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Effect of postnatal HIV treatment on clinical mastitis and breast inflammation in HIV-infected breastfeeding women

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Abstract

Background—The relationship between mastitis and antiretroviral therapy among HIV-positive, breastfeeding women is unclear.

Methods—In the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study, conducted in Lilongwe, Malawi, 2369 mother-infant pairs were randomized to a nutritional supplement group and to one of three treatment groups: maternal antiretroviral therapy (ART), infant nevirapine (NVP) or standard of care for 24 weeks of exclusive breastfeeding and 4 weeks of weaning. Among 1,472 HIV-infected women who delivered live infants between 2004 and 2007, we estimated cumulative incidence functions and sub-distribution hazard ratios (HR) of mastitis or breast inflammation comparing women in maternal ART (n=487) or infant nevirapine (n=492) groups to the standard of care (n=493). Nutritional supplement groups (743 took, 729 did not) were also compared.

Results—Through 28-weeks post-partum, 88 of 1472 women experienced at least one occurrence of mastitis or breast inflammation. The 28-week risk was higher for maternal ART (RD 4.5, 95% confidence interval (CI): 0.9, 8.1) and infant NVP (RD: 3.6, 95%CI: 0.9-6.9) compared to standard of care. The hazard of late-appearing mastitis or breast inflammation (from week 5-28) was also higher for maternal ART (HR: 6.7, 95%CI: 2.0, 22.6) and infant NVP (HR: 5.1, 95%CI: 1.5, 17. 5) compared to the standard of care.

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A complete list of institutions and individuals involved in the BAN study is shown in the online supplemental material (appendix 2).

Conclusions—Mastitis or breast inflammation while breastfeeding is a possible side effect for women taking prophylactic ART and women whose infants take NVP, warranting additional research in the context of postnatal HIV transmission.

INTRODUCTION

Mastitis is defined as inflammation of the breast, generally associated with lactation.[1] Mastitis ranges in severity from mild, asymptomatic inflammation that is usually non-infectious in origin, to severe, clinically evident mastitis, which manifests as redness, swelling of the breast, fever or systemic infection. Among all breastfeeding women, incidence varies widely, from 2 to 30%.[2–4] Mastitis is an unwelcome complication for all breastfeeding women, but especially for HIV-infected women. HIV-infected and uninfected women who breastfeed are not differentially affected[5,6], but HIV-infected women with mastitis are more likely to transmit HIV to their infants compared to women without mastitis if they are not taking antiretroviral therapy (ART). [7–13]

Mastitis can arise from factors associated with maternal health, infant health or both. Maternal causes of mastitis include poor breastfeeding practices due to insufficient knowledge or education about breastfeeding, blocked ducts, cracked nipples[14,15] or a compromised maternal immune system, which can cause mastitis through systemic mechanisms that increase susceptibility to infection or reduce milk supply in response to poor nutrition, stress and maternal fatigue.[2,14,16] Infant factors associated with mastitis include poor latching and inadequate suckling, both of which could be exacerbated by poor infant health. Some causes of mastitis, including insufficient breast drainage, change in frequency of feedings and mixed feeding,[14,15] are difficult to attribute to either maternal or infant origin.

The relationship between mastitis and either maternal ART or daily infant nevirapine (NVP) while breastfeeding has yet to be established. The objective of this study was to describe the incidence, severity, and timing of mastitis among breastfeeding women who are HIV-infected and to evaluate whether maternal ART, daily infant NVP or a nutritional supplement influence patterns of incident mastitis. We conducted an exploratory analysis comparing the risk of mastitis between women receiving maternal ART, women whose infants are taking NVP and women in the standard of care group. We expected that women taking a nutritional supplement to support exclusive breastfeeding to be healthier, so we also hypothesized that mastitis or breast inflammation would be lower for mother-infant pairs taking a nutritional supplement compared to those who were not.

