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HIV transmission and 24-month survival in a randomized trial of HAART to prevent MTCT during pregnancy and breastfeeding in Botswana (The Mma Bana Study)

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Abstract

Objectives—Highly active antiretroviral therapy (HAART) for prevention of mother-to-child HIV transmission (MTCT) may impact long-term survival of mothers and children.

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Design—Randomized clinical trial.

Methods—HIV–infected pregnant women with CD4 ≥200 cells/mm^3 were randomly assigned to abacavir, zidovudine, lamivudine (Arm A) or lopinavir–ritonavir, zidovudine–lamivudine (Arm B) from week 26–34 gestation through planned weaning by 6 months postpartum. Women with baseline CD4 <200 received nevirapine–zidovudine–lamivudine indefinitely (Obs arm), as did randomized women later qualifying for treatment.

Results—Among 560 randomized and 170 observational women enrolled, there were 14 deaths (1.9%); 1 antenatally (Obs), 3 from delivery though 6 months postpartum (1 Arm A, 2 Obs), and 10 from 6–24 months postpartum (5 Arm A, 3 Arm B, 2 Obs). Time to death or CD4 <200 was shorter in Arm A vs. B (p=0.03). Of 709 live-born children, 97% breastfed for median 5.8 months. Of 37 (5.2%) deaths by 24 months, 9 were before breastfeeding initiated (3 Arm A, 2 Arm B, 4 Obs); 6 while breastfeeding (1 Arm A, 2 Arm B, 3 Obs); and 22 after weaning (9 Arm A, 11 Arm B, 2 Obs). Only 8 children (1.1%) were HIV-infected at 24 months (6 Arm A, 1 Arm B, 1 Obs), all before 6 months.

Conclusions—Low MTCT was maintained through extended follow-up in all arms. Disease progression appeared slower after discontinuing protease inhibitor-based HAART, but a concerning number of maternal deaths occurred after stopping either regimen. Strategies to improve maternal and child survival in the post-intervention period are required.

Keywords

HIV; MTCT; Botswana; Africa; Antiretrovirals; Infant Survival; Maternal Health

INTRODUCTION

Highly active antiretroviral therapy (HAART) started in pregnancy and continued through 6 months of breastfeeding can reduce mother-to-child HIV transmission (MTCT) as low as 1%, allowing safer breastfeeding where infant formula is unsafe or unavailable [1–6]. The World Health Organization (WHO) recommends maternal HAART or infant nevirapine prophylaxis as options to prevent breastfeeding MTCT [7], but limited data exist for long-term maternal and child outcomes with these strategies. Prevention of MTCT (PMTCT) beyond the intervention period, maternal survival after HAART cessation, long-term child survival, and avoiding potential toxicities remain important concerns [8–11].

We present final 24-month maternal and child outcomes from a randomized clinical trial of maternal HAART used for PMTCT in Botswana. Six-month virologic suppression and PMTCT findings were previously reported [1]. This report includes final PMTCT efficacy results beyond the intervention period; CD4 cell count and treatment re-initiation data over time; and pre-specified morbidity and mortality comparisons through the end of follow-up at 24 months postpartum.

METHODS

Trial Design and Study Population

Between July 2006 and May 2008, HIV-infected treatment naïve pregnant women choosing to breastfeed enrolled in the Mma Bana Study (meaning “mother of the baby” in Setswana) in southern Botswana.

Women with CD4 cell counts ≥ 200 cells/mm^3 and no AIDS-defining illness were randomized to receive either abacavir (300 mg) (ABC) / zidovudine (300 mg) (ZDV) / lamivudine (150 mg) (3TC) co-formulated as Trizivir (GlaxoSmithKline) twice daily (Arm A) or lopinavir (400 mg) / ritonavir (100 mg) (LPV/r) with ZDV (300 mg) / 3TC (150 mg) co-formulated as Kaletra (Abbott) / Combivir (GlaxoSmithKline) twice daily (Arm B). Randomized women initiated HAART between 26–34 weeks gestation and continued through weaning or 6 months postpartum (whichever first). Women meeting Botswana government treatment criteria (+ cell counts < 200 cells/mm^3 [changed to < 250 cells/mm^3 after May 2008] or AIDS-defining illness) at any time continued or re-started HAART according to government guidelines. HAART for treatment was generally nevirapine (200 mg) (NVP) / ZDV (300 mg) / 3TC (150 mg) twice daily (following a 2 week lead-in period of 200 mg once-daily NVP), but was individualized within available treatment guidelines.

Women with CD4 cell counts < 200 cells/mm^3 or with AIDS-defining illness received indefinitely the standard-of-care NVP-based treatment listed above from enrollment between 18–34 weeks gestation, and were followed observationally (Obs arm).

Infants received single-dose NVP (6 mg) at birth, and ZDV (4 mg/kg twice daily) from birth through 4 weeks. HIV-infected children were offered HAART according to government treatment guidelines. Women were counseled to exclusively breastfeed and wean three days before the 6 month study visit. Infants were provided free formula from weaning and mothers were encouraged to introduce age-appropriate complementary foods beginning at six months.

The Health Research Development Committee from Botswana and the Harvard School of Public Health Human Subjects Committee approved the study protocol and amendments. An independent Data and Safety Monitoring Board reviewed safety and efficacy data approximately every 6 months. Participants signed written consent approved by the ethical review boards.

