Risk factors for early mortality in children on adult fixed-dose combination antiretroviral treatment in a central hospital in Malawi

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Objectives: In children aged less than 15 years, to determine the cumulative proportion of deaths occurring within 3 and 6 months of starting split-tablet adult fixed-dose combination antiretroviral therapy (ART) and to identify risk factors associated with early deaths.

Design: A retrospective cohort analysis.

Methods: Data were collected and analysed from ART patient master cards and the ART register of all children registered for treatment between July 2004 and September 2006 in the ART clinic at Mzuzu Central Hospital, northern Malawi.

Results: A total of 439 children started on ART, of whom 220 (50%) were male; 37 (8%) were aged less than 18 months, 172 (39%) 18 months to 5 years, and 230 (52%) were 6–14 years. By September 2006, 49 children (11%) had died, of whom 35 (71%) died by 3 months and 44 (89%) by 6 months. The cumulative incidence of death at 3, 6, 12 and 24 months after ART was 8, 12, 13 and 15%, respectively. After multivariate analysis, being in World Health Organization clinical stage 4, having severe wasting and severe immunodeficiency were factors significantly associated with 3-month mortality and 6-month mortality, respectively.

Conclusion: Although children do well on ART, there is high early mortality. Scaling up HIV testing and simple diagnostic tests for infants and children, expanding routine provision of cotrimoxazole prophylaxis, and investigating the role of nutritional interventions are three measures that, if implemented and expanded countrywide, may improve ART outcomes.

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Introduction

Since 2003, Malawi, along with other sub-Saharan African countries, has been making good progress in scaling up antiretroviral therapy (ART), and by September 2006, 69 547 patients had been placed on treatment from 102 public sector facilities (source: HIV Unit, Ministry of Health, Malawi). Initially, children were

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poorly served as a result of concerns over the use of split tablets and a lack of trained expertise in managing paediatric treatment. Since 2006, however, the national ART guidelines have been modified to incorporate more details about the management of children on ART, health workers have been trained, and regional pharmacokinetic and clinical studies [1–4] have provided reassuring data that split-tablet, adult fixed-dose combination (FDC) therapy in children is associated with good outcomes. More children now access therapy, and by September 2006, 4612 children aged 14 years or younger had started ART (source: HIV Unit, Ministry of Health, Malawi).

In Malawi, treatment outcomes for patients on ART are monitored monthly using ART patient master cards [5]. By September 2006, 7983 patients (11%) started on ART were known to have died. Of these deaths, 70% occurred in the first 3 months of treatment (source: HIV Unit, Ministry of Health, Malawi). In adults, this high early mortality is attributed to severe malnutrition, being in World Health Organization clinical (WHO) stage 4 or having a low baseline CD4 lymphocyte count [6–8]. The limited data from Africa show that children do well on ART, and have a better survival probability than HIV-infected children given no therapy [9]. Reports from Uganda and Côte d'Ivoire, however, suggest high early mortality similar to that seen in adults [2,3]. We therefore undertook a review of the paediatric ART records from Mzuzu Central Hospital, north Malawi, to determine the cumulative proportion of deaths that occur within 3 and 6 months of starting ART, and to identify risk factors associated with early mortality.

Methods

Background

Mzuzu Central Hospital is the main referral hospital in the northern region of Malawi. Through the Rainbow Clinic, it has provided free ART to eligible HIV-infected patients since July 2004 in accordance with national guidelines [10,11].

HIV-infected children, who are considered eligible for ART by WHO clinical or immunological criteria [12], undergo a thorough clinical assessment before starting therapy, and their guardians receive pre-ART counseling and education about how to administer split tablets. The clinical assessment includes a nutritional evaluation [13] and measurement of CD4 lymphocyte count and percentage performed on a Beckman Coulter EPICS XL-MCL flow cytometer (Beckman Coulter, Fullerton, California, USA).

Treatment for the first 2 weeks is with a single daily split-tablet, FDC, of stavudine 30 mg (T30) or 40 mg (T40)/lamivudine 150 mg/nevirapine 200 mg (procured from Cipla, Mumbai, India, under the trade name of Triomune) in the morning followed by a single daily split-tablet of stavudine 30 mg or 40 mg/lamivudine 150 mg in the evening, the lower dose of nevirapine is to reduce the risk of skin reactions. Provided there are no side effects, split tablets, FDC, T30 or T40, are then given twice a day. Split-tablet doses are based on body weight according to national guidelines [10,11]. Since December 2005, all children have been treated with the stavudine 30 mg formulation only [11], as these provide a higher dose of nevirapine compared with stavudine for all weight bands: pharmacokinetic studies in Malawi showed that children were underdosed with nevirapine when half to quarter tablets of T40 were used [14,15]. Children are also given cotrimoxazole preventive therapy at the same time as ART, with dosages based on body weight according to national guidelines.

