Antiretroviral treatment for children

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Objective. To describe the response of children during their first year on highly active antiretroviral therapy (HAART).

Design. Retrospective, descriptive.

Setting. Tertiary, referral hospital.

Subjects. All HIV-infected children commenced on HAART from 1 August 2002 until 31 December 2004.

Outcome measures. Children were retrospectively restaged using the WHO 4-stage clinical classification and CDC immunological staging system. After commencing HAART, patients were assessed at monthly intervals for the first 6 months and thereafter mostly 3-monthly. Baseline and 6-monthly CD4 counts and viral loads were performed.

Results. Of 409 children commenced on HAART, 50.6% were < 2 years old, 62.7% had severe clinical disease and 76.6% had severe immune suppression. After 1 year, 65.8% were alive and continued HAART at the hospital, 11.2% had been transferred to another antiretroviral site, 15.4% had died, 4.6% were lost to follow-up and treatment had been discontinued in 2.9%. Kaplan-Meier survival estimate for 407 children at 1 year was 84% (95% confidence interval (CI) 80 - 87%). On multivariate analysis, survival was adversely affected in children with WHO stage 4 v. stage 2 and 3 disease (adjusted hazard ratio (HR): 5.26 (95% CI 2.25 - 12.32), $p = 0.000$), age < 12 months (adjusted HR: 2.46 (95% CI 1.48 - 4.09), $p = 0.001$) and CD4 absolute count (per 100 cell increase) (adjusted HR: 0.93 (95% CI 0.88 - 0.98), $p = 0.013$). In a separate multivariate model including only children with an initial viral load ($N = 367$), viral load ≥ 1 million copies/ml (adjusted HR: 1.84 (95% CI 1.03 - 3.29)) and taking a protease inhibitor (PI)-based regimen (adjusted HR: 2.25 (95% CI 1.10 - 4.61)) were additionally independently associated with poorer survival; however, young age was not a significant predictor of mortality, after adjusting for viral load ($p = 0.119$). After 1 year of HAART 184/264 (69.7%) of children had a viral load < 400 copies/ml. Comparative analysis showed significant improvements in growth, immunological status and virological control.

Conclusion. HAART can improve the health of many HIV-infected children with advanced disease, including those aged less than 2 years in resource-limited settings.

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The World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched their '3 by 5' initiative in December 2003. The principal aim was to mobilise the world to provide highly active antiretroviral therapy (HAART) to 3 million people living with HIV/AIDS in low- and middle-income countries by the end of 2005.[1] By June 2005 approximately 1 million people were receiving HAART in these countries, giving an estimated average coverage rate of 15%. Of an estimated 600 000 children in sub-Saharan Africa who required HAART, less than 5% were receiving therapy.[2] Consequently, the United Nations Children's Emergency Fund (UNICEF) along with the WHO and UNAIDS have begun to mobilise global forces to intensify perinatal prevention programmes, and extend care, particularly in the provision of co-trimoxazole prophylaxis to HIV-exposed children and HAART to all infected children in poor countries.[3]

From 1996 onwards triple combination antiretroviral (ARV) therapy has been used to treat HIV-infected children.[4,5] Since then a large body of research has been published attesting to the benefits of HAART in children. Although in general virological control has been more difficult to achieve in children compared with adults, the risks of progression to end-stage disease or AIDS and death have been significantly attenuated in children treated with HAART.[4,5] Furthermore, improvements in growth and body composition parameters, reduced frequency and severity of infectious complications, decreased hospitalisation rates and reversal or prevention of organ-specific damage have been achieved.[6-9] Long-term survival is possible and some perinatally infected children have already reached their second or third decade of life.[10,11] Research has also documented some concerns associated with HAART including the overall negative impact of HIV infection on quality of life among children, emergence of viral resistance, long-term metabolic complications, and the challenges of managing these problems.[10,12]

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Several studies on paediatric ARV treatment programmes in middle- and low-income countries have documented favourable responses to HAART.[13-16] At Red Cross War Memorial Children's Hospital (RCH) a donor-funded ARV treatment programme for children was started in August 2002. Initial experience of this programme was reported on in 2004.[17] Between February and November 2004, after the Western Cape province of South Africa began providing HAART to public sector patients, the donor-funded programme was fully integrated with the provincial programme. At the end of March 2006 RCH was therefore one of 37 accredited public sector institutions in the Western Cape managing children on HAART. At the time, 16 300 patients were receiving HAART in the province of whom 2009 (12.3%) were children. In this report we describe the response of children during their first year on HAART at our institution.