Study Procedures and Monitoring

Women were evaluated at least monthly from enrollment through delivery, and infants were enrolled and evaluated at birth. Women and children were evaluated at months 1–7, 9, 12, 15, 18, and 24. Telephone follow-up was conducted to determine 24-month vital status when unknown. After 6 months postpartum, maternal CD4 cell count testing occurred at least 6-monthly (3-monthly for those off HAART with CD4 cell counts < 400 cells/mm^3). Infant HIV DNA PCR testing occurred at birth, 1, 6, and 12 months, and HIV ELISA at 18 months. Child hematology testing (hemoglobin, white blood cell count, absolute neutrophil

count, and platelets) occurred at birth, 1, 3, 6, and 18 months. Additional laboratory monitoring was performed as previously described through 6 months [1].

Pre-specified Study Objectives and Definitions

Time to maternal and child death, child HIV-infection or death, and time to first of death or CD4 cell count < 200 cells/mm^3 in mothers were pre-specified study arm comparisons. Definitions for MTCT timing were as previously reported.[1] Child weight for age z-scores were based on WHO norms [12] and small-for-gestational age assessment was determined by Botswana-specific norms [13].

Statistical Analysis

Event rates were estimated using Poisson regression and differences between event rates were assessed using exact methods appropriate for small numbers of events. Factors associated with child mortality were assessed with a Poisson regression model fitted using generalized estimating equations. In this modeling, follow-up was divided into successive one-month intervals starting from birth and risk of death during an interval was evaluated by baseline and time-dependent factors; for the latter, the last available value at or before each interval was used. Univariate factors were first assessed, and those with p-value < 0.20 were included in multivariable models. Backwards variable selection was used to include factors with p-value < 0.05 in final models. For continuous variables, differences between means were assessed using the t-test. Time-to-event data were analyzed using the Kaplan-Meier estimator and the log rank test. The proportion of subjects with grade 3/4 events was compared using Fisher's exact test.

P-values < 0.05 were interpreted as statistically significant. Analyses were performed using SAS, Version 9.2 (SAS Institute, Cary, NC) and StatXact, Version 8.0 (Cytel Inc., Cambridge, MA).

Role of the Funding Source

The study sponsor had no role in study design; in collection, analysis, or interpretation of data; or in writing or submitting this manuscript.

RESULTS

In total, 730 women were enrolled (285 Arm A, 275 Arm B, 170 Obs) (Figure 1). Baseline characteristics were well-balanced by randomization arm (Table 1). At 24 months, survival status was available for 714 (98%) women; 612 (84%) women had completed the protocol or died (including 19 of those with stillbirths), and 102 (14%) women were confirmed to be alive by telephone follow-up (Figure 2A).

HAART treatment and CD4 Cell Count Changes

At 6 months postpartum, 13 women (5%) in Arm A and 7 (3%) in Arm B had met treatment criteria and continued HAART. Between 6 and 24 months, 31 (11%) in Arm A and 33 (12%) in Arm B re-started HAART (Figure 2C). Thus 84 women (15%) in Arms A and B received HAART after their PMTCT intervention completed: 81 met CD4 cell count criteria

to start, 2 had an AIDS-defining illness, and 1 started for PMTCT during another pregnancy. Among these 84 women, the median month for restarting HAART was 12 months postpartum. Of those who re-started, 3 (4%) had a baseline CD4 cell count at enrollment in pregnancy > 500 cells/mm^3, 12 (14%) from 351–500 cells/mm^3, 33 (39%) from 251–350 cells/mm^3, and 36 (43%) from 200–250 cells/mm^3. Although 85% in arms A and B remained off HAART after 6 months, mean CD4 cell count increased from baseline to 24 months in all groups: +68 cells/mm^3 (Arm A), +100 cells/mm^3 (Arm B), and +282 cells/mm^3 (Obs) (p=0.11 for Arm A vs. B). At 24 months or upon re-starting HAART (whichever first), mean CD4 cell count change was significantly lower in Arm A vs. Arm B (+20 vs. +71 cells/mm^3, p=0.005).

Maternal Survival and Adverse Events

Fourteen mothers died (1.9%) (Table 2). One death occurred antenatally after HAART initiation (Obs); 3 between delivery and 6 months postpartum (1 Arm A, 0 Arm B, 2 Obs); and 10 between 6 and 24 months postpartum (5 Arm A, 3 Arm B, 2 Obs). Among randomized women, deaths occurred across baseline CD4 cell count strata (4 had baseline CD4 200–350 cells/mm^3, 2 had baseline CD4 351–500 cells/mm^3, and 3 had baseline CD4 >500 cells/mm^3). Most deaths among randomized women occurred after stopping HAART; 8 deaths occurred from 6–24 months postpartum (1.0/100 person-years), whereas only 1 death occurred between HAART initiation and 6 months (0.3/100 person-yrs) (RR= 3.8, 95% CI=0.5, 167.2; p=0.29). Of the 8 post-intervention deaths, 3 had re-started HAART (0.9, 4.2, and 5.1 months prior to death), and 5 women had not re-started HAART as treatment at the time of death; the last CD4 cell counts for these 5 women were 304, 399, 482, 518, and 886 cells/mm^3, drawn at a median of 3.8 months (range 0.4, 8.9) before death. Among all 5 observational women who died, the last CD4 cell count before death was < 250 cells/mm^3. Causes of maternal death are detailed below Table 2. In a planned analysis, time to death or CD4 < 200 cells/mm^3 was shorter in Arm A vs. Arm B (p=0.03); in Arm A there were 21 CD4 cell count events and 6 deaths, and in Arm B there were 10 CD4 cell count events and 3 deaths.