Once started on ART and cotrimoxazole preventive therapy, children are followed up, first at 2 weeks and thereafter at 4-week intervals, with assessments and drugs distributed from the ART clinic. Treatment outcomes, compliance with clinic visits, and drug adherence are monitored and recorded on ART treatment master cards and the ART register [5].

Data collection and statistical analysis

Only those children who started ART at Mzuzu Central Hospital were enrolled in the study: children who had transferred in from other ART facilities, had not complied with clinic visits or showed less than 95% drug adherence based on pill counting within the first 6 weeks of ART were excluded. Characteristics, WHO clinical stage and outcomes of children on ART were recorded from the ART master card and ART register [5]. Cut-off points for CD4 lymphocyte counts or percentages at different age groups were those that related to the category of severe immunodeficiency: less than one year, less than 1500 cells/μl/less than 25%; 1–3 years, less than 750 cells/μl/20%; 3–5 years, less than 350 cells/μl/15%; more than 5 years, less than 250 cells/μl/15% [11,12].

The characteristics of children between each age group were compared using the chi-squared test. The cumulative incidence of death was determined using the Kaplan–Meier method. Baseline factors related to early mortality within 3 and 6 months of starting ART were determined by the Cox proportional hazards model. The multivariate model (using 95% confidence intervals) included independent variables that were significant at the $P < 0.05$ level. Data analysis was carried out using the SAS system for Windows (version 9.1; SAS Institute Inc., Cary, North Carolina, USA).

Ethical approval

The Malawi National Health Science Research Committee does not require studies that use routine programmatic data collection to be formally submitted

for ethical or scientific approval. This study was thus not formally submitted to the Research Committee. General measures are provided in the Rainbow Clinic to ensure patient confidentiality, consent for HIV testing, and support for children and guardians upon receiving a positive HIV test result.

Results

Characteristics of children on antiretroviral therapy

Between July 2004 and September 2006, 3908 patients started on ART at Mzuzu Central Hospital. A total of 483 children were aged less than 15 years, of whom 34 had been transferred in and 10 showed either poor compliance (two) or poor drug adherence (eight). These children, whose baseline characteristics were similar to those enrolled, were excluded from the study. Of 439 enrolled children, 220 (50%) were boys. The median age was 6 years [interquartile range (IQR) 2.9–9.7 years]. A total of 37 children (8%) were aged less than 18 months (range 3.6–16.9 months; IQR 12–15.6 months), 172 (39%) were aged 18 months to 5 years (range 1.5–5.9 years; IQR 2.2–4.5 years) and 230 (52%) were aged 6–14 years (range 6–14 years; IQR 7.5–11.5). The main characteristics of children in each of these age groups are shown in Table 1. The main difference was that children aged less than 18 months were significantly more likely to have an advanced WHO clinical stage and severe wasting compared with the other children.

Treatment outcomes and risk factors associated with early death

By September 2006, the treatment outcomes of the 439 children ever started on ART were: 306 (69%) alive and on ART; 38 (8.6%) lost to follow-up despite attempts at active tracing; and 46 (10.4%) permanently transferred out to another ART facility. Of those who were alive, the percentage of children with a CD4 cell count indicating they were not severely immunodeficient increased from 54% at baseline ($n = 408$) to 75% at 3 months ($n = 209$) to 85% at 6 months ($n = 138$). A total of 49 children (11%) died, of whom 35 (71%) died in the first 3 months and 44 (89%) in the first 6 months of treatment. The cumulative incidence of death at 3, 6, 12 and 24 months after ART was 8, 12, 13 and 15%, respectively. The relationship between the main baseline characteristics and early death is shown in Table 2. By multivariate analysis, children in WHO clinical stage 4, with severe wasting and with a CD4 cell count below the threshold for severe immunodeficiency had a significant risk of early death at 3 or 6 months.

Table 1. Baseline characteristics of children started on antiretroviral therapy according to age groups at Mzuzu Central Hospital, Malawi.