Methods

This retrospective study describes a public sector ARV treatment programme for HIV-infected children. The study took place at Red Cross War Memorial Children's Hospital, a tertiary referral hospital affiliated to the University of Cape Town. All children who started treatment between 1 August 2002 and 1 December 2004 were included. The study documented the outcomes of children during their first year on HAART. The Research Ethics Committee of the University of Cape Town approved the study.

Children were selected to start HAART according to established clinical and immunological criteria. The first 122 children were enrolled according to criteria derived from the Paediatric European Network for the Treatment of AIDS (PENTA) recommendations. 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.[18] The remaining 287 children were enrolled according to criteria derived from the WHO's 2003 recommendations for children. Children with modified WHO clinical stage 2 or 3 disease *or* a low CD4 percentage irrespective of disease stage (< 20% if < 18 months old or < 15% if > 18 months old) qualified for HAART.[19] In addition to the clinical and/or immunological criteria all children were required to have an identifiable caregiver who could take responsibility for the administration of the medication.

Triple combination ARV therapy comprising of 2 nucleoside reverse transcriptase inhibitors (NRTIs) plus either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) was administered according to conventional paediatric dosing recommendations.[20] The choice of individual drugs was determined by funding constraints, availability of home refrigeration required to store temperature-sensitive drug formulations, and previous exposure to perinatal nevirapine. Children who had been exposed to perinatal nevirapine were given a PI-based regimen in keeping with the national treatment guidelines of South Africa.[21] The monitoring plan included monthly clinical assessments for the first 6 months of therapy and thereafter mostly 3-monthly reviews, baseline and 6-monthly CD4 counts and viral loads (due to financial constraints, the viral load at 6 months was omitted in the first 122 children unless they were enrolled in parallel research studies), and regular biochemical and haematological evaluations.

For the purpose of this analysis, all children were retrospectively re-staged at the time of starting HAART according to the latest WHO 4-stage clinical classification and the CDC immunological staging system.[22,23] Weight-for-age, height-for-age and weight-for-height z-scores were calculated using EpiInfo 2000, version 1.0, Division of Surveillance and Epidemiology, CDC, Atlanta, Georgia. Moderate underweight, stunting and wasting were defined as weight-for-age z-score (WAZ) < -2, height-for-age z-score (HAZ) < -2 and weight-for-height z-score (WHZ) < -2 respectively. Severe underweight, stunting and wasting were defined as WAZ < -3, HAZ < -3 and WHZ < -3 respectively.[24] Data were analysed using Stata version 8.0, College Station, Texas, USA and StatsDirect software, version 2.5.5, 2006, Cheshire, UK. The probability of survival was determined using Kaplan-Meier analysis and log-rank tests were used to compare survival times between strata. The Cox proportional hazards model was used for multivariate analysis. Patient characteristics found to be associated with mortality ($p < 0.1$) on univariate analysis were included in the multivariate model, and removed by a backward selection procedure if $p > 0.05$. Separate models were estimated for all children, and on the subset on whom initial viral load was measured. The regimen variable (PI v. NNRTI) was then added to both models to assess whether regimen was independently associated with survival. The Wilcoxon signed ranks test was used to compare continuous data. The chi-square test was used to compare categorical data. A p-value of < 0.05 was regarded as statistically significant.

Results

By the end of December 2004, 409 children had been enrolled on the ARV treatment programme. The median age (interquartile range) at enrolment was 23 months (8.9, 54.6), 207/409 (50.6%) were less than 24 months old and the female-to-male ratio was 182:227. Baseline clinical staging was available for 407 children: 3 (0.7%) had WHO stage 2 disease, 149 (36.6%) WHO stage 3 disease and 255 (62.7%) WHO stage 4 or advanced clinical disease. CD4 percentages and/or absolute counts were available for 406 children at the start of ARV therapy. The median CD4 percentage (interquartile range) was 11.7% (7, 17.3), 266/402 (66.2%) had a CD4 percentage < 15%

