Clinical and immunological outcomes of a national paediatric cohort receiving combination antiretroviral therapy in Uganda

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Objective: We aimed to evaluate clinical and immunological outcomes of paediatric patients receiving combination antiretroviral therapy (cART) enrolled in The AIDS Support Organization (TASO) Uganda national HIV/AIDS programme.

Design: Observational study of patients (age <14 years) enrolled in 10 clinics across Uganda for which TASO has data.

Methods: We extracted patient demographic, immunological and clinical outcomes from the TASO databases regarding age, sex, cART regimen, CD4 cell count and WHO stage at initiation, tuberculosis, mortality and adherence. Outcomes were analysed using Pearson's rank–order correlations, Wilcoxon's rank sum tests, Cox proportional hazard model and survivor functions.

Results: Of the total 770 HIV children on cART, median age was 9 years (interquartile range, 5–13 years), and median follow-up time was 377 days (interquartile range, 173–624 days). Seven hundred and fifty-one children (97.5%) initiated nonnucleoside reverse transcriptase inhibitor-based regimens. Three hundred and sixty-five children (47.5%) initiated cART with severe immune suppression (CD4 cell percentage <15). Of the 18 (2.3%) children that died, mortality was associated with lower CD4 cell percentage at initiation (B coefficient −0.144, standard error 0.06, $P = 0.02$). Of the total, 229 (30%) were single or double orphans and more likely to initiate cART at an older age (mean age, 9.25 vs. 8.35 years, $P = 0.02$) and have a lower CD4 cell count (median, 268 vs. 422 cells/μl, $P \leq 0.0001$) and CD4 cell percentage (median 12.8 vs. 15.5%, $P = 0.02$) at initiation. Pulmonary tuberculosis was present in 43 (5.6%) patients at initiation and 21 (2.3%) after cART. Almost all patients (94.9%) demonstrated more than 95% adherence.

Conclusion: Children on cART in Uganda demonstrate positive clinical outcomes. However, additional support is required to ensure timely cART access among orphans and young children. © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins

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Introduction

There were approximately 2.1 [95% confidence interval (CI), 1.9–2.4] million children (age <14 years) living with HIV/AIDS globally in 2006 [1]. Access to combination antiretroviral therapy (cART) among children remains limited worldwide, with only 115 500 (15%) of clinically eligible children currently receiving treatment [1]. Studies in high-income countries have demonstrated that cART use among children effectively reduces morbidity [2], hospital admissions [3] and increases long-term survival [4]. Studies in low-resource settings have demonstrated good early outcomes among children receiving cART [5]. A number of small studies have evaluated the impact of cART on paediatric populations in sub-Saharan Africa [6–10]. However, few have examined paediatric cART outcomes from large regional networks [11]. We present the first clinical and immunological outcomes of a national paediatric population receiving cART in Uganda.

Patients and methods

Programme

An estimated 110 000 children were living with HIV/AIDS in Uganda at the end of 2006. Of these children, 5800 were receiving cART, representing about 14% coverage among those in clinical need [1,12]. The AIDS Support Organization (TASO) initiated a national paediatric cART programme in 2004, one of the largest in the country. TASO currently has paediatric patients at 11 clinical sites throughout the country: Entebbe, Gulu, Jinja, Masaka, Masindi, Mbale, Mbarara, Mulago, Rukungiri, Tororo and Soroti. These primary healthcare clinics are located in urban centres of towns and service both urban and rural populations. Partners involved in HIV testing refer newly diagnosed HIV-positive children to the TASO clinic nearest to patients' respective homes.

TASO provides a range of services including HIV testing (enzyme-linked immunosorbent assay and western blot), clinical care, provision of cART and psychosocial support. Criteria for clinical admittance into the TASO paediatric cART programme are based on WHO and Ugandan Ministry of Health Guidelines. Children are eligible for cART if they have WHO paediatric stage III, advanced stage II or stage I with CD4 cell percentage less than 15%, for those less than 18 months, and less than 20% for those more than 18 months of age [13]. All suspected children are screened for tuberculosis (TB) at admission and at cART initiation. The Uganda Ministry of Health National Antiretroviral Treatment and Care Guidelines for Adults and Children has not yet been updated to reflect WHO's newest recommendations for clinical staging and immunological classification [14]. Current paediatric guidelines in Uganda are produced by The African Network for the Care of Children Affected by AIDS (ANNECA).