METHODS

Participants and Study Design

We performed a secondary analysis of data from the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study. The BAN study was a randomized controlled trial among HIV-infected women and their breastfeeding infants.[17] Enrollment for BAN took place in Lilongwe, Malawi between April 2004 and September 2009 and mother-infant pairs were followed for 48 weeks after delivery. Mothers and infants received peripartum antiretroviral

prophylaxis at delivery and for 7 days after birth. Mother-infant pairs who met primary and secondary eligibility criteria[17] were assigned to one of six treatment groups using a 3-by-2 factorial design and permuted-block randomization. They were randomized to one of three antiretroviral treatment groups and to a nutritional supplement group. Treatment lasted for the duration of breastfeeding. Women were counseled to exclusively breastfeed for the first 24 weeks, then rapidly wean between 24 and 28 weeks. Women received guidance about exclusive breastfeeding consisting of two antenatal counseling sessions, counseling and lactation consultation at delivery, reminders at each study visit, and all women were visited at home for counseling between 24 and 28 weeks during the breastfeeding cessation period. Women were followed for 48 weeks, barring dropout or maternal or infant death.

As in previous analyses from the BAN study, mother-infant pairs whose infants tested HIV-positive in the first 2 weeks of life were excluded. We also excluded mothers who delivered after July 14, 2007, when data collection from the breast exam ceased. For treatment and nutritional group analyses, mother-infant pairs were excluded if they if they had mastitis at delivery or if they did not have any visits after randomizaiton to characterize infant breastfeeding status. All women provided informed consent. The protocol was approved by the Malawi National Health Science Research Committee and the institutional review boards at the University of North Carolina at Chapel Hill and the US Centers for Disease Control and Prevention.

Data Collection and Measurements

Treatment Groups—Mothers in mother-infant pairs randomized to maternal ART (mART) received combination therapy with three drugs twice daily through 28 weeks—300mg of Zidovudine (ZDV), 150mg of 3TC (lamivudine) and a third drug. The third drug changed from 200mg nevirapine (NVP) for the first 39 women, 1250 mg nelfinavir for the next 134 women and Kaletra (400mg lopinavir plus 100mg ritonavir) for the remaining women. Those randomized to the infant NVP group received a daily dose of NVP for infants, which increased according to infant age, ranging from 10 to 30 mg per day. Pairs in the standard of care group did not receive any treatment after 7 days postpartum, consistent with Malawian guidelines at the time. Unless explicitly stated, “treatment groups” refers to both maternal ART or infant NVP groups, usually in comparison to the standard of care.

Nutritional Supplement—Women were also randomized to take or not take a nutritional supplement, which was a high-energy, high protein food supplement with 100% of the recommended dietary allowance of micronutrients.[18]

Mastitis or Breast Inflammation while Breastfeeding—Our outcome measure indicated whether women had mastitis or breast inflammation while breastfeeding. For all women, a breast exam was scheduled for 2, 6, 12, 18, 24 and 28 weeks postpartum or if they answered “yes” to a screening question at a non-breast exam visit until July 2007. Women were categorized as having mastitis or breast inflammation while breastfeeding if they had a diagnosis of clinical mastitis or breast infection reported as an adverse event (AE); if during a breast exam, their breasts were discolored or shiny, hard, lumpy, hot, painful or tight; or if they had tender axilla nodes, cracks, blood, rash, exudate, open or oozing sores on breast or

areola (Appendix 1). Over the course of the BAN study the breast exam was increasingly not conducted during expected study visits unless breast health issues were indicated at screening and eventually the breast exam was stopped entirely in July 2007. As a consequence, women were sometimes missing data from a breast exam visit. Based on the BAN protocol and implementation before July 2007, we assumed women without a breast exam at an expected visit did not have mastitis. The average case of severe mastitis lasts 2 weeks,[19] so the start date for mastitis or breast inflammation was set to two weeks before the study visit if visits were 4 or more weeks apart. If visits were less than 4 weeks apart, the start date was the midpoint between two study visits.

Breastfeeding Cessation Visit—Breastfeeding cessation date was the first visit where women indicated that they stopped nursing with no evidence of breastfeeding in subsequent visits (Appendix 1).