Grade 3/4 diagnoses, laboratory events, and hospitalizations were higher in the observational arm than in the randomized arms (Table 2). More neutropenias occurred in Arm A compared with Arm B (p=0.014), but Grade 3/4 events were otherwise similar by randomized treatment arm. For the entire study period, 82 (11.2%) women had a grade 3/4 diagnosis (29 [10.2%] Arm A, 23 [8.4%] Arm B, 30 [17.6%] Obs) with corresponding event rates per 100 person years (95% CI) of 5.1 (3.4, 7.4), 4.2 (2.7, 6.3), and 8.4 (5.7, 12.0), respectively. Ninety-four women (13%) had a subsequent pregnancy.

Child Breastfeeding and HIV Infection

Of 709 live-born infants, survival status was available at 24 months for 691 (97%) children; 601 (85%) children had completed the protocol or died, and 89 (13%) were confirmed to be alive and 1 was confirmed to be dead at 24 months by telephone follow-up (Figure 2B). Among 687 (97%) who breastfed, breastfeeding was stopped prior to 5 months in 173 (25%), and was reported beyond 7 months in only 3 (< 1%) children (Figure 2D). Only identified as HIV-infected through 18 months (6 [2.1%] Arm A, 1 [0.3%] Arm B, 1 [0.6%]

Obs). This number was unchanged from 6 months. Exposure to breast milk was reported in 1 child beyond the 18 month ELISA, but a subsequent post-weaning ELISA was negative.

Child Survival and Adverse Events

There were 37 (5.2%) child deaths in the study period. Of these, 9 were before breastfeeding initiated (3 Arm A, 2 Arm B, 4 Obs) including 7 children < 3 days of age. Six deaths occurred while breastfeeding (1 Arm A, 2 Arm B, 3 Obs), and 22 after weaning (9 Arm A, 11 Arm B, and 2 Obs). There was no significant difference in child survival between arms A and B (p=0.71) or between randomized and observational arms (p=0.69).

Child mortality was significantly increased after weaning. Thirteen deaths occurred within 3 months of weaning and 9 occurred >3 months after weaning. No child had illness listed as a reason for weaning, and no deaths occurred within 5 days of last breastfeeding, making reverse causality (illness as a reason for weaning) unlikely. Among infants who initiated breastfeeding, the death rate during breastfeeding was 2.1/100 person-years, compared with 7.9/100 person-years within 3 months of weaning (RR = 3.7, 95% CI=1.3, 12.0; p=0.007). Beyond 3 month of weaning, the death rate declined to 1.0/100 person-years (compared with 7.9/100 person-years < 3 months from weaning, RR = 7.5, 95% CI=3.2, 18.4; p<0.001). Child deaths are detailed in a footnote to Table 2.

Two of 8 HIV-infected children died. HIV-infection or death occurred in 43 (6.1%) children; 18 (6.4%) Arm A, 16 (5.9%) Arm B, 9 (5.8%) Obs. There was no significant difference in HIV-free survival between arms A and B (p=0.74).

Grade 3/4 child diagnoses and hospitalizations did not differ significantly by maternal treatment arm (Table 2). For the entire study period, 111 children (15.7%) had a grade 3/4 diagnosis (47 [16.6%] Arm A, 40 [14.8%] Arm B, and 24 [15.4%] Obs) with a corresponding event rate per 100 person years (95% CI) of 12.6 (9.7, 16.1), 9.3 (6.8, 12.5), and 9.9 (6.6, 14.3), respectively. Grade 3/4 child hematologic findings through 24 months did not differ by maternal study arm (p=0.19). Beyond 6 months, child grade 3/4 anemia and neutropenia declined in all arms, occurring in 36 (5.5%) and 19 (2.9%) children, respectively. Through 24 months, 162 (22.8%) children were hospitalized, without a significant difference by maternal arm (p=0.95).

Risk Factors for Child Mortality

Risk factors for child mortality are presented in Table 3. Significant univariate risk factors included preterm delivery, being a twin, lower weight-for-age z-score, being within 3 months of weaning, and the child's age. Both weaning within 3 months (RR=4.07, 95% CI 1.62, 10.22) and the child's age by 3-month age group (p=0.02) were significant risk factors for mortality when independently modeled, but co-linearity prevented their inclusion in the same model. Additional adjusted risk factors in the model including child age were preterm delivery (RR=3.4 for < 37 vs. ≥ 37 weeks gestation, 95% CI 1.5, 7.8), and lower child weight for age z-score (RR=1.6 per 1 z-score lower, 95% CI 1.2, 2.2). Child mortality risk was greatest for children in the 6 to < 9 month age group.

