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## Stopping the Control Arm in Response to the DSMB: Mother's Choice of HIV Prophylaxis during Breastfeeding in the BAN Study

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### Abstract

The Data and Safety Monitoring Board (DSMB) for the Breastfeeding, Antiretrovirals, and Nutrition study, a clinical trial aimed to prevent postnatal HIV transmission, recommended halting randomization to the enhanced standard-of-care (control) arm. The 67 mother-infant pairs on the control arm and less than 21 weeks postpartum at the time of the DSMB recommendation were read a script informing them of the DSMB decision and offering them the the maternal or infant antiretroviral interventions for the remainder of the 28-week breastfeeding period. This paper describes the BAN study response to the DSMB decision and what the women on the control arm chose, when given a choice to start the maternal or infant antiretroviral interventions.

### Keywords

Postnatal HIV transmission; breastfeeding; antiretorival prophylaxis

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

## Introduction

Breast milk transmission accounts for almost half of the estimated 420,000 HIV infections among children, annually [1]. Most of these infections occur in sub-Saharan Africa, where replacement feeding from birth is neither feasible nor safe due to cost, lack of a safe water supply, and increased risk of infant morbidity and mortality [2, 3].

Prevention of HIV transmission during breastfeeding was evaluated in the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study that randomized mothers and their infants to one of three study arms—with 28-weeks of postnatal antiretroviral prophylaxis given to the mother, infant, or neither [4, 5]. In March 2008, the Data and Safety Monitoring Board (DSMB) overseeing the BAN study recommended halting enrollment to the control arm based on interim findings that HIV transmission was significantly reduced among infants on one of the antiretroviral intervention arms compared to the control arm. The BAN Study stopped enrollment to the control arm, and all women who were on that arm and less than 21 weeks postpartum were offered the maternal or infant antiretroviral interventions for the remainder of the 28-week breastfeeding period. Thus, the BAN Study provides a case study in how to respond to a DSMB recommendation and offers an opportunity to evaluate women's choice regarding initiation of antiretroviral prophylaxis for prevention of postnatal HIV transmission.

## Methods

At an urban healthcare facility in Lilongwe, Malawi, the BAN Study enrolled HIV-infected mothers who met prenatal and postnatal screening criteria ([www.thebanstudy.org](http://www.thebanstudy.org); ClinicalTrials.gov number, NCT00164736) [4, 5]. The prenatal criteria included  $\geq 14$  years of age, CD4 cell count  $\geq 250/\text{mm}^3$  ( $\geq 200/\text{mm}^3$  before July 24, 2006), hemoglobin  $\geq 7$  g/dl, alanine aminotransaminase  $< 2.5$  times the upper limit of normal, and no serious complications of pregnancy. The postnatal criteria included infant birth weight  $\geq 2000$  g, no severe congenital malformations or other conditions incompatible with life, and no maternal condition which would preclude initiation of the antiretroviral prophylaxis. To prevent intrapartum HIV transmission, all mothers and their infants received a single dose of nevirapine at delivery, the standard of care at the time, and daily zidovudine and lamivudine for one week postpartum [6, 7]. Within 7 days of delivery, mother-infant pairs were randomized according to a factorial design to one of two nutritional study arms to prevent maternal depletion and one of three postnatal antiretroviral arms—with 28 weeks of antiretrovirals given to the mother, infant or neither—to prevent HIV transmission during breastfeeding. The maternal antiretroviral regimen was a standard triple drug regimen. The infant regimen was 28 weeks of daily nevirapine syrup with dosage increasing with age. All enrolled participants received a family maize supplement, medical care, and counseling on rapid breastfeeding cessation from 24 to 28 weeks. The mother-infant pairs were followed for up to 14 postpartum visits through 48 weeks after delivery. Infants were tested for HIV infection at birth and weeks 2, 12, 28 and 48, and those who were HIV positive were referred for care.

On March 26, 2008, an independent DSMB of the National Institute of Allergy and Infectious Diseases met and reviewed interim results from the first 1,857 mother-infant pairs who had received treatment assignment. The report from this meeting stated that 1) the HIV transmission rate was significantly higher among infants on the control arm compared to infants on one of the antiretroviral intervention arms (later found to be the infant nevirapine arm) and 2) the DSMB recommended stopping enrollment to the control arm, but continuing randomization to both the antiretroviral intervention arms. The BAN study implemented the DSMB recommendations on March 27, 2008. In addition, the BAN Study team offered

mothers currently on the control arm and less than 21 weeks postpartum the choice of the maternal or infant antiretroviral intervention through 28 weeks postpartum. Investigators prepared a script, in local Chichewa, explaining the DSMB recommendations (English translation shown in Appendix). The revised protocol was approved by the Malawi National Health Science Research Committee and institutional review boards at University of North Carolina at Chapel Hill and the U.S. Centers for Disease Control and Prevention. Beginning April 14, 2008, women were read the script informing them of their choice to stay on the control arm or initiate one of the two antiretroviral interventions, and specimens were collected to determine maternal CD4 count and infant HIV status. The mothers returned one week later. Mother-infant pairs with either a maternal CD4 count  $<250$  cells/ $\mu$ l or an HIV-infected infant were referred for care, but remained in study follow-up, while the remaining mother-infant pairs were offered their chosen intervention until 28-weeks postpartum or breastfeeding cessation, whichever occurred first.

