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Infant HIV-Free Survival in the Era of Universal Antiretroviral Therapy for Pregnant and Breastfeeding Women: A Community-Based Cohort Study from Rural Zambia

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Abstract

Background: Lifelong antiretroviral therapy (ART) is now recommended for all HIV-infected pregnant and breastfeeding women; however, few have described overall infant outcomes in this new era for the prevention of mother-to-child HIV transmission (PMTCT). **Methods:** As part of an assessment of PMTCT program impact, we enrolled a prospective cohort study in four predominantly rural districts in Zambia. HIV-infected mothers and their newborns (≤30 days old) were recruited and followed at 6 weeks, 6 months, and 12 months postpartum; infant specimens were tested via HIV DNA PCR. In Kaplan-Meier analyses, we estimated overall infant HIV-free survival and then stratified by district, community, and maternal ART use. We investigated the relationship between community-level 12-month, self-reported maternal ART use and infant HIV-free survival via linear regression. **Results:** From June 2014 to November 2015, we enrolled 827 mother-infant pairs in 33 communities. At 12 months, small proportions of infants had died (2.8%), were HIV-infected (3.0%), or were lost to follow-up (4.3%). Overall, infant HIV-free survival was 99.0% (95%CI: 98.0–99.5%) at 6 weeks, 97.5% (95%CI: 96.1–98.4%) at 6 months, and 96.3% (95%CI: 94.8–97.4%) at 12 months. Women reporting ART use at enrollment had higher infant HIV-free survival than those who did not (97.4% vs. 89.0%, p=0.01). Differences were noted at the district and site levels (p=0.01). In community-level analysis, no relationship was observed between 12-month infant HIV-free survival and self-reported maternal ART use (p=0.65). **Conclusion:** While encouraging, these findings highlight the need for rigorous monitoring and evaluation of PMTCT services at the population level.

Key words: prevention of mother-to-child HIV transmission, PMTCT, HIV-free survival, impact, Zambia, sub-Saharan Africa

Introduction

Tremendous gains have been made worldwide to eliminate mother-to-child transmission of HIV. From 2009 to 2015, the annual number of new pediatric HIV infections dropped by 60%; as a result, over 1.2 million new pediatric HIV infections were averted.[1] The provision of universal antiretroviral therapy (ART) for pregnant and breastfeeding women – known as the "Option B+" approach – has played a critical role in the success of global programs to prevent the mother-to-child transmission of (PMTCT). Initiated during pregnancy and breastfeeding and continued for life, ART can reduce vertical HIV transmission to less than 2%.[2,3] There is strong evidence for improved maternal survival and decreased horizontal HIV transmission as well.[4] Importantly, the Option B+ policy is aligned with international HIV treatment recommendations, which have moved towards universal ART for all HIV-infected adults and children.[5] First implemented in Malawi in 2011,[6] this strategy has since expanded to many settings of high HIV prevalence in sub-Saharan Africa.[1]

To date, assessments of Option B+ programs have focused largely on HIV-infected mothers. Many studies have emphasized programmatic indicators, such as uptake, retention, and adherence.[7-11] Others have focused on maternal health outcomes, including immune recovery.[12] Surprisingly, there are comparatively few reports of infant health in the context of Option B+, especially for broader – and perhaps more informative – outcomes such as HIV-free survival.[13] To address this gap in the medical literature, we evaluated the population-level impact of Option B+ services in Zambia via a large cohort of HIV-exposed infants and their HIV-infected mothers.

Methods

Setting

We targeted 33 sites in the peri-urban and rural settings of Zambia's Lusaka Province. All participated in the Better Health Outcomes through Mentoring and Assessment (BHOMA) project, an initiative to improve the quality of primary care through community- and facility-based interventions.[14] Like many African countries, PMTCT policy in Zambia has changed rapidly. In 2010, the Ministry of Health endorsed the World Health Organization's "Option A" strategy: antenatal zidovudine monotherapy, peripartum nevirapine (with a week-long tenovofir/emtricitabine "tail"), and infant nevirapine prophylaxis during breastfeeding.[15] Due to logistical challenges – and a growing desire to align PMTCT policy with general adult HIV guidelines – the Ministry of Health announced a policy shift to Option B+ in January 2013, with roll-out beginning the following year.[16] Our study coincided with the start of Zambia's adoption and implementation of Option B+.