and 41/402 (10.2%) had a CD4 percentage ≥ 15%. According to the CDC classification 18/406 (4.4%) had no immune suppression (immune category 1), 77/406 (19%) moderate immune suppression (immune category 2) and 311/406 (76.6%) severe immune suppression (immune category 3). At baseline the median viral load (interquartile range) was 380 000 copies/ml (140 000, 1 292 000), and 111/367 (30.2%) had an initial viral load > 1 million copies/ml. The nutritional status of the children at the start of ARV therapy showed that 116/408 (28.4%) were moderately underweight, 116/408 (28.4%) severely underweight, 129/406 (31.8%) moderately stunted, 142/406 (35.2%) severely stunted, 55/390 (14.1%) moderately wasted and 26/390 (6.7%) severely wasted. The children were initiated on an ARV treatment regimen comprising two NRTIs plus either a PI (208/409 (50.9%)) or an NNRTI (201/409 (49.1%)).

After 1 year on ARV therapy, 269/409 (65.8%) were alive and continued to be managed at RCH, 46/409 (11.2%) had been transferred to another ARV treatment site for continuation of HAART, 63/409 (15.4%) had died, 19/409 (4.6%) were lost to follow-up and treatment had been discontinued in 12/409 (2.9%) because of sub-optimal adherence. The Kaplan-Meier survival estimate for all children (N = 407) at 1 year was 84% (95% confidence interval (CI) 80 - 87%). Survival for WHO clinical stage 2 (N = 3), stage 3 (N = 149) and stage 4 (N = 255) was 100%, 96% (95% CI 91 - 98%) and 77% (95% CI 71 - 82%) respectively (Fig. 1). On univariate analysis, survival was adversely affected in children with WHO stage 4 v. stage 2 and 3 disease (hazard ratio (HR): 6.19 (95% CI 2.67 - 14.36), p = 0.000), age < 12 months (HR: 2.81 (95% CI 1.71 - 4.61), p = 0.000), those with a viral load ≥ 1 million copies/ml (HR: 2.80 (95% CI 1.63 - 4.80, p = 0.000) and those on a PI regimen (HR: 3.84 (95% CI 2.12 - 6.96), p = 0.000). Survival was unaffected by gender, CDC immunological category, absolute CD4 count and CD4 percentage. On multivariate analysis of all children, after adjusting for WHO clinical stage and age, the absolute CD4 count did affect survival. In a separate multivariate model including only children on whom an initial viral load was done (N = 367), more severe WHO clinical stage, lower absolute CD4 count, viral load ≥ 1 million copies/ml and taking a PI-based regimen were independently associated with poorer survival; however, age was no longer a significant predictor of mortality (p = 0.119) (Table I).

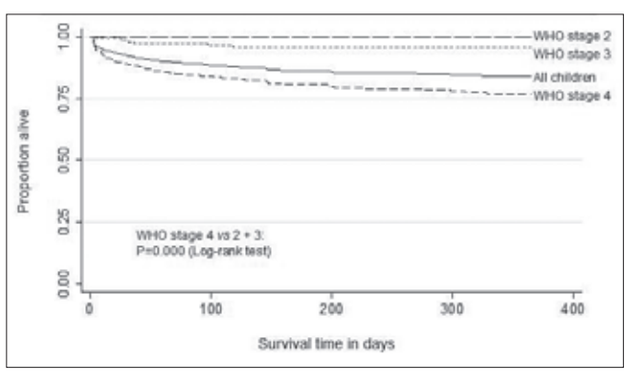

Fig. 1. Kaplan-Meier survival estimates by WHO clinical stage.

One-year viral load results were available for 264/269 children who continued their management at RCH throughout the first year on HAART. The proportion of these children with a viral load less than 400 copies/ml was 184/264 (69.7%). A further 26/264 (9.8%) had a viral load between 400 and 5 000 copies/ml. A more detailed analysis of the cohort after 1 year of HAART is presented in Table II. This analysis is confined to children with complete results at both baseline and 1 year, for each parameter evaluated.