Exact methods were used to determine factors associated ( $p<0.05$ ) with choosing an antiretroviral intervention over remaining on the control arm in univariate logistic regression using SAS version 9.2. Maternal factors evaluated were age group, education, marital status, parity, CD4 count at screening, body mass index at 4 weeks post-partum, and occurrence of clinical or laboratory serious adverse events [5]. Infant characteristics evaluated were history of a laboratory or clinical adverse event and age in weeks and weight-for-length z-score at the time of decision.

## Results

On March 26, 2008, 97 mother-infant pairs were on the control arm and within the 28-week postpartum intervention period (Figure 1). Of these, 26 were beyond 21 weeks postpartum and 4 were lost to follow-up prior to April 14, 2008. Given the choice to switch to either the maternal or infant antiretroviral intervention, about half (47.8%,  $n=32$ ) chose to stay on the control arm. Mothers who chose an antiretroviral intervention ( $n=35$ ) were significantly more likely to choose the maternal (85.7%) over the infant (14.3%) regimen ( $p<0.001$ ).

None of the maternal factors considered were associated with choosing an antiretroviral intervention (Table 1). Although not significant, a higher proportion of the women who chose an intervention (48.6%,  $n=17$ ) had more than a primary school education compared to those who chose to remain on the control arm (28.1%,  $n=9$ ). Neither the mother's CD4 count at screening nor her experience of an adverse event postpartum was associated with choosing an antiretroviral intervention.

The odds of a mother choosing an antiretroviral intervention decreased 20% for each week of infant age ( $p<0.001$ ) (Table 1). Infant weight-for-length at the time of the choice was also associated with choosing an antiretroviral intervention ( $p=0.002$ ). Mothers of infants with higher weight-for-length were more likely to choose an intervention compared to mothers of infants with lower weight-for-length (OR=2.33 for one z-score difference in weight-for-length). Age and weight-for-length remained significant in a multivariable model, adjusting each variable for the other (age  $p$ -value =0.001; weight-for-length  $p=0.006$ ). Serious adverse events among infants prior to mothers choosing whether to switch to an antiretroviral intervention was not associated with the mother's decision.

## Discussion

Our study team responded swiftly to the DSMB recommendations but faced the hurdle of what to do with women already randomized to the control arm. We decided to inform the women and offer them a choice. Almost half of the mothers in the BAN study who were

offered the maternal or infant antiretroviral interventions chose to remain on the control arm. Mothers were more likely to choose an intervention if they were in the earlier postpartum period, with a longer time remaining for breastfeeding and prophylaxis use. The only other independent factor associated with choosing an intervention was infant weight-for-length, which may be an indicator of general well-being of the infant and potentially their mother. Initiation of the BAN study interventions at delivery has demonstrated efficacy for prevention of HIV transmission during breastfeeding [5], but the effectiveness of these regimens when started later in the postnatal period remains unclear. Women enrolled in the BAN study were receptive to randomization to an antiretroviral intervention, and when given the choice to start an intervention, they may have intuitively chosen what makes sense scientifically: the less time remaining on the study, the lower potential benefit of the antiretroviral prophylaxis compared to the risk for side effects and resistance upon stopping.

Among mothers choosing an intervention, significantly more chose the maternal regimen. Knowledge of the benefits of antiretroviral therapy for treatment of HIV disease may have increased the motivation for the maternal regimen. Alternatively, mothers may prefer that they assume any risk of antiretroviral prophylaxis rather than their infants. To better understand mothers' motivations, future research should ask women why they prefer one method over another.

## Conclusions

Early stopping of randomization to a control arm upon evidence for clinical benefit of an intervention arm in a factorial design creates ethical and scientific difficulties as well as opportunities. Foremost, investigators must reassess the best interests of the participants on the control arm and rapidly respond accordingly. If investigators decide to offer control participants the option of study interventions, they can evaluate participant preference. The World Health Organization recently issued new guidelines for the prevention of mother-to-child transmission recommending the provision of antiretrovirals to the mother or infant during breastfeeding to prevent postnatal HIV transmission [8]. The BAN study suggests that, when given the choice of postnatal antiretroviral prophylaxis, mothers may prefer the maternal regimen.

## Abbreviations

<b>DSMB</b>	Data Safety and Monitoring Board
<b>BAN</b>	Breastfeeding, Antiretrovirals, and Nutrition Study

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The BAN Study was carried out in accordance with *the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans*.

The BAN Study Team:

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## Appendix

“Dear BAN Study Participant:

Thank you for taking part in this important study. UNC Project appreciates your help. As you know, we are gathering information so we can better understand HIV infection. Part of this study is trying to find the best way to prevent your baby from getting HIV through breastfeeding. No one at present knows the best way to protect babies when the mother is infected with HIV. In BAN all mothers get one dose of Nevirapine at delivery. Also, all mothers and babies get 7 more days of HIV medicines. This is to prevent the baby from getting infected with HIV at birth and in the first 7 days of breastfeeding.

