Prevention of HIV-1 Transmission Through Breastfeeding: Efficacy and Safety of Maternal Antiretroviral Therapy Versus Infant Nevirapine Prophylaxis for Duration of Breastfeeding in HIV-1-Infected Women With High CD4 Cell Count (IMPAACT PROMISE): A Randomized, Open-Label, Clinical Trial

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Background: No randomized trial has directly compared the efficacy of prolonged infant antiretroviral prophylaxis versus maternal antiretroviral therapy (mART) for prevention of mother-to-child transmission throughout the breastfeeding period.

Setting: Fourteen sites in Sub-Saharan Africa and India.

Methods: A randomized, open-label strategy trial was conducted in HIV-1–infected women with CD4 counts ≥350 cells/mm^3 (or ≥country-specific ART threshold if higher) and their breastfeeding

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PROMISE Study Team Members are listed in Appendix 1

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HIV-1–uninfected newborns. Randomization at 6–14 days postpartum was to mART or infant nevirapine (iNVP) prophylaxis continued until 18 months after delivery or breastfeeding cessation, infant HIV-1 infection, or toxicity, whichever occurred first. The primary efficacy outcome was confirmed infant HIV-1 infection. Efficacy analyses included all randomized mother–infant pairs except those with infant HIV-1 infection at entry.

Results: Between June 2011 and October 2014, 2431 mother–infant pairs were enrolled; 97% of women were World Health Organization Clinical Stage I, median screening CD4 count 686 cells/mm^3. Median infant gestational age/birth weight was 39 weeks/2.9 kilograms. Seven of 1219 (0.57%) and 7 of 1211 (0.58%) analyzed infants in the mART and iNVP arms, respectively, were HIV-infected (hazard ratio 1.0, 96% repeated confidence interval 0.3–3.1); infant HIV-free survival was high (97.1%, mART and 97.7%, iNVP, at 24 months). There were no significant differences between arms in median time to breastfeeding cessation (16 months) or incidence of severe, life-threatening, or fatal adverse events for mothers or infants (14 and 42 per 100 person-years, respectively).

Conclusions: Both mART and iNVP prophylaxis strategies were safe and associated with very low breastfeeding HIV-1 transmission and high infant HIV-1–free survival at 24 months.

Key Words: breastfeeding, HIV-1, prevention of perinatal HIV-1 transmission, antiretroviral therapy (ART), nevirapine

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INTRODUCTION

Substantial progress has been made toward preventing perinatal transmission of HIV-1 in the developing world, but questions remain as to the relative safety and efficacy of various antiretroviral regimens. In the Antepartum Component of a large randomized multicountry clinical trial, *Promoting Maternal Infant Survival Everywhere* (PROMISE), we showed that maternal antiretroviral therapy (mART) during pregnancy and intrapartum can reduce perinatal HIV-1 transmission to ~0.5% in Sub-Saharan African settings.[1] However, breastfeeding-associated HIV-1 exposure and potential transmission continues in breastfed HIV-exposed infants living in resource-limited settings. Although World Health Organization (WHO) guidelines recommend that all HIV-1–infected pregnant women initiate lifelong ART, adherence to ART, particularly postpartum, has proven to be a major challenge; postpartum viral rebound has been observed in 31% of women starting ART during pregnancy who had initial viral suppression and 22% of women receiving preconception ART had detectable viremia at first antenatal visit.[2–4] Thus, evaluation of the safety and efficacy of alternative strategies, such as infant prophylaxis, to reduce postnatal infection remains important.[5]

Based on previous clinical trial data, the following 2 strategies have been shown to be safe and effective in preventing postnatal HIV-1 transmission: (1) providing ART to the lactating woman, thereby reducing breastmilk viral load; or (2) providing daily single-drug antiretroviral (ARV) prophylaxis to the breastfeeding infant, maintaining prophylactic infant ARV blood levels throughout the period of HIV-1 transmission risk.[6–13] Previous studies, however, focused on interventions only given through the first 6–12 months of breastfeeding and there were additional late infections related to breastfeeding transmission when breastfeeding continued after prophylaxis stopped. Because increased morbidity and mortality have been associated with weaning compared with continued breastfeeding through the second year of life in HIV-1–exposed infants, breastfeeding beyond 12 months, and interventions to reduce HIV-1 transmission during breastfeeding will be required to maximize infant HIV-1–free survival.[14–16]

A few studies have evaluated the safety and efficacy of prolonged maternal or infant prophylaxis, but only through 12 months.[11,12] No previous randomized trial has directly compared the efficacy and safety of prolonged infant ARV prophylaxis with maternal ART throughout the duration of breastfeeding into the second year of life. We report results from the PROMISE trial's Postpartum Component, which randomized breastfeeding HIV-1–infected women with high CD4 cell count and their HIV-1–uninfected infants at 6–14 days postpartum to either mART or infant nevirapine (iNVP) prophylaxis to prevent HIV-1 transmission during breastfeeding.

METHODS

Study Design and Participants

PROMISE was a randomized, open-label strategy trial sponsored by the U.S. National Institutes of Health conducted at 14 health facility–based research sites in 7 countries: India (1 site), Malawi (2), South Africa (5), Tanzania (1), Uganda (1), Zambia (1), and Zimbabwe (3). HIV-1–infected postpartum women were recruited from 2 sources: women completing the PROMISE Antepartum Component[1] and women first identified as HIV-1–infected during active labor, and hence received no ARV during pregnancy ("late presenters").

