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Adherence to extended postpartum antiretrovirals is associated with decreased breastmilk HIV-1 transmission: Results of the BAN study

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Abstract

Objective—Estimate association between postpartum antiretroviral adherence and breastmilk HIV-1 transmission

Design—Prospective cohort study

Methods—Mother-infant pairs were randomized after delivery to immediately begin receiving 28 weeks of either triple maternal antiretrovirals (zidovudine, lamivudine, and either nevirapine, nelfinavir, or lopinavir-ritonavir) or daily infant nevirapine as part of the Breastfeeding, Antiretrovirals, and Nutrition study. Associations between postpartum antiretroviral adherence and rate of breastmilk HIV-1 transmission were estimated using Cox models. We measured adherence over four postpartum time intervals using pill count, suspension bottle weight, and maternal self-report. Adherence was categorized and lagged by one interval. Missing adherence measures were multiply imputed. Infant HIV-1 infection was determined by DNA PCR every 2-6 weeks. The primary endpoint was infant HIV-1 infection by 38 weeks of age among infants alive and uninfected at 5 weeks.

Results—Analyses included 1479 mother-infant pairs and 45 transmission events. Using pill count and bottle weight information, 22-40% of mother-infant pairs at any given interval were <90% adherent. Having ≥90% adherence was associated with a 52% (95% CI 3-76%) relative reduction in the rate of breastmilk HIV-1 transmission, compared with having <90% adherence when controlling for study arm, breastfeeding status, and maternal characteristics. Complete case analysis rendered similar results (n=501; relative reduction 59%, 95% CI 6-82%).

Conclusion—Non-adherence to extended postpartum ART regimens in ‘real world’ settings is likely to be higher than that seen in BAN. Identifying mothers with difficulty adhering to antiretrovirals, and developing effective adherence interventions, will help maximize benefits of ARV provision throughout breastfeeding.

Keywords

adherence; antiretroviral; breastfeeding; HIV transmission; PMTCT

INTRODUCTION

The World Health Organization (WHO) recommends that pregnant and breastfeeding women with HIV infection receive antiretroviral therapy (ART) either throughout breastfeeding or lifelong in an effort to achieve global goals of eliminating new infant HIV infections and keeping their mothers alive.[1] Effective implementation of this WHO guidance relies on adherence to prescribed antiretroviral (ARV) regimens.[2] Maintaining ARV adherence has been challenging for patients, and predicting who will be non-adherent and intervening in an effective way has been challenging for prevention of mother-to-child HIV transmission (PMTCT) programs.[3-8] Almost one half of postpartum patients included

in a recent meta-analysis did not maintain an adherence level thought to be needed for virologic suppression (>80%).[9]

Non-adherence to ART and PMTCT regimens may occur for several reasons, including: time and financial costs of accessing care, stigma, forgetfulness or changes in routine, and side effects of medications.[6, 10-15] Among non-pregnant or breastfeeding adults, >95% adherence is thought to be needed to maintain virologic suppression when unboosted protease inhibitors (PI) are included in the ART regimen.[16] Pharmacokinetic boosting of PIs with drugs such as ritonavir has been used to extend the plasma half-life of the active PI by inhibiting drug metabolism.[17, 18] With boosted PIs, 80% adherence may be sufficient for non-pregnant or breastfeeding adults to achieve virologic suppression.[19-21]

Despite the efficacy of ART in PMTCT, transmission does occur even in the context of closely monitored clinical trials for poorly understood reasons.[22-26] In this paper, we use data from a recent randomized PMTCT trial in Malawi to: 1) estimate adherence to postpartum maternal triple ARVs or daily infant NVP using pill counts, bottle weights, and maternal self-report; 2) compare characteristics of mother-infant pairs by adherence category; and 3) quantify the effect of adherence to both maternal triple ARVs and extended daily infant NVP on breastmilk HIV-1 transmission.

METHODS

The Breastfeeding, Antiretrovirals and Nutrition (BAN) trial was conducted in Malawi between 2004 and 2010 using a factorial design to assess the benefit and safety of antiretroviral medications given either to infants or mothers to prevent HIV transmission during breastfeeding.[22] Mothers were recruited at antenatal clinics in Lilongwe. Eligibility criteria for mother-infant pairs included the following: antibody-confirmed maternal HIV infection, maternal CD4 ≥250 cells/μL (≥200 cells/μL before July 24, 2006), no previous antiretroviral drug use (including single dose NVP), infant birth weight ≥2000 grams, no infant or maternal condition that would preclude the use of a study drug, and able to enroll within 36 hours of delivery.[22]

