Treatment outcomes of antiretroviral therapy among pediatric patients in Zewditu Memorial Hospital, Addis Ababa, Ethiopia

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Abstract

There are a few studies in resource-limited settings describing the various treatment outcomes and the factors that are associated with ART outcomes. Studies in the African region have reported tangible clinical benefits for early diagnosis and initiation of ART such as low mortality and high survival time. This study determined the factors influencing the outcome of ART in children enrolled in an ART program of a hospital. This was a quantitative retrospective design using electronic medical records of children enrolled for ART in Zewditu Memorial Hospital, Ethiopia from March 2005 to March 2012. The median age at the initiation of ART was 7.9 years, the mortality rate was 2.3 per 100 person-years, the mean survival time was 81 months. Of the children who died, 53% died during the first 3 months of treatment initiation. The probability of survival at 24 months was 0.93. On univariate analysis, age, marital status of parents, parental survival, co-trimoxazole prophylaxis, WHO clinical stage, baseline functional status, weight-for-age and height-for-age, were found to be significantly associated with death. On adjustment for confounding, absence of co-trimoxazole prophylaxis and poor baseline functional status remained strong predictors of mortality. This study confirms the prophylactic effect of co-trimoxazole in reducing mortality and morbidity. Since children who were bedridden at initiation of ART were very much likely to die earlier than those who were active, it can be concluded that early initiation of ART has an enormous benefit in prolonging life and improving the quality of life of HIV infected individuals.

Keywords: Pediatric ART, treatment initiation, mortality, survival, health status

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Introduction

Ethiopia is one of the first countries which were hard hit by the HIV/AIDS epidemic. According to the World Health Organization (WHO), adult HIV prevalence in Ethiopia in 2011 was estimated at 1.5 percent (WHO, 2010). In 2010, approximately 1.2 million Ethiopians were living with HIV/AIDS, of which 79,871 were children under the age of 15 years. In Ethiopia, antiretroviral therapy (ART) has been made accessible to the population since 2005 (Akalu et al., 2010). The introduction of combination ART has resulted in striking reductions in HIV-related mortality and morbidity. Although data are accumulating on the long-term effectiveness of ART among adults, few data are available on long-term outcomes from ART among children beyond two years of follow-up (Janssens et al., 2007; Kamya et al., 2007; Sanne et al., 2009).

There are a few studies in resource-limited settings describing the various treatment outcomes and the factors that are associated with ART outcomes. A cohort of 2938 children in Zambia initiated on ART, the median age at enrollment was 81 months and, and 72.4% in WHO stage III or IV. At the time of analysis, 5.4% had withdrawn from care and 13.0% were at least 30 days late for follow-up. Of the remaining 2398 children, 198 (8.3%) died over 3018 child-years of follow-up. Of these deaths, 56.6% occurred within 90 days of therapy initiation (Bolton-Moore et al., 2007). Investigations in these pediatric cohorts from Zambia by (Bolton-Moore et al., 2007) and in Côte d'Ivoire by (Fassinou et al., 2004) have shown that treatment improves immunological, hematological, and growth outcomes, and results in mortality rates lower than those observed in the pre-antiretroviral era. Other countries in the region like South Africa have also reported tangible clinical benefits for children accessing the national ART program such as low mortality in infants and those with advanced disease highlightswith early diagnosis of HIV infection and commencement of ART (Janssens et al., 2007).

In a retrospective cohort study of children who had started ART between October 2004 and May 2006 in Lilongwe, Malawi, 41 (15.9%) of the 258 children died, 185 (71.7%) were alive, and 32 (12.4%) had defaulted (Fetzer et al., 2009). Most of the children were in WHO clinical stage III (56%) and IV (37%). Factors strongly associated with mortality and defaulting were age <18 months and WHO stage IV. Research has indicated that the outcome of lost-to-follow-up (LTFU) studies differs across settings. A study from South Africa showed zero LTFU as compared to two Ethiopian studies, which reported LTFU of 3.2% (Asfawesen et al., 2011) and 13.5% (Workneh, Girma, & Woldie, 2009). As already stated, there are a few studies which investigate treatment outcomes of children receiving ART. This article determined the factors influencing the outcome of ART in children enrolled in an ART program of Zewditu Memorial Hospital. The findings of the study will infom possible ways of improvement in HIV treatment.

