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Early Antiretroviral Therapy Initiation and Mortality Among Infants Diagnosed with HIV in the First 12 Weeks of Life: Experiences from Kinshasa, DR Congo and Blantyre, Malawi

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ABBREVIATED TITLE: Early Infant HIV Diagnosis in Malawi and DR Congo

RUNNING HEAD: HIV Diagnosis and Treatment

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Background: Based on clinical trial results, the WHO recommends infant HIV testing at age 4-6 weeks and immediate antiretroviral therapy (ART) initiation in all HIV-infected infants. Little is known about the outcomes of HIV infected infants diagnosed with HIV in the first weeks of life in resource-limited settings. We assessed ART initiation and mortality in the first year of life among infants diagnosed with HIV by 12 weeks of age.

Methods: Cohort of HIV-infected infants in Kinshasa and Blantyre diagnosed before 12 weeks to estimate 12-month cumulative incidences of ART initiation and mortality, accounting for competing risks. Multivariate models were used to estimate associations between infant characteristics and timing of ART initiation.

Results: 121 infants were diagnosed at a median age of 7 weeks (interquartile range 6-8). The cumulative incidence of ART initiation was 46% (95% CI: 36%, 55%) at 6 months and 70% (95% CI: 60%, 78%) at 12 months. Only age at HIV diagnosis was associated with ART initiation by age 6 months, with a subdistribution hazard ratio of 0.70 (95% CI: 0.52, 0.91) for each week increase in age at DNA PCR test. The 12-month cumulative incidence of mortality was 20% (95% CI: 13%, 28%).

Conclusions: Despite early diagnosis of HIV, ART initiation was slow and mortality remained high, underscoring the complexity in translating clinical trial findings and WHO guidance into real-life practice. Novel and creative health system interventions will be required to ensure that all HIV infected infants achieve optimal treatment outcomes under routine care settings.

INTRODUCTION

Morbidity and mortality among untreated HIV-infected children is exceptionally high,[1,2] with almost 50% of perinatally-infected children estimated to die within the first year of life and 20% estimated to die within the first three months of life.[1] Early initiation of antiretroviral therapy (ART) has been shown to significantly reduce the risk of mortality. In a landmark clinical trial (CHER study), asymptomatic infants (median age 7.4 weeks) with a CD4% >25 who were randomized to immediate ART experienced a large (75%) reduction in mortality compared to infants who were randomized to initiate ART based on immunologic or clinical eligibility criteria.[3] The World Health Organization (WHO) amended the guidelines in 2008 to recommend immediate initiation of ART in all children diagnosed with HIV in the first two years of life, independent of clinical and immunologic markers of immunosuppression.[4]

Translating evidence from clinical trials into practice and achieving similar results in routine care settings can be difficult, particularly in resource-limited settings. Although the roll-out of ART has been dramatic, the treatment of HIV-infected infants in sub-Saharan Africa has lagged behind that of older children and adults. In 2014, overall, only 32% of HIV-infected children were accessing antiretroviral treatment compared to 41% of eligible adults.[5] Timely initiation of ART for perinatally-infected infants is particularly challenging, in large part due to the complexity of early infant HIV diagnosis (EID) at four to six weeks of age.[4,6] Several barriers to accessing EID have been highlighted in prior studies, including cultural resistance to testing, lack of laboratory infrastructure, weak sample transport networks, poor communication between laboratories and primary care clinics, weak linkages between EID and pediatric HIV care and treatment programs, non-availability of pediatric-appropriate antiretroviral formulations, and loss to follow-up at all stages of the EID cascade, including between delivery and testing.[7-10]

Little is known about the outcomes of HIV-infected infants diagnosed through EID in resource-constrained settings. Using data from two HIV research and treatment programs in the Democratic Republic of Congo (DRC) and Malawi, we assessed early infant ART (EIART) initiation and mortality in the first year of life among infants diagnosed with HIV prior to 12 weeks of age.

MATERIALS AND METHODS

Study population

The study population included HIV-infected infants diagnosed with HIV following EID performed prior to 12 weeks of age in Blantyre, Malawi (between July 2008 and August 2011) and Kinshasa, Democratic Republic of Congo (DRC) (between August 2009 and August 2012).