All mothers and infants enrolled in BAN received one dose of NVP at delivery or birth and seven days of zidovudine and lamivudine postpartum; no antepartum antiretrovirals were given.[22] Mother-infant pairs were randomized after delivery to immediately begin one of the following postpartum PMTCT prophylaxis regimens: 1) 28 weeks of maternal triple antiretrovirals (maternal ARV); 2) 28 weeks of infant NVP; or 3) no further drugs postpartum (enhanced control).[22] Mothers were also randomized to either receive or not receive a lipid-based nutrient supplement throughout breastfeeding.[22] All mothers were advised to breastfeed exclusively for the first 24 weeks postpartum with weaning between 24 and 28 weeks.[22] Details of the drug regimens and nutrition supplement have been reported previously.[27-29]

Ethical approval was obtained from the Malawi National Health Science Research Committee and the institutional review boards at the University of North Carolina at Chapel Hill and the U.S. Centers for Disease Control and Prevention.

Study design

Mother-infant pairs randomized to the two treatment arms of BAN, maternal ARV (n=849) and infant NVP (n=852) were included. We excluded mother-infant pairs that were randomized to the enhanced control arm (n=668), and infants who had one of the following outcomes between birth and four weeks of age: HIV infection (n=86), death (n=6), lost to follow-up (n=84), or unknown breastfeeding status (n=46). Information on first-born multiples was used when multiple births occurred (n=31). Our analysis thus included a total of 1479 mother-infant pairs at risk of breastmilk HIV transmission between 5 and 38 weeks of age. Weeks were chosen based on adherence measure availability and to allow for the delayed effect of non-adherence on transmission.

Data analyses

Breastmilk HIV-1 transmission was determined by Roche Amplicor 1.5 DNA PCR (Roche Molecular Systems, Pleasanton, CA, USA) at 2, 12, 28, and 48 weeks to indicate infant HIV-1 status. PCR-positive results were confirmed by testing an additional blood specimen, and the window of infection was narrowed with tests of infant dried blood-spot specimens taken at 4, 6, 8, 18, 24, 32, and 36 weeks. The primary outcome was breastmilk transmission, defined as first positive infant PCR test between 5 and 38 weeks of age. The secondary outcome was time until either first detection of infant HIV-1 infection or infant death by 38 weeks. Death ascertainment procedures have been described previously.[27]

The main exposure of interest was adherence to the prescribed postpartum ARV regimen. We measured adherence two ways: 1) maternal ARV pill counts or infant NVP suspension bottle weights, taken by trained pharmacy staff (hereafter referred to as “adherence”); and 2) maternal self-report, using a standardized questionnaire (used in sensitivity analyses, hereafter referred to as “self-reported adherence”). Only pill counts and bottle weights measured on contiguous visits were used. Adherence was then calculated for the following time intervals: 2-4, 8-12, 13-18, and 24-28 weeks of age. Pill counts and bottle weights were not collected during weeks 5-7, and 19-23. For analysis purposes, the unobserved adherence during weeks 5-7 and 19-23 were assumed to be equal to the observed adherence during weeks 8-12 and 24-28, respectively. Adherence was calculated using the difference in the number of pills or grams returned at the current visit and the number distributed at the previous visit, compared to the number of pills or grams expected to be consumed between visits if perfectly compliant under BAN dosing regimens. [27]

Because all three prescribed ARV drugs are necessary for full regimen activity, we made separate calculations for each drug and used the lowest percentage of the three to define a mother's ARV adherence at a given interval. A cutoff of 90% was then used to dichotomize adherence (<90% adherent=non-adherent, ≥90% adherent=adherent). The choice of adherence cutoff was based on previous studies and the expected adherence distribution.[30]

Self-reported adherence was measured at 4, 8, 21, and 28 weeks postpartum and based on the mother's answer to the following question: “During the past three days excluding today, have you/your baby missed any doses of (name of each individual antiretroviral

prescribed)?" Self-reported adherence was considered a time-varying dichotomous variable (≥1 reported missed dose of *any* drug; no reported missed doses of *any* drugs).

Potential confounding variables consisted of randomization assignment, baseline demographic characteristics and health status information (Table 1), and time-dependent breastfeeding status. All covariates were measured as part of the BAN trial. Frequencies, means, and medians were also calculated, as appropriate, to compare characteristics of mother-infant pairs by exposure (adherence) and outcome (HIV-1 status) category. Binomial regression models using generalized estimating equations (GEE) and an exchangeable correlation matrix were used to test whether or not adherence changed over time.