DISCUSSION

Low MTCT was maintained through extended follow-up in all arms of this randomized clinical trial in Botswana, with no additional MTCT beyond the 6 month intervention period. Time to maternal death or CD4 < 200 cells/mm^3 was shorter in the triple NRTI arm than the PI arm, and a concerning number of maternal deaths occurred after stopping HAART used for PMTCT. Child mortality was highest within 3 months of weaning.

Our MTCT findings are encouraging, and support the high efficacy of maternal HAART for preventing breastfeeding transmission when full viral suppression is achieved (93% of women in our study had HIV RNA < 400 copies/mL throughout the breastfeeding period [1]). Breastfeeding transmission rates in our study are in accord with smaller studies [3, 6] but were lower than other large clinical trials in Africa [2, 4, 8]. We believe that starting HAART by the early third trimester of pregnancy in most women, achieving high levels of HAART adherence and viral suppression through 6 months, and excellent compliance with the recommendation to wean by 6 months (with almost all children being weaned by 7 months), reduced MTCT risk in our study. In Malawi, where HAART from delivery to 28 weeks postpartum was evaluated and 48-week results reported, 4% overall MTCT occurred in the maternal HAART arm, with 30% of transmissions occurring after the intervention period [8]. We can only explain the difference in post-intervention MTCT rates by different levels of adherence to weaning recommendations in the two studies.

The randomized comparison between NRTI and PI-based HAART was notable for several significant and non-significant trends favoring PI-based PMTCT. A planned analysis of time to death or CD4 cell count < 200 cells/mm^3 favored PI-based HAART, and appeared to be driven by a difference in the CD4 cell count endpoint (11 more events in Arm A) than death (3 more endpoints in Arm A). Although HIV RNA suppressed faster in Arm A than Arm B [1], the overall CD4 cell count increase was greater in Arm B. Mortality, hospitalizations, and adverse events did not differ by randomization arm, but there was limited power to detect significant differences. The study was powered to detect virologic differences between randomized arms, and was not powered to detect a difference in MTCT. However, 6 Arm A transmissions vs. 1 Arm B transmission was noteworthy; further data are required to evaluate this difference.

Among randomized women, mortality increased after HAART was discontinued, with all but one death occurring in the post-intervention period. This trend was not statistically significant, but the absolute mortality risk of 1.4% in the 18 months after stopping HAART is of concern. Current guidelines in Botswana,[14] and newer WHO guidelines [7], support continuous treatment for women with CD4 <350 cells/mm^3, providing greater security against rapid health declines before treatment initiation. These data are supported by several studies that highlight a survival benefit when HAART is started between CD4 cell counts of 200–350 cells/mm^3 rather than < 200 cells/mm^3 [15–17]. WHO also supports continuous treatment for all postpartum women following HAART initiation for PMTCT (Option B+) [18], and the fact that 5 deaths occurred among women with baseline CD4 cell counts >350 cells/mm^3 may support this recommendation as well.

Although child mortality in our study was lower than others in Africa [2, 4, 8, 10, 19–21], we identified a clear period of risk during the first 3 months after weaning. The post-weaning period for most children, from 6 to 9 months, had a higher mortality than the first 3 months of life, which is a striking finding that contrasts the normal pattern of reduced mortality risk as a child ages [22, 23]. This same pattern has been described in other studies of HIV-exposed uninfected children after weaning [8, 20, 24–27]. Most children in our study were weaned before the 6-month visit, consistent with WHO recommendations at the time but earlier than current WHO guidelines developed by expert consensus. Few data exist to guide the decision about the optimal time to wean in the setting of ongoing MTCT risk. Relatively rapid weaning during the 3 days prior to the 6-month visit was also recommended (to avoid prolonged mixed feeding with formula or other foods), but it remains unknown how this strategy compares with a more gradual period of weaning.

Because of similarities in enrollment characteristics and location, cautious comparisons can be made with our previous PMTCT study (the Mashi Study) [24, 28, 29], where a non-HAART PMTCT intervention (zidovudine with or without single-dose NVP) was used in the setting of maternal HAART availability for treatment (CD4 < 200 cells/mm^3 or AIDS) for most of the study. Although comparisons are underpowered for small differences, maternal deaths were similar in the two studies (1.9% in Mma Bana, 2.0% in Mashi breastfeeding arm). Child HIV infection or death through 24 months was significantly lower in the Mma Bana Study (6.1%) than in either the breastfeeding arm (15.0%) or formula feeding arm (13.5%) of the Mashi Study (both $p < 0.001$). Excluding HIV-infected children, there was also a trend for reduced child mortality in Mma Bana (5.0% in Mma Bana compared with 8.4% in Mashi formula feeding arm [p=0.016] and 6.4% in Mashi breastfeeding arm [p=0.32]). Larger studies directly comparing maternal and infant PMTCT strategies may be required to determine whether maternal HAART has a positive impact on infant survival among HIV-exposed but uninfected infants.

The strength of our study was the randomized design and strict adherence to treatment and weaning recommendations by study participants. The most important limitation was lack of power to detect small differences between treatment groups, particularly a difference in MTCT. As with other studies conducted in Africa, determining exact causes of maternal and child mortality was a challenge because of limited diagnostic testing.