In BAN we are studying whether there are ways of preventing your baby from getting HIV. We do this by either giving HIV medicines to you or your baby or neither after the first 7 days. For the last two and a half years, an independent committee has been looking at our results on a regular basis. They are looking to see if one of those groups is doing better than the other. On March 26<sup>th</sup> 2008, they met and decided that we should no longer put mothers or infants in the group where neither receives extra medicines. Instead, they should be offered the chance to be in one of the other groups. They decided this because there is less chance of the baby getting HIV from breastmilk when either the mother or infant take medicine during breastfeeding. Women and infants who take these medicines can become sick from them. However, the benefit of taking the medicines is more than the risk of becoming sick. Please remember, babies who get the Nevirapine dose at delivery with 7 days of HIV medications have a smaller chance of getting HIV compared to the Malawi standard of only taking a single dose of nevirapine.

Since you were in the group that only took HIV medicines for the first 7 days, you can now choose between one of these three options:

1. You can continue to be followed on the study without you or your baby starting the new medicines. This will mean there is a small risk of your baby getting HIV through the breast milk but no side effects from the medicines.

OR

2. You can begin giving your baby nevirapine syrup until you stop breastfeeding or 28 weeks whichever comes first. There may be a smaller risk of your baby getting HIV. However, there is a small chance the medicines may not agree with your baby and may make him sick.

OR

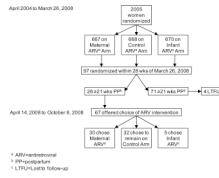
3. You can begin taking the HIV medicines Combivir (1 tablet) and Aluvia (2 tablets). You would take these medicines each twice a day until you stop breastfeeding or 28 weeks, whichever comes first. This will mean that your baby may have a smaller chance of getting HIV. But you will have a small chance of the medicines not agreeing with you and could make you sick.

The chance of your child getting HIV depends on how long you breastfeed. It also depends on how long you will keep breastfeeding. If your child is already 24 weeks switching may not make a difference since the child would be stopping breast feeding soon anyway.

If you have understood this letter, we ask you to sign it. It states that you understand this information. Also, please circle your choice.”

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**Figure 1.**  
Implications of halting enrollment to the control antiretroviral arm of the BAN Study.



**Table 1**

Maternal and infant characteristics of mother-infant pairs who chose an antiretroviral intervention compared to those remaining on the control arm in the BAN Study.

	Number Choosing to:		Odds Ratio (95% CI) <sup>a</sup>	P-value <sup>a</sup>
	Start Antiretrovirals	Remain on Control Arm		
<b>Maternal Factors<sup>b</sup></b>				
Age				0.68
< 23 years	14	10	Ref	
23 – 27 years	9	11	0.59 (0.15, 2.26)	
> 27 years	12	11	0.78 (0.21, 2.86)	
Marital status				1.00
Other	2	1	Ref	
Married	33	31	0.54 (0.00, 10.80)	
Total number of pregnancies				0.28
1	3	4	Ref	
2	14	7	2.57 (0.33, 22.82)	
3+	18	21	1.14 (0.17, 8.83)	
Education level of mother				0.14
≤ Primary education	18	23	Ref	
> Primary education	17	9	2.38 (0.78, 7.63)	
BMI 4 weeks postpartum				0.58
< 21.5 kg/m <sup>2</sup>	10	10	Ref	
21.5 – 24 kg/m <sup>2</sup>	12	14	0.86 (0.23, 3.21)	
> 24 kg/m <sup>2</sup>	13	8	1.61 (0.40, 6.73)	
BMI at time of choice				0.42
< 21.5 kg/m <sup>2</sup>	10	11	Ref	
21.5 – 24 kg/m <sup>2</sup>	12	14	0.94 (0.26, 3.47)	
> 24 kg/m <sup>2</sup>	13	7	2.00 (0.49, 8.66)	
CD4				0.46
< 400	11	12	Ref	
400 – 500	10	12	0.91 (0.24, 3.42)	
> 500	14	8	1.88 (0.50, 7.46)	
Maternal SAE <sup>c</sup> prior to choice				0.66
No	33	29	Ref	
Yes	2	3	0.59 (0.05, 5.53)	
<b>Infant Factors</b>				
Age of infant at choice (weeks)			0.80 (0.69, 0.90)	<0.001
Weight-for-length <sup>d</sup> at choice			2.33 (1.26, 6.64)	0.002
Infant SAE <sup>c</sup> prior to choice				0.56
No	26	26	Ref	
Yes	9	8	1.49 (0.41, 5.88)	



<sup>a</sup> Odds ratios, confidence intervals (CIs), and p-values were generated by exact logistic regression with each factor as the sole covariate.

<sup>b</sup> Maternal characteristics assessed at baseline (enrollment) visit unless stated otherwise.

<sup>c</sup> SAE = serious adverse event.

<sup>d</sup> Weight-for-height Z-Score.