Study activities

We conducted a prospective cohort study as part of a larger initiative to measure PMTCT impact at the population level. Trained community health workers from our target facilities identified potential candidates for the study. HIV-infected women and their HIV-exposed newborns (≤ 30 days of life) were recruited at the health facility or via the community-based networks from the BHOMA project.[14] Maternal HIV infection was confirmed through review of medical records (e.g., antenatal card) or via on-site rapid HIV antibody testing by trained personnel. Eligible mother-infant pairs were given information about the study objectives and procedures; those wishing to participate provided written informed consent.

At enrollment, we collected baseline demographic and medical information. At subsequent visits – scheduled at 6 weeks, 6 months, 12 months, and 18 months of infant life – mothers gave an update on their own health and that of their child, including HIV treatment status. Infants were tested for HIV via DNA PCR at enrollment, 6 weeks, 6 months, and 12 months of life. At 18 months of life, in accordance with Zambian national guidelines, rapid HIV antibody tests were used. Children who initially tested HIV-positive had a repeat test done; those with confirmed HIV infection were immediately referred to the nearest HIV treatment facility. In an effort to maximize participant retention, study visits were conducted at either at the clinic or at the household, based on the participant's stated preference.

Our original target was 40 HIV-infected/-exposed mother-infant pairs per site, or 1,320 mother-infant pairs overall. This sample size was based on practical considerations (e.g., duration of enrollment) and on what was deemed an acceptable level of precision within estimates of HIV-free survival at the community level (+/– 11%). As the study began enrolling, however, we became aware of the significant heterogeneity in clinic volumes and HIV prevalence among sites. In some communities, full enrollment was completed in a matter of months; in others, only a few participants could be enrolled over the course of a year. Ultimately, we closed enrollment after 19 months (prior to reaching our original target) due to financial and time constraints related to project funding. Our study protocol was reviewed and approved by the University of Zambia Biomedical Research Ethics Committee (Lusaka, Zambia) and the University of North Carolina Institutional Review Board (Chapel Hill, NC, USA).

Statistical analysis

The primary outcome of this cohort study was HIV-free survival among HIV-exposed infants, a metric that considers the direct (i.e., preventing vertical HIV transmission) and indirect (i.e.,

improving child survival) benefits often associated with PMTCT programs.[13] In our study, infants were categorized as having met the study outcome if they died or were diagnosed with HIV (see above). Infant HIV-free survival represents the proportion of infants who did not meet these study endpoints – i.e., they were alive and HIV-uninfected. We originally proposed to measure infant HIV-free survival at 18 months; however, over the course of the study, this was changed to 12 months to allow for extended recruitment at slowly enrolling sites.

We estimated overall infant survival and HIV-free survival using Kaplan-Meier analyses. We pooled data from all sites and then stratified our analysis by reported maternal ART use at enrollment and by district. We also calculated estimates for infant HIV-free survival for each participating community. Because of their relatively small sample sizes, we excluded four sites that enrolled fewer than 10 participants (Chongwe I [n=6], Chongwe J [n=7], Rufunsa C [n=8], Rufunsa E [n=2]). Further, we investigated potential factors associated with infant HIV infection or death, the two study endpoints used to generate infant HIV-free survival. We identified exposure variables that were associated with infant HIV infection or death at a $p \leq 0.05$ level in univariate analyses. These used to construct a multivariable Cox proportional hazards model. Robust standard errors were used to adjust for within-person clustering; maternal ART use was treated as a time-varying exposure.

Our secondary outcome was use of maternal antiretroviral drugs at 12 months, which was based on participant self-report. We calculated overall and site-specific proportions of reported antiretroviral drug use at each visit; missing values were considered non-use. Similar to our primary outcome, we calculated a pooled overall estimate, and then stratified by district and by community. Finally, we plotted site-level estimates for infant HIV-free survival and reported

maternal antiretroviral drug use to evaluate the linear relationship between these two outcomes. All statistical analyses were conducted using Stata version 14.1 (College Station, TX, USA).