Statistical Analysis

We estimated the cumulative incidence of the first occurrence of mastitis or breast inflammation while breastfeeding and evaluated the type and timing of symptoms over time. Participants were randomized to one of six arms in the original study and we assumed exchangeability between groups for this nested study. For all treatment analyses, the standard of care group was the referent and we assumed adherence to assigned intervention arms.[20]

To account for competing risks (i.e., breastfeeding cessation, infant or maternal death), the proportional sub-distribution hazards model was employed to estimate hazard ratios of mastitis or breastfeeding inflammation while breastfeeding.[21–23] The proportional hazards assumption was tested by adding an interaction term between group and time. The proportionality assumption was violated for both treatment and nutritional group analyses ($P < 0.01$), so an interaction term with time and type of treatment was included in the final models. Since causes of early and late mastitis differ, a dichotomous interaction term for time (0 to 4 weeks, or 5-28 weeks) was included allowing the treatment effect in the first 4 weeks to differ from weeks 5-28. Cumulative incidence was estimated using the Breslow estimator of the cumulative sub-distribution hazard function.[21–23] Risk differences (RD) were calculated using cumulative incidence estimates and confidence intervals were computed using the bootstrap. In the hazards models, baseline viral load and baseline CD4 count were assessed as potential effect measure modifiers, using an alpha=0.15 threshold for interaction term retention. Person-time after 28 weeks from delivery and after July 14, 2007 was (non-informatively) administratively right-censored. Women were considered lost to follow-up if the date of their last infant feeding questionnaire (to determine breastfeeding status) occurred prior to the end of the 28-week follow-up period.

Sensitivity Analyses—All analyses were repeated using a different definition of mastitis that was more severe than in the primary analyses (Appendix 1). The narrow definition identified mastitis occurrences diagnosed at a routine postpartum visit. We also conducted a sensitivity analysis using a multiple imputation approach to examine possible bias associated with the assumption that women with missing outcome data did not have mastitis. For the

primary analyses, missing outcome data were assumed to be missing, such that women without mastitis were more likely to be missing breast exam data. The multiple imputation analysis assumed data were missing at random, so women without a breast exam had the same probability of mastitis as women with a similar covariate distribution who had a breast exam. Values of the missing outcome (mastitis) were imputed using covariates selected a priori, including a breast health screening question (any breast health issues, none), treatment arm, nutritional supplement, visit, age (continuous), baseline CD4 count (continuous), baseline plasma viral load (continuous, log10 transformed and if undetectable, set to the lower limit of detection minus one), detectable viral load (detected, not detected), marital status (married, not married) and parity (1, ≥ 2). Hazard ratios were estimated separately for each imputation dataset and combined across datasets to account for uncertainty within- and between- imputations.

RESULTS

Among 2369 mother-infant pairs enrolled and randomized to participate in the BAN study, 1554 infants were delivered before July 7, 2007 and eligible for the present study. We excluded 82 pairs whose infants were HIV-positive within their first 2 weeks, leaving 1472 mother-infant pairs in our descriptive analyses of mastitis and breastfeeding signs and symptoms. Analysis by treatment group consisted of 1317 mother-infant pairs since we additionally excluded 155 (10%) women without a follow-up visit after randomization to obtain breastfeeding status. Over the 28-week follow-up period, 194 (15%) mother-infant pairs were lost to follow-up, 50 (4%) infants acquired HIV and 52 (4%) pairs experienced a competing event (12 infants died, 1 mother died and 39 stopped breastfeeding before the rapid weaning period at 24 weeks).

For 92.8% of visits where a breast exam was supposed to occur, information about the health of women's breasts was available from a screening question, the breast exam or both. For visits where a breast exam was supposed to occur, many women (50.8%) did not receive a breast exam. Frequency of missing breast exam data was similar for all treatment arms, over all expected visits. For those who were screened about their breast health history, most (99.8%) who were missing breast exam data reported no breast pain or discomfort at screening.

Most women breastfed for at least 24 weeks, many had two or more previous children (62%), and the median age was 25 (Table 1). During the 28-week study period, 102 women had at least one occurrence of mastitis or breast inflammation while breastfeeding. We focused on the first occurrence of mastitis or breast inflammation while breastfeeding. Most symptoms occurred either in the first few weeks after delivery or near the end of the study period (Figure 1). The most common symptoms of discomfort associated with breastfeeding identified by study nurses during the breast exam were breasts that were lumpy, hard, cracked, painful, hot, discolored or shiny. For women in the maternal ART group, occurrence of mastitis was highest for women on NVP-based regimens (20%, 6/30), followed by women taking Combivir only (16%, 3/19), then Nelfinavir-based regimens (10%,11/113) with the lowest incidence among those taking a Lopinavir-Ritonovir-based regimens (5%, 14/268).