The PROMISE Postpartum Component was designed to compare the relative efficacy and safety of mART versus daily iNVP prophylaxis for prevention of breastmilk HIV-1 transmission. Women who intended to breastfeed and planned to remain in the study site area through 24 months postpartum were eligible. Randomization occurred at the postpartum week 1 (day 6–14 after delivery) visit. Inclusion criteria for women (within 30 days before enrollment in the Postpartum Component) were as follows: CD4 count ≥350 cells/mm^3 (or ≥ the country-specific ART initiation threshold if it was >350 cells/mm^3); hemoglobin >7.0 grams/dL; white blood cell count >1500 cells/mm^3; absolute neutrophil count >750 cells/mm^3; platelets >50,000 cells/mm^3; alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal; and estimated creatinine clearance of ≥60 mL/min. Inclusion criteria for infants were: ≤14 days of age; birth weight ≥2.0 kg; uninfected [negative HIV-1 nucleic acid test (NAT) on a specimen drawn before the week 1 visit]; hemoglobin ≥10 g/dL; white blood cell count ≥1500 cells/mm^3; absolute neutrophil count ≥750 cells/mm^3; platelets ≥50,000 cells/mm^3; and ALT ≤2.5 × upper limit of normal. For multiple births, a mother–infant pair was enrolled only if all live infants

could be enrolled. Exclusion criteria included positive infant HIV-1 NAT result on a specimen drawn before study entry or NAT result not available or a life-threatening condition.

Before obtaining informed consent and during follow-up, women were regularly informed of the current and evolving country-specific guidelines for preventing perinatal HIV-1 transmission and for ART initiation and other options for prevention outside PROMISE. The study was approved by local and collaborating institutional review boards and other relevant regulatory authorities and was reviewed for safety and efficacy by an independent Data and Safety Monitoring Board.

Randomization

Women enrolled in the PROMISE Antepartum Component[1] continued their antepartum randomized regimen [zidovudine alone (ZDV) or ZDV/lamivudine (3 TC)/lopinavir boosted with ritonavir (LPVr) or tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)/LPVr] until assessment for the Postpartum Component at the postpartum week 1 visit (day 6–14 after delivery). Late-presenting women who had not been enrolled in the PROMISE Antepartum Component were enrolled in labor or within 5 days after delivery; those in labor received intrapartum single-dose nevirapine (sdNVP) with a TDF/FTC tail until the postpartum week 1 visit. All infants received daily NVP through age 6 weeks as recommended by WHO guidelines.[17]

Mother–infant pairs were randomized at the week 1 postpartum visit to 1 of 2 prophylaxis regimens (in a 1:1 ratio): mART or iNVP. TDF/FTC/LPVr was the study-preferred mART regimen. TDF/FTC fixed dose combination tablets containing 300 mg/200 mg orally daily plus LPV/r fixed dose combination tablets, 2 tablets of 200 mg/50 mg orally twice daily were recommended dosage. Women who experienced intolerance, toxicity, or clinical, immunologic, or virologic failure were allowed to receive other 3 ARV regimens selected by their provider. Infant NVP was prescribed using age-based NVP dosing (Birth to 6 Weeks—birth weight ≥2500 gm, 15 mg and for birth weight 2000–2499 gm, 10 mg; >6 weeks to 6 months—20 mg; >6 months–9 months—30 mg; >9 months to cessation of BF or 18 months, whichever is first—40 mg). Randomized regimen was continued until 42 days after last breastmilk exposure (2 weeks after breastfeeding cessation, defined as no breastmilk exposure for >28 days) or age 18 months, whichever came first. The randomized regimen was discontinued if infant HIV-1 infection was diagnosed or if mother or infant had severe toxicity. A web-based, central computer randomization system used permuted block allocation with stratification by country and the antepartum/intrapartum maternal ARV prophylaxis [maternal ART versus ZDV/sdNVP versus ZDV/sdNVP (late presenter) versus none (late presenter)].[18]

Procedures

Maternal visits occurred at weeks 1 (6–14 days postpartum, entry), 6, and 14 postpartum, and then every 12 weeks through week 74 postpartum. General medical history and limited physical examination were obtained at each visit. Complete blood count was performed at all visits and chemistry safety laboratories (ALT, aspartate aminotransferase, creatinine, alkaline phosphatase, total bilirubin, and albumin) were also obtained except at week 62. CD4 cell counts were performed at all visits except week 6 postpartum. Pregnancy tests were obtained if pregnancy was suspected. Infant visits occurred at postpartum weeks 1, 6, 10, 14, 18, 22, and 26, then every 12 weeks until week 98, with a final visit at week 104. History and physical evaluation were performed at all visits. HIV-1 NAT, complete blood count, and stored plasma were collected at every visit except week 10; ALT was obtained at weeks 1 and 6. For infants randomized to iNVP, ALT was performed at week 26 and every 12 weeks while receiving NVP. An HIV-1 antibody test could be substituted for NAT if the infant was >18 months old and had ceased breastfeeding. Infants diagnosed with HIV infection were referred to the local treatment clinic to initiate ART; study follow-up continued regardless of infection status.