A time-to-event Cox model was used to assess the association between adherence and the rate of breastmilk HIV-1 transmission and breastmilk HIV-1 transmission or infant death by 38 weeks of age, adjusting for potential prognostic factors. Hazard ratios represent the transmission rate for mother-infant pairs that were ≥90% adherent relative to the transmission rate of pairs <90% adherent; relative reduction is defined as one minus the hazard ratio. Adherence was included in the Cox model as a time-varying covariate, lagged by one interval to ensure the exposure occurred prior to the outcome. Therefore, adherence was associated with transmission in the subsequent time interval. Mother-infant pairs lost to follow-up were censored at the time of their last PCR negative HIV-1 test.

Effect measure modification was assessed by comparing unadjusted and adjusted hazard ratio estimates and 95% confidence intervals using an interaction term between adherence and the variable of interest. Covariates producing adjusted hazard ratio estimates different enough to be clinically or programmatically relevant were considered effect measure modifiers. A directed acyclic graph (DAG) was used to identify potential confounders and a minimally sufficient adjustment set.[22, 27, 31] Given the limited number of outcomes, more parsimonious models were generated by removal of potential confounders that had minimal effect on the hazard ratio estimate or precision.

Multiple imputation was used to account for missing adherence measures.[32]. Adherence was assumed to be missing at random. The probability of being adherent for each missing adherence measure was predicted from a fitted logistic regression model comprised of variables believed a priori to be predictive of adherence and for which there was minimal missing data. Covariates used to predict adherence included ARV study arm, maternal age (continuous), parity (0, ≥1), marital status, (married, not married), education status (≤primary, >primary), baseline maternal CD4+ category (200-350, 351-500, >500), baseline maternal hemoglobin (<11mg, ≥11mg), previous visit(s) adherence, time-dependent breastfeeding status, infant's outcome, and log survival time. Missing adherence measures were imputed based on the logistic regression predicted probabilities of being ≥90% adherent or <90% adherent. Five hundred complete data sets were imputed. Unadjusted and adjusted Cox models were then fit to obtain parameter and variance estimates for each of the 500 datasets, and these estimates were combined to obtain a final mean hazard ratio estimate and 95% confidence interval.[33]

Two main sensitivity analyses were conducted to address self-reported adherence and baseline maternal viral load. First, we compared self-reported adherence with pill count and bottle weight adherence, and compared the association between adherence and breastmilk HIV-1 transmission using each adherence measurement method. To do this, self-reported adherence was considered as the main exposure in sensitivity analyses, instead of pill count or bottle weight adherence. Second, we assessed the impact of adjustment for baseline maternal viral load, which was not included in the main regression analyses. Baseline maternal viral load information was not available for 3 mother-infant pairs, including one mother-infant pair who experienced a HIV-1 transmission event. Due to the known association between viral load and HIV transmission, we included log10-transformed baseline maternal viral load in both the imputation and analysis models as a sensitivity analysis.

All data analyses were conducted using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

A total of 1479 mother-infant pairs and 45 transmission events were included in analyses (Figure 1). The median maternal age was 26 years [interquartile range (IQR): 23 to 29]. Most mothers were married (93%) and reported at least one previous live birth (87%) (Table 1). Among those randomized to maternal ARVs, most received a boosted protease inhibitor regimen of zidovudine, lamivudine, and lopinavir-ritonavir (79%) (Table 1). Mothers had a median baseline CD4+ count of 477 per uL (IQR: 330 to 582), a median baseline log10 viral load of 4.1 copies per milliliter of blood (IQR: 3.6 to 4.7), and a median hemoglobin of 10.8 grams per dL (IQR: 10.0 to 11.7). The median infant birth weight was 3.0 kg (IQR: 2.7 to 3.3).

The overall postnatal MTCT rate was 5.1 infections per 100 person-years (95% confidence interval (CI) 3.8-6.8); rates by maternal and infant NVP arm were 5.4 (95% CI 3.6-8.1) and 4.9 (95% CI 3.2-7.4) infections per 100 person-years, respectively. Overall, mean pill count or bottle weight adherence was 87% [median 0.98; IQR: 0.82 to 1.00], and did not meaningfully differ by study arm (maternal arm 87%, infant arm 86%). Adherence changed over time in both the maternal and infant arm ($p<0.001$), but no consistent pattern was identified (Table 2).

Among all mother-infant pairs with at least one pill count or bottle weight adherence measure, 22-40% were <90% adherent at any given interval (maternal ARV arm 24-42%, infant NVP arm 17-51%) (Table 2). A larger proportion of mother-infant pairs with a HIV-1 transmission event were <90% adherent (41%) during any given interval compared with mother-infant pairs whose infants remained HIV-uninfected (33%) (Table 2), but the difference was not statistically significant ($p=0.1$). The postnatal MTCT rate between 5-38 weeks of infant age was 3.0 infections per 100 person-years (95% CI 1.7-5.4) for adherent intervals, and 7.4 infections per 100 person-years (95% CI 4.7-12.3) for non-adherent intervals.