Results

From June 2014 to November 2015, we enrolled 827 HIV-infected mothers and their HIV-exposed infants across 33 communities in Lusaka Province (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/D112). 199 mother-infant pairs were enrolled in Chilanga District (5 sites), 325 were enrolled in Chongwe district (14 sites), 253 were enrolled in Kafue District (9 sites), and 50 were enrolled in Rufunsa District (5 sites). Of 827 enrolled mother-infant pairs, 36 (4.3%) were lost to follow-up or had withdrawn, 23 (2.8%) infants had died, and 22 (3.0%) infants had a confirmed HIV infection in the first year of life (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/D113). Nearly 80% reported an institutional delivery, either at a government facility or a mission hospital or clinic. Almost all (99.4%) were breastfeeding at time of enrollment (Table, Supplemental Digital Content 3, http://links.lww.com/INF/D114). High rates of breastfeeding were reported throughout the follow-up period: 98.1% (95%CI: 96.8–98.9%) at 6 weeks; 96.3% (95%CI: 94.6–97.5%) at 6 months; and 84.8% (95%CI: 81.9–87.4%) at 12 months.

In pooled Kaplan-Meier analysis, survival among HIV-exposed infants was 99.6% (95% confidence interval [CI: 98.9–99.9%) at 6 weeks, 97.8% (95%CI: 96.5–98.6%) at 6 months, and 97.1% (95%CI: 95.7–98.1%) at 12 months. HIV-free survival among HIV-exposed infants was 99.0% (95%CI: 98.0–99.5%) at 6 weeks, 97.5% (95%CI: 96.1–98.4%) at 6 months, and 96.3% (95%CI: 94.8–97.4%) at 12 months. In stratified analyses, we found that infants whose mothers reported ART use at enrollment had higher subsequent rates of infant HIV-free survival than those who did not (97.4% vs. 89.0%, p=0.01; Table 2). Significant differences were also

observed at the district level (p=0.01; Table 2), with HIV-free survival ranging from 93.2% (95%CI: 89.1–95.8%) in Kafue to 99.5% (95%CI: 96.4–99.9%) in Chilanga. Infant HIV-free survival by community is shown in Figure 1 (p=0.01).

In univariate analysis, several factors were associated with infant HIV infection or death, the two adverse outcomes used to generate HIV-free survival; these were included in our multivariable Cox proportional hazards model. Two continuous variables were associated with these study endpoints: years of education (adjusted hazard ratio [AHR]: 0.89, 95%CI: 0.80–0.98) and parity (AHR: 0.81, 95%CI: 0.71–0.92). Among categorical variables, women who reported an institutional delivery were less likely to report infant HIV infection or death compared those who delivered outside of a health facility (AHR: 0.48, 95%CI: 0.23–0.99). Marriage (AHR: 0.81, 95%CI: 0.32–1.35) and reported use of maternal ART (AHR: 0.52, 95%CI: 0.21–1.27) both trended towards a protective effect, but neither was statistically significant.

At the time of enrollment, 724 of 827 (87.6%) women reported using antiretroviral drugs. This figure declined gradually over time: 85.7% (95%CI: 83.2–88.0%) at 6 weeks, 82.6% (95%CI: 79.8–85.1%) at 6 months, and 80.5% (95%CI: 77.7–83.2%) at 12 months. In stratified analyses, the 12-month estimates for antiretroviral use was highest in Chilanga District (84.4%, 95%CI: 78.6–86.4%), followed by Chongwe (82.4%, 95%CI: 77.9–86.4%), Kafue (77.1%, 95% CI: 71.4–82.1%), and Rufunsa Districts (70.0%, 95%CI: 55.4–82.1%). At the community level, reported use of maternal antiretroviral drugs varied significantly at 12 months (p=0.001), ranging from 55.6% (Chongwe L) to 100% (Chongwe E; Figure 1). We were unable to identify a linear relationship between infant HIV-free survival and reported maternal antiretroviral drug use at 12 months (p=0.65, Figure 2).

Discussion

In this rural, community-based cohort study, we provide empiric data about infant outcomes in the era of universal ART for pregnant and breastfeeding women. We found HIV-free survival to be generally high at 12 months of infant life. We observed significant heterogeneity in maternal antiretroviral drug use at one year postpartum but, at the site level, usage rates did not correlate with infant outcomes.