The 4-week risk of mastitis or breast inflammation while breastfeeding was 3.8% (95%CI: 2.8, 4.9) and the 28-week risk was twice as high. The 28-week risk of mastitis or breast inflammation while breastfeeding was higher for women in the maternal ART and infant NVP groups compared to the standard of care (Table 2, Figure 2a). For severe mastitis, the 4-week risk while breastfeeding was 2.5% (95%CI: 1.7, 3.4), but similar for all treatment groups. The 28-week risk of severe mastitis was 5.7% (95%CI: 4.3, 7.1) and higher for maternal ART and infant NVP compared to the standard of care.

In the first 4 weeks after delivery, there were no differences in the hazard of mastitis or breast inflammation across all treatment groups (Table 3). After the first 4 weeks, the hazard was higher in the maternal ART and infant NVP groups compared to the standard of care (Table 3). We examined modification of the effect of assigned treatment group on the outcome by baseline viral load (below and above median) and CD4 count (<350, >350). Women in the maternal ART group had a slightly higher hazard of late mastitis (after 4 weeks postpartum) or breast inflammation while breastfeeding if they had a low baseline CD4 count or high baseline viral load; however, in all cases the interaction terms did not meet the a priori criteria ($p < 0.15$) for inclusion. Moreover, confidence intervals were wide and overlapping the point estimates (results not shown). For the nutritional supplement analysis, neither the 28-week risk (Table 2) nor the hazard (Table 3) of mastitis or breast inflammation while breastfeeding differed between groups.

In our primary analyses, we used a definition of mastitis or breast inflammation that was broader than mastitis generally diagnosed in clinical practice. As a sensitivity analysis, we repeated all analyses with a stricter definition of mastitis, which resulted in a lower overall incidence, but similar trends over time and comparisons between treatment groups and nutritional groups (Table 3). In a multiple imputation analyses for missing outcomes, the 28-week cumulative incidence of mastitis or breast inflammation while breastfeeding was 12.4% (95%CI: 9.6,15.2) and the 28-week risk differences obtained from the imputation analysis were similar in magnitude to estimates in Table 2: maternal ART (RD: 5.6, 95%CI: −0.3,12.5) and infant NVP (RD: 3.5, 95%CI: −1.4, 8.4) compared to the standard of care. Compared to the primary analysis, hazard ratios for early mastitis or breast inflammation from the imputation analysis were similar (maternal ART HR: 1.1, 95%CI: 0.5, 2.2 and infant NVP HR: 1.0, 95%CI: 0.5, 1.9), while late mastitis or breast inflammation findings were closer to the null (maternal ART HR: 2.1, 95%CI: 0.7, 5.7 and infant NVP HR: 1.8, 95%CI: 0.7, 5.0).

COMMENT

We evaluated whether maternal ART or daily infant NVP treatment affected the incidence of mastitis or breast inflammation among breastfeeding, HIV-infected women. To our knowledge, this study is the first to explore the relationship between maternal or infant prophylactic ART, a maternal nutritional supplement and the incidence of mastitis or breast inflammation among breastfeeding, HIV-infected women. The 28-week incidence of mastitis or breast inflammation while breastfeeding was higher among women taking maternal ART and women whose infants took daily NVP compared to women in the standard of care group, where no ART was provided.

The mechanism of action responsible for the elevated 28-week incidence of mastitis or breast inflammation while breastfeeding in both treatment arms is not straightforward, though we have several theories. One possibility is that following initiation of maternal ART, women may have experienced a partial recovery of the immune system in response to maternal ART, though the timing may not line up. With immune reconstitution, which occurs betwen 4-8 weeks after initiation of ART,[24–26] women could be more capable of mounting an inflammatory response to milk stasis, clogged ducts, a bacterial infection or other antigens in the breast. Another theory for women in the maternal ART group comes from the variation in the incidence of mastitis by treatment regimens. The type of maternal ART regimen could influence milk production, the taste of the milk, or the proportion of fat, protein or nutrients contained in breastmilk. For women in the infant NVP group, elevated incidence of late mastitis or breast inflammation could stem from effects of introducing a non-breastmilk substance (i.e., daily NVP). While most infants are considered to be exclusively breastfed if they take medication,[27] it is conceivable that daily NVP in infant saliva could irritate the mother's nipple, or side effects of infant NVP, like oral lesions, conjunctivitis or blistering[28] could affect the quality and frequency of feeding, suckling, latch or other factors associated with mastitis or breast inflammation.

