Initial experience of a public sector antiretroviral treatment programme for HIV-infected children and their infected parents

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Objective. To describe the initial experience of treating HIV-infected children and their infected parents with antiretroviral therapy.

Design. Prospective, cohort study.

Setting. Tertiary, referral hospital.

Patients. HIV-infected children and their parents.

Methods. This report focuses on the early response of children to highly active antiretroviral therapy (HAART). Children were followed up at 4-weekly intervals. Monitoring included initial and yearly viral load measurements, baseline and 6-monthly CD4 counts and 4-weekly adherence checks.

Results. Between August 2002 and June 2003, 80 children were enrolled in the programme, representing a follow-up period of 23.9 patient-years. Seventy-five children had severe clinical disease, severe immune suppression, or a combination of the two. The response of children who had received HAART for ≥ 6 months (N = 17) was assessed. There was no change in mass z-score (p = 0.11) or length z-score (p = 0.37), but a significant increase in CD4 percentage ($p < 0.0001$) during the first 6 months of therapy. Six-month viral loads were available for 12 children. There was a significant drop in viral load (p = 0.001) and 9 achieved undetectable levels by 6 months. Most children achieved ≥ 85% adherence. By June 2002, 67 children (84%) were relatively well, 1 had B-cell lymphoma, 7 (8.8%) had died, 4 (5%) were lost to follow-up and 1 was withdrawn from the programme. Of 57 children who completed 3 months of HAART, 12 were admitted a total of 17 times for infectious complications. There were no severe drug reactions. Three of 7 mothers on HAART received treatment through the programme.

Conclusion. These initial results suggest that many HIV-infected children in the public sector will benefit from antiretroviral therapy. However, both ambulatory and inpatient facilities are required to manage children on HAART comprehensively.

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Over the past 5 years there has been a significant change in approach to the HIV/AIDS epidemic in sub-Saharan Africa. Previously, prevention measures were particularly emphasised. It is now acknowledged that prevention and comprehensive care which includes the provision of antiretroviral therapy are mutually reinforcing elements of an effective response to the epidemic.[1] This shift in thinking was further strengthened by a recent World Health Organisation (WHO) publication[2] on the delivery of highly active antiretroviral therapy (HAART) in resource-limited settings.

The changing environment contributed to our decision to develop an antiretroviral treatment programme for public sector patients at Red Cross Children's Hospital (RCCH) at the beginning of 2002. The programme, which is donor funded, builds on an established ambulatory service for HIV-infected children and their infected parents. The principal objective is to extend access to HAART to as many children and/or their infected parents as possible. Secondary objectives include evaluating the effectiveness of the antiretroviral treatment programme, developing the clinical expertise required to treat large numbers of children and the establishment of a parallel research agenda. While HAART is widely used to treat children in rich countries, there are virtually no reports from sub-Saharan Africa on the use or effectiveness of HAART in children treated within the public sector. In this report we document our initial treatment experience and discuss several challenges facing the public health sector.

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Methods

This prospective, cohort study describes the initial experiences of a public sector antiretroviral treatment programme for HIV-infected children and their infected parents at RCCH. This report focuses primarily on the early response of children to

HAART. The study period extended from August 2002 to the end of June 2003. The Research Ethics Committee of the University of Cape Town approved the study. Written consent was obtained from the parents or caregivers before enrolment.

Children were selected to start antiretroviral therapy according to clinical and immunological criteria derived from the Paediatric European Network for the Treatment of AIDS (PENTA) recommendations.[3] Briefly, children with Centers for Disease Control (CDC) clinical category C or immune category 3 disease and those with CDC clinical category B disease plus a low CD4 percentage (< 20% if < 12 months old or < 15% if > 12 months old) qualified for treatment and were considered for enrolment.[4] These treatment guidelines are similar to the WHO recommendations for HIV-infected children in resource-limited settings.[2] Several social criteria were included in the selection process, primarily to ensure that the caregivers understood the implications of antiretroviral therapy and made a long-term commitment to the programme. Parents were selected for treatment based on guidelines established by the WHO, i.e. adults with WHO category III and IV disease and/or a CD4 count < 0.2 x 10^9/l were offered treatment.[2]

The preferred first-line therapy for HIV-infected children was stavudine, lamivudine plus ritonavir (children < 10 kg or < 3 years old) or efavirenz (children > 10 kg or > 3 years old). The monitoring plan included 4-weekly clinical review, initial and yearly viral load measurements, baseline and 6-monthly CD4 counts and regular chemistry and haematology evaluations. Several of the children were co-enrolled on parallel research studies and have had more frequent viral load measurements performed.

At each 4-weekly visit the unused medication of each child was checked and the percentage of each antiretroviral administered was determined. Mass and length z-scores were calculated using EpiInfo 2000, version 1.0, Division of Surveillance and Epidemiology, CDC, Atlanta, Georgia. Data were analysed using StatsDirect software, version 2.2.3, Cheshire, UK and Microsoft Excel. Wilcoxon's signed ranks test was used to compare related samples. A p-value of < 0.05 was regarded as statistically significant.