Discussion

The treatment programme at RCH is an integral component of a complex network of primary, secondary and tertiary ARV treatment sites that was established by the HIV/AIDS Directorate of the Western Cape from March 2004 onwards to respond to the HIV epidemic among children in the province. Through donor funds several institutions, including RCH, began treating children before 2004 but all have since been incorporated into the provincial network.[17] Central to the provincial response to the paediatric epidemic is a successful perinatal prevention programme. The perinatal programme has undergone significant improvement in the last few years and could in the foreseeable future reduce the absolute perinatal transmission rate to less than 5%. This should decrease the paediatric HIV burden and ultimately lead to improved care for children with established infection. The development of treatment sites for children has generally lagged behind adult care. However, this problem has largely been corrected and at

Table I. Predictors of death in children receiving HAART

	Adjusted HR	95% CI	p-value
Cox-proportional hazards model for all children (N = 407)			
WHO stage 4	5.26	2.25 - 12.32	0.000
Age < 12 months	2.46	1.48 - 4.09	0.001
CD4 absolute count (per 100 cell increase)	0.93	0.88 - 0.98	0.013
Cox-proportional hazards model for children on whom initial viral load was measured (N = 367)			
WHO stage 4	3.84	1.45 - 10.20	0.007
CD4 absolute count (per 100 cell increase)	0.90	0.84 - 0.96	0.002
Viral load ≥ 1 million	1.84	1.03 - 3.29	0.041
PI-based regimen	2.25	1.10 - 4.61	0.026

Adjusted HR = adjusted hazard ratio; 95% CI = 95% confidence interval; PI = protease inhibitor.

Table II. Comparison of status at baseline and 1 year after commencing HAART

Parameter	Baseline	1 year	*p*-value
Median WAZ; IQR	-2.17; -3.09, -1.12	-0.93; -1.66, -0.13	0.000
Moderate underweight	76/266 (28.6%)	42/266 (15.8%)	0.000
Severe underweight	73/266 (27.4%)	9/266 (3.4%)	0.000
Median HAZ; IQR	-2.51; -3.41, -1.72	-1.92; -2.67, -1.14	0.000
Moderate stunting	89/264 (33.7%)	77/264 (29.2%)	0.3
Severe stunting	89/264 (33.7%)	46/264 (17.4%)	0.000
Median WHZ; IQR	-0.63; -1.77, 0.4	0.43; -0.37, 1.14	0.000
Moderate wasting	34/254 (13.4%)	3/254 (1.2%)	0.000
Severe wasting	18/254 (7.1%)	3/254 (1.2%)	0.000
Median CD4%; IQR	12.0; 7.2, 17.2	24.0; 18.74, 30.0	0.000
CD4% < 15%	173/261 (66.3%)	28/261 (10.7%)	0.000
CD4% ≥ 25%	26/261 (10.0%)	118/261 (45.2%)	0.000
Median log10 VL; IQR	5.54; 5.15, 6.08	2.6; 2.6, 3.27	0.000
VL > 10^6 copies/ml	69/241 (28.6%)	3/241 (1.2%)	0.000
VL < 400 copies/ml	0/241	168/241 (69.7%)	0.000

IQR = interquartile range; WAZ = weight-for-age z-score; HAZ = height-for-age z-score; WHZ = weight-for-height z-score; VL = viral load.

the end of March 2006, 37/43 (86%) ARV treatment sites in the province were treating children.[25]

This retrospective study addressed the effectiveness of HAART in a setting characterised by high unemployment and low rates of secondary school completion among caregivers.[26] As with many retrospective studies some of the data were not available for analysis. Furthermore, children were retrospectively restaged using the latest WHO clinical staging system and the CDC immunological staging system. While immunological classification is based on objective criteria, retrospective clinical staging is dependent on the quality and availability of the clinical records. The latest WHO staging guidelines include clinical case definitions for each staging criterion, which does improve the objectivity of staging.[22] Furthermore, the impact of HAART on the frequency and severity of infectious complications and on hospitalisation rates was not evaluated. Despite these limitations, we believe that the results of this study are an accurate reflection of the response to HAART at our institution.

Baseline characteristics described the clinical condition of the children at the time of starting HAART. Striking features were the high frequency of advanced, WHO clinical stage 4 disease (62.7%), advanced immune suppression (76.6%) and pervasive nutritional deficiencies. The median age of 23 months, the high proportion of children below 2 years of age and the adverse survival associated with an age of less than 1 year reflect the high burden of severe disease among young children treated at our institution. These findings are consistent with natural history studies of paediatric HIV infection in Africa that have reported mortality rates in excess of 50% by the age of 2 years.[27] In contrast, previous publications on paediatric ARV treatment programmes from low- and middle-income countries have documented limited experience with treating children less than 2 years of age.[13,15,16] Treating young infected children may be particularly challenging as they often have complex medical problems, the state of knowledge of the use of ARVs in the very young is incomplete and obtaining blood samples for monitoring may be technically challenging. For these reasons health professionals have generally been reluctant to treat young children with HIV infection.[28] Special attention is needed to ensure that health institutions in resource-limited settings are adequately capacitated to address the medical needs of this vulnerable group.