Outcomes

The primary efficacy outcome was confirmed infant HIV-1 infection, defined as positive HIV-1 NAT from a specimen drawn at any postrandomization visit, confirmed by a positive HIV-1 NAT on a second specimen drawn at a subsequent time point. Cases of uncertain infant HIV-1 infection status were reviewed, blinded to arm assignment, by an independent 4-member committee who made the definitive determination of infant HIV-1 infection status and timing. Infant HIV-1–free survival (infant alive and not HIV-1–infected) and infant death were secondary efficacy outcome measures. All HIV-1 NATs were performed in laboratories certified by the Division of AIDS (DAIDS) Virology Quality Assurance Program.

The DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, 2004 Version 1.0 (clarification August 2009) was used to grade adverse events.[19] For women, the primary safety outcome was a composite of grade 2 hematologic, renal, or hepatic abnormalities or grade ≥3 adverse events or death, whichever occurred first. For infants, the primary safety outcome was a composite of grade ≥3 adverse events or death, whichever occurred first. Secondary safety outcomes included the individual components of the primary composite outcomes.

Statistical Analyses

The original target sample size was 4650 mother–infant pairs (approximately 3100 from the Antepartum Component and approximately 1550 late presenters), providing ≥90% power to detect a difference between groups in cumulative postnatal transmission at breastfeeding cessation of approximately 3% versus 5%, with 2-sided type I error of 5% and allowing for loss-to-follow-up (10%) and interim efficacy monitoring (3%). These projected cumulative postnatal transmission rates were anticipated based on the following information and assumptions: postnatal transmission rates through 6 months postpartum would be approximately 1%–3% among

early presenters (based on the MITRA[20] and MITRA-PLUS[21] studies) and approximately 5%–7% among late presenters (based on the SWEN[7] and PEPI-Malawi[8] studies); late presenters would represent 33% of all study participants; the postnatal transmission rate would increase by an average of 0.35% per month after 6 months postpartum (half the estimated rate reported in a meta-analysis[22]); and a projected average breastfeeding duration across all sites of approximately 9 months.

In July 2014, because of slow accrual, the sponsor (NIAID) decided to stop enrollment to all PROMISE Components when the Antepartum Component reached its accrual target for breastfeeding women or on October 1, 2014, whichever came first. The sponsor's decision was based in part on revised power calculations that used using the same approach as the original power calculations but with the anticipated postnatal transmission rates updated based on the smaller observed percentage of late presenters enrolled (6%) and the longer observed median duration of breastfeeding (15 months). The revised power calculations indicated that a projected total accrual of 2436 mother–infant pairs by October 1, 2014, would provide 85% power to detect a difference between groups in cumulative postnatal transmission at breastfeeding cessation of approximately 3.2% versus 6%.

All analyses used the intent-to-treat principle with 1 prespecified exception: mother–infant pairs who had a positive infant HIV-1 NAT result on a specimen drawn before or on the randomization date were excluded from the efficacy analyses. The risk period for the primary efficacy and safety analyses was the time from randomization until 56 days after the last exposure to breastmilk or 18 months postpartum, whichever came first. The risk period was extended until 24 months postpartum in secondary efficacy and infant safety analyses. The a priori analysis plan specified that the primary efficacy and safety analyses would be censored at the recommended minimum duration of breastfeeding at each enrolling site (at the time of the study design, this was 6 or 12 months), due to concerns that the PROMISE postbreastfeeding maternal randomization of mART women to continue or stop mART could induce longer breastfeeding in the mART arm, which could introduce bias. Sensitivity analyses were also conducted which did not censor at the recommended minimum duration of breastfeeding.

Comparisons between randomization arms and estimation of effect sizes used time-to-event analyses with the Cox proportional hazards regression model. The distributions of time until the first event occurred were summarized using Kaplan–Meier plots. Statistical significance was defined as a 2-sided P-value < 0.05 for all analyses except efficacy; efficacy analyses used a group-sequential repeated confidence interval (RCI) for the hazard ratio in cumulative postnatal transmission using the Lan–DeMets approach with an O'Brien-Fleming type 1 error spending function (for the final analysis, the confidence coefficient was 96%, to preserve an experiment-wise type I error rate of 0.05). The RCI indicated the range of hazard ratio values that were consistent with the observed data; if the RCI excluded 1.0, this would indicate a statistically significant difference between arms and if the RCI included 1.0, the width of the RCI would indicate the ability of the study to rule out a difference between treatment arms (the narrower the RCI, the stronger the evidence of equivalence). Two interim efficacy analyses were performed during the conduct of the study.

