

CHILDREN'S ADHERENCE TO HAART

Paul Roux, MB ChB, MPhil (Bioethics), FCP (Paed), MD
Paediatric HIV/AIDS Service, Grootte Schuur Hospital, Cape Town

CHALLENGES IN PAEDIATRIC ADHERENCE

Highly active antiretroviral therapy (HAART) can achieve control of viral replication in HIV-1-infected children who adhere to therapy, but there are two major challenges to its successful use:

- Complex regimens which include multiple medications and dosing intervals, and
- Formulations that are difficult for caregivers to prepare or are unpalatable. Such medications will be less likely to be administered to a child.

Fortunately these problems can be overcome.

A few points worth noting when prescribing HAART in developing countries are, firstly, that a low-price HAART regimen is not necessarily the cheapest option if it adds complexity to administration (crushing, suspending and carefully measuring volumes of water). Although the paediatric suspensions are more expensive than other dosage forms, i.e. tablets, powders and capsules, they facilitate the preparation by caregivers, ease administration, and as a result, improve adherence. In fact, the majority of charity-funded HAART programmes have opted for relatively expensive, but simple, suspension-based regimens because in the long term the costs and outcomes are better.

Secondly, if caregivers are not well prepared for adherence issues before starting HAART, or if regimens are too onerous to follow, treatment is likely to fail. Every effort should be made to see the burden of adherence from the caregiver's point of view. Meticulous attention to detail offers the greatest likelihood of making HAART a successful venture. *The key element to adherence lies in the amount of time and care the health care worker can devote to the effort of explaining the purpose and practice of adherence.*

Unfortunately, South African children have rarely been enrolled as subjects in drug trials, and therefore few local paediatricians in public or academic practice have been able to gain experience in using HAART. Clinical experience with antiretrovirals has mostly been restricted to physicians in private practice and those engaged in drug trials.

WHAT WE 'KNOW' SO FAR – A REVIEW OF THE LITERATURE

A review of published work conducted internationally reveals what has been learnt about paediatric adherence so far.

The so-called PENTA 1 trial¹ conducted by the Paediatric European Network for Treatment of AIDS studied parents' attitudes to their HIV-infected children being enrolled into a placebo-controlled trial. When asked to describe the degree of interference with daily life that the administration of the medication caused, 43% of parents described it as 'moderate' or 'great'. Caregivers' concerns included forgetting to administer doses of medication, taste of medicine, and volume of trial medication. The findings underline the importance of trying to develop and evaluate innovative ways of helping families with these problems.

In a study looking at adherence to antiretroviral therapy and *Pneumocystis carinii* prophylaxis, in HIV disease in children, conducted by Eldred *et al.*² in 1998, 60% of parents reported $\geq 80\%$ adherence over a prior 7-day period. Adherence was found to be correlated with:

- simple regimens (twice daily) and
- belief in ability to adhere, and
- were uncorrelated to sociodemographics or belief in efficacy.

A more recent article³ confirmed adherence as a determinant of response to HAART in children. One hundred and ninety-three children were enrolled in the study, which compared various combinations of d4T, 3TC, nevirapine, zidovudine and zalcitabine. From this group, 125 completed full data sets of 3-monthly questionnaires. Seventy per cent of the 125 achieved complete adherence, while 30% were non-adherent. There was 84% adherence for zidovudine and 68% for zalcitabine. Most difficulties were found with zalcitabine, and included poor taste, patient refusal, and scheduling problems. Adherence was found to be directly correlated with efficacy: full adherence (FA) was seen in 92% of children with a decrease in viral load greater than or equal to $2 \log_{10}$ and in 64% of children with smaller than $2 \log_{10}$ decrease in viral load.

In another, smaller adherence trial⁴ in 2001, 44 children with a mean age of 9.4 years were studied. There was a mean burden of 8.1 pills or syrup doses, and 54.5% of children also required food restrictions. Mothers administered the medication in 58% of cases. It was shown that 20 - 30% had missed at least 1 dose in 3 days. The main problems cited were:

- too many pills, too many doses
- difficulty swallowing pills
- taking medication at school, and when away from home
- refusal to take medication and spitting up medication, and
- food interactions.