Complete case

A total of 501 mother-infant pairs had complete pill count or bottle weight adherence information (complete cases). Of these, 146 (29%) were always ≥90% adherent and 35 (7%) were never ≥90% adherent (Table 3).

Among complete cases, 23 experienced a breastmilk HIV-1 transmission event by 38 weeks of age (maternal ARV arm: 18, infant NVP arm: 5), and 28 experienced the composite outcome of breastmilk HIV-1 transmission or infant death by 38 weeks (maternal ARV arm: 21, infant NVP arm: 7). Having >90% adherence was associated with a 60% relative reduction in the rate of breastmilk HIV-1 transmission by 38 weeks of age among complete cases, compared with having <90% adherence (Hazard Ratio (HR) 0.40; 95% CI 0.17-0.91) (Table 4). Adjustment for maternal age, baseline maternal CD4+ count, baseline maternal hemoglobin level, time-dependent breastfeeding status, and study arm had little impact (HR 0.41, 95% CI 0.18-0.94) (Table 4).

Multiple imputation

Adherence measured by pill count and bottle weight was imputed for 29% (431/1479) of mother-infant pairs at 4 weeks, 27% (387/1411) at 12 weeks, 29% (401/1375) at 18 weeks, and 43% (560/1310) at 28 weeks. No variables were significant predictors of adherence at all time points.

Having ≥90% pill count or bottle weight adherence was associated with a 50% relative reduction in the rate of breastmilk HIV-1 transmission by 38 weeks of age, compared with having <90% adherence [unadjusted HR 0.50, 95% CI 0.25-0.99] when using multiply imputed data (Table 4). The estimated hazard ratio was similar when unadjusted Cox models were fit separately for each study arm [maternal ARV HR 0.51, 95% CI 0.21-1.21; infant NVP HR 0.48, 95% CI 0.16-1.44) (Table 4). Adjustment for potential confounding did not meaningfully change the hazard ratio estimate (HR 0.48; 95% CI 0.24-0.97) (Table 4).

Composite outcome: breastmilk HIV-1 transmission or infant death

Associations between adherence and the composite outcome of breastmilk HIV-1 transmission or death did not appreciably differ from those using only HIV-transmission as the outcome (unadjusted HR 0.58, 95% CI 0.32-1.04; adjusted HR 0.59, 95% CI 0.33-1.06).

Sensitivity analyses

A total of 541 mother-infant pairs had complete self-reported adherence information. Of these, 22 experienced a breastmilk HIV-1 transmission event (maternal ARV arm: 16, infant NVP arm: 6). Overall, 92% of mothers self-reported missing no pills in the last three days. Self-reported adherence was similar by study arm (infant NVP: 0.93, maternal ARV: 0.90). Among complete cases, reporting missing no pills in the prior 3 days (100% self-reported adherence) was associated with a 74% relative reduction in the rate of breastmilk HIV-1 transmission, compared with those self-reporting <100% adherence during the last three days (HR 0.26, 95% CI 0.09-0.71) and after adjusting for study arm, time-dependent breastfeeding status, and baseline maternal age, CD4+ count, and hemoglobin. The

association remained similar when using multiply imputed self-reported adherence (n=1479, adjusted HR 0.33, 95% CI 0.14-0.78).

Including baseline maternal viral load in the imputation and analysis model resulted in a nearly identical association between pill count or bottle weight adherence and the rate of breastmilk HIV-1 transmission (complete case HR 0.40, 95% CI 0.18-0.92; imputed HR 0.49, 95% CI 0.25-0.97), compared to models that did not adjust for baseline maternal viral load. Similarly, including the control arm in analyses and allowing for potential differential detection of HIV among the infant NVP arm resulted in similar findings (supplemental material).

DISCUSSION

We have shown that adherence to antiretroviral regimens needs to be maintained throughout the breastfeeding period to maximize efforts to prevent breastmilk HIV-1 transmission and improve infant HIV-free survival. The strong association found between very high (≥90%) adherence and transmission is striking, reinforcing the importance of maintaining mother-infant pairs in HIV care and providing effective adherence counseling messages. To our knowledge, this study was the first in a resource-limited setting that assessed adherence over time to an extended postpartum prophylaxis regimen using pill count, bottle weight, and maternal self-report. The extent of missing adherence data in our study underscores the difficulty in consistently assessing adherence to postpartum antiretroviral medications, even in a well-monitored clinical trial with intensive follow-up.