In Blantyre, EID activities were implemented as part of a research study that assessed the effect of HIV on the neurodevelopment. HIV-exposed infants identified through prevention of mother-to-child transmission (PMTCT) activities at two public health facilities were referred to study staff for EID services. HIV-infected infants were referred back to the primary care facility for clinical management and ART initiation. The Kinshasa data come from two centralized HIV prevention, care and treatment sites (one primary health center and one pediatric hospital) providing family-centered care. The referral network for the two centralized sites includes 90 maternities providing routine PMTCT services. HIV-exposed infants were identified through routine PMTCT activities. Before 2011, all HIV-exposed infants were referred for EID and clinical management at one of the two centralized sites. In the decentralized model implemented in 2011, all ART eligible pregnant women and their exposed infants were referred to a centralized site for care, while women not yet eligible for ART had the option of receiving EID

for their exposed infants at the level of the maternity with referral for care to a centralized site if their infant was HIV-infected.[11-14]

Available PMTCT services in Malawi consisted of single dose nevirapine before July 2009. Between July 2009 and January 2010 the regimen changed to include zidovudine from 28 weeks of gestation until a week after delivery, with the addition of nevirapine for the week following delivery. After delivery, single dose nevirapine was given to the infant within 72 hours and zidovudine was given for seven days. In the DRC, before 2010 mothers who were not yet eligible for ART received single dose nevirapine, as did their infants. Once the national guidelines changed to include Option A in 2010, the regimen changed to zidovudine prophylaxis from as early as 14-weeks gestation up to seven days postpartum, with infants receiving a daily prophylactic regimen of nevirapine from birth until six weeks after weaning or for six days after birth if they were not breastfed. Due to inconsistent availability of zidovudine and presentation to care later in pregnancy, some women continued to receive single dose nevirapine on its own or in addition to zidovudine even after 2010.

In both cities, EID was performed using DNA PCR (version 1.5 of the Amplicor HIV-1 DNA test kit, Roche, Basel, Switzerland) on dried blood spots (DBS) collected via heel prick. In Blantyre, confirmatory testing was done by DNA PCR on a second blood spot of the original DBS card or by an HIV RNA viral load test (version 1.5 of the Amplicor HIV-1 Monitor, Roche) on a subsequently collected peripheral blood sample. In Kinshasa, confirmatory testing was done by DNA PCR on a new DBS sample. An infant was considered HIV-infected if the confirmatory test was also positive. In accordance with the 2008 WHO guidelines,[4] all HIV-infected infants under two years of age were eligible to receive ART (standard of care during study period was

nevirapine/stavudine/lamivudine in Malawi and zidovudine/lamivudine/lopinavir/ritonavir or zidovudine/lamivudine/nevirapine in the DRC).

The study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill, the Ethics Committee of the Kinshasa School of Public Health, and the University of Malawi College of Medicine Review Board. Parents or guardians of all children included in the analysis provided written informed consent.

Measurements

The primary outcomes of interest were ART initiation and mortality in the first 12 months of life. Covariates included age at first infant HIV test, gender, receipt of any PMTCT prophylactic regimen (based on current recommendations) by infant and/or mother, and breastfeeding status (exclusive breastfeeding or not), maternal ART status, severity of immunodeficiency (CD4%<25 or ≥25), anemia, and growth failure measured at time of infant HIV diagnosis. The hemoglobin cut points for severe, moderate, and mild anemia were defined according to the WHO recommendations for children under five (<7 g/dl, 7-9.9 g/dL, and 10-10.9 g/dL, respectively).[15] Growth failure was defined as having a weight-for-age z-score (underweight) or height-for-age z-score (stunted) less than two standard deviations for the weight and height measured between HIV diagnosis and 17 weeks of age. Z-scores were derived from the WHO Child Growth Standards[16]. Severity of immunodeficiency and anemia were determined from the first available CD4% and hemoglobin values measured before 15 weeks of age.