	< 18 months ($N = 37$)	18 months to 5 years ($N = 172$)	6–14 years ($N = 230$)	Total ($N = 439$)
Sex				
Male	19 (51%)	91 (53%)	110 (48%)	220 (50%)
Female	18 (49%)	81 (47%)	120 (52%)	219 (50%)
Orphan (*n*)	37	167	218	422
Non	33 (89%)	109 (65%)	66 (30%)[a]	208 (49%)
Single – lost one parent	4 (11%)	47 (28%)	83 (38%)	134 (32%)
Double – lost both parents	0	11 (7%)	69 (32%)	80 (19%)
WHO clinical stage				
1 & 2 with low CD4 cell count	0	11 (7%)	23 (10%)	34 (8%)
3	0	128 (74%)	177 (77%)	305 (69%)
4	37 (100%)[b]	33 (19%)	30 (13%)	100 (23%)
Body mass index (*n*)	37	169	216	422
Median (kg/m^2) (IQR)	13.7 (12.4–14.1)	15.3 (13.7–16.4)	14.7 (13.6–16.0)	14.8 (13.6–16.1)
Weight for height[d]				
< 70%	6 (16%)[b]	13 (8%)	11 (5%)	30 (7%)
70–79%	9 (24%)	30 (18%)	23 (11%)	62 (15%)
> 80%	22 (60%)	126 (74%)	182 (84%)	330 (78%)
CD4 cell count (*n*)	30	165	213	408
Median (cells/μl) (IQR)	861 (514.7–1373)	546 (372–911)	220 (102–373)	364 (160–660)
Above standard threshold	11 (37%)	107 (65%)[c]	99 (46%)	220 (54%)
CD4 cell percentage				
Median (%) (IQR)	15.2 (9.5–20.6)	15 (10–20)	9.2 (5.3–14.7)	11.8 (7.1–17.3)
Above standard threshold	8 (27%)	70 (42%)[c]	51 (24%)	129 (32%)
Initial ART treatment				
T40-based	17 (46%)	85 (49%)	106 (46%)	208 (47%)
T30-based	20 (54%)	87 (51%)	124 (54%)	231 (53%)

ART, Antiretroviral therapy; IQR, interquartile range; T30, single daily split-tablet of stavudine 30 mg/lamivudine 150 mg/nevirapine 200 mg; T40, single daily split-tablet of stavudine 40 mg/lamivudine 150 mg/nevirapine 200 mg; WHO, World Health Organization. The superscripts ([a],[b],[c]) refer to variables in children in the age groups 6–14 years[a], less than 18 months[b], and 18 months to 5 years[c] that are significantly different from those seen in the other age groups, at $P < 0.05$. [d]Unexplained moderate malnutrition with wasting not responding to standard therapy defined as weight for height 70–79% on two measurements 3 months apart was classified as WHO stage 3; severe malnutrition with wasting defined as weight for height < 70% was considered as WHO stage 4.

Table 2. Factors associated with early deaths at 3 months and 6 months in children started on antiretroviral therapy in Mzuzu Central Hospital.

	Dead/alive on ART (%)		Univariate analysis hazard ratio (95% CI)		Multivariate analysis hazard ratio (95% CI)	
	3 months	6 months	3 months	6 months	3 months	6 months
Age group						
<18 months	7/30 (18.9)	9/28 (24.3)	3.6 (1.5–9.0)	3.9 (1.8–8.7)	0.8 (0.3–2.6)	1.1 (0.4–3.1)
18 months to 5 years	13/159 (7.6)	16/156 (9.3)	1.2 (0.5–2.4)	1.2 (0.6–2.2)	0.8 (0.3–1.8)	0.8 (0.4–1.7)
6–14 years	15/215 (6.5)	19/211 (8.3)	1.0	1.0	1.0	1.0
Sex						
Male	18/202 (8.2)	20/199 (9.1)	1.0 (0.5–1.9)	0.8 (0.5–1.5)		
Female	17/202 (7.8)	24/196 (10.9)	1.0	1.0		
WHO clinical stage						
1, 2 or 3	12/327 (3.5)	18/321 (5.3)	1.0	1.0	1.0	1.0
4	23/77 (23.0)	26/74 (26.0)	8.1 (4.0–16.4)	6.4 (3.5–11.6)	5.5 (2.2–14.0)	4.3 (1.9–9.6)
Weight for height						
<70%	9/21 (30.0)	9/21 (30.0)	9.3 (4.1–20.9)	6.8 (3.1–14.6)	2.9 (1.0–7.7)	2.3 (0.9–5.9)
70–79%	9/53 (14.5)	11/51 (17.7)	3.2 (1.4–7.1)	2.7 (1.3–5.6)	1.8 (0.7–4.8)	1.8 (0.8–4.1)
>80%	12/318 (3.6)	18/312 (5.5)	1.0	1.0	1.0	1.0
Baseline CD4 cell count						
Above threshold	10/210 (4.5)	13/207 (5.9)	1.0	1.0	1.0	1.0
Below threshold (for severe immunodeficiency)	20/168 (10.6)	26/162 (13.8)	2.5 (1.2–5.4)	2.6 (1.3–5.0)	2.1 (1.0–4.6)	2.6 (1.1–4.5)
Baseline CD4 cell %						
Above threshold	8/121 (6.2)	8/121 (6.2)	1.0	1.0		
Below threshold (for severe immunodeficiency)	22/257 (7.9)	31/248 (11.1)	1.3 (0.6–2.9)	1.8 (0.8–4.0)		
Initial ART (*n*)						
T40-based	16/192 (7.7)	22/186 (10.6)	1.0	1.0		
T30-based	19/212 (8.2)	22/209 (9.5)	1.2 (0.6–2.3)	1.1 (0.6–2.0)		