Methods and Materials

Study design

This was a quantitative retrospective design using an electronic database of children enrolled in the ART program in Zewditu Memorial Hospital which is a pioneer hospital in Ethiopia to

roll out ART since 2004. The study population consisted of the electronic medical records of children enrolled for ART from March 2005 to March 2012. All electronic medical records (N=786) of the children enrolled for ART were included in the study. The inclusion criteria were HIV-positive children who were younger than 18 years who started ART as of March 2005 and had complete intake form, registers, and follow-up forms. Electronic records of patients diagnosed outside the hospital (transfer-in) and children who had not started on ART (Pre-ART) were excluded. Those who died due to competing causes of death were also excluded from the analysis. This study utilized both electronic database and the clinical charts as a source of the required data. For the purpose of data collection from the ART charts and the electronic database, a data abstraction tool was developed, and data was abstracted by a trained data clerk and a nurse who have previous experience in similar ART data collection from the database.

Ethical clearance for the study was granted by the Research and Ethics Committee at UNISA, Department of Health Studies. Permission to conduct the study and access records was obtained from the Research Ethics Committee of the Regional Health Bureau and the hospital administration, Addis Ababa. Only patients' ART unique identification number was used and the names of the patients was not identified by the researchers who collected the data.

Data analysis

Data was captured into excel spreadsheet and were analyzed using the IBM SPSS version 20 Statistical software. Descriptive statistics were carried out to explore the socio-demographic characteristics of the children and the caregivers/parents, the clinical characteristics of the children and the outcome rates. A life table was used to estimate the cumulative survival of children. Descriptive survival analysis was carried out to assess the survival time among the various predictors (socio- demographic and the baseline clinical characteristics) using Kaplan-Meir procedure. Factors which were found to be statistically significant ($p<0.05$) in the univariate model were subjected to the multivariate analysis using the Cox regression model to control the effect of confounding variables. Mortality rate was expressed as deaths per 100 person-years and was calculated by adding up the total follow-up time which was converted to years (as the record was in months the total divided by 12), and the total number of deaths divided by the obtained person-years.

Results

Socio-demographic characteristics

The mean age at initiation of ART was 7.6 years ± 3.8 years, the minimum and the maximum ages being 2.4 months and 15 years, respectively. The median age was 7.9 years (IQR= 4.7 to 7.9 years). About a quarter (25.9%) of the children were under five years, 41% were between 5-10 years and one-third were above ten years of age. There was almost equal male to the female proportion (50.3% males). At the initiation of ART, just above a quarter of the children had both parents alive, while either of the parents was alive in 31% and neither of the parents was alive for 19.1% of the children. This means, at least 50% were orphans. Information was missing in 23.4% of the records. About 50% of the children lived with their biological parents (one or both parents), 25% lived with guardians or relatives, while 0.8% lived in an orphanage (Table 1).

Table 1: Baseline socio-demographic characteristics of HIV-infected children on ART

Variables	Category	Frequency (%)
Age group in years	<1 year	43 (5.5)
	1-5 years	160 (20.4)
	6-9 years	321 (40.8)
	10–14 years	248 (31.6)
	15 years and above	14 (1.8)
Sex	Boy	395 (50.3)
	Girl	391 (49.7)
Parents survival status	Father alive	134(17.1)
	Mother alive	109 (13.9)
	Both alive	208(26.5)
	Neither alive	150(19.1)
	Not established	184 (23.4)
Marital status of parents	Married	168 (21.4)
	Divorced	34 (4.3)
	Widowed	117 (14.9)
	Single	80 (10.2)
	Not established	386 (49.2)
Child lived with	Parent/s	400(50.9)
	Guardian	123 (15.6)
	Grandpa	59 (7.5)
	Siblings	17 (2.2)
	Orphanage	6 (0.8)
	Others	180 (22.9)

