development of resistance. It is the equivalent of monotherapy, which should generally be avoided at all costs.

Consider cross-resistance

Cross-resistance can be defined as phenotypic resistance to one drug resulting from mutations (genotypic) selected by another drug.[22] There is no cross-resistance between the different classes of ARVs. For the nucleoside reverse transcriptase inhibitor (NRTI) class there may be cross-resistance, e.g. zidovudine (ZDV) and stavudine (d4T) 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.[22] With the NNRTIs, on the other hand, there is a high level of cross-resistance. Generally it can be assumed that if a patient has failed any of the NNRTIs, there will be high-level resistance to the other NNRTIs. Cross-resistance in the protease inhibitor (PI) class depends on the PI concerned. Some PIs, e.g. atazanavir, amprenavir and nelfinavir, develop specific primary mutations first which do not confer cross-resistance to other PIs. Only after prolonged treatment with a failing PI will secondary mutations occur that confer cross-resistance to other PIs.

Genotyping may help to clarify whether cross-resistance may be present or not. The help of an expert can be invaluable in this situation.

Consider drugs used for PMTCT

Numerous studies have confirmed that resistance to nevirapine (NVP) can occur where mothers and their babies each receive one dose of NVP for prevention of mother-to-child transmission (PMTCT). There are emerging data in adults suggesting reduced efficacy of future NNRTI-containing regimens.[23] It is therefore advisable to avoid NVP and efavirenz as part of first-line therapy in this situation. Consult the SA HIV Clinicians Paediatric ART Guidelines on p. 18 of this issue, where other ARV drugs have been used for MTCT prophylaxis.

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

Resistant HIV-1 virus with the hallmark lamivudine (3TC) resistance mutation, M184V, has reduced viral fitness, i.e. it replicates at a reduced rate and may also reverse resistance to ZDV, d4T and tenofovir (TDF). For this reason, there may be value in adding 3TC in a salvage situation even though there is documented resistance to it. The data, however, are conflicting.[24,25]

An example would be a patient who was on 3TC in the first regimen and developed resistance to it. He subsequently fails his second regimen. For his third regimen, it is to be hoped that adding in 3TC as a 4th drug in addition to the 3 new active drugs will maintain the weaker 3TC-resistant virus, which will replicate more slowly and be easier to control than wild-type virus. It has been shown that 3TC monotherapy in patients who have failed multiple drugs results in slower disease progression than no therapy at all.[26]

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 CYP3A4 enzyme that metabolises the PI. This results in much higher levels of the PI and may overcome minor degrees of PI resistance.

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.

Structured treatment interruptions (STIs)

This approach should only be used on the advice of an expert. There are three situations in which one might consider stopping therapy:

- **Infants**. Since paediatric HIV infection takes place in the setting of an immature immune system, treating with ARVs may allow the immune system to mature. A baby who has had several months of ART may cope without ART for several years because the immune system is now mature enough to produce viral suppression. A study is

currently underway in South Africa to study this phenomenon. Until the results are published, this practice is not recommended.

- **Infants and children with immune reconstitution**. This is a situation in which the patient's CD4 count has recovered but he or she is now failing the current regimen virologically. Here 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 threshold for starting ART, a new regimen can be started. Some patients may be able to go for several years without needing ART, by which time more effective or safe agents may have become available.
- **Multidrug-experienced children**. Adult data reveal that there is no place for STIs in a salvage situation.[27-29] The CD4 count drops rapidly and patients are at risk of developing an opportunistic infection. The only possible reason to stop treatment in this situation is in order to resolve an adherence problem.

Mega- or giga-HAART

There are some adult data on the efficacy of empiric multidrug regimens,[30,31] but these are complex and poorly tolerated and often have unfavourable drug interactions. A feeding gastrostomy tube may be used to simplify the administration of so many medications.[32]

Quality of life in end-stage disease

In patients who have used up all possible options and who are failing or are unable to tolerate a mega-HAART regimen, there may be a place for reducing the number of drugs the patient is taking in order to make life more tolerable. Frequently patients taking mega-HAART do not tolerate it. A feeding gastrostomy tube may simplify taking all those medications,[32] but if this does not help, or if the patient really cannot tolerate the drugs, there may be a role for simplifying the regimen. Even if a regimen is failing, it will delay disease progression compared with no drugs. It is therefore inadvisable to stop the ART completely in this situation. Rather, with the help of an expert, reduce the number of agents to a more tolerable regimen. As mentioned above, 3TC should always be included in such a regimen.

New antiretroviral drugs

New agents are being developed, or may already have been launched overseas, that will be active against resistant virus. Drugs such as TDF and tipranavir may be useful in the highly ART-experienced patient. It is always useful to find out from an expert if there are any new drugs available that could potentially help a patient. Even if they have not been registered in this country yet, they may be accessible through a 'Section 21' authorisation from the Medicines Control Council.

CONCLUSION

Changing ART is a highly complex field, which can have a major impact on a child's future if not done correctly. For this reason it is strongly recommended that an expert is consulted before changing any child's ART. This article is intended to show the complexity of the subject and the issues that need to be taken into account, and *not* as a guide to doing it yourself.

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