The results highlighted the need for improved formulations and better counselling tailored to meet individual treatment.

In another paediatric study⁵ two characteristics of caregivers were identified as associated with non-adherence. One was inability to describe the medication, and the other was non-attendance at appointments. This study confirmed that adherence of 90% or higher is associated with a virological response.

Caregivers of children enrolled in clinical trials are often more thoroughly counselled and supported than in ordinary clinical practice. This has been found to impact on efficacy and adherence to HAART.⁶ Over the first 180 days it was found that even among clinical trial subjects only 58% were totally compliant, and a non-detectable viral load was recorded in only 52% of patients. Only 3 patients (10%) maintained a viral load < 400 copies/ml. The trial confirmed that there is a high risk of treatment failure unless there is adherence.

WHAT WE THINK WE KNOW – AN ANALYSIS OF CONSENSUS

HIVATIS⁷ website lists reasons why children fail to comply with treatment and barriers to adherence:

Failure of compliance

- unpalatable medicines
- difficult formulations
- problems around meals
- non-disclosure to others
- hiding/re-labelling medicines
- defaults at clinic
- midday doses.

Barriers to adherence:

- denial and fear
- misinformation
- distrust

- fear and lack of belief in medications
- low self-esteem
- unstructured chaotic life
- lack of family support.

PROMOTING ADHERENCE TO HAART – SUFFICIENT COUNSELLING AND SUPPORT

It is obvious from what we know that parents/caregivers require detailed, in-depth and ongoing counselling in order to provide comprehensive care to children receiving HAART. Medical staff require sufficient time to explain:

- child-proof tops on medicine bottles
- 'colour-coding' of medicines
- the importance of keeping accurate 'diary cards' of administration of doses of medication (Fig. 1), and
- the critical importance of adherence.

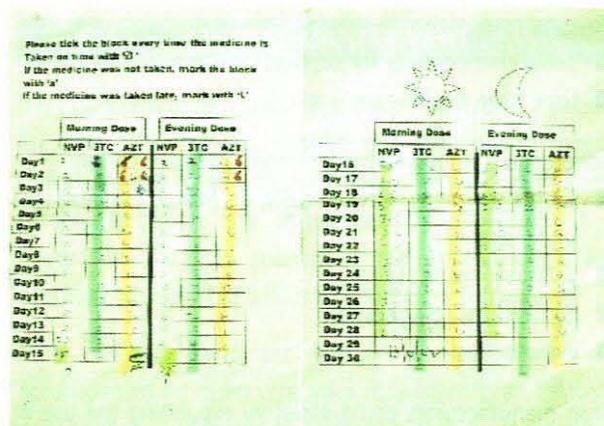


Fig. 1. A well-used diary card.

As infected children require correct nutritional support and timeous and adequate treatment of intercurrent infections, caregivers need to be informed about both of these issues. The necessary measures to protect against opportunistic infections need to be explained, together with the importance of adherence to any prophylactic medications for opportunistic infections.

Caregivers need to understand the critical importance of continuity of care. Clinics must run on a 'no wrong days' basis, and caregivers should also have access to a 24-hour emergency/help line for information and support.

Only when physicians are sure that all of the above are in place should HAART be considered. Then and only then should HAART be commenced.

ADHERENCE – FIRST WORLD V. THIRD WORLD

In a sophisticated First-World trial, Reddington *et al.*⁸ reported on their interview of 90 children's parents that:

- 17% had missed a dose in the previous 24 hours
- 43% had missed at least 1 dose in the previous week.
- non-adherent caregivers tended to consider adherence impossible, needed more practical help with

administration, and were less likely to have told school/day care about treatment.

Interventions thought to be helpful included:

- better tasting medicines (81%)
- longer dosing intervals (72%)
- medications not requiring refrigeration (63%)
- telephone advice (62%)
- follow-up call (52%)
- pill organiser (56%).