In summary, we report very low MTCT through 24 months of child age in all arms of this study. A significantly shorter time to maternal death or CD4 < 200 cells/mm^3 was noted for women randomized to NRTI-based HAART, and despite relatively preserved 24-month CD4 cell counts in the cohort as a whole, there did not appear to be a survival benefit for women beyond the intervention period. These findings support current WHO recommendations for a higher CD4 cell count threshold to continue lifelong treatment [7], and to consider lifelong treatment for all women who start HAART for PMTCT [18]. Child HIV-free survival in our trial surpassed any previous African PMTCT cohort of which we are aware, but it can still be improved. Further study is required to determine whether maternal HAART plays a role in promoting child survival, and whether the mortality risk after weaning can be reduced by biomedical interventions or by modification of weaning age and techniques.

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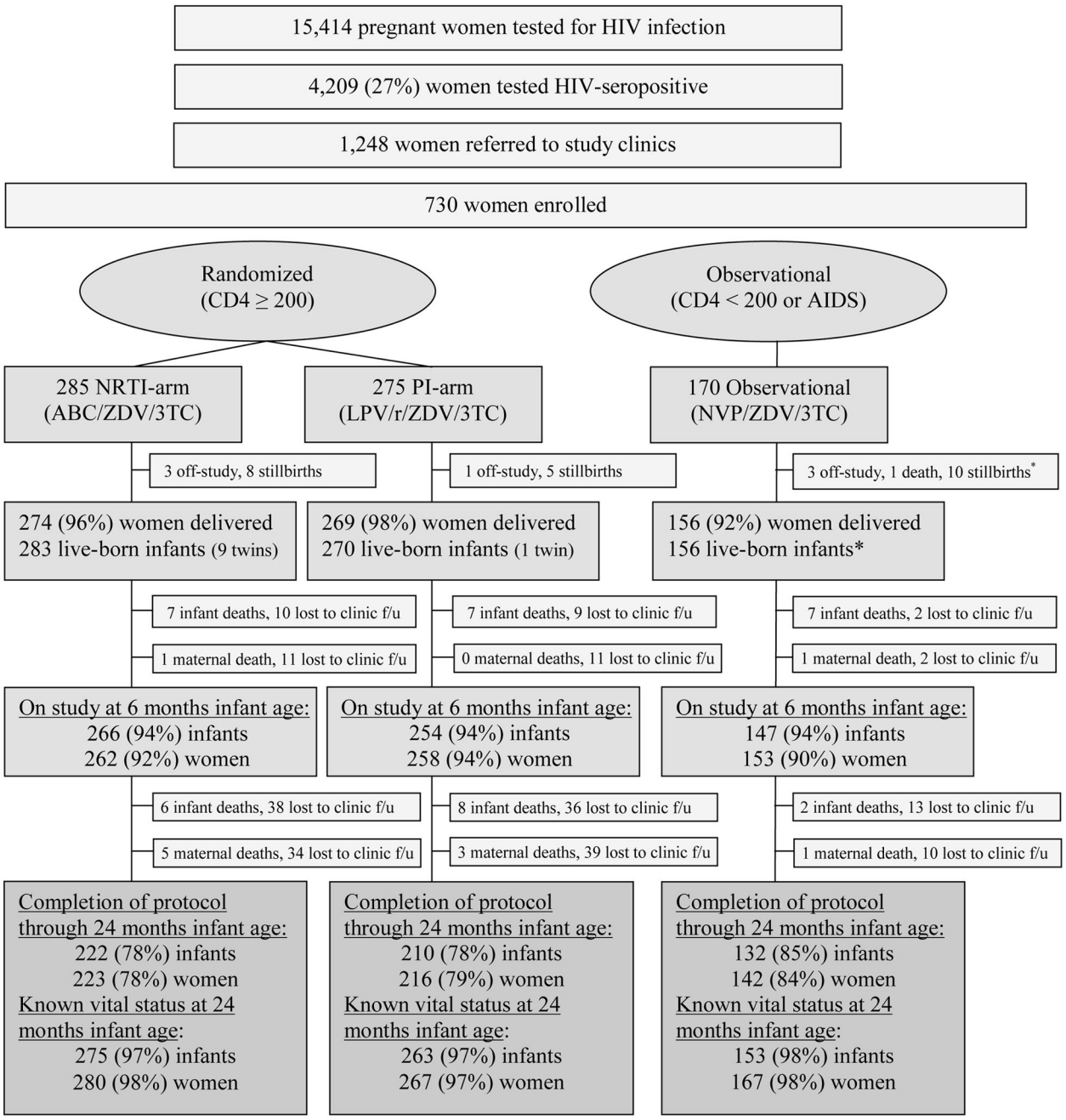

Figure 1. Enrollment and Follow-up of Study Participants

* One woman had a live twin and a stillborn twin and was categorized as having a live delivery. One woman died 18 days after delivery of a stillborn, and one woman died 12 months after delivery of a stillborn.