Data collection

The administrative headquarters of TASO Uganda and the Mbale Regional Referral Hospital Review Board approved this study. Clinicians at each site complete standardized patient forms detailing patient demographics, as well as clinical, psychosocial and drug utilization data at each patient visit. These data are then hand-entered, in duplicate, into the TASO data collection database at each site. Patients are provided with a unique confidential identification number.

A field adherence monitoring team equipped with motorcycles is responsible for active patient retention and follow-up. Patients who fail to show for any appointment or patients who have requested home-based care are visited by the field adherence monitoring team. The team consists of medical attendants who conduct HIV testing, adherence counselling, clinical observation and provide cART.

All TASO clinical sites were included in the study, with the exception of Mulago, for which the data is captured under a separate collaboration with Baylor College of Medicine, who administer TASO's Mulago paediatric site. We extracted data at each TASO site on demographic details about paediatric patient age, sex and orphan status at initiation; clinical cART outcomes about mortality and presence of TB at initiation confirmed with X-ray; and immunological outcomes including absolute CD4 T-cell count at initiation, change in CD4 T-cell count, CD4 percentage and WHO staging. $CD4^+$ T-cell counts and percentages are provided only to children initiating cART without WHO-defined stage symptoms. Patients will not routinely receive second CD4 cell count tests if they are clinically responsive to therapy. Patients return for regularly scheduled clinic appointments. Patient adherence to cART was defined as greater than or less than 95% and determined by pharmacy refill records, 3-day self-report and drug-possession ration, whereby the number of pills returned should coincide with the number previously dispensed.

Analysis

Two of the authors (M.J. and E.M.) conducted all analyses. We used descriptive statistics to address patient characteristics. We used the Pearson's rank–order correlations to assess relationships between mortality and CD4 cell percentage and *a priori* determined covariates. We used Wilcoxon's rank sum tests for two samples (NPAR1-WAY procedure) to determine differences between male and female children. We used Cox proportional hazard model and survivor functions with the product-limit method (Kaplan–Meier) to take into account censored data. We used multivariable regression to determine the impact of a-priori determined covariates on the initiation

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of cART, including CD4 cell percentage, absolute CD4 T-cell count, orphan status and age. All *P* values are exact. All tests of significance are two-sided, with a *P* value of less than 0.05 indicating that an association was statistically significant. We used SAS (version 9.1) for all calculations [15].

Results

Demographic, clinical and immunological characteristics of TASO's paediatric cART cohort are described in Table 1. As of January 2008, 770 HIV-positive children were receiving cART from TASO. The median age of paediatric cART patients was 9 years at initiation [interquartile range (IQR), 5–13]. The average period of clinical follow-up among the cohort was a median 377 days (IQR, 173–624 days).

At initiation, 365 (47.5%) of children had CD4 cell percentage below 15%, considered severe immunological suppression [14]; 129 (16.8%) initiated with CD4 cell percentage between 15 and 24% and 67 (8.8%) children initiated with no evidence of immunological suppression (CD4 cell percentage >25%). Information on CD4 cell percentage was unavailable for the remaining 106 (26.8%) children who were admitted into TASO's paediatric cART program on the basis of WHO stage III or advanced stage II.

Almost all children, 751 (97.5%), initiated a cART regimen using nonnucleoside reverse transcriptase inhibitor (NNRTI)-based therapy. The remaining 19 (2.5%) initiated cART on protease inhibitor-based regimens. Six children switched regimens because of the emergence of toxicity-related adverse events, including nausea, skin rash and neuropathy. Among those receiving cART, 414 (54%) children were girls. Female children initiated cART at an older median age, 9.22 years (standard deviation 4.54), than boys ($P = 0.06$). Female CD4 cell percentage ($P = 0.02$), but not absolute counts ($P = 0.12$), was slightly higher. For all children, older age predicted lower CD4 cell percentage ($P \leq 0.0001$) and absolute CD4 cell count ($P = 0.014$). The average CD4 cell percentage change from baseline over the period of evaluation was 5.8% (95% CI,

Table 1. Population demographic, immunological and clinical characteristics.

