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Survival of HIV Infected Children Born to Mothers Enrolled in a PMTCT Program in a Resource Poor Setting*

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ABSTRACT

Background: Pediatric HIV is a leading cause of morbidity and mortality worldwide. The substantial expansion in PMTCT has generated information on rates of transmission and associated factors, but there are limited studies on disease progression and mortality in vertically infected children, especially from resource poor settings. **Methods:** A birth cohort study was initiated in 2002 to focus on the role of a single dose of nevirapine in HIV transmission before Highly Active Antiretroviral Therapy (HAART) was readily available. The enrolment of women and subsequent follow up of the children occurred at 3 peri urban clinics around Harare. **Findings:** 479 women were HIV infected. From these, 93 (19%) children became HIV infected, 182 (38.0%) uninfected and 204 (43%) lost to follow up before HIV diagnosis. Of the HIV infected children, 40 (43%) died before the fifth birthday, 26 (28%) were lost to follow up and 27 (29%) were alive five years after maternal enrolment prior to availability of cART. **Conclusion:** In this setting, there was unacceptable high mortality from HIV infected children and loss to follow up prior to availability of HAART. A small proportion of HIV vertically infected children is surviving in resource poor settings without antiretroviral therapy.

Keywords: HIV Infected Children Outcome; Mortality; Loss to Follow Up

1. Introduction

Highly prevalent mother to child HIV transmission has given rise to pediatric AIDS mortality, especially in countries where resources are few. It has been difficult to follow up HIV exposed infants, so that timely diagnosis of HIV infection can be made which results in appropriate treatment, care and support. Several studies have reported short term survival of HIV exposed children from vertical transmission [1-4]. The substantial interest in PMTCT has generated information on short term survival of vertically infected children both in the pre Highly Active Antiretroviral Therapy (HAART) and post HAART era particularly in developed countries [3-6]. On the other hand, there is very little information on long-term survival of these children in resource poor settings where follow up is a challenge. Child mortality is independently associated with maternal HIV status and maternal death, with pediatric infection resulting in approximately a four fold increase in mortality by the age of two years compare to HIV unexposed infants [7]. To determine the proportion of children whose mothers had enrolled in the Better Health for the African Mother and Child cohort and were surviving at 5 years of age, a cross sectional study of HIV infected children was carried out between 2007 and 2008 prior to universal access of antiretroviral drugs in Zimbabwe.

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2. Methods

The study was conducted at three primary maternal child health clinics in peri-urban areas around Harare (namely Epworth, Seke North and St Mary's) in Zimbabwe.

The initial study was a cohort study of HIV infected pregnant women who had been enrolled in a PMTCT program between 2002 and 2003. The follow up of mothers and children occurred up until 15 months of post natal age and ceased. We describe cross-sectional characteristics of HIV exposed children after a five year follow up visit.

The pregnant women were enrolled into the cohort study from 36 weeks of gestation, after obtaining informed consent. The aim of the initial study was to explore the role of sexually transmitted infections in pregnancy outcome. Pre and post HIV test counseling were offered as part of the national PMTCT program. Baseline characteristics collected included sociodemographic information, medical history of sexually transmitted infections, gynecological examination findings and specimen collection for full blood counts, serology for herpes simplex type 2 and syphilis, and high vaginal swabs for culture. All HIV infected women were given a single dose of nevirapine at delivery; their infants received a single dose of nevirapine, according to the national guidelines at that time (HIVNET 012) [8]. The infants were then followed up at 6weeks, 4 months, 9 months and 15 months and HIV status determined by HIV DNA PCR (Roche Diagnostics, Indianapolis, USA) if the children were aged less than 15 months, and rapid HIV antibody tests, Determine (Abbott Diagnostics, Illinois, USA) and Oraquick (abbott before 15 months and antibody tests at 15 months. The proportion of HIV infected infants has been reported [9].