On July 7, 2015, the sites were instructed to inform all maternal participants about the START trial results[23], which demonstrated statistically significant benefits of starting ART early compared with delayed initiation, and offer ART to those who were not receiving it. In November 2015, the Data and Safety Monitoring Board recommended that the primary PROMISE analyses should include only follow-up through July 6 to minimize bias if large numbers of women in the iNVP arm chose to start ART or the women who chose to take ART were systematically different than those who did not. Statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

Between June 6, 2011, and October 1, 2014, a total of 2431 mother–infant pairs (including 13 pairs of twins) were enrolled (1220 randomized to mART and 1211 to iNVP) from sites in Malawi (32%), South Africa (23%), Zimbabwe (22%), Uganda (16%), Zambia (2%), Tanzania (2%), and India (3%). Ninety-five percent of mother–infant pairs in each arm were previously enrolled in the PROMISE Antepartum Component (42% randomized to Maternal ZDV Arm and 53% randomized to a Maternal Triple ARV Arm) and 5% were late-presenting women enrolled at delivery or within 5 days after delivery. Nearly all (1207, 98.9%) of the mothers in the mART arm started the preferred study-supplied mART regimen and nearly all (1204, 98.9%) of the infants in the iNVP arm started on daily NVP. A patient flow diagram is shown in Supplemental Digital Content, http://links.lww.com/QAI/B102.

Table 1 summarizes selected baseline characteristics of mothers and infants at study entry. The median time to breastfeeding cessation was 16 months (70 weeks) with no statistically significant difference between arms ($P = 0.70$). Kaplan–Meier probability estimates for continued breastfeeding at age 6, 9, 12, 18, and 24 months were 93.3%, 86.2%, 81.0%, 34.3%, and 12.5%, respectively.

The efficacy analysis included 2430 of the 2431 enrolled mother–infant pairs (1 infant born to a late-presenting mother was found to have been HIV-1–infected at time of randomization and was excluded from the efficacy analysis). Thirty-five infants (22 in the mART and 13 in the iNVP arm, 1.5%) had no postrandomization HIV-1 testing results and were censored at the date of randomization; 10 infants (6 mART and 4 iNVP) died of non-HIV (5 infants) or unknown causes (5 infants) without any record of HIV testing, 10 (7 mART and 3 iART) were not able to get to clinic, 9 (6 mART and 3 iNVP) had consent withdrawn, and 6 (3 mART and 3 iNVP) could not be contacted (Supplemental Digital Content, http://links.lww.com/QAI/B102). Maternal and infant baseline characteristics (maternal RNA and CD4, infant gestational age, and birth weight) were similar for the 22 mART and 13 iNVP arm infants.

TABLE 1. Baseline Characteristics of Women and Infants by Study Arm

Maternal Characteristic	Maternal ART (N = 1220)	Infant NVP Prophylaxis (N = 1211)	Total (N = 2431)
Age (years)			
Median (IQR)	26 (23–30)	26 (23–30)	26 (23–30)
Race			
Black African	1178 (97%)	1168 (96%)	2346 (97%)
Asian*	41 (3%)	42 (3%)	83 (3%)
Colored	1 (0%)	1 (0%)	2 (0%)
Weight (kg)			
# missing	0	0	0
Median (IQR)	61.0 (54.9–69.8)	61.0 (54.7–69.1)	61.0 (54.8–69.4)
Previous PROMISE treatment arm			
Antepartum component—LPV/r + ZDV/3 TC	508 (42%)	497 (41%)	1005 (41%)
Antepartum component—LPV/r + TDF/FTC	140 (11%)	149 (12%)	289 (12%)
Antepartum component—ZDV + sdNVP	506 (41%)	503 (42%)	1009 (42%)
Late presenter component—none	42 (3%)	39 (3%)	81 (3%)
Late presenter component—intrapartum ZDV + sdNVP	24 (2%)	23 (2%)	47 (2%)
Gestational age at antepartum randomization			
# missing (includes late presenters)	67	62	129
Median (IQR)	26.3 (21.4–30.7)	26.3 (21.7–31.4)	26.3 (21.6–31.1)
HIV-1 viral load (copies/mL) obtained at delivery or entry visit (week 1 postpartum)			
# missing	2	3	5
Median (IQR)	220 (40–1029)	400 (40–1960)	322 (40–1422)
Below assay limit of detection	499 (41%)	379 (31%)	878 (36%)
<400	276 (23%)	296 (24%)	572 (24%)
400–1000	136 (11%)	139 (11%)	275 (11%)
1000–<10,000	196 (16%)	278 (23%)	474 (19%)
10,000–< 100,000	91 (7%)	105 (9%)	196 (8%)
100,000–< 200,000	12 (1%)	9 (1%)	21 (1%)
≥200,000	10 (1%)	5 (0%)	15 (1%)
Screening CD4 count (cells/mm^3)			
Median (IQR)	682.5 (555–870)	691 (550–868)	686 (553–869)
350–<400	37 (3%)	49 (4%)	86 (4%)
400–<450	70 (6%)	57 (5%)	127 (5%)
450–<500	88 (7%)	90 (7%)	178 (7%)
500–<750	550 (45%)	522 (43%)	1072 (44%)
≥750	475 (39%)	493 (41%)	968 (40%)
WHO clinical stage†			
Clinical stage I	1174 (96%)	1182 (98%)	2356 (97%)
Clinical stage II	45 (4%)	28 (2%)	73 (3%)
Clinical stage III	1 (0%)	1 (0%)	2 (0%)
# of live infants at entry			
1	1213 (99%)	1205 (100%)	2418 (99%)
2	7 (1%)	6 (0%)	13 (1%)