	Girls ($n = 414$)	Boys ($n = 356$)	*P*
	9.22 (4.54)	8.08 (4.31)	0.06
WHO stage at initiation			
1	8 (2.0%)	9 (2.5%)	0.84
2	201 (48.8%)	172 (48.6%)	
3	141 (34.2%)	110 (31.1%)	
4	21 (5.1%)	17 (4.8%)	
Data missing	41 (9.9%)	46 (13.0%)	
CD4% at initiation			
>25	46 (11.1%)	21 (5.9%)	0.02
15–24	74 (18.0%)	55 (15.5%)	
<15	195 (47.3%)	170 (47.9%)	
Data missing for children	97 (23.5%)	109 (30.7%)	
CD4 cell count >200 at initiation			
Yes	197 (47.8%)	146 (41.1%)	0.12
No	173 (42.0%)	161 (45.4%)	
Data missing for children	42 (10.2%)	48 (13.5%)	
Median CD4% at initiation (IQR range)	12 (7–19)	11 (5.5–17)	0.11
Orphanhood			
Yes	123 (29.9%)	106 (29.9%)	0.82
No	160 (38.8%)	138 (38.3%)	
Data missing for children	132 (31.3%)	112 (31.8%)	
Median age (IQR)			
	9 (6–13)	9 (6–12)	0.53
Baseline CD4 (% SE)	11.4 (6.6–16.3)	10 (5–16)	0.33
WHO stage at initiation			
1	4 (3.3%)	2 (1.9%)	0.84
2	70 (57.8%)	65 (62.5%)	
3	41 (33.9%)	33 (31.7%)	
4	6 (3.2%)	4 (3.9%)	
TB at initiation	20 (6.1%)	23 (8.5%)	0.26
Adherence			
<95%	18 (5.1%)	15 (5.1%)	0.36
>95%	335 (94.9%)	280 (94.9%)	
Median weight at initiation (SD)	25.7 kg (27.2)	21.5 kg (12.9)	0.03
Median age			
Death	12 (2.8%)	6 (1.6%)	0.58

IQR, interquartile range; TB, tuberculosis.

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Table 2. Presenting clinical manifestations at initiation of combination antiretroviral therapy.

	Girls	Boys
Respiratory infection (bronchopneumonia, upper respiratory tract infection, bronchial asthma)	64	40
Gastrointestinal infection (diarrhoea, gastroenteritis, gastritis)	7	7
Skin infection (fungal skin infection, skin sepsis, eczema, psoriasis, boil, seborrhoeic dermatitis, prurigo, Herpes simplex labialis)	32	21
Oral infection (glossitis, oral candidiasis, tonsillitis)	2	2
Sinus infection (sinusitis, coryza)	4	1
Others (urinary tract infection, helminthiasis, malaria, otitis media/externa, myalgia, arthritis, psychosis, vaginal candiditis)	14	16

−35−55%), and the average CD4 cell count increased by 205 cells/μl (−1931 to 3267 cells/μl). Age was not significantly associated with CD4 cell percentage change ($r = -0.07$, $P = 0.30$). There was no statistically significant difference in CD4 cell percentage change between boys and girls (median change zero for both, meaning there was no net change. Mean change was 5.5 for boys and 6.3 for girls ($P = 0.38$). Baseline CD4 cell percentage was inversely correlated with CD4 cell percentage change ($r = -0.30$, $P < 0.0001$).

Opportunistic infections are presented in Table 2. Using logistic regression, we found that orphanhood ($P = 0.02$) and increased follow-up time ($P = 0.0001$) were associated with the presence of opportunistic infections. Over the course of the study period, 18 (2.3%) children died. The causes were all advanced AIDS occurring within the first 6 months of therapy (63% of all deaths). Among these, mortality was predicted by initial CD4 cell percentage counts (B coefficient −0.144, SE 0.06, $P = 0.02$) but not absolute CD4 T-cell counts [odds ratio (OR), 0.99; 95% CI, 0.99−1.00; $P = 0.28$]. TB was present in 43 (5.6%) patients at initiation and 21 (2.3%) after cART. The latter cases of TB may represent immune reconstitution inflammation syndrome. Patients presenting with TB had lower initiating CD4 cell percentage (median 11.34 vs. 13.88%, $P = 0.08$). Adherence was clinically excellent (>95%) in 93.5% of patients.