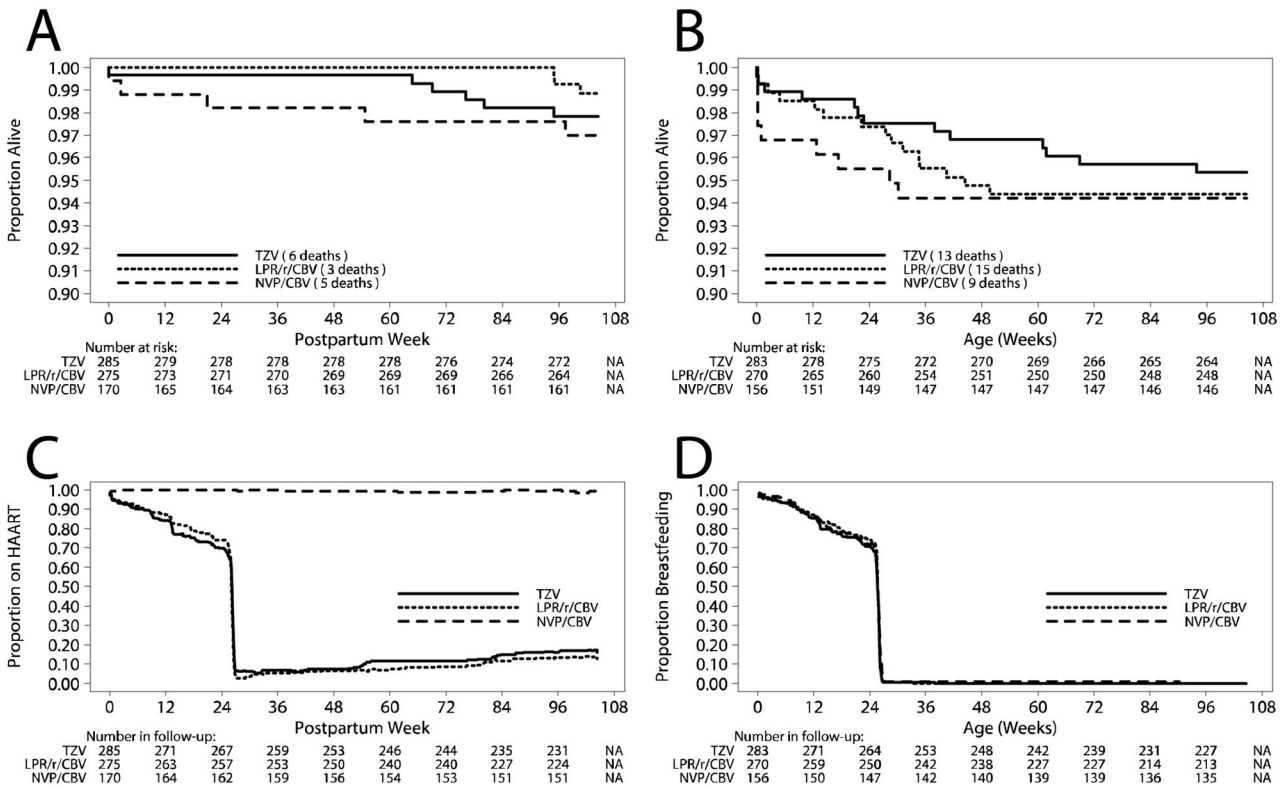

Figure 2. Maternal Survival (A), Child Survival (B), Maternal HAART Status (C), and Child Breastfeeding Status (D), by Study Arm*

* Note: the range for the vertical axis is 0.9–1.0 in panels A and B, and 0–1.0 in panels C and D.

Table 1

Maternal and Child Characteristics, by Study Arm.

Maternal characteristics at enrollment	Observational arm (NVP/ZDV/3TC) N=170	Arm A (ABC/ZDV/3TC) N=285	Arm B (LPV/r/ZDV/ 3TC) N=275
Study site, N %			
City	58 (34)	99 (35)	98 (36)
Town	31 (18)	53 (19)	52 (19)
Village	81 (48)	133 (47)	125 (45)
Median (Q1, Q3) age at enrollment, years	29 (25, 33)	26 (23, 31)	25 (23, 30)
Education, N (%)			
None or primary	41 (24)	57 (20)	57 (21)
Secondary	126 (74)	211 (74)	208 (76)
University	3 (2)	17 (6)	10 (4)
Personal monthly income, in US dollars, N (%)			
None	75 (44)	146 (51)	146 (53)
< 100	42 (25)	66 (23)	62 (23)
101–200	31 (18)	34 (12)	38 (14)
>200	22 (13)	38 (13)	29 (11)
Electricity in the home, N (%)	69 (41)	94 (33)	98 (36)
Median (Q1, Q3) gestational age at enrollment, wks	26.1 (22.6, 28.4)	27.1 (26.4, 29.9)	27.1 (26.4, 29.9)
Median baseline CD4 cell count, cells/mm^3 Q1, Q3	147 115, 183	393 305, 514	403 297, 514
Median baseline HIV-1RNA, copies/mL (Q1, Q3)	51,700 (14,400, 179,000)	13,300 (2,340, 50,900)	9,100 (2,210, 39,900)
≥100,000 copies/mL, N (%)	63 (37)	44 (15)	36 (13)
< 1,000 copies/mL, N (%)	10 (6)	42 (15)	47 (17)
Maternal HAART Status			
Stopped HAART ≤ 6 months	7 (4)	272 (95)	266 (97)
Continued HAART past 6 months for treatment	163 (96)	13 (5)	7 (3)
Re-started HAART for treatment	--	31 (11)	33 (12)