Infant Characteristic	Maternal ART (N = 1227)	Infant NVP Prophylaxis (N = 1217)	Total (N = 2444)
Sex			
Male	622 (51%)	614 (50%)	1236 (51%)
Female	605 (49%)	603 (50%)	1208 (49%)
Gestational age at birth (wk)			
# missing	0	0	0
Median (IQR)	39 (38–40)	39 (38–40)	39 (38–40)
<34	10 (1%)	8 (1%)	18 (1%)
34–<37	113 (11%)	135 (11%)	268 (11%)
≥37	1084 (88%)	1074 (88%)	2158 (88%)
Birth weight (gm)‡			
# missing	9	6	15
Median (IQR)	2910 (2600–3230)	2900 (2600–3200)	2900 (2600–3200)
2000–< 2500	149 (12%)	183 (15%)	332 (14%)
≥2500	1069 (88%)	1028 (85%)	2097 (86%)

*Include women from the Indian subcontinent and natives of India.

†Two women had WHO Stage III at entry, but were tuberculosis-negative and had CD4 >350 copies/ml and therefore, did not require ART for their own health.

‡The birth weight is the infant weight closest to birth and within 0–5 days postpartum. Using the determination closest to birth (not restricting to 0–5 days postpartum) provided similar summary statistics. All infants had weight of at least 2000 grams.

Eighteen infants were diagnosed with HIV-1 infection at a postrandomization visit; 14 were included in the primary analysis (4 were censored at the country-recommended minimum

duration of breastfeeding: 6 months for 1 infant and 12 months for 3 infants) and all were included in the secondary analysis through 24 months postpartum.

In the primary analysis, infant HIV-1 infection occurred in 7 infants of 1219 mother–infant pairs randomized to mART and 7 of 1211 randomized to iNVP. The HIV-1 transmission rates in both arms were much lower than anticipated and the 96% RCI was quite wide (0.3–3.1), indicating very limited ability to rule out differences between arms due to the small number of infants who were HIV-1 infected (Fig. 1A and Table 2). Sensitivity analyses that did not censor at the minimum recommended duration of breastfeeding provided similar results (not shown).

In the secondary analysis, which included all follow-up data, there were 8 cumulative infections among 1218 mother–infant pairs randomized to mART and 10 among the 1211 randomized to iNVP. For the 18 infected infants, the median infant age at HIV-1 infection was 38 weeks (range, 13–62 weeks) in the mART arm and 50.5 weeks (range, 6–75 weeks) in the iNVP arm. The cumulative probability of infection at 24 months was 0.9% (95% CI: 0.6% to 1.5%) (Fig. 1B and Table 2). The probability of infant HIV-1 infection/death at 24 months in the mART arm was 2.9% (95% CI: 2.0% to 4.1%), and in the iNVP arm was 2.3% (95% CI: 1.5% to 3.4%), resulting in HIV-1–free survival at 24 months of 97.1% in the mART and 97.7% in the iNVP arm (Fig. 1C and Table 2).

All 2431 women are included in the safety analysis; 15 had no postrandomization visit (9 in mART and 6 in iNVP) and were censored at date of randomization. There was no significant difference in time to the first composite safety endpoint between arms ($P = 0.98$ and $P = 0.61$) and the incidence rates of adverse events were similar in the 2 arms (Table 3). Sensitivity analyses that did not censor at the minimum recommended duration of breastfeeding provided similar results (not shown). Three maternal deaths occurred (2 in the mART and 1 in the iNVP arm) during the perinatal HIV-1 transmission risk period; no death was judged related to study intervention. Of the 1207 women in the mART arm who started on the study recommended regimen, 9 (<1%) stopped the recommended regimen because of toxicity.

All 2444 infants are included in the safety analysis; 4 had no postrandomization visit information (2 in each arm)