Statistical analysis

Descriptive statistics were used to characterize the study population at infant enrollment and at age 12 months. Competing risk cumulative incidence functions[17] were computed to estimate the 12-month cumulative incidence of infant ART initiation, stratified by city. Infants

contributed follow-up time from birth until the event of interest (ART initiation), competing event (death), or censoring event (loss to follow-up [LTFU], transfer out, 12 months of age, or end of data collection (August 2013 for Kinshasa, no administrative censoring for Blantyre), whichever occurred first. Infants were considered LTFU on their last attended clinic visit date following two (Blantyre) or three (Kinshasa) failed tracking attempts after a missed appointment. The same approach was used to estimate 12-month cumulative incidences of death, except there were no competing risks to account for.

To determine predictors of ART initiation by six months of age, we used the SAS macro %PSHREG[18] to implement the proportional subdistribution hazards model of Fine and Gray.[17,19] Bivariate and multivariate subdistribution hazard ratios (in text referred to as HR), as well as corresponding 95% confidence intervals (CI), were generated. In these analyses, infants contributed follow-up time from birth until the event of interest (ART initiation by age six months, a competing event (death), or a censoring event (LTFU, transfer of care to another facility, six months of age, or end of data collection), whichever occurred first.

All analyses were performed using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina). We conducted a complete case analysis, excluding observations with missing values for covariates. All tests of statistical significance were two-sided and the threshold for statistical significance was $p < 0.05$.

RESULTS

Between 2008 and 2012, 2593 children underwent DNA PCR testing at the EID programs: 1305 at the two centralized HIV care and treatment sites in Kinshasa and 1288 in the Blantyre clinics. Of these children, 121 (4.7%) were diagnosed with HIV by age 12 weeks of age: 38 (2.9%) in Kinshasa and 83 (6.4%) in Blantyre. Median age at HIV diagnosis for these

121 children was seven weeks (interquartile range: 6-8 weeks) and similar between the two countries (Table 1).

Despite the availability of routine PMTCT services, in 16% (18) of infants (9% (3) in Kinshasa and 19% (15) in Blantyre) neither the mother nor the infant had received any antiretroviral drugs for PMTCT (Table 1). Overall, 8% (9) of women were receiving antiretroviral treatment. At time of HIV diagnosis, 80% (94) of infants were exclusively breastfed, 21% (23) were underweight, and 34% (36) were stunted. About half of all infants had a CD4% below 25 (63% (17) in Blantyre and 43% (15) in Kinshasa), but CD4% was not available for all infants in Blantyre.

During the first 12 months of life, 75 (62%) children initiated ART. ART was initiated at a median age of 6.2 months (27 weeks, range 9.1 to 51.4 weeks), at a younger age in Kinshasa (24 weeks) than Blantyre (33 weeks) (Figure 1). The 12-month cumulative incidence of ART initiation was 70% (95% CI 60%, 78%), and was higher in Kinshasa (82%, 95% CI: 64%, 92%) than Blantyre (64%, 95% CI: 51%, 74%) (p=0.017). The 6-month cumulative incidence of ART initiation was 46% (95% CI 36%, 55%), and was also higher in Kinshasa (54%, 95% CI: 37%, 69%) than in Blantyre (42%, 95% CI: 30%, 53%) (p=0.12). Of the 46 infants who did not start ART in the first 12 months of life, 17 (40.0%) died and 15 (32.6%) were LTFU.

In bivariate analysis (Table 2), age at HIV diagnosis (p=0.02) was predictive of ART initiation by six months of age, with a hazard ratio of 0.79 (95% CI: 0.65, 0.95) for each week increase in age at DNA PCR test. Country, gender, exclusive breastfeeding, receipt of infant or maternal antiretrovirals for PMTCT, and underweight status of the child were not associated with timing of ART initiation. In multivariate analysis (Table 2), age at DNA PCR test remained

independently associated (p<0.01) with ART initiation by six months of age (HR, 0.70; 95% CI: 0.52, 0.91).