Results

At the end of June 2003, 80 children had been enrolled on the antiretroviral treatment programme, representing a total follow-up period of 23.9 patient-years. Two of the 80 children were siblings.Thirty-seven children (46.3%) were enrolled in the 3-month period from April to the end of June 2003. Mean age (95% confidence interval) at enrolment was 50.5 months (CI 41.8 - 59.2 months). The female-to-male ratio was 31:49. Seventy-five children had severe clinical disease (CDC clinical category C), severe immune suppression (CDC immune category 3) or a combination of severe clinical disease and severe immune suppression. The remaining 5 children had moderate clinical disease and moderate immune suppression. These results indicate that the selection process was being followed. Over 90% of the children were started on the preferred first-line regimens.

The response of children who had received HAART for ≥ 6 months (N = 17) was assessed. There was no significant change in mass z-score (p = 0.11) or length z-score (p = 0.37). There was a significant increase in CD4 percentage (p < 0.0001) and absolute CD4 count (p = 0.0013) over the first 6 months of therapy (Fig. 1, left). Six-month viral load data were available for 12 children co-enrolled on parallel research studies. There was a significant drop in viral load (p = 0.001), with 9 of the 12 children achieving undetectable viral loads by 6 months (Fig. 1, right). Of the 3 children who failed to achieve undetectable viral loads by 6 months, 1 developed B-cell lymphoma approximately 9 months into treatment. The other 2 children were siblings with excellent recorded adherence patterns. They are being investigated for viral resistance. Most children achieved greater than 85% adherence (Fig. 2).

At the end of June, 67 (84%) of the children were relatively well, the majority having shown improvements in their clinical status. One child was deteriorating with a B-cell lymphoma and 1 was withdrawn from treatment because of consistently

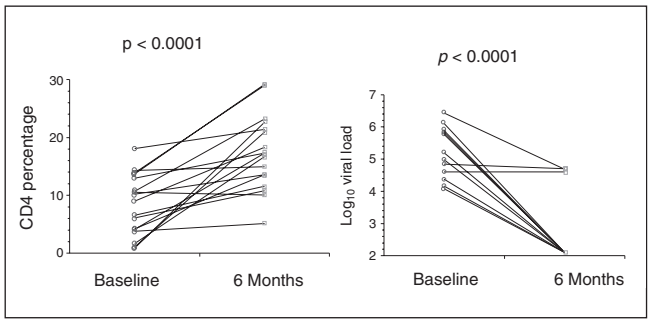

Fig. 1. Changes in CD4 percentage (N = 17) and $\log_{10}$ viral load (N = 12) during the first 6 months of antiretroviral therapy.

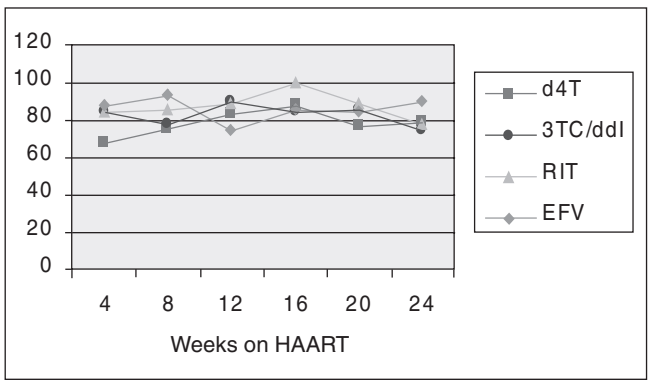

Fig. 2. Percentage of children achieving ≥ 85% adherence at each 4-weekly visit.

poor adherence. Seven (8.8%) died during the study period. Four children died within 2 weeks of commencing HAART, 1 due to *Pneumocystis carinii* pneumonia and 3 associated with presumed sepsis. Three children died between 4 and 6 weeks after starting HAART. All 3 had culture-proven bacterial infections.

Four (5%) of the children were lost to follow-up. All had been cared for by their mothers. Their ages at enrolment ranged from 5 to 72 months and the duration of treatment before exiting the programme ranged from 4 to 19 weeks. Their initial CD4 percentages ranged from 4.2% to 15.8% and the initial viral loads ranged from 2 600 to 2.4 million copies/ml. Three of the 4 children exhibited poor adherence patterns, i.e. adherence for most drugs below 75%. Adherence was not documented for the fourth child.

At the time of analysis only 57 children had completed 3 months of HAART. Twelve of these children were admitted a total of 17 times during the initial 3 months on HAART. The median time from start of antiretroviral therapy to first admission was 19 days (range 11 - 65 days). Fig. 3 records the spectrum of diagnoses during admission. Four of 9 patients admitted with lower respiratory tract infection had a positive blood culture for bacterial organisms. No severe adverse events were recorded. However, 2 children experienced problems with ritonavir. The first child developed persistent nausea and vomiting soon after initiating therapy and the second child did not tolerate the taste. Both were successfully managed by substituting ritonavir with efavirenz.

