Antiretroviral Adherence Associated with Reduced Breastmilk HIV-1 Transmission: the BAN Study

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INTRODUCTION

BACKGROUND

Postnatal HIV-1 transmission occurred in the Breastfeeding, Antiretrovirals and Nutrition (BAN) study despite well-controlled implementation of either maternal triple antiretrovirals (ARV) or daily infant nevirapine (NVP) throughout 28 weeks of breastfeeding.

One possible explanation for transmission is suboptimal antiretroviral adherence.

Quantifying the association between adherence and breastmilk transmission will have important implications for prevention of mother-to-child HIV transmission (PMTCT) efforts.

OBJECTIVES

We used data from BAN, a recent randomized PMTCT trial in Malawi, to:

1) Estimate adherence to postpartum maternal triple ARV and extended daily infant NVP using pill counts, suspension bottle weights, and maternal self-report;

2) Compare the characteristics of mother-infant pairs by adherence category; and

3) Quantify the effect of adherence to both maternal triple ARV and extended daily infant NVP on breastmilk HIV-1 transmission.

METHODS

THE BAN STUDY

Randomized control trial in Lilongwe, Malawi (2004-2010) to assess the benefit and safety of ARVs given to HIV-infected mothers or their infants to prevent breastmilk HIV transmission

Select eligibility criteria:

- Maternal HIV infection with CD4 ≥ 250 and no prior ARV use
- Infant birth weight ≥ 2000 grams
- No infant or maternal condition that would preclude use of study drug

Mother-infant pairs randomized to receive:

- 28 weeks of antiretrovirals given to mother only (maternal ARV)
- 28 weeks of daily NVP given to infant only (infant NVP)
- Single-dose NVP and 1 week of Combivir given to mother and infant (control)

Mothers advised to exclusively breastfeed for first 24 weeks, with weaning at 24-28 weeks

STUDY POPULATION

1701 mother-infant pairs randomized to extended postpartum ARV regimen
849 to Maternal Regimen
852 to Infant NVP Regimen

222 were excluded
86 Had infections ≤ 4 weeks of age
6 Died ≤ 4 weeks of age
84 Were lost to follow-up ≤ 4 weeks of age
46 Had unknown breastfeeding status

1479 mother-infant pairs included

725 assigned to maternal ARV regimen
23 Had infections at 5-38 weeks
11 Died at 5-38 weeks (2 HIV-1 infected)
62 Were lost to follow-up at 5-28 weeks

754 assigned to infant NVP regimen
22 Had infections at 5-38 weeks
12 Died at 5-38 weeks (2 HIV-1 infected)
62 Were lost to follow-up at 5-28 weeks

METHODS

DATA ANALYSIS

We measured adherence over four time intervals from 2-28 weeks postpartum using pill count, suspension bottle weight, and maternal self-report. Adherence was treated as a time-varying exposure. Missing adherence measures were multiply imputed.

Pill count and bottle weight 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.

Self-reported adherence was 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)?"

Infant HIV infection was determined by polymerase chain reaction every 2-6 weeks using the Roche Amplicor 1.5 DNA assay.

Cox models were used to estimate the association between postpartum adherence and the rate of breastmilk HIV-1 transmission by 38 weeks of age.

RESULTS

Table 1. Baseline characteristics of 1479 mother-infant pairs.

	N	(%)
Antiretroviral randomization		
Maternal antiretroviral	725	(49)
Infant nevirapine	754	(51)
Nutritional randomization		
No supplement	733	(50)
Received supplement	746	(50)
Mothers:		
Age (years)		
15-25	720	(49)
26-35	680	(46)
36-45	76	(5)
Education		
Primary school only	941	(64)
More than primary school	536	(36)
Married		
No	110	(7)
Yes	1369	(93)
Parity		
0	193	(13)
>=1	1280	(87)
CD4+ count per mm^3		
200-350	450	(30)
351-500	478	(32)
>500	551	(37)
Hemoglobin (g/dl)		
< 11	783	(53)
>= 11	696	(47)
ARV Regimen†		
Nevirapine based	20	(3)
Nelfinavir based	124	(18)
Lopinavir/ritonavir based	556	(79)
Infants:		
Sex		
Female	752	(51)
Male	727	(49)
Birth weight (kg)		
<2.5	106	(7)
>=2.5	1370	(93)

† Among those randomized to maternal ARV

Between 22-40% of mother-infant pairs at any given interval were <90% adherent using pill count and bottle weight.

Among mother-infant pairs with complete pill count and bottle weight information (n=501), 146 (29%) were always ≥ 90% adherent and 35 (7%) were never ≥ 90% adherent. No variables were significant predictors of adherence at all time points.

5-10% of mothers at any given interval self-reported missing ≥ 1 dose of maternal or infant ARV medication over the last 3 days.

Having ≥ 90% pill count or bottle weight adherence was associated with a 52% (95% CI 3-76%) relative reduction in the adjusted rate of HIV-1 transmission by 38 weeks of age, compared with having <90% adherence.

Reporting missing no pills in the prior 3 days (100% self-reported adherence) was associated with a 67% (95% CI 22-86%) relative reduction in the adjusted rate of HIV-1 transmission, compared with those self-reporting <100% adherence in the prior 3 days.

Associations between adherence and a composite outcome of breastmilk HIV-1 transmission or infant death by 38 weeks of age did not appreciably differ from those using only HIV-transmission as the outcome.

Table 2. Adherence as a risk factor for breastmilk HIV-1 transmission 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)
Pill Count or Bottle Weight Adherence								
≥ 90% adherent vs. < 90% 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)
Self-reported Adherence								
100% adherent vs. < 100% adherent	0.40	(0.17, 0.94)	0.33	(0.14, 0.78)	0.29	(0.11, 0.79)	0.26	(0.09, 0.71)

*Adjusted for study arm, time-dependent breastfeeding status, and the following baseline maternal characteristics: continuous age, CD4+ category, and dichotomous hemoglobin

CONCLUSIONS

Antiretroviral adherence was associated with a 52-67% relative reduction in the rate of breastmilk HIV-1 transmission by 38 weeks of age.

Being able to predict who will be non-adherent would help in developing tailored and targeted adherence interventions, and to intervene before transmission occurs. We found no baseline covariates to be consistently associated with non-adherence in our study, therefore a more generic intervention that is simple and can be applied to everyone may be required in some settings.

The extent of non-adherence in this heavily monitored clinical trial setting has important implications for adherence counseling messages, antiretroviral resistance concerns, and local PMTCT program planning efforts.

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