Non-adherence to ART has been associated with higher HIV viral loads in pregnant women, and compliance to short-course maternal zidovudine has been associated with decreased HIV-1 vertical transmission.[12, 34, 35] Maternal ARV adherence rates had a negative but not statistically significant correlation with MTCT rates in a recent meta-analysis.[9] However, most studies in the meta-analysis used short-course ARV regimens and reported only antepartum adherence.[9] In contrast, we measured postpartum adherence over four time intervals, and allowed adherence to vary over time. In addition, we used methods that account for missing adherence measures, infants lost to follow-up, and infant death.

The number of transmission events was relatively small despite the large sample size, reducing the precision of our estimates and preventing comparisons by study arm. However, we observed a substantial effect of adherence on breastmilk HIV-1 transmission despite the small number of transmission events.

Adherence levels found in BAN are similar to reported adherence from other randomized controlled trials of either extended infant or maternal antiretroviral prophylaxis during breastfeeding, and to a pooled postpartum adherence estimate.[9, 23, 24, 26, 36] However, direct adherence comparisons are difficult due to differences in definition and measurement of adherence across trials. Adherence may be measured using a variety of approaches ranging in sophistication, but all are imperfect.[37] Self-reported adherence has the most potential for bias (usually in the form of overestimating adherence) due to recall and social desirability bias, but is the measurement tool most often used because it is easy and

inexpensive to administer.[37] Adherence measurements based on pill count and suspension bottle weight are subject to manipulation, but are thought to have greater validity and take into account adherence over the entire monitoring period, rather than just the three days prior to the self-report assessment visit.[38] A consensual adherence measurement method is needed to facilitate inter-study comparisons. In our study, self-reported adherence was higher than adherence measured by pill count and bottle weight, with poor agreement between the two measures (supplemental material). However, both adherence measures resulted in a consistent association with breastmilk HIV-1 transmission, increasing the confidence in our findings.

We were unable to determine an adherence threshold for transmission prevention despite assessing multiple adherence cutoffs (e.g.: 80% and 95%) and imputing adherence as a continuous measure. Our findings suggest that the association between adherence and transmission is a continuum, with higher adherence leading to higher protection against transmission (results not shown). In addition, while determinants of maternal versus infant adherence likely differ, we were unable to ascertain such differences in this study.

When adherence data are skewed, presenting only one measure of central tendency (e.g., mean or median) may fail to convey the characteristics of the adherence distribution, and be misleading. For example, median adherence in our study was 98%, suggesting that no further action is needed to maintain high levels of postpartum adherence. Mean adherence was 87%, suggesting that some work is needed to improve adherence, but adherence remained high. In contrast, 22-40% of mother-infant pairs in our study were <90% adherent during each interval, suggesting that increased focus is needed to improve postpartum adherence. Variation in measures exemplifies the skewed left adherence distribution and implies that some mother-infant pairs had very low adherence, and that some had intermittent non-adherence. Given that transmission is associated with non-adherence, there is a need to consistently emphasize adherence throughout the postpartum period.

BAN study nurses counseled mothers on adherence, referencing pill counts and bottle weights. The extent of adherence monitoring and counseling in BAN greatly exceeds that conducted in most non-clinical trial settings. In ‘real-world’ settings, retention in HIV care as measured by non-missed appointments is generally used as a crude proxy for adherence, with other direct adherence measures rarely conducted. However, a patient's care-seeking and drug-taking behaviors are not necessarily synonymous.

Non-adherence did not account for all transmission events. Transmission may have occurred despite perfect adherence due to imperfection in our adherence measure, delay between maternal initiation of antiretrovirals and virologic suppression, antiretroviral drug resistance, or other unidentified processes. The number of visits that could be used to assess adherence resulted in inconsistent and extended time intervals between adherence measures. Adherence was held constant during the interval, and lagged to ensure the exposure occurred before the outcome. Therefore, measured adherence may not be the true adherence in the period immediately before transmission.