It is assumed by many health care professionals that adherence is not good in developing populations, but South African triallists Orrell *et al.*⁹ have asserted that this is not true in a clinical trial setting. Strategies that will improve adherence include:

- education regarding the disease and HAART
- preparatory visits to the clinic
- cues, reminders
- social and community support
- time from health care workers.

Adherence is improved by commonsense medication:

- simple regimens – twice daily, no mixing (suspensions under age 3)
- palatable medications
- no need for refrigeration
- 'Adaptacaps'.

Drug manufacturers could assist by expanding the use of the 'Adaptacaps', which currently only comes with nevirapine. The device facilitates drawing up of medicine into a syringe for administration. (Fortunately it also happens to fit onto a lamivudine top.) There is a commercially available universal adapter made by Apex.

AIDING ADHERENCE

In a small group of poor responders, Gigliotti *et al.*¹⁰ studied the impact of directly observed therapy (DOT) on viral load and found that it was highly effective.

In one study,¹¹ gastrostomy tubes were inserted into 17 patients with poor compliance. This did result in a decrease in viral load, but the biggest drop was seen in those in whom the HAART schedule was changed at the time of insertion. Additionally, the procedure reduced the administration time for drugs to less than 5 minutes. It would appear to be a less practical means of improving adherence but an interesting approach.

WHAT WE MIGHT BE ABLE TO RESEARCH – A LIST OF ASSUMPTIONS WORTH TESTING

Certain assumptions that treaters currently hold but that have not been tested include:

- promotion of **demand** rather than adherence
- encouragement of maternal self-esteem
- arrangement of cohort bookings to promote alliances between mothers
- organisation of a buddy system for 'reciprocal DOTS'
- reward for good performance
- pride in access, therapeutic programmes, and national success.

These may well be worth testing.

SUMMARY

- Non-adherence is common everywhere, but adherence is entirely possible in our setting.
- Commonsense interventions promote adherence.
- Not all manufacturers are prioritising adherence.
- Families need support to achieve adherence.
- Adherence requires commitment from health care workers.
- Health care workers need time to train caregivers.
- Extraordinary measures are sometimes indicated.

We must commit resources and innovative thought to local adherence programmes.

REFERENCES

1. Paediatric European Network for Treatment of AIDS. Parents' attitudes to their HIV-infected children being enrolled into a placebo-controlled trial: The PENTA 1 trial. Paediatric European Network for Treatment of AIDS. *HIV Med* 1999; **1**: 25-31.
2. Eldred LJ, Wu AW, Chaisson RE, Moore RD. Adherence to antiretroviral and + prophylaxis in HIV disease. *J Acquir Immune Defic Syndr Hum Retroviral* 1998; **18**: 117-125.
3. Van Dyke RB, Lee S, Johnson GM, *et al.* Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have human immunodeficiency virus infection. *Pediatrics* 2002; **109**: e61.
4. Pontali E, Feasi M, Toscanini F, *et al.* Adherence to combination antiretroviral treatment in children. *HIV Clin Trials* 2001; **2**: 466-473.
5. Katko E, Johnson GM, Fowler SL, Turner RB. Assessment of adherence with medications in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2001; **20**: 1174.
6. Watson DC, Farley JJ. Efficacy of and adherence to highly active antiretroviral therapy in children infected with human immunodeficiency virus type 1. *Pediatr Infect Dis J* 1999; **18**: 682-689.
7. HIVATIS.ORG website.
8. Reddington C, Cohen J, Baldillo A, *et al.* Adherence to medication regimens among children with human immunodeficiency virus infection. *Pediatr Infect Dis J* 2000; **19**: 1148-1153.
9. Orrell C, Bekker LG and Wood R. Adherence to antiretroviral therapy - achievable in the South African context? *S Afr Med J* 2000; **91**: 483-484.
10. Gigliotti F, Murante BL, Weinberg GA. Short course directly observed therapy to monitor compliance with antiretroviral therapy in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2001; **20**: 716-718.
11. Shingadia D, Viani RM, Yogev R, *et al.* Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in paediatric patients with human immunodeficiency virus. *Pediatrics* 2000; **105**: E80.