Overall, 11% (95% CI: 6%, 18%) of infants died by six months of age and 20% (95% CI: 13%, 28%) died by 12 months of age (Figure 2). Mortality in the first year of life was higher in Blantyre than in Kinshasa with a 12-month cumulative incidence of 27% (95% CI: 17%, 39%) in Blantyre versus 8% (95% CI: 2%, 20%) in Kinshasa (p=0.04).

DISCUSSION

Among infants diagnosed with HIV in the first 12 weeks of life in Blantyre, Malawi and Kinshasa, DRC, we found that few children received immediate ART, a high proportion failed to initiate ART by six months of age, and one in five infants died before reaching one year of age.

The association between earlier DNA PCR testing and earlier ART initiation in our analysis highlights the importance of removing barriers to EID, including inadequate recording of HIV exposure and maternal HIV status on patient records, maternal non-disclosure, insufficient awareness of EID, high cost and logistical complexity of HIV DNA PCR tests, and LTFU after diagnosis given the need for a return visit. Development of an accurate, cheap point-of-care assay for EID has the potential to optimize the outcome of perinatally-infected infants.

During the pre-ART era, when an estimated 36% of perinatally-infected children died within the first year of life,[20] findings of retrospective cohort studies observed that starting ART in the first six to 12 months of life decreases mortality and improved clinical outcomes.[21-24] Our results extend these finding by assessing the one year outcomes in infants participating in a PMTCT-linked EID program. While the 20% mortality rate we observed in the first year of life among infants diagnosed with HIV at a median age of 7 weeks (IQR 6-8) is an improvement compared to the pre-ART era, it is much higher than the mortality observed in infants

randomized to immediate ART in the CHER study (4% over a median follow-up of the full cohort of 40 weeks) conducted in South Africa. We believe the discrepancy between the trial and implementation data is due to several factors. First, the CHER study excluded children with evidence of immunosuppression (CD4% <25). Similar to observations in other studies[23], we found that half (52%) of young infants already have signs of immunosuppression at time of infant HIV diagnosis. Expanding eligibility for immediate ART to all infants, including those with immunosuppression in the first weeks of life, will result in higher mortality rates than what was observed in the restricted trial population. Another important difference is the median age of ART initiation. Under the CHER trial conditions, all children were tested for HIV prior to age 6 weeks and ART initiation was achieved by age 7.4 weeks (IQR: 6.6, 8.9).[3] In our analysis, we included children receiving EID before age 12 weeks to take into account of the delays that often occur under real world conditions. In this population, ART initiation occurred at a median age of 6.2 months. Delays in ART initiation occur as children need to return for their EID HIV test result, which is often delayed given the difficulties with transportation and communication between the centralized laboratory and the primary care clinics. Furthermore, upon diagnosis, children often need to be referred for ART initiation as this is not yet available at primary care in many settings, again resulting in further delays.

While the delays in ART initiation were present in both cities, rates of ART initiation were higher and 12-month mortality was lower in Kinshasa compared to Blantyre, with no deaths occurring between 3-12 months in the Kinshasa patients, likely due in part to higher ART initiation rates. While the numbers are relatively small and theses differences need to be confirmed, the differences may be explained by the fact that the HIV care and treatment program in Kinshasa received a high level of international financial and technical assistance, including

intensive monitoring and evaluation, whereas HIV-infected infants in Blantyre were referred to routine public HIV care and treatment program. Furthermore, a strong family-centered program, which was the focus of the Kinshasa program, has been shown to result in improved infant outcomes.[14] We envision that the shift to Option B+ in Malawi and DRC may result in improved infant HIV care and treatment[25] by overcoming some of the barriers to timely ART initiation including stigma,[26,27] loss to follow up, [28-30] and fear of finding out an infant's status.[26,27] There is existing evidence that increasing access to combination antiretroviral therapy for mothers results in improved retention of HIV-exposed infants,[14] a finding which may be promising for improved linkage to care and retention of infants born to HIV-infected mothers in the setting of Option B+.