Given the severity of the clinical and immunological status of the children at baseline and the high proportion of young children in the programme, the overall estimated survival after 1 year of 84% (95% CI 80 - 87%) was reasonable. The probability of survival on HAART after 1 year in a study conducted in Côte d'Ivoire was 91% (95% CI 82.1 - 95.6%). In that study 107 children were enrolled, hence the wider 95% confidence interval, the median age at enrolment was 7.2 years, which was higher than in our study, and severe clinical disease was present in only 12.8%, suggesting that children enrolled in that study were relatively less ill at the start of HAART.[13] The marked, but expected, predictable pattern of decline in 1-year survival between children with WHO stage 2 and 3 disease (96% (95% CI 91 - 98%)) compared with those with WHO stage 4 disease (77% (95% CI 71 - 82%)) and the adverse effect of viral load ≥ 1 million on survival in our study suggests that the high proportion of children enrolled with severe disease adversely affected overall survival rates. While the Côte d'Ivoire study showed significantly lower survival in children with a CD4 percentage < 5%, interestingly in our study survival was not associated with CD4 percent or CDC immunological category.[13] However, on multivariate analysis higher absolute CD4 counts were independently associated with improved survival, with a 7% (95% CI 2 - 12%) reduction in mortality for every 100-cell increase in CD4 count. In the present study, univariate

analysis and the multivariate model on all children suggest that children under 1 year of age experience adverse survival. However, the separate multivariate model in children in whom an initial viral load was measured showed that after adjusting for viral load, age does not affect survival. This suggests that poorer survival in very young children is due to their more severe disease rather than their age *per se*. While univariate analysis and the multivariate submodel including viral load showed greater mortality in children receiving a PI-based regimen, this was not confirmed in the main multivariate model for all children in the study. The apparent adverse effect of a PI-based regimen may therefore largely be due to preferential administration of PIs to younger children who tended to have more severe disease. Alternatively, regimen and age were co-linear variables, which may explain why age was excluded and replaced with regimen in the multivariate submodel analysis.

Table II summarises the effect of 1 year of HAART on growth, immune reconstitution and viral replication in children for whom complete data existed. Notably, of 264 children who remained on HAART at RCH 69.7% had a viral load below 400 copies/ml. This result is consistent with published efficacy studies where the percentage of children with viral loads < 400 copies/ml varied between 63% and 87%.[29] The future management of the 30.3% of children with detectable viral loads is of concern. Current national treatment guidelines have made provision for two rounds of ARV therapy. Beyond second-line therapy there is no specific recommendation for the provision of salvage regimens.[21] This particular issue has to be confronted in South Africa and other middle-income countries where resources exist to manage patients beyond second-line therapy and where a sizeable proportion of children are likely to fail second-line therapy in the near future.

After 1 year on HAART, 11.3% of the children had been transferred to another ARV treatment site for ongoing care. Most were referred to their local community clinics in the greater Cape Town region. This development represents another important component of the provincial paediatric programme, namely the provision of treatment for infected children at the most appropriate level within the health care system. Referral of clinically stable children on HAART to community institutions accompanied by the transfer of appropriate paediatric clinical skills is a necessary strategy in countries with high HIV prevalence rates. This approach will alleviate the congestion experienced at referral hospitals, allowing them to address the more technically challenging aspects of the disease, including children with complex pathology, serious infectious complications, adverse events including immune reconstitution inflammatory syndrome, and many of the younger children. The success of this initiative, which has gained momentum over the last year, is best illustrated with the official provincial statistics. At the end of March 2004, 78.4% (537/685) of all children treated with HAART in the province were managed at the three paediatric referral hospitals in Cape Town namely RCH, Groote Schuur Hospital and Tygerberg Hospital.[30] At the end of March 2006, this figure had declined to 49.5% (995/2009) of the total number of children on treatment.[25] Furthermore, the referral hospitals in Cape Town have been actively involved in developing the clinical capacities of health professionals at community institutions and providing telephonic and on-site consultation support to these institutions.

In conclusion, while this study has demonstrated that HAART is able to improve the health of many HIV-infected children with advanced disease, including those less than 2 years of age in a middle-income country, it has generated concern about treatment beyond second-line therapy.

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