At the 5 year follow up visit, HIV infected women who had been enrolled in the BHMAC study were identified from registers and traced to their homes where information on survival of their children was collected. HIV infected children were also identified from pediatric follow up clinics and blood was collected for CD4 counts.

2.1. Data Handling and Analysis

Information was collected with the data collecting tool and results were analyzed using Stata version 10.0 (College Station, Texas, USA). Cox proportional hazard ratios were used to determine baseline factors associated with child mortality. Characteristics of survivors were also described using percentages for categorical variables and mean (standard deviations) for continuous variables.

2.2. Ethics

The mothers or legal guardians signed an informed consent. The study was approved by the Medical Research Council of Zimbabwe (MRCZ) and the Norwegian ethical review committee.

3. Results

Figure 1 shows the follow up of HIV infected infants born from the recruited mothers, 27 out of 93 (29%) HIV infected children survived. There were no significant differences in maternal baseline characteristics, notably haemoglobin $p = 0.563$, total lymphocyte count $p = 0.557$, age $p = 0.067$ and disclosure of HIV status to partner $p = 0.733$ between the 204 children who were lost before HIV diagnosis and those tested for HIV. **Table 1** shows unadjusted hazard ratios for predictors of child mortality. Breast feeding at 4 months was protective of death $p = 0.002$, which is reflected at 6 weeks and 9 months but not statistically significant. We were able to postulate causes of mortality by verbal autopsy in 27 patients. Of these, 13 (48%) died from pneumonia, 13 (48%) from diarrhea and 1 (4%) from asthma.

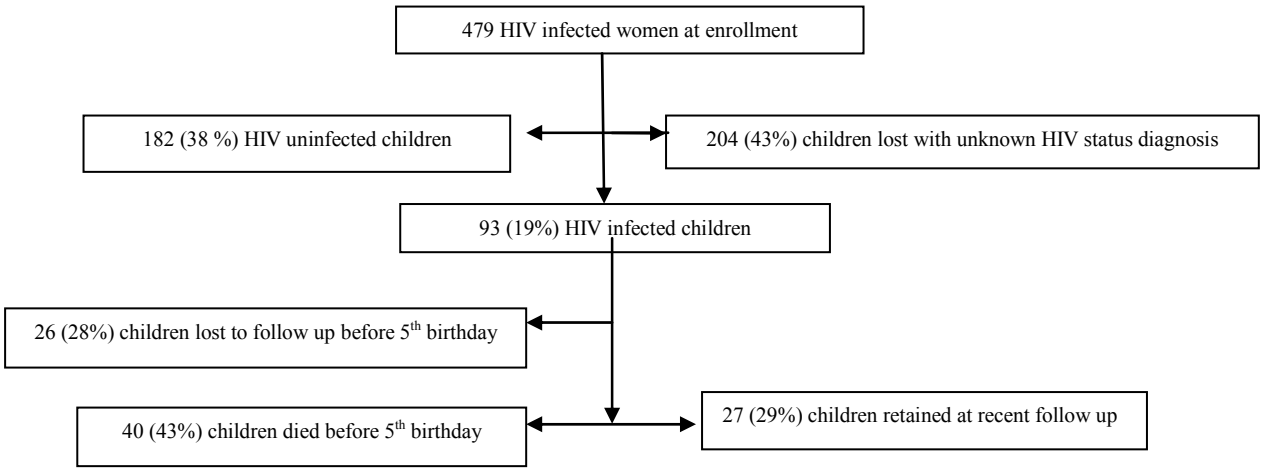

Figure 1. Follow up and retention of HIV infected infants in the cohort.

Table 1. Unadjusted hazard ratio for predictors of child mortality.