Baseline clinical characteristics

The weight-for-age of the children was below the third percentile (very low weight) in about 60%, and height-for-age (stunted) was below the third percentile in about 64% of the children. At the initiation of the ART, nearly two-thirds of the children were severely ill with advanced clinical disease (WHO stage III & IV). Table 2 presents the baseline clinical characteristics of HIV-infected children and their parents or caregivers. The baseline CD4 count was available for the majority 763 (97.1%) of children, 48% had CD4 count less than 200 cells/uL. The results indicated that the CD4 count decreased with increasing age (Figure 1).

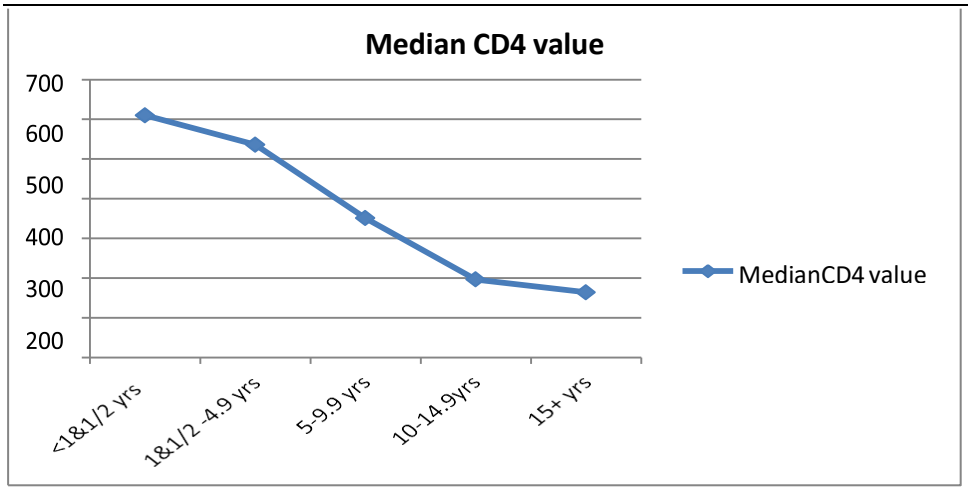

Figure 1: Median CD4 value with age group of HIV-infected children on HAART

The baseline CD4% was available for 76% of the 203 under-five children. Viral load pattern could not be assessed since it was not determined on a regular basis. Over thirds (62.8%) of the children's functional status was active, 32.6% were ambulatory, and 4.6% were bed-ridden. Clinical criteria with low CD4 count accounted for about 87% of the candidates to initiate ART.

Treatment outcomes

Of the total 786 children, 11.8% were on INH prophylaxis for TB, and about 90% were on co-trimoxazole prophylaxis. At the initiation of ART regimen just more than half were on the AZT-based regimen, while about 42% were on the stavudine-based regimen, and the rest, 4.5%, were on other regimens (Table 2).