Our results reinforce the need to focus on maintaining adherence to meet PMTCT goals. Furthermore, the extent of non-adherence in this heavily monitored clinical trial setting has important implications for adherence counseling messages, local PMTCT program planning efforts, and global modeling exercises predicting MTCT elimination. We measured adherence through 28 weeks postpartum. The time lag between maternal antiretroviral initiation and virologic suppression may partly explain the strong association found between what is generally deemed as very high adherence and breastmilk transmission, as very high adherence may be more important for preventing transmission during the first months of ARV initiation. Assessment of adherence and adherence-related outcomes throughout one to two years of breastfeeding is urgently needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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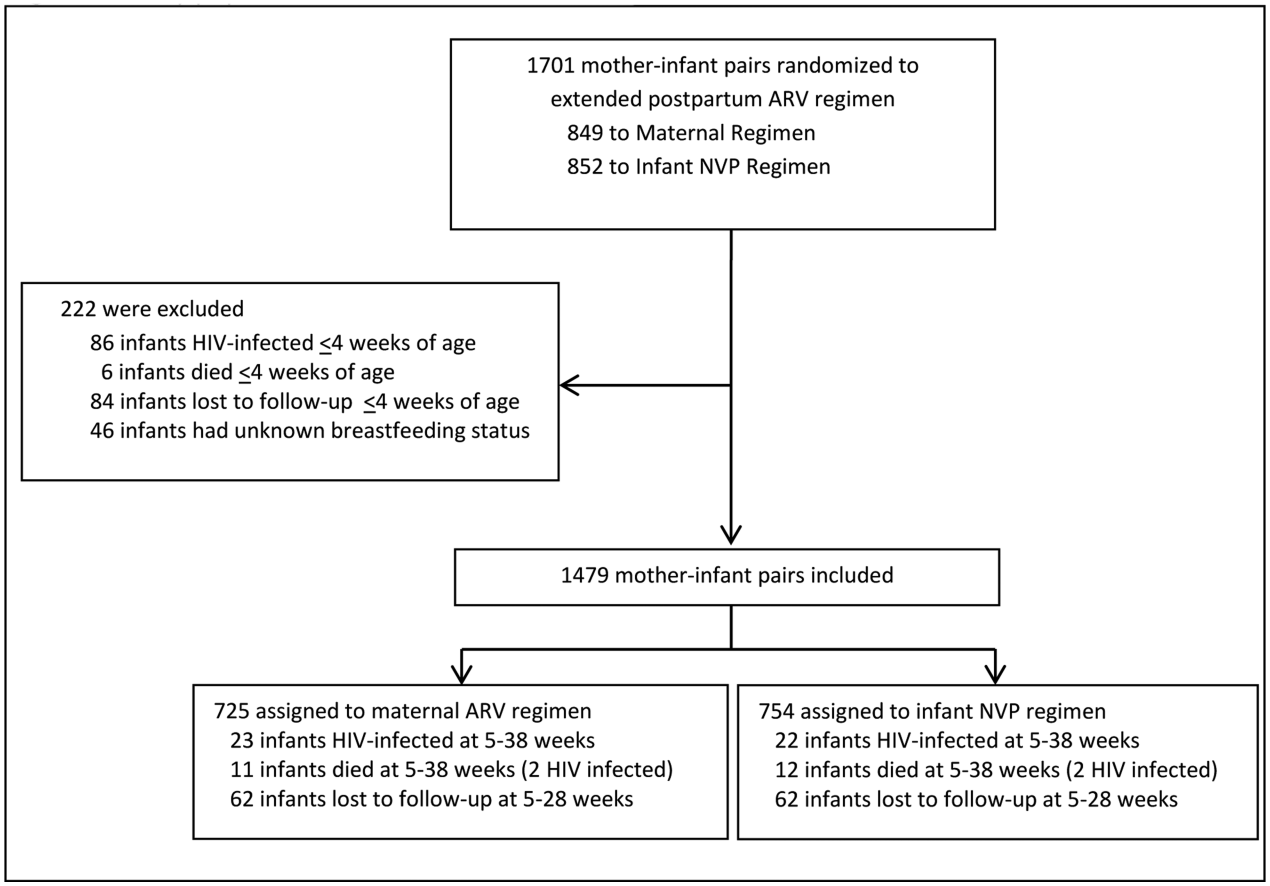

Figure 1.
Study population and outcomes

Table 1

Baseline characteristics of 1479 mother-infant pairs.