Of all children receiving cART, 229 (30%) were either single or double orphans. Compared with nonorphans, orphans were more likely to initiate cART at an older age (OR, 1.04; 95% CI, 1.006−1.08; $P = 0.02$), with lower baseline CD4 cell count (median 268 cells/μl, SE 25.5 vs. median 422 cells/μl, SE 23; $P \leq 0.0001$) and CD4 cell percentage (median 12.8%, SE 0.84 vs. median 15.5%, SE 0.75; $P = 0.02$) and with more advanced WHO staging (OR, 0.74; 95% CI, 0.55−0.99; $P = 0.028$).

Discussion

Our study represents the first national clinical and immunological outcome evaluation of children receiving cART in Uganda. These findings contribute to the limited collection of studies evaluating paediatric cART outcomes in sub-Saharan Africa. We found that children receiving cART in Uganda achieved excellent adherence, important CD4 cell percentage increases and good survival. However, certain groups are importantly missing, including young boys and infants.

The survival rate among our paediatric cART patients is consistent with studies from high-income and other African settings [4,16]. Among those children who died, our finding that CD4 cell percentage at initiation predicted their death is similar to outcomes found in other paediatric cART cohorts [4,9,16,17]. In our judgment, these children initiated cART too late, when they were already severely immune compromised and at a high risk for AIDS-related opportunistic infections.

Children receiving cART in Uganda achieved a mean increase of 5.5% in CD4 cell percentage over the study period. This is slightly lower than CD4 cell percentage changes observed in some other sub-Saharan African countries. In one study in Kenya, children receiving cART had an average of 7.4% increase in CD4 cell percentage after 6 months of therapy [18]. In South Africa, median change in CD4 cell percentage was 10.2% at 6 months [19]. A large Zambian cohort of 4975 children found that patients' CD4 cell percentage increased by a median of 10.8% [20]. In Cote D'Ivoire, mean CD4 cell percentage change was 14.8% at 6 months [9]. The immunological responses exhibited by cART-receiving children in Uganda are also consistent with outcomes from children in industrialized countries, where patients' CD4 cell percentage has been found to increase significantly within the first year on cART [3].

Our study has certain strengths and limitations to consider. Our analysis did not include paediatric patients from Mulago Hospital, which houses TASO and Uganda's largest paediatric HIV patient population. It is difficult to estimate what impact the exclusion of Mulago Hospital data had on our findings. Although the 10 primary health clinics included in our analysis serve both peri-urban and rural populations, Mulago Hospital largely serves the urban population of Kampala. Studies from South Africa suggest that cART patients accessing

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major hospitals in urban areas have higher transportation costs and wait times than those in rural and peri-urban communities [21], which may adversely affect adherence and clinical outcomes. Meanwhile, studies in rural Uganda and Zambia demonstrated that cART patients could have excellent outcomes irrespective of long travel distances, assisted by home-based programs [22,23]. A recent study on paediatric cART patients at Mulago Hospital found that 89.4% ($n = 170$) of children were at least 95% adherent according to 3-day recall measurements, and 94.1% were adherent according to clinic-based pill counts [24]. These adherence rates are slightly lower than those of patients in the 10 sites in our analysis. However, it is not possible to ascertain whether this difference is statistically significant or how it would impact our findings.

One of the major strengths is that 100% of patients in our study were effectively followed up. Although many programmes in Africa are affected by major loss to follow-up [21], our programme employs a special mobile team on motorcycles that consistently tracks patients. This model is now being implemented by other organizations throughout Africa. Our data monitoring and adherence counselling is superior to that found in more developed settings, as TASO has specifically employed adherence counsellors and database managers at each TASO site. Our technique of measuring adherence is optimal, as it combines several validated techniques, preventing reliance on caregiver self-reports that often prove to be inaccurate [25]. We recognize that monitoring adherence in children is a major methodological challenge. However, our methods of adherence measurement are similar to those currently in use in developed settings.