The use of prospectively collected data on infants diagnosed at two different resource-poor settings are important strengths of this assessment of infant outcomes which, to our knowledge, is the first report of infant outcomes under routine PMTCT and EID implementation at primary care. It is estimated that in 2014 a quarter of women still did not have access to any PMTCT regimens. [5] Our data provide valuable context for the reality and challenges of implementing HIV prevention and treatment in the real world setting. The challenges encountered in the settings described here have relevance for the implementation a wide variety of current and future public health guidelines that go beyond the specific EID guidelines that are the focus of this work. Several limitations should be noted. First, despite the aggregation of two databases, the limited sample size prohibited assessment of the causal effect of timing of ART on mortality. Furthermore, due to delays in availability of test results and the need for referral for HIV care and ART, some children were lost to follow up and others died before ART could be initiated. In the analysis, we tried to take this into account by treating death as a competing risk.

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Figure Legend

Figure 1. Twelve-month cumulative incidence of ART initiation in Kinshasa, Democratic Republic of Congo and Blantyre, Malawi

Figure 2. Twelve-month cumulative incidence of death in Kinshasa, Democratic Republic of Congo and Blantyre, Malawi

TABLE 1. Characteristics of 121 HIV-infected infants at enrollment

	Overall (N=121)	Blantyre (N=83)	Kinshasa (N=38)	*p*-value[a]
Age in weeks at first DNA PCR test, median (IQR)	7 (6-8)	7 (6-8)	7 (6-8)	0.07
Gender, N (%)				0.42
F	70 (58)	46 (55)	24 (63)	
M	51 (42)	37 (45)	14 (37)	
Exclusive breastfeeding, N (%)				0.28
No	23 (20)	14 (17)	9 (26)	
Yes	94 (80)	68 (83)	26 (74)	
Missing	4	1	3	
Infant or maternal PMTCT regimen, N (%)				0.20
No	18 (16)	15 (19)	3 (9)	
Yes	95 (84)	65 (81)	30 (91)	
Missing	8	3	5	
Maternal ART, N (%)				0.02
No	110 (92)	78 (96)	32 (84)	
Yes	9 (8)	3 (4)	6 (16)	
Missing	2	2	0	
CD4%, N (%)				0.12
25+	30 (48)	10 (37)	20 (57)	
<25	32 (52)	17 (63)	15 (43)	
Missing	59	56	3	
Stunted, N (%)				0.93
No	71 (66)	46 (67)	25 (66)	
Yes	36 (34)	23 (33)	13 (34)	
Missing	14	14	0	
Underweight, N (%)				
No	85 (79)	59 (84)	26 (68)	0.05
Yes	23 (21)	11 (16)	12 (32)	
Missing	13	13	0	
Anemia, N (%)				0.07
Normal	13 (20)	8 (20)	5 (21)	
Mild	13 (20)	9 (23)	4 (17)	
Moderate	30 (47)	15 (38)	15 (63)	
Severe	8 (13)	8 (20)	0 (0)	
Missing	57	43	14	

[a] *p*-Values are for the comparison of Blantyre versus Kinshasa.

Note: Enrollment characteristics were measured by 15 weeks of age, except for weight and height, which were measured by 17 weeks of age. Analysis includes first available measurement for each child.

TABLE 2. Predictors of ART initiation by six months of age

	Subdistribution hazard ratio (95% confidence interval)	*p*-Value
Bivariate Analysis		
Kinshasa vs. Blantyre	1.58 (0.88, 2.74)	0.12
Each week increase in age at PCR test	0.79 (0.65, 0.95)	0.02
Female vs. Male	1.36 (0.78, 2.46)	0.29
Exclusive breastfeeding vs. Not	0.97 (0.50, 2.05)	0.93
CD4% <25 vs. 25+	0.77 (0.37, 1.55)	0.45
Any PMTCT regimen v None	0.92 (0.44, 2.23)	0.45
Maternal ART vs. No maternal ART	1.06 (0.32, 2.60)	0.91
Underweight vs. Not	1.00 (0.48, 1.89)	0.99
Multivariate Analysis*		
Kinshasa vs. Blantyre	1.57 (0.78, 3.07)	0.21
Each week increase in age at PCR test	0.70 (0.52, 0.91)	0.01
Female vs. Male	1.46 (0.77, 2.90)	0.27
Exclusive breastfeeding vs. Not	0.60 (0.28, 1.41)	0.14
Any PMTCT regimen vs. None	0.86 (0.37, 2.34)	0.76
Underweight vs. Not	1.40 (0.59, 3.07)	0.43