Maternal characteristics at enrollment	Observational arm (NVP/ZDV/3TC) N=170	Arm A (ABC/ZDV/3TC) N=285	Arm B (LPV/r/ZDV/ 3TC) N=275
Characteristics of live-born infants at birth	**N=156**	**N=283**	**N=270**
Median gestational age, weeks (Q1, Q3)	39.4 (38.4, 40.3)	39.3 (37.9, 40.3)	39.0 (37.4, 40.0)
Preterm (< 37 weeks gestation), N (%)	16 (10)	42 (15)	61 (23)
Very preterm (<32 weeks gestation), N (%)	2 (1)	4 (1)	8 (3)
Median birthweight, kilograms (Q1, Q3)	2.9 (2.6, 3.2)	3.0 (2.7, 3.3)	2.9 (2.6, 3.2)
Low birth weight (<2.5 kilograms), N (%)	23 (15)	37 (13)	45 (17)
Very low birth weight (<1.5 kilograms), N (%)	3 (2)	4 (1)	1 (<1)
Child Weaning Status			
Never breastfed	6 (4)	10 (4)	6 (2)
Weaned before 5 months	36 (23)	71 (25)	66 (24)
Weaned 5–6 months	87 (56)	175 (62)	175 (65)
Weaned 6–7 months	22 (14)	20 (7)	15 (6)
Weaned after 7 months or weaning not reported	5 (3)	7 (2)	8 (3)

Table 2

Maternal and Child Deaths, Grade 3 or 4 Diagnoses and Hospitalizations through 24 Months

	Obs Arm (NVP/ZDV/3TC)	Arm A (ABC/ZDV/3TC)	Arm B (LPV/r/ZDV/3TC)
Maternal Events*	**N=170**	**N=285**	**N=275**
Deaths†	5 (3%)	6 (2%)	3 (1%)
Women with at least one grade 3 or 4 diagnosis‡	30 (18%)	29 (10%)	23 (8%)
Women with at least one grade 3 or 4 lab event**	54 (32%)	54 (19%)	42 (15%)
Anemia	19 (11%)	15 (5%)	13 (5%)
Neutropenia	24 (14%)	23 (8%)	9 (3%)
Women with at least one hospitalization	47 (28%)	48 (17%)	41 (15%)
Child Events*	**N=156**	**N=283**	**N=270**
Deaths&	9 (6%)	13 (5%)	15 (6%)
Children with at least one grade 3 or 4 diagnosis∞	24 (15%)	47 (17%)	40 (15%)
Children with at least one grade 3 or 4 lab event#	70 (45%)	132 (47%)	136 (50%)
Anemia	37 (24%)	45 (16%)	53 (20%)
Neutropenia	38 (24%)	48 (17%)	53 (20%)
Children with at least one hospitalization	37 (24%)	65 (23%)	60 (22%)

*Events graded using Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, National Institues of Health, December 2004.

†Maternal deaths (also included as grade 3 or 4 diagnoses when known): NRTI-arm – extrapulmonary TB (3), postpartum hemorrhage, bleeding disorder/hemorrhage, diarrhea/sepsis, vulvar cancer, drowning; PI-arm – pulmonary TB, diarrhea/hepatic/renal failure, unknown (febrile illness, back pain); Observational Arm – *Pneumocystis jirovicii* pneumonia, toxoplasmosis, congestive heart failure from probable cardiomyopathy, nevirapine hypersensitivity reaction (Stevens-Johnson Syndrome) followed by sepsis, bowel obstruction.

‡Grade 3 or 4 maternal diagnoses included: NRTI arm – preeclampsia/eclampsia (4), postpartum hemorrhage (2), pulmonary or extrapulmonary tuberculosis (confirmed or suspected) (3), gastroenteritis or diarrhea, hepatitis, rash, Stevens Johnson Syndrome, cardiomyopathy (2), congestive heart failure, pulmonary hypertension, cellulitis, hypertension (postpartum) (3), premature rupture of membranes, prolapsed umbilical cord, psychosis, hernia, vaginal candidiasis, herpes simplex, vulvar cancer, renal failure, suspected mitochondrial toxicity, thrombocytopenia/ hemorrhage, intrauterine fetal demise (8); PI arm – preeclampsia/eclampsia (2), pregnancy-induced hypertension (1), postpartum hemorrhage (2), pulmonary or extrapulmonary tuberculosis (confirmed or suspected) (2), bacterial pneumonia, gastroenteritis or diarrhea, hepatitis (1), deep vein thrombosis (3), fracture (2), mastitis, oligohydramnios, pneumonia, postoperative peritonitis, premature rupture of membranes, syphilis, rash, Stevens Johnson Syndrome, intrauterine fetal demise (5); observational arm – preeclampsia/eclampsia (5), pregnancy-induced hypertension (1), pulmonary or extrapulmonary tuberculosis (confirmed or suspected) (7), bacterial pneumonia (2), gastroenteritis or diarrhea, rash (3), cardiomyopathy or heart failure (3), abruptio placenta (2), acute renal failure, appendicitis, cerebral toxoplasmosis, cholangitis, chorioamnionitis (2), diabetes, esophageal candidiasis, gastritis (6), gestational diabetes, nevirapine hypersensitivity reaction (2), Stevens Johnson Syndrome, pancreatitis, *Pneumocystis jirovicii* pneumonia, post-cesarean wound infection, sepsis (2), social harm, hepatitis, appendicitis, intestinal obstruction, chronic headache, intrauterine fetal demise (11).