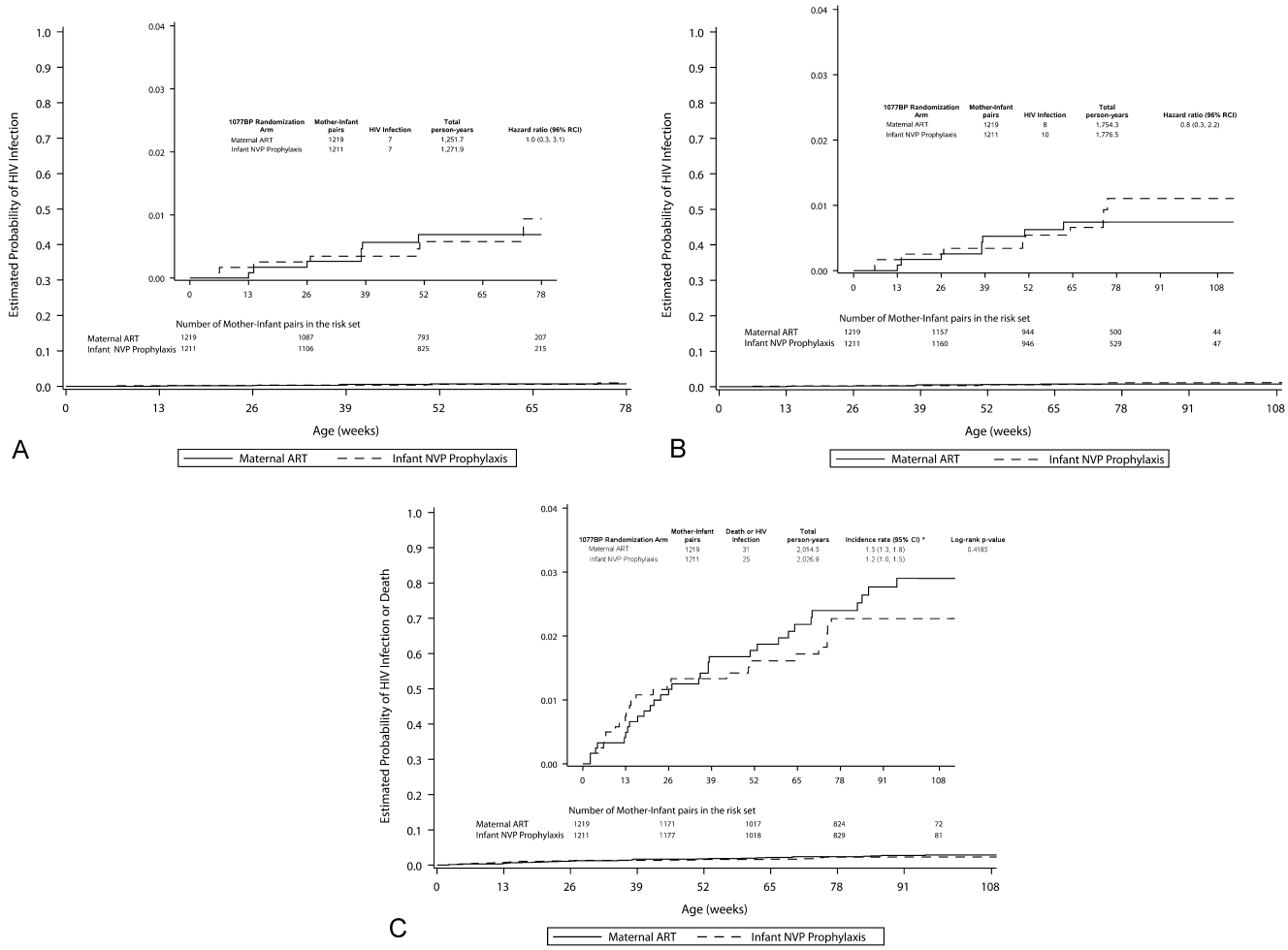

FIGURE 1. A, Probability of infant HIV-1 infection through 78 weeks censored at the recommended minimum duration of breastfeeding at each enrolling site. (primary analysis). B, Probability of infant HIV-1 infection through 108 weeks without censoring at the recommended minimum duration of breastfeeding at each enrolled site. (secondary analysis). C, Probability of infant HIV-1 infection or death through 108 weeks.

TABLE 2. Probability of HIV-1 Infection or HIV-1 Infection/Death by Study Arm: Primary and Secondary Analyses

Age	Maternal ART	Infant NVP Prophylaxis	Overall
Probability of HIV-1 infection % (95% confidence interval)			
Primary analysis (follow-up time is censored per planned analysis specifications)*			
6 mo	0.3 (0.1 to 0.8)	0.3 (0.1 to 0.8)	0.3 (0.1 to 0.6)
9 mo	0.6 (0.3 to 1.3)	0.3 (0.1 to 0.9)	0.5 (0.2 to 0.8)
12 mo	0.7 (0.3 to 1.4)	0.6 (0.3 to 1.3)	0.6 (0.4 to 1.1)
18 mo	0.7 (0.3 to 1.4)	0.9 (0.4 to 2.3)	0.8 (0.4 to 1.5)
Secondary analysis (includes all infections and total duration follow-up)†			
24 mo	0.7 (0.4 to 1.5)	1.1 (0.6 to 2.1)	0.9 (0.6 to 1.5)
Probability of HIV-1-infection or death % (95% confidence interval)			
Secondary analysis (includes all infections and total duration follow-up)†			
6 mo	1.2 (0.7 to 2.0)	1.2 (0.8 to 2.1)	1.2 (0.8 to 1.7)
9 mo	1.7 (1.1 to 2.6)	1.3 (0.8 to 2.2)	1.5 (1.1 to 2.1)
12 mo	1.8 (1.2 to 2.7)	1.6 (1.0 to 2.5)	1.7 (1.2 to 2.3)
18 mo	2.4 (1.6 to 3.5)	2.3 (1.5 to 3.4)	2.3 (1.8 to 3.1)
24 mo	2.9 (2.0 to 4.1)	2.3 (1.5 to 3.4)	2.6 (2.0 to 3.4)

*Primary analysis: postrandomization to end of transmission risk period, 18 months postpartum, or minimum recommended duration of breastfeeding at site (whichever occurs first).

†Secondary analysis: postrandomization to 24 months postpartum.

and were censored at date of randomization. There was no significant difference in time to the first composite safety endpoint between arms ($P = 0.99$) and the incidence rates of adverse events were similar in the 2 arms (Table 3). Sensitivity analyses that did not censor at the minimum recommended duration of breastfeeding provided similar results (not shown). In addition, among infants randomized to iNVP, safety assessments beyond week 6 did not demonstrate increased incidence of liver or skin toxicity compared with the mART arm (Table 3). Of the 1204 infants in the iNVP arm who started on the study recommended regimen, 20 (<2%) stopped the recommended regimen because of toxicity.