Due to the high frequency of missing CD4 data, this variable was not included in the multivariate analysis

Figure 1

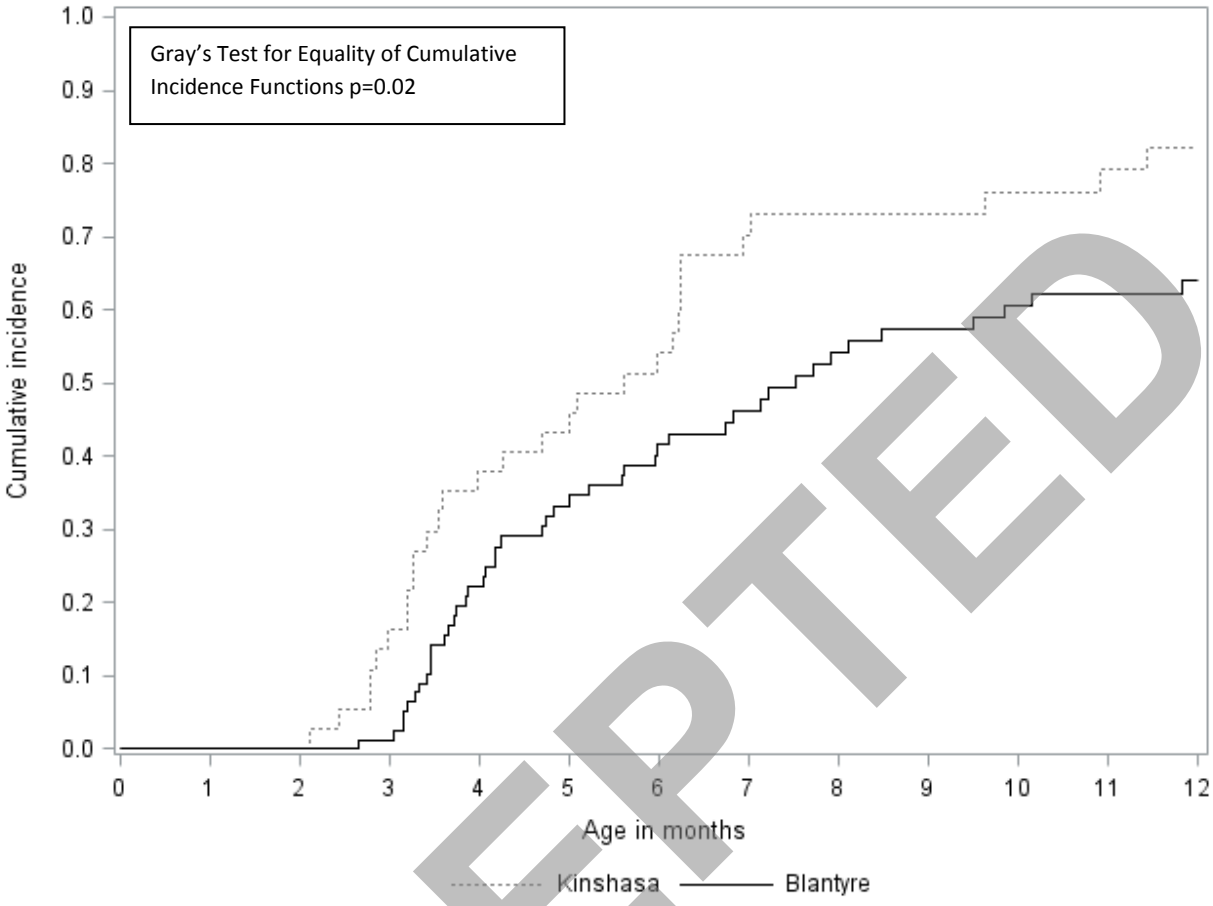

Figure 2