	Total* (N=1479)		HIV-1infected infant** (N=45)		HIV-1 uninfected infant† (N=1434)	
	N	(%)	N	(%)	N	(%)
Antiretroviral randomization						
Maternal antiretroviral	725	(49)	23	(51)	702	(49)
Infant nevirapine	754	(51)	22	(49)	732	(51)
Nutritional randomization						
No supplement	733	(50)	17	(38)	716	(50)
Received supplement	746	(50)	28	(62)	718	(50)
Mothers:						
Age (years)						
15-25	720	(49)	30	(67)	690	(48)
26-35	680	(46)	14	(31)	666	(47)
36-45	76	(5)	1	(2)	75	(5)
Education						
Primary school only	941	(64)	29	(64)	912	(64)
More than primary school	536	(36)	16	(36)	520	(36)
Married						
No	110	(7)	5	(11)	105	(7)
Yes	1369	(93)	40	(89)	1329	(93)
Parity						
0	193	(13)	8	(18)	185	(13)
>1	1280	(87)	37	(82)	1243	(87)
CD4+ count per mm^3						
200-350	450	(30)	20	(44)	430	(30)
351-500	478	(32)	13	(29)	465	(32)
>500	551	(37)	12	(27)	539	(38)
Plasma viral load copies/mL						
≤1,000	147	(10)	1	(2)	146	(10)
1,001-10,000	425	(29)	7	(16)	418	(29)
>10,000	904	(61)	36	(82)	868	(61)
Hemoglobin (g/dl)						
<11	783	(53)	35	(78)	748	(52)
≥11	696	(47)	10	(22)	686	(48)
ARV Regimen‡						
Nevirapine based	20	(3)	0	(0)	20	(3)
Nelfinavir based	124	(18)	5	(22)	119	(18)
Lopinavir/ritonavir based	556	(79)	18	(78)	538	(79)
Infants						
Sex						
Female	752	(51)	23	(51)	729	(51)

	Total* (N=1479)		HIV-1infected infant** (N=45)		HIV-1 uninfected infant† (N=1434)	
	N	(%)	N	(%)	N	(%)
Male	727	(49)	22	(49)	705	(49)
Birth weight (kg)						
<2.5	106	(7)	7	(16)	99	(7)
≥2.5	1370	(93)	38	(84)	1332	(93)

* Maternal plasma viral load was not available for 3 mothers, ARV regimen information was not available for 25 mothers randomized to maternal ARV arm, and infant birth weight was not available for 3 infants

** Infant tested PCR-positive for HIV-1 between 5 and 38 weeks of age

† Includes 16 infants that tested PCR-positive for HIV-1 after 38 weeks of age

‡ Among those randomized to maternal ARV arm.

Table 2

Pill count and bottle weight adherence for mother-infant pairs with ≥1 adherence measure.

		Percent adherence				Dichotomous adherence
	n	Mean	SD*	Median	IQR**	% non-adherent†
Maternal + Infant regimen						
Overall		0.87	0.22	0.98	0.82-1.00	33
Week 4	1048	0.86	0.23	0.98	0.82-1.00	34
Week 12	1024	0.91	0.19	1.00	0.91-1.00	22
Week 18	974	0.87	0.19	0.97	0.76-1.00	37
Week 28	750	0.82	0.27	0.96	0.74-1.00	40
Maternal regimen						
Overall		0.87	0.21	0.97	0.85-1.00	32
Week 4	571	0.86	0.22	0.96	0.82-1.00	37
Week 12	552	0.89	0.19	0.98	0.89-1.00	26
Week 18	522	0.91	0.17	0.99	0.90-1.00	24
Week 28	401	0.81	0.27	0.94	0.73-1.00	42
Infant regimen						
Overall		0.86	0.23	1.00	0.78-1.00	34
Week 4	477	0.86	0.24	1.00	0.81-1.00	31
Week 12	472	0.92	0.19	1.00	0.95-1.00	17
Week 18	452	0.82	0.20	0.87	0.67-1.00	51
Week 28	349	0.82	0.27	0.98	0.74-1.00	39
HIV-infected infants						
Overall		0.84	0.26	0.96	0.83-1.00	41
Week 4	30	0.85	0.22	0.93	0.84-1.00	47
Week 12	24	0.89	0.22	0.99	0.89-1.00	29
Week 18	18	0.82	0.30	0.98	0.75-1.00	39
Week 28	11	0.71	0.35	0.83	0.45-1.00	55
HIV-uninfected infants						
Overall		0.87	0.22	0.98	0.82-1.00	33
Week 4	1018	0.86	0.23	0.99	0.82-1.00	34
Week 12	1000	0.91	0.19	1.00	0.91-1.00	22
Week 18	956	0.87	0.19	0.97	0.76-1.00	37
Week 28	739	0.82	0.27	0.96	0.74-1.00	40

*SD=standard deviation

**IQR=Interquartile range

†Having less than 90% pill count or bottle weight adherence is considered non-adherent.