Table 2: Baseline clinical characteristics of HIV-infected children on ART

Variables	Category	Frequency (%)
Weight for age	<3rd centile	477(60.7)
	≥3rd centile	303 (38.5)
	<3rd centile	504(64.1)
Height for age	≥3rd centile	270 (34.4)
Opportunistic infection/s	Yes	234 (29.8)
	No	552 (70.2)
On TB treatment	Yes	23 (2.9)
	No	763 (97.1)
INH prophylaxis	Yes	93 (11.8)
	No	693 (88.2)
Co-trimoxazole prophylaxis	Yes	708 (90.1)
	No	78 (9.9)
WHO Stage	Stage I	43 (5.5)
	Stage II	224 (28.6)
	Stage III	374 (47.8)
	Stage IV	142 (18.1)
CD4 (cells/uL) group (n=768)	0-49	81 (10.5)
	50-99	75 (9.8)
	100-199	211 (27.5)
	200-349	185 (24.1)
	350-999	172 (22.4)
	1000-2999	28 (3.6)
	3000+	16 (2.1)
Baseline Functional status	Active	479 (62.8)
	Ambulatory	249 (32.6)
	Bed-ridden	35 (4.6)
Reason for being eligible for ART	Clinical + CD4	680 (86.5)
	CD4 only	70 (8.9)
	Clinical only	32 (4.1)
	Others	4 (0.5)
ART Regimen (n=786)	AZT+3TC+NVP	387 (49.2)
	d4T +3TC+NVP	304 (38.7)

The outcomes after the initiation of ART have been presented on mortality and survival, immunologic failure, drug toxicity and defaulting. The overall median follow-up period of the children was 41 months (IQR, 16-66 months), with minimum and maximum follow-

up period of 2.4 months and 88 months respectively. Among the 786 children, 479 (60.9%) were alive and receiving treatment, 62 (7.9%) died, 87 (11.1%) defaulted (81 dropped out, 4 lost-to-follow-up and 2 stopped follow-up), and 158 (20.1%) were transferred out to various health institutions where the treatment could be continued.

Treatment failure and drug toxicity

The immunologic failure occurred in 2.2% (n=17) of the total number of children on ART. Drug regimen switch was done to ABC/ddI/LVP for the immunologic failure cases, 154 (19.6%) children had ART regimen substitution, 90% of which was due to drug toxicity and 7% due to TB treatment. All of the cases of the failure occurred during the first three years of initiation of therapy, i.e., in 2005-2007.

Survival and Mortality rates

The total survival time was 31,883 months (2656.9 person-years), and considering the sixty-two cases of death during the study period, the mortality rate becomes 2.3 per 100 person- years. The mean survival time was 81.1months (95 CI: 79.5-82.8). With regard to time of death, 32.3% died within the first month, 48.4% within the first two months, and 53.2% during the first three months of initiation of treatment. The cumulative probabilities of survival at 6, 12, 24, 30, 36 and 60 months was 95%, 94%, 93%, 93%, 92%, and 91%, respectively (Figure 2).