Sixty-five mothers were alive at enrolment, 11 had died and the whereabouts of 3 was unknown. The median maternal CD4 count was 0.353 x 10^9/l (range 0.006 - 0.704). At the end of June, 7 mothers were receiving HAART, 3 having obtained therapy at RCCH and 4 from other treatment programmes within the Cape Metropolitan region. The primary caregiver was the mother (63 children), maternal grandmother (5 children), maternal great grandmother (1 child), sister (1 child) or aunt (5 children), and 5 children were in foster care. The mean age ± standard deviation of the primary caregiver was 31.6 ± 9.3 years.

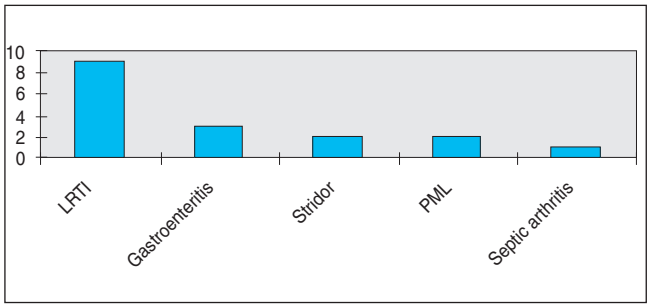

Fig. 3. Reasons for hospitalisation during the first 3 months of HAART (total number of admissions = 17). (LRTI = lower respiratory tract infection, PML = progressive multifocal leuco-encephalopathy).

Discussion

The antiretroviral treatment programme at RCCH is currently one of few programmes examining the practical implications of therapy for public sector patients. With a national antiretroviral programme being planned, we elected to report our early observations so as to assist other South African institutions preparing for the national roll-out. Although the programme at RCCH is still relatively new, the initial results suggest that many children do benefit from treatment. Seventy-five per cent of the children who had viral load assessments done at 6 months had undetectable levels. These early results are better than published reports from rich countries, which show that only 25 - 40% of children experience viral load suppression below the limits of detection.[5] The high levels of drug adherence are encouraging and are probably the reason for the favourable response of many children. Adherence to ritonavir was excellent, particularly in view of the fact that the suspension is extremely unpalatable. These results probably indicate that the initial education and support that the patients received was appropriate. The key to ongoing success is to ensure that high levels of adherence are maintained.[6-8] We are currently considering a number of strategies for improving patient support including a regular support group, small group discussion and more intensive support for caregivers of children with consistently poor patterns of adherence.

The programme at RCCH started within an ambulatory clinic setting. Some children developed serious medical events during the early stages of therapy, particularly infectious complications relating to ongoing immune suppression or immune reconstitution disease.[9] These problems are more common in children with advanced clinical disease and/or severe immune suppression. To optimise the care of these children an inpatient consultation service was initiated. The recent WHO publication[2] makes little reference to the need for inpatient facilities during the early phase of HAART. Our experience suggests that this is an important consideration as there are many children in South Africa with advanced HIV infection who urgently require HAART to improve their quality of life.

Enrolment accelerated during the 3 months up to the end of June owing to the growing confidence and efficiency with which staff members approached their clinical responsibilities. Interestingly, there was no significant improvement in the growth of the first group of children during the initial 6 months of HAART. However, there was a small subset of children who showed marked increase in mass z-score.

Of concern is that 4 children have already been lost to the programme, despite extensive counselling and a commitment from the caregivers that they would maintain a long-term

relationship with the clinic. This problem is not unique to HIV infection but could potentially undermine the long-term effectiveness of antiretroviral treatment programmes in South Africa if not adequately addressed. Suboptimal adherence patterns, present in 3 of the 4 children, may be a risk factor which identifies those at risk of being lost to follow-up.

Treatment models for HIV-infected children in South Africa will to some extent be determined by the effectiveness of mother-to-child-transmission (MTCT) interventions. At present an estimated 80 000 HIV-infected children are born in South Africa annually.[10] Intervention based on nevirapine can be expected to reduce MTCT by 40 - 50%.[11] Further significant reductions are possible if triple combination prophylaxis is offered to pregnant HIV-infected women.[12] Consequently, the paediatric HIV burden will be further reduced and the potential for improved care for HIV-infected children significantly increased. Particular attention should be given to the training of doctors, nurses and pharmacists in the practical aspects of administering antiretroviral therapy to ensure that institutions are fully prepared to manage large numbers of children. A particular problem identified at RCCH is that staff members not directly linked to the programme were less rigorous about optimising drug administration during hospital admission. This issue should be addressed with adequate education.

Recently, the initial lessons of a community clinic-based antiretroviral programme for adults were published.[13] In the present study, we describe the early experience of a hospital-based programme for children and their infected parents. Both reports may spark debate about which treatment models should be employed to roll out antiretroviral therapy throughout South Africa. Our early observations suggest that an integrated family model offers the best option for managing HIV-infected children comprehensively. Although most of the therapy may eventually be administered at primary care level, inpatient facilities at secondary or tertiary care institutions must be geared towards managing children with complications arising from treatment.

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