Table 3

Characteristics of mother-infant pairs with complete adherence information (n=501)

	Total*	Always ≥90% adherent (n=146)		<90% adherent for ≥1 interval (n=355)		Never ≥90% adherent (n=35)**	
	N	n	%†	n	%†	n	%†
ARV randomization							
Maternal antiretroviral	328	99	(30)	229	(70)	23	(7)
Infant nevirapine	173	47	(27)	126	(73)	12	(7)
Nutritional randomization							
No supplement	230	71	(31)	159	(69)	17	(7)
Received supplement	271	75	(28)	196	(72)	18	(7)
Mothers:							
Age (years)							
15-25	208	66	(32)	142	(68)	18	(9)
26-35	265	78	(29)	187	(71)	17	(6)
36-45	27	2	(7)	25	(93)	0	(0)
Education							
Primary school only	316	90	(28)	226	(72)	19	(6)
More than primary school	184	55	(30)	129	(70)	16	(9)
Married							
No	35	10	(29)	25	(71)	1	(3)
Yes	466	136	(29)	330	(71)	34	(7)
Parity							
0	55	22	(40)	33	(60)	5	(9)
≥1	445	124	(28)	321	(72)	30	(7)
CD4+ count per mm^3							
200-350	162	46	(28)	116	(72)	11	(7)
351-500	151	41	(27)	110	(73)	11	(7)
>500	188	59	(31)	129	(69)	13	(7)
Plasma viral load copies/mL							
≤1,000	52	20	(38)	32	(62)	1	(2)
1,001-10,000	135	42	(31)	93	(69)	3	(2)
>10,000	313	83	(27)	230	(73)	31	(19)
Hemoglobin (g/dl)							
<11	262	74	(28)	188	(72)	20	(8)
≥11	239	72	(30)	167	(70)	15	(6)
ARV Regimen‡							
Nevirapine based	9	4	(44)	5	(56)	1	(11)
Nelfinavir based	46	13	(28)	33	(72)	6	(13)
Lopinavir/ritonavir based	273	82	(30)	191	(70)	16	(6)
Infants							
Sex							

	Total*	Always ≥90% adherent (n=146)		<90% adherent for ≥1 interval (n=355)		Never ≥90% adherent (n=35)**	
	N	n	%†	n	%†	n	%†
Female	262	67	(26)	195	(74)	20	(8)
Male	239	79	(33)	160	(67)	15	(6)
Birth weight (kg)							
<2.5	36	17	(47)	19	(53)	3	(8)
≥2.5	465	129	(28)	336	(72)	32	(7)

*Maternal age, education, parity, and viral load are missing for 1 mother

**Columns are not mutually exclusive. Those 'never ≥ 90% adherent' are also included in the '<90% adherent for ≥1 interval' column.

†Row percentages are presented

‡Among those randomized to maternal ARV arm

Table 4

Estimates of adherence as a risk factor for breastmilk HIV-1 transmission and a composite outcome of breastmilk HIV-1 transmission or infant death by 38 weeks of age, among those HIV-1 uninfected at 5 weeks.*

	Imputed adherence				Complete case			
	Unadjusted		Adjusted**		Unadjusted		Adjusted**	
	Hazard Ratio	(95% CI)	Hazard Ratio	(95% CI)	Hazard Ratio	(95% CI)	Hazard Ratio	(95% CI)
Breastmilk HIV-1 transmission								
Maternal and Infant Regimen								
Adherent vs non-adherent	0.50	(0.25, 0.99)	0.48	(0.24, 0.97)	0.40	(0.17, 0 .91)	0.41	(0.18, 0.94)
Adherence by study arm								
Maternal ARV adherent vs. non-adherent	0.51	(0.21, 1.21)	0.49	(0.20, 1.19)	0.44	(0.17, 1.11)	0.44	(0.17, 1.12)
Infant NVP adherent vs. non-adherent	0.48	(0.16, 1.44)	0.47	(0.16, 1.40)	0.31	(0.05, 1.87)	0.32	(0.05, 1.91)
Breastmilk HIV-1 transmission or infant death								
Maternal and Infant Regimen								
Adherent vs non-adherent	0.58	(0.32, 1.04)	0.59	(0.33, 1.06)	0.42	(0.20, 0.89)	0.44	(0.21, 0.94)
Adherence by study arm								
Maternal ARV adherent vs. non-adherent	0.51	(0.23, 1.08)	0.53	(0.24, 1.17)	0.38	(0.16, 0.91)	0.40	(0.17, 0.95)
Infant NVP adherent vs. non-adherent	0.66	(0.28, 1.59)	0.65	(0.27, 1.55)	0.58	(0.13, 2.63)	0.61	(0.13, 2.75)

*Having greater than or equal to 90% pill count or bottle weight adherence is considered adherent; less than 90% adherence is considered non-adherent.

**Adjusted for maternal age, CD4+, hemoglobin, and time-dependent reported breastfeeding status. Study arm was included as a confounding variable in combined maternal and infant regimen models. Adherence by study arm models included an interaction term between adherence and study arm.