Thirty infant deaths occurred within the minimum recommended breastfeeding duration, and an additional 8 thereafter (Table 3). Of the 30 deaths in the primary analysis, 16 were infants randomized to mART (incidence rate: 1.2 per 100 person-years; 95% CI: 1.0 to 1.5 per 100 person-years) and 14 in infants randomized to iNVP (incidence rate: 1.1 per

TABLE 3. Number of Women and Infants Who Experienced Adverse Events by Study Arm (Primary Analysis: Randomization to End of Transmission Risk Period, 18 Months Postpartum, or the Minimum Recommended Duration of Breastfeeding, Whichever Came First)

Adverse Event	Maternal ART	Infant NVP	Total
Women	N = 1211	N = 1205	N = 2416
Composite (grade >3 adverse events or grade 2 laboratory or death)*	159 (13.1%)	161 (13.4%)	320 (13.2%)
Composite (grade >3 adverse events/laboratory or death)†	59 (4.9%)	66 (5.5%)	125 (5.2%)
Death	2 (0.2%)	1 (0.1%)	3 (0.1%)
Grade >3 signs/symptoms	22 (1.8%)	24 (2.0%)	46 (1.9%)
Grade >2 laboratory	141 (11.6%)	140 (11.6%)	281 (11.6%)
Grade >2 hematology	128 (10.6%)	119 (9.9%)	247 (10.2%)
Grade >2 chemistry	18 (1.5%)	27 (2.2%)	45 (1.9%)
Grade >3 laboratory	38 (3.1%)	42 (3.5%)	80 (3.3%)
Grade >3 hematology	35 (2.9%)	27 (2.2%)	62 (2.6%)
Grade >3 chemistry	3 (0.2%)	15 (1.2%)	18 (0.7%)
Infant	N = 1225	N = 1215	N = 2440
Composite (grade >3 adverse events or death)‡§	427 (34.9%)	426 (35.1%)	853 (35.0%)
Death	16 (1.3%)	14 (1.2%)	30 (1.2%)
Grade >3 signs/symptoms	61 (5.1%)	44 (3.6%)	105 (4.3%)
Grade >3 laboratory	383 (31.3%)	385 (31.7%)	768 (31.5%)
Grade >3 hematology	383 (31.3%)	384 (31.6%)	767 (31.4%)
Grade >3 chemistry§	0 (0%)	2 (0.2%)	2 (0.1%)
Grade ≥3 ALT (wk 1 and 6 assessment)	0 (0%)	2 (0.2%)	2 (0.1%)
Grade ≥3 ALT (week 26, 28, 50, 62, and 74 assessment)	NA	5 (0.4%)	NA

*Incidence rates were 14.4 per 100 person-years (95% CI: 12.4 to 16.6 per 100 person-years) in women in the mART arm and 14.1 per 100 person-years (95% CI: 12.2 to 16.3 per 100 person-years) in women in the iNVP arm, and not significantly different between arms ($P = 0.98$).

†Incidence rates were 5.0 per 100 person-years (95% CI: 4.2 to 5.9 per 100 person-years) in mART and 5.4 per 100 person-years (95% CI: 4.6 to 6.4 per 100 person-years) in iNVP, and not significantly different between arms ($P = 0.61$).

‡Incidence rates were 42.5 per 100 person-years (95% CI: 37.9 to 47.5 per 100 person-years) for infants in the mART and 42.0 per 100 person-years (95% CI: 37.5 to 47.0 per 100 person-years) in infants in the iNVP arm, and not significantly different between arms ($P = 0.99$).

§Includes ALT from week 1 and 6 visit only because infants randomized to the mART arm did not have ALT assessed at subsequent study visits.

100 person-years; 95% CI: 0.9 to 1.3 per 100 person-years), and not significantly different between arms ($P = 0.72$). The Kaplan–Meier estimates of probabilities of infant death at 6, 9, 12, and 18 months postpartum were 1.0% (95% CI: 0.6% to 1.5%), 1.1% (95% CI: 0.7% to 1.6%), 1.1% (95% CI: 0.7% to 1.6%), and 1.7% (95% CI: 1.1% to 2.6%), respectively. The secondary analysis included all 38 infant deaths (23 in the mART and 15 in the iNVP arm); and the cumulative probability of infant death at 24 months was 1.7% (95% CI: 1.3% to 2.4%). No infant death was attributed to study regimen and no HIV-1–infected infant died.