**Maternal grade 3 or 4 laboratory events included: anemia, neutropenia, thrombocytopenia, potassium, sodium, alkaline phosphatase, glucose, creatinine, SGOT, SGPT, bilirubin, amylase, lipase.

[&]Child deaths (also included as grade 3 or 4 diagnoses when known): maternal NRTI arm -- neonatal sepsis (3), gastroenteritis (4), respiratory distress, pneumonia, or aspiration (3), meningitis (1), car accident (1), and unknown (1); maternal PI arm -- respiratory distress, pneumonia, or aspiration (4), tuberculosis (1), hydrocephalus (1), gastroenteritis (7), neonatal sepsis (1), and unknown (1); maternal observational arm -- respiratory distress, pneumonia, or aspiration (5), gastroenteritis (3), and neonatal sepsis (1)

[∞]Grade 3 or 4 child diagnoses included: Maternal NRTI arm – neonatal sepsis (9), sepsis (1), gastroenteritis (22), dysentery (1), respiratory distress, pneumonia, or aspiration (21), tuberculosis (1), meningitis (5), eczema (2), malaria; maternal PI arm – neonatal sepsis (3), sepsis (3), gastroenteritis (19), dysentery (1), respiratory distress, pneumonia, or aspiration (10), tuberculosis (2), meningitis (1), hydrocephalus (1), varicella (1), failure to thrive (2), burns; maternal observational arm – neonatal sepsis (3), gastroenteritis (7), respiratory distress, pneumonia, or aspiration (14), hypoxic encephalopathy (1), social harm, cellulitis.

[#]Grade 3 or 4 child laboratory events included: anemia, neutropenia, thrombocytopenia, potassium, sodium, glucose, SGOT, SGPT, bilirubin, amylase.

Table 3

Baseline and Time-Dependent Risk Factors for Child Death

Selected Maternal and Child Risk Factors for Child Mortality	Univariate RR (95% CI)	p-value	Multivariate RR (95% CI)	p-value
Baseline maternal CD4 count (per 50 cells/mm^3 higher)	1.01 (0.95, 1.08)	0.69	--	
Baseline maternal HIV-1 RNA (per $\log_{10}$ copies/mL higher)	1.01 (0.63, 1.62)	0.96	--	
Maternal age (per year higher)	0.94 (0.87, 1.01)	0.085	--	
Maternal income (reference: > $130 per month)		0.13	--	
None	2.25 (0.29, 17.49)			
< $65	4.63 (0.59, 36.42)			
$66–$130	4.76 (0.57, 39.86)			
Maternal education (reference: Senior Secondary)		0.63	--	
None/Primary	1.36 (0.38, 4.87)			
Junior Secondary	1.61 (0.54, 4.80)			
Marital status single (reference: married)	2.15 (0.65, 7.18)	0.21	--	
Electricity in house (reference: no electricity)	0.77 (0.34, 1.76)	0.54	--	
Maternal PMTCT regimen (reference: NVP/CBV)		0.65	--	
TZV	1.14 (0.39, 3.36)			
LPV/r/CBV	1.55 (0.55, 4.41)			
Child sex male (reference: female)	2.17 (0.98, 4.83)	0.056	--	
Child PCR positive at birth (reference: negative)	7.15 (0.79, 64.40)	0.079	--	
Preterm Delivery (< 37 weeks gestation)	5.14 (2.41, 10.94)	<0.001	3.43 (1.51, 7.82)	0.003
Small for gestational age (< 3rd percentile)	1.50 (0.35, 6.43)	0.58	--	
Child is a twin	5.72 (1.88, 17.41)	0.002		
Child PCR positive	4.81 (0.57, 40.92)	0.15		
Maternal CD4 cell count change from baseline (per 50 cells/mm^3 higher)	1.07 (0.99, 1.16)	0.082		
Maternal HIV RNA ≥ 400 copies/mL	0.78 (0.23, 2.63)	0.69	--	
Child weight for age z-score (per 1 z-score lower)	1.92 (1.38, 2.67)	<0.001	1.64 (1.20, 2.24)	0.002
Child age (reference: 0 to < 3 months)		0.006		0.022
3 to < 6 months	1.03 (0.33, 3.18)		1.40 (0.46, 4.28)	
6 to < 9 months	1.42 (0.49, 4.10)		2.23 (0.76, 6.53)	
9 to < 12 months	0.73 (0.21, 2.59)		1.24 (0.36, 4.33)	
12 to < 15 months	0.38 (0.08, 1.86)		0.64 (0.13, 3.24)	

Selected Maternal and Child Risk Factors for Child Mortality	Univariate RR (95% CI)	p-value	Multivariate RR (95% CI)	p-value
≥ 15 months	0.13 (0.03, 0.63)		0.20 (0.04, 1.07)	
Child feeding[a] (reference: still breastfeeding)		0.004		0.009
Weaned within 3 months	3.37 (1.34, 8.47)		4.07 (1.62, 10.22)	
Weaned > 3 months prior	0.44 (0.16, 1.21)		0.60 (0.21, 1.66)	

[a] Modeled separately, excluding child age, because of co-linearity with child age.