Predictor	Hazard ratio (95% confidence interval)	p value (cox regression)
Sex N = 85		
Male		
Female	0.81 (0.41 - 1.61)	0.549
Delivery weight (g) N = 80		
<2500 (%)		
≥2500 n (%)	0.88 (0.31 - 2.50)	0.816
Head circumference at birth (cm)	0.90 (0.75 - 1.07)	0.228
Length at birth (cm)	0.99 (0.89 - 1.09)	0.796
Breast feeding at 6 weeks		
No		
Yes	0.56 (0.17 - 1.83)	0.336
Breast feeding at 4 months		
No		
Yes	0.25 (0.11 - 0.60)	0.002
Breast feeding at 9 months		
No		
Yes	0.51 (0.16 - 1.58)	0.241
Baby ever breastfed N = 86		
No		
Yes	0.82 (0.29 - 2.32)	0.712
Mother died N = 93		
No		
Yes	2.54 (0.78 - 8.26)	0.121

From 27 Children who survived (**Figure 1**), 23 children were not on antiretroviral therapy at the 5 year follow up visit. **Table 2** shows children's characteristics at the 5 year follow up visit. Six out of 23 children (26%) were eligible for antiretroviral therapy (cART) but not yet on cART.

Table 2. Children's characteristics at 5 year follow up visit.

Children's characteristics at 5 years follow up visit not receiving ART.	N = 23
Sex	
Male (%)	13(57%)
Female	10 (43%)
Age in months (SD)	56 (11)
Mean CD4 counts (SD)	1044(741)
Mean CD4 percentages (N = 22) (SD)	24(13)
Number eligible for ART (<350/<15%)	6(26%)

4. Discussion

The results depict an unacceptably high mortality of HIV infected children in the cohort and loss to follow up rate before and after HIV diagnosis. About 43% died before the 5th birthday which supports the urgent need of the prevention of mother to child transmission of HIV and the early diagnosis and treatment of HIV infection in children in Zimbabwe. As expected, mortality has been shown to be higher among HIV infected children compared to HIV-exposed but uninfected children [10]. Several studies have reported early mortality in HIV infected infants but few on long term outcome in Africa [11,12]. Kuhn *et al.* reported 77.1% mortality by 24 months in Zambia among HIV infected children [13].

Avoidance of breastfeeding eliminates the risk of HIV transmission through breast milk but is detrimental to child survival. Increased infant morbidity and mortality have been reported in several sub-Saharan African countries [14-17] in non-breastfed infants. In our study, the protective association of breast feeding was evident at 4 months but not statistically significant at 6 weeks and 9 months. This could be explained by the small numbers of HIV infected children. Although not statistically significant, the hazards ratio for children whose mothers died was more than twice. Studies from Africa have shown that maternal death is associated with child mortality. Mothers who have advanced HIV disease are unlikely to care for their children adequately and/or may carry infectious pathogens which are harmful to their children [18-20]. Marinda *et al.* identified low birth weight and male sex as risk factors of mortality in HIV exposed children [21]. Our results show a similar tendency.

Approximately one-third of HIV-infected children in sub-Saharan Africa who have no access to antiretroviral therapy are estimated to die by 1 year of age, and approximately one-half are estimated to die by 2 years of age [22]. However, these estimates are based on a limited number of observational and prospective studies [7].

The national program in Zimbabwe introduced HAART in 2008. It was during this time when the health delivery system faced a lot of socioeconomic challenges, so accessibility of the national program was somewhat limited. The majority of the children demised before HAART was the public domain although a few in the private sector could access the drugs. PMTCT coverage increased from 22% in 2007 to 42.6% in 2008 in Zimbabwe [23,24]. In 2009, 56% of HIV-positive pregnant women received antiretroviral (ARVs) for PMTCT and only 35% of HIV-exposed infants received prophylactic ARVs for PMTCT [25].

Unfortunately in this study there was a significant loss to follow up before and after diagnosis of HIV infection of children who participated in the study. We were unable to measure HIV viral loads of remaining HIV infected children. In conclusion, in this resource poor setting, there was a high mortality of HIV exposed children pre and post diagnosis.

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