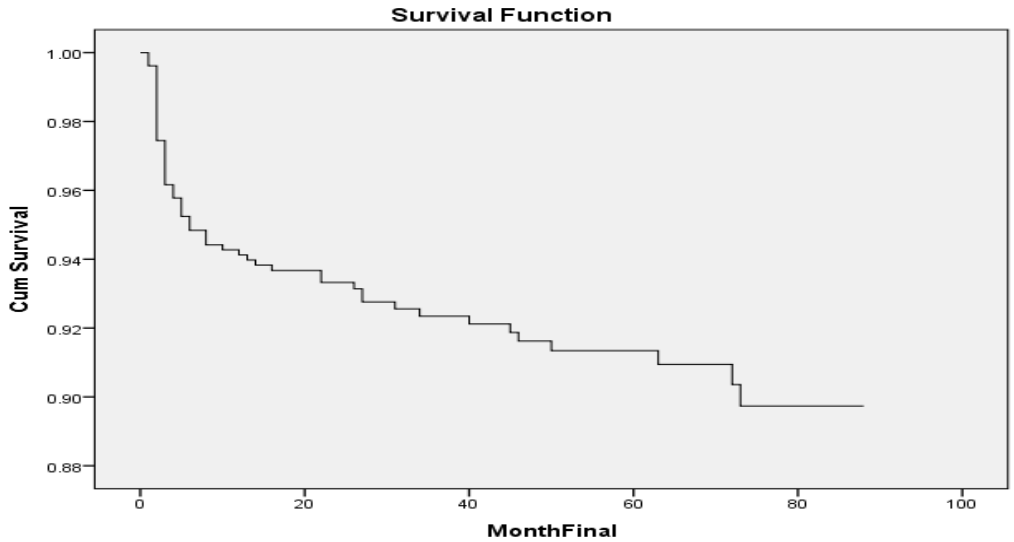

Figure 2: Probability of survival among HIV-infected children on HAART

Predictors considered to influence the outcome of survival in the study were socio-demographic and the baseline clinical characteristics. Each factor was initially analyzed through univariate statistical procedure. Among the various characteristics considered in the study, as presented above, those found to be significantly ($p<0.05$) associated with the outcome of death were age, marital status of parents, parental survival, co-trimoxazole prophylaxis, WHO clinical stage, baseline functional status, weight-for-age and height-for-age. Factors which were found to be significant on the univariate procedure were subjected to the multivariate analysis using Cox regression model.

Baseline WHO Clinical stages and baseline CD4 categories

Shorter mean survival time was associated with WHO baseline stage IV disease (advanced HIV disease) as compared to the other stages, and the difference was statistically significant (p value= 0.00). Children with stage IV disease lived five months shorter than those with stage I disease. The estimated survival time was longer for those with CD4 200-349/mm3 and 350-999 mm3 by 11 months as compared to those of baseline CD4 category of 0-49/ mm3. However, with further increment in CD4 count, there was no difference. Children on INH prophylaxis lived an average of 85 months which is five months more than those who were not on INH prophylaxis (p=0.006). Children on co-trimoxazole prophylaxis lived an average of 82.5 months while those who were not on the prophylaxis lived markedly shorter by about 24 months (p=0.006).

Discussion

The mean age at initiation of ART was 7.8 years old, and the relatively late age of initiation in most African ART programs result in poor treatment outcomes. In most cases, ART initiation occurs when the disease is advanced (Asfawesen et al., 2011; Bolton-Moore et al., 2007; Janssens et al., 2007; Koye, Ayele, & Zeleke, 2012; Mokgatle & Madiba, 2015; Sanne et al., 2009; Wamalwa et al., 2010). Late initiation of ART is common among children, and it is related to the fact that most children are orphaned, and they depend on caregivers who are mainly from economically challenged contexts for their access to health care services. Besides orphan-hood, other variables that were found to influence the late initiation and late diagnosis are the younger age of the child, marital status of caregiver, WHO clinical stage, baseline functional status, weight-for-age, and height-for-age.

At the initiation of ART, just above a quarter of the children had both parents alive, while either of the parents was alive in 31% and neither of the parents was alive in 19.1%. This means that at least 50% of the children were orphans and vulnerable and explained part of the reasons for late initiation of ART. The findings is not different from other studies conducted in Ethiopia and other countries in the region (Fassinou et al., 2004; Fetzer et al., 2009; Janssens et al., 2007; Mokgatle & Madiba, 2015; Wamalwa et al., 2007; Workneh et al., 2009).

Children who were bedridden had a mean period of survival shorter by 24 months and 20 months than those who were ambulatory and active, respectively. Ambulatory children were nearly five times more at risk of dying than the active children, and the bed-ridden children were about nine times more at risk of dying than the active ones. The finding of poor treatment outcomes and a higher risk of death of children with bedridden functional status than those who are active as well as ambulatory was also found in studies from the region (Biadgilign, Reda, & Digaffe, 2012; Fetzer et al., 2009; Janssens et al., 2007; Tadesse, Haile, & Hiruy, 2014; Wamalwa et al., 2007). This indicates that treatments with anti-retroviral drugs would have the best efficacy if provided at the earliest stage of the clinical condition of the patient. Poor functional status of patients with HIV/AIDS is a reflection of their level of viremia and immunological status as measured by blood viral load

and CD4 levels, respectively. In the current study set-up, viral load has been determined very rarely and could not be assessed in the study. Taking the CD4 level into account, the study showed the expected association.