DISCUSSION

The PROMISE study is the first randomized trial to conduct a head-to-head comparison of mART and iNVP for postnatal HIV-1 transmission through up to 18 months of breastfeeding in asymptomatic women with high CD4 counts who did not meet treatment criteria at the time the study was conducted. Although the cumulative postnatal HIV-1 transmission rates in both the mART and iNVP arms were much lower than anticipated in sample size calculations, which greatly limited the study's statistical power to detect a difference in transmission risk between arms, the findings demonstrate that both mART and iNVP regimens were highly efficacious, with 12- and 24-month postnatal infection rates of 0.6% and 0.9%, respectively, and high rates of HIV-1–free survival at 24 months (>97%). The high under-two year survival rates (1.7% infant mortality) were particularly noteworthy compared with prevailing rates in most of the settings where the study was conducted.[24]

Two contemporary studies, ANRS 12174 and the Uganda PROMOTE trial, demonstrated similar survival rates but at 50 weeks of follow-up. ANRS 12174 randomized HIV-1–uninfected breastfed infants to either LPV/r or 3 TC through cessation of breastfeeding or 50 weeks. HIV-1–free survival at 50 weeks was 96% in both study arms.[11] HIV-1–infected women in the PROMOTE study were randomized between 12 and 28 weeks of pregnancy to either a LPV/r or efavirenz-based regimen that was continued for 48 weeks of breastfeeding. HIV-1–free infant survival at 8 weeks postpartum was 92.9% in the LPVr arm and 97.2% in the efavirenz arm.[12]

HIV-1 transmission rates in these studies were also low. In the PROMOTE study, HIV-1 infection occurred during breastfeeding in 1 infant in the LPV/r arm. Infections rates after 50 weeks in the ANRS 12174 study were 1.4% in the LPV/r arm and 1.5% in the 3 TC arm. To date, there is only 1 study that has compared the efficacy of mART and infant prophylaxis. The Breastfeeding, Antiretrovirals and Nutrition Study (BAN) compared a control regimen of intrapartum sdNVP plus 7 days of ZDV/3 TC in all women followed by a randomization into 1 of 3 groups: extended mART prophylaxis or daily iNVP prophylaxis given for up to 7 months of exclusive breastfeeding or no further ARV prophylaxis in mothers or infants. Although not designed nor powered to directly compare the efficacy of mART and iNVP, study findings indicated that both mART and the iNVP arms were superior to the 1-week control arm (3%, 1.8%, and 6.4%, respectively) at 28 weeks after delivery.[10] It should be noted that the women in BAN received only sdNVP and 7 days of ZDV/3 TC as prophylaxis for perinatal transmission, whereas 95% of the PROMISE cohort had been followed in the antepartum component and received either mART or ZDV. In addition, women in the BAN study were only enrolled if their CD4 count was greater than or equal to 200 or 250 cells/mm^3 (depending on time of enrollment), whereas women enrolled in the PROMISE cohort had CD4 cell counts ≥350 cells/mm^3 (or ≥the country-specific ART initiation threshold if it was >350 cells/mm^3). These underlying differences in subject selection likely explain the higher HIV transmission rates observed in the BAN study.

In addition, no safety concerns were observed in both mART and iNVP arms of the study. Less than 1% of women and 2% of infants discontinued their study regimen because of toxicity. Concerns have been raised about the potential infant toxicity from ingestion of ARVs in breastmilk of mothers receiving ART. Our study found no evidence of increased rates of toxicity in breastfeeding infants of mothers receiving tenofovir-based ART compared with breastfeeding infants whose mothers were not receiving ART. These data are also reassuring regarding the safety of TDF/FTC pre-exposure prophylaxis by breastfeeding, uninfected women at risk of HIV, and their infants.[25–27] Similarly, the prolonged use of daily NVP prophylaxis by HIV-1–uninfected infants for up to 18 months was not associated with elevated infant toxicity, including skin and liver toxicity, compared with infants not receiving NVP.

The median infant age to breastfeeding cessation in the study was 16 months, with 86% of infants still not having achieved complete breastfeeding cessation by 9 months, decreasing to 34% by 18 months. This is longer than what was originally hypothesized during the design of the trial and likely reflects changing guidelines on breastfeeding by HIV-1–infected women as well as changing habits among Sub-Saharan women during the trial. This prolonged duration of breastfeeding puts the HIV-1–exposed infant at risk of infection should there be suboptimal ART adherence by the mother. Approximately 67% of infections occurred after 6 months of age and 33% after 12 months of age, with infections continuing to occur through 24 months.

During the conduct of the PROMISE randomized trial, the WHO guidelines for prevention of perinatal HIV-1 transmission were modified in 2013 to recommend maternal ART through at least the duration of breastfeeding; current guidelines recommend lifelong ART for all HIV-1–infected individuals, including pregnant and breastfeeding women.[17,28] Despite these recommendations, due to postpartum adherence problems, many women experience rebound viremia, resulting in continued postnatal transmission.[3,4,29] The PROMISE data demonstrate that mART and iNVP have similar efficacy and safety profiles through up to 24 months of breastfeeding, indicating that although treatment for breastfeeding women is a priority, prolonged use of iNVP is an effective and safe alternative, for example, for women who refuse or do not adhere to ART, have persistent viremia, or who temporarily stop ART for toxicity.[5] However, for women who refuse or are not adherent to ART, similar barriers to iNVP administration may exist.

Our data underline the importance of providing postpartum support for women receiving ART because we observed a continuing risk of infant postnatal infection for the duration of breastfeeding even when effective interventions were being provided. A variety of approaches will be needed to achieve an HIV-1–free generation, including interventions to support ART adherence and postpartum retention in care for women and ensuring the availability of equally effective and safe infant prophylaxis alternatives for situations in which maternal ART may be insufficient to protect the breastfeeding infant.

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