We measured infant HIV-free survival in our primary outcome, a metric that considers the effectiveness of PMTCT interventions alongside indirect infant survival benefits that may accompany enhanced health services.[13] At 12 months of life, our pooled estimate was 96.3%; by community, they ranged from 93.2% to 99.5%. These rates are comparable to those observed in survey studies from sub-Saharan Africa. Buzdugan and colleagues, for example, measured population HIV-free survival between 9-18 months of life across 157 communities in Zimbabwe. Prior to the introduction of the 2010 Option A strategy for PMTCT, HIV-free survival was estimated at 89.6% (95%CI: 87.1–92.1%); two years after implementation, this had increased to 95.1% (95%CI: 93.6–96.6%).[17] In a nationally representative sample in Rwanda – before the implementation of more efficacious PMTCT regimens – HIV-free survival was measured at 91.9% (95%CI: 90.4–93.3%) between 9 and 24 months.[18] In a pilot program of universal combination antiretroviral regimens for HIV-infected pregnant women – conducted in Zambia's Kafue District in 2009-2010 – we observed an HIV-free survival of 89% (95%CI: 83–94%) at 24 months.[19] These four communities were also part of the current study.

Our findings are consistent with prior cohorts as well. In a meta-analysis by Chikhungu and colleagues, pooled estimates from 10 studies showed a 12-month HIV-free survival of 89.8% (95%CI: 86.4–93.2%). When limited to the three studies of lifelong maternal ART – including

two in the setting of universal HIV treatment – the estimate was slightly higher at 91.8% (95% CI: 87.7–95.9%).[20] Similar to other studies,[21,22] the high rates of continued breastfeeding observed in our cohort (84.8% at 12 months) likely contributed to the overall HIV-free survival. At approximately 80%, our reported antiretroviral use at 12 months postpartum is similar to other regional studies, but below the "90-90-90" thresholds endorsed worldwide.[23] In the Malawi national PMTCT program, for example, 76.8% (95%CI: 76.3–77.3%) were retained in care at 12 months following ART initiation; at 24 months, this figure was estimated at 70.8% (95%CI: 70.3–71.4%).[8] Myer, *et al.* described similar trends in a cohort South African women who initiated ART during pregnancy and attained virologic suppression (<50 copies/mL). At 12 months postpartum, 70% maintained virologic suppression; however, 8% had minor virologic episodes (<50 to 1,000 copies/mL), and 22% had at least one major episode (>1,000 copies/mL).[24]

We recognize the potential for biases with our self-reported measure of ART adherence. Despite attempts to minimize such reporting biases (e.g., employment of community health workers, home study visits), participants may have inaccurately reported ART use out of perceived social desirability. Our study question ("are you taking antiretroviral drugs now?") could have led to misclassification if antiretroviral drugs were confused with other prescribed medicines (e.g., cotrimoxazole). Generally, such factors could lead to an over-reporting of ART use. They could also contribute to the observed differences in reported ART use in pregnancy and at time of enrollment. It should be noted that participants were asked the same question about ART use at each of the study visits. This approach enhanced the internal validity of the outcome, particularly when analyzing trends over time.

At the community level, we observed a significant heterogeneity in ART continuation rates in the 12 months after delivery. While the Option B+ policy was included in the Zambian PMTCT guidelines in 2013-2014, the implementation of services was not immediate, particularly in peri-urban and rural sites. Similar to other settings, the model of service delivery may have varied.[25] In addition, implementation may have been slowed by existing health infrastructure constraints, often exacerbated by the increased demands of the Option B+ services. In an analysis of 42 health facilities in Lusaka Province, Mutale and colleagues showed the variation in health systems performance across different domains (i.e., patients and communities, human resources, service capacity, finance, governance, service provision, overall vision).[26] Understanding ART use in the context of health system capacity could help to identify high-leverage points for implementation support.

At the individual level, use of combination antiretroviral regimens during pregnancy leads to improved infant HIV-free survival.[19,27] As part of our analysis, we investigated whether a similar association could be demonstrated at the population level. Interestingly, in aggregate, we did not show relationship between these programmatic outcomes (i.e., continued maternal ART use) and health outcomes (i.e., infant HIV-free survival). With only 29 facilities and surrounding communities – our unit of analysis – we likely had insufficient statistical power, especially given the narrow range of HIV-free survival at the facility/community level. This highlights the challenge of translating individual-level associations to meaningful population-level metrics for monitoring and evaluation. Our reliance on self-reported adherence measures – and its potential for misclassification – may have contributed to this lack of association observed between maternal ART use and infant HIV-free survival.