ART, Antiretroviral therapy; CI, confidence interval; T30, single daily split-tablet of stavudine 30 mg/lamivudine 150 mg/nevirapine 200 mg; T40, single daily split-tablet of stavudine 40 mg/lamivudine 150 mg/nevirapine 200 mg; WHO, World Health Organization.

Discussion

This study shows that children starting ART with split tablets of stavudine–lamivudine–nevirapine had a good overall treatment outcome. There was, however, a high early mortality by 3 and 6 months after starting treatment. Significant risk factors for this were children assessed at WHO clinical stage 4, and children with severe wasting and severe immunodeficiency.

This operational research study has some limitations. First, in assessing children for eligibility for ART, bacterial infections, and particularly presumed sepsis, in most cases could not be confirmed because of a lack of sophisticated laboratory facilities. Some children might thus have been incorrectly staged. Second, exact causes of death could not be determined as there are no postmortem facilities available. Third, nearly 9% of patients were lost to follow-up. Previous studies in tuberculosis patients lost to follow-up identified that a significant proportion had in fact died [16], and thus we have most probably underestimated the mortality rate in this study. Fourth, there is a concern that Malawi's current ART split-tablet regimen underdoses children with the nevirapine component, and this might be a risk factor for early death. Unfortunately, we have no pharmacokinetic information on nevirapine levels in children in this study. We are, however, partly reassured by a study in Thailand on 34 children treated with split tablets of Triomune, which showed satisfactory plasma concentrations of nevirapine [4]. Furthermore, of those children who survived, there was evidence of good immunological recovery, and there were no significant differences in early mortality between children treated with a regimen of T40 or T30. This study in the routine system has strengths in that it reflects the national system, the same treatment regimens used in Mzuzu Central Hospital are those used throughout the country, and standardized treatment outcomes mean that results can be interpreted in all ART facilities in the country.

The high early mortality and identified risk factors in children are similar to those found in adults [6–8]. Specific reasons for early mortality include: late diagnosis of HIV, particularly in the youngest children; late presentation of patients who thus come to health facilities with advanced HIV disease; and life-threatening complications such as bacteraemia. Drug-induced adverse reactions or immune reconstitution disease are other possible causes of early death, although we think these are unlikely as the frequency of serious adverse reactions to first-line ART or severe immune reconstitution disease in Malawi is low.

Preventing these early deaths will be a challenge. First, HIV testing and simple diagnostic tests, as an entry point to care, must be scaled up for infants, children in nutritional rehabilitation units, under-5 clinics and in hospital wards, and better links made with prevention of mother-to-child transmission (PMTCT) programmes for the follow-up of patients. Second, in Malawi, approximately 40% of children with malnutrition are HIV infected [17]. Although it is important to address the underlying factors related to malnutrition, such as infection, there is interest in providing nutritional interventions, particularly through comprehensive home-based services [18,19]. Whether such interventions can reduce early mortality is not known and controlled trials are needed to provide definitive answers. Third, cotrimoxazole prophylaxis for children must be scaled up and integrated with PMTCT, as this intervention can clearly reduce morbidity and mortality before children need ART [20]. The final challenge is to scale up PMTCT to prevent children becoming HIV infected in the first place.

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