We did not have complete CD4 cell counts of all children at initiation. The lack of complete CD4 cell counts reflects the diversity of settings in which TASO works in Uganda. In conflict-affected Gulu District, for example, CD4 cell count evaluations were not possible for all children, and some initiated cART on the basis of clinical symptoms [26]. Indeed, this is a common circumstance in many resource-poor settings [27]. We also do not have routine patient data on viral load or resistance testing and cannot be sure of the exact number of treatment failures; mortality provides the strongest inference of treatment success. Finally, as with any cohort study, it is possible that there are confounding variables that we are unaware of. We tried to control for these by using a-priori explanations of bias.

Adherence rates among our paediatric cohort were exceptional, with 93.5% of children demonstrating perfect adherence. This finding runs contrary to suggestions that paediatric adherence to cART is difficult because of tablet size, syrup palpability and dependence on unreliable primary caregivers [28]. Adherence rates exhibited by children in our study exceed those of other high and low-income settings. Children in several North American and European cART studies have demonstrated suboptimal adherence rates, ranging from 58 to 81% [29–32]. In sub-Saharan Africa, paediatric adherence to cART has also been found to be less positive, with rates ranging from 77% in Cote D'Ivoire [33] to 87.4% in South Africa [19]. Qualitative studies in Uganda have found that complete HIV disclosure, in which child and caregiver are aware of infection, and strong parental relationships predicted good adherence [34]. A likely explanation for our positive findings is the focus on adherence counselling and monitoring that TASO has employed since initiating cART care.

A concerning finding from our study is the older age of most children. A pooled analysis of mortality from studies of HIV-infected African infants and children identified mortality proportions of 35% at 1 year and 53% at 2 years of age [21]. In our cohort, only six one-year olds and 33 two-year olds were initiated on treatment. The Uganda Ministry of Health recommends the use of antibody tests for infants only once they have lost their mothers' antibodies [35]. However, the use of simplified nucleic acid-based amplification assays in Uganda has shown to effectively diagnose HIV among infants and may play an important role in increased uptake of HIV treatment and care among this age group [36]. Providing cART to infants represents an important treatment support challenge that is further complicated when children lack the presence of parents.

Our finding that orphans were more likely to initiate cART at an older age than nonorphans is consistent with the only other study examining cART outcomes among orphans in Kenya [10]. Our finding that orphanhood is a predictor of lower CD4 cell count and percentage at initiation implies the need for more active case finding of HIV-positive orphans eligible for cART. Early initiation of cART among children is important to fully suppress the viral load, protect the immune system from further deterioration, facilitate growth and optimize early childhood neurodevelopment [37]. Timely access to HIV care and treatment for orphans is particularly important in light of their added socio-economic disadvantage as compared with nonorphaned children. Studies have found that AIDS orphans are more likely to be food insecure and have limited access to basic material goods. They are more likely to acquire sexually transmitted infections during adolescence, to experience psychological distress and to drop out of school or achieve education levels below that which are age appropriate [38,39].

Challenges remain in the effective use of cART among paediatric populations, particularly in resource-limited settings. Paediatric cART coformulations remain largely unavailable, and limited data exists about antiretroviral pharmokinetics and toxicity among children [28].

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National governments need to develop standardized systems for promoting early infant diagnosis of HIV, ensure follow-up of children identified as HIV exposed, enhance prevention of mother-to-child transmission services and link diagnosed children to HIV care, social support services and treatment [40].

Our evaluation represents the first national report of clinical and immunological outcomes in children receiving cART in Uganda. These findings contribute to a limited number of studies evaluating paediatric cART outcomes in resource-limited settings. Children in our cohort achieved adherence levels exceeding those in many high-income and African contexts, significant CD4 cell count recovery and good long-term survival. Therapeutic outcomes in our paediatric population may be improved by accelerating case finding among specific vulnerable groups, including orphans and very young children.

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