We recognize several strengths of our study. In line with published guidance from the World Health Organization,[28] we employed a prospective cohort approach to minimize recall and reporting biases. We maintained high patient retention (>95%) to address an important potential weakness of this design. We sought a "real world" perspective from non-urban settings; to accomplish this, we streamlined study activities and engaged participants at both the facility and community levels. We acknowledge important limitations as well. First, despite intensive efforts to identify and enroll eligible mother-infant pairs, we faced substantial recruitment challenges in some of the smaller and more remote facilities. Participant outcomes from these sites were under-represented in our pooled analysis, which we addressed by reporting community-level estimates. Second, for logistical reasons, we truncated our primary outcome from 18-month to 12-month HIV-free survival. Lengthier follow-up could provide definitive early childhood outcomes for HIV, particularly if HIV testing were performed after breastfeeding cessation. Third, our population was likely enriched with women who sought institutional antenatal care and delivered at health facilities. Although we recruited from communities, we did not sample at the household level because of the intensive nature of such an approach. Finally, we did not conduct detailed adherence evaluations (e.g., pill counts, pharmacy record reviews) nor did we obtain more objective measures of drug ingestion (e.g., direct observation, drug levels), even in a subset of participants. Haas, et al. has shown the decreasing probability of maintaining adequate adherence (defined as $\geq$90%) over time[7] – even among those reporting taking ART – and this should be considered when interpreting our results.

In summary, we demonstrated encouraging infant outcomes in the era of Option B+ in peri-urban and rural Zambia. Our estimates for infant HIV-free survival remained relatively stable, despite a wide range of maternal ART continuation at 12 months. Our study highlights the ongoing need

for program monitoring and evaluation, and its role for improving Option B+ services. Alternative approaches, including household surveys, may be more efficient and less time-consuming, but such methodologies require validation.

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Legend:

Figure 1: Infant HIV-free survival and reported maternal antiretroviral continuation at 12 months by clinic and surrounding community**.** Four clinics were not included in the stratified analysis because of low enrollment figures: Chongwe I (n=6), Chongwe J (n=7), Rufunsa C (n=8), and Rufunsa E (n=2).

Figure 2: Comparison of community-level infant HIV-free survival and maternal antiretroviral use at 12 months following delivery

Supplemental digital content 1: Figure. Location of 33 participating communities in Lusaka Province

Supplemental Digital Content 2: Figure Enrollments and retention of HIV-exposed infants enrolled from 33 communities in Lusaka Province

Supplemental Digital Content 3 Table. Maternal characteristics of the study cohort, overall and stratified by district

Table 1: Kaplan-Meier analysis of infant outcomes at 6 weeks, 6 months, and 12 months in pooled analysis of participants from 33 communities in Lusaka Province, Zambia

Infant outcome	**6 weeks**	**6 months**	**12 months**	**p**
Overall survival	99.6% (98.9–99.5%)	97.8% (96.5–98.6%)	97.1% (95.7–98.1%)	–
Overall HIV-free survival	99.0% (98.0–99.5%)	97.5% (96.1–98.4%)	96.3% (94.8–97.4%)	–
HIV-free survival by district				0.01
Chilanga	100% (n/a)	100% (n/a)	99.5% (96.4-99.9%)	
Chongwe	99.4% (97.5-99.8%)	98.1% (95.8-99.2%)	96.8% (94.2-98.3%)	
Kafue	97.9% (95.1-99.1%)	95.0% (91.3-97.1%)	93.6% (89.7-96.1%)	
Rufunsa	97.9% (85.8-99.7%)	95.7% (83.9-98.9%)	95.7% (83.9-98.9%)	
HIV-free survival by maternal antiretroviral use at enrollment				<0.01
Yes	99.1% (98.1-99.6%)	98.1% (96.8-98.9%)	97.4% (95.9-98.4%)	
No	97.9% (91.7-99.5%)	92.4% (84.7-96.3%)	89.0% (80.6-94.0%)	

Figure 1

Figure 2