Our study found the mean survival time on initiation of ART of about 81 months, and the mortality rate was 2.3 per 100 person-years. This is slightly less than in a facility-based retrospective study among HIV-positive children in Northwest Ethiopia where mortality rate was 4.0 deaths per 100 child-years (Koye et al., 2012). Over time, studies have shown good treatment outcomes regarding survival time on treatment, and to date we have perinatally HIV-infected children reaching adolescent stage and beyond (Callens et al., 2009; Davies et al., 2009; Jacobson et al., 1994; Kim et al., 2012; Little et al., 2007; Nuwagaba-Biribonwoha et al., 2010; Organization, 2010; Shiau et al., 2013; Sutcliffe et al., 2011). However, a study conducted among a cohort of 135 Kenyan children followed for a median of 21 months after ART initiation, found mortality rate of 8.4 deaths per 100 child-years (Wamalwa et al., 2010). With regard to time of death, early mortality rate (during the first three months) was 63.4%, which is higher than the current finding (53.2%) (Koye et al., 2012). Similar early mortality rate has been demonstrated in another African study (Asfawesen et al., 2011). The trend of early death emphasizes the need for strict follow-up and monitoring system in place, immediately following the initiation of therapy.

In this study, children on co-trimoxazole prophylaxis lived about 24 months more than those who were not on the prophylaxis. Children who were not on co-trimoxazole prophylaxis were more than three times at risk of dying than those who were on the prophylaxis. Other studies have also shown that co-trimoxazole prophylaxis reduces morbidity and mortality. A clinical trial on 534 Zambian children with HIV infection children found that co-trimoxazole reduced the mortality rate and hospital admissions Wamalwa et al., 2007). The value of co-trimoxazole in reducing the morbidity and mortality associated with HIV infection has been well established. Co-trimoxazole has been shown to be associated with a 25–46% reduction in mortality among individuals infected with HIV in sub-Saharan Africa. These improvements in survival are due to the antibiotic effect of the drug resulting in substantial reductions in severe disease events such as pneumonia, malaria, and diarrhea. WHO recommends co-trimoxazole for all infants exposed to HIV and all symptomatic children with HIV infection (WHO clinical stages 2, 3 or 4) and all children with HIV infection who have a CD4 count < 25% (WHO, 2007).

It is noted that the main study limitation is the study design, since the study used secondary data, the inevitable missing of information mainly on social history has resulted in limited assessment of potential predictors of mortality. Though the sample size was high, the generalizability to other set-ups in other countries is limited.

Conclusions

The study found that late initiation of ART among children is a predictor of poor treatment outcomes such as short survival period and treatment failure. Early initiation of ART has an enormous benefit in prolonging life and improving the quality of life of infected individuals. In addition, the finding of the high rate of early death emphasizes the need for strict follow-

up and monitoring system as soon as the patient has been admitted to HIV care.

Age, marital status of parents, parental survival, co-trimoxazole prophylaxis, WHO clinical stage, baseline functional status, weight-for-age, and height-for-age were found to be significantly associated mortality. However, on adjustment through multivariate analysis, factors most strongly associated with mortality were co-trimoxazole prophylaxis and baseline functional status of the children. In this study, mortality as a treatment outcome was associated with the absence of co-trimoxazole prophylaxis and poor baseline functional status of the children on ART. Hence, the current study confirms the prophylactic effect of co-trimoxazole in reducing mortality and morbidity. Since children who were bedridden at the initiation of ART were very much likely to die earlier than those who were active, it can be concluded that early initiation of ART has an enormous benefit in prolonging life and improving the quality of life of the affected individuals.

These conclusion prompt for recommendations of strict follow-up and monitoring system as soon as a child is admitted to HIV care; strict alignment to the protocol of administering co-trimoxazole prophylaxis; strengthening of HIV screening programs for detection of HIV infection atthe earliest age possible and early initiation of treatment is recommended.

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