Another possible explanation for higher incidence of mastitis in treatment arms is that the study may have suffered from ascertainment bias. Participants and study staff were not blinded to the treatment arm. Unintentionally, nurses or physicians may have more carefully observed or asked questions about the breast health of mother-infant pairs who were randomized to a treatment arm. Women in the maternal or infant treatment groups could have been looking for treatment-related issues compared to women without an intervention. Alternatively, women not taking treatment may have been more carefully observed or cared for if providers knew they were in a non-treatment arm. Missing outcome data is unlikely to contribute since breast exams were missing with similar frequency across treatment arms and visits. These theories about how maternal or infant prophylactic ART influences mastitis or breast inflammation are speculative and will require additional efforts to disentangle how these biological and design factors influence the incidence of mastitis.

The overall 28-week risk of mastitis or breast inflammation for all enrolled women was 7.5%, which was lower than the 3-month risk (10.0% in Zimbabwe[11]) and the 6-month risk (20% in Zambia[29] and 17% in South Africa[6]) of mastitis in similar cohorts of HIV-infected, African women where a similar definition of clinical mastitis was used. The analysis decision about missing outcome data—that women who were missing breast exam data did not have mastitis—could explain why the observed incidence of mastitis was lower than expected among women enrolled in BAN. In a sensitivity analysis where missing values for mastitis or breast inflammation were imputed with the same probability as women with observed data and similar covariate distributions, incidence estimates were higher, hazard ratios lower and risk differences were similar to the primary analyses. Based on the BAN protocol, communication with study staff and screening data, women who were missing breast exam data were less likely to have breast health issues, so the primary analysis estimates are probably less biased. The estimates from the multiple imputation analysis serve as an upper bound for the incidence of mastitis if the assumptions made about missing data for the primary analysis were misled.

For women in this BAN sub-study, the hazard of mastitis or breast inflammation was highest immediately after delivery, decreased quickly during the first 4 weeks of breastfeeding and stayed low for the remainder of the 28-week follow-up period. The timing of mastitis or breast inflammation in our population was similar to previous estimates where mastitis was most common in the first month after delivery.[3,30] Several studies, with similar follow-up, identified a spike in mastitis between 14-28 weeks[29,31] in relation to mixed feeding or weaning. We did not see a late spike in mastitis, but BAN protocol instructed women to rapidly wean between 24-28 weeks and considered completion of breastfeeding cessation to be a competing risk. While the hazard of mastitis and breast inflammation while breastfeeding decreased at the end of follow-up, individuals who had an event in the last few weeks of follow-up, when solid foods were introduced, had more symptoms than women with mastitis after delivery.

In our cohort, baseline viral load and CD4 count did not modify the effect of treatment on mastitis or breast inflammation, as we hypothesized. We also did not see a modifying effect of nutritional supplementation on the incidence of mastitis or breast inflammation. Others observed similar absence of effects of a nutritional supplement on subclinical mastitis,[5,32,33] with the exception of one instance[34] where healthier (with higher baseline CD4) HIV-infected women who took either of two vitamin supplements (one consisting of vitamin B-complex, C, and E & one consisting of vitamin A + b-carotene) had an increased risk of mastitis.

The BAN study was ideally designed to study the concerns that face HIV-infected, breastfeeding women in the context of lifelong ART in resource-limited settings. As a sub-study of a large, randomized trial, we assumed treatment assignment arms were exchangeable at baseline. BAN also had good retention for a postpartum study in a resource-limited setting, losing only 12% at 28 weeks.[17] However, despite strong retention in BAN overall, this cohort may be subject to selection bias if women who were not included in this sub-study or those who were lost to follow-up had different rates of mastitis compared to women included in this sub-study. Our results may also be subject to bias due to misclassification. The definition of mastitis or breast inflammation while breastfeeding was based on a range of clinical signs and symptoms. We conducted sensitivity analyses with a definition of severe mastitis and while the 28-week incidence was lower, the trends over time and between treatment groups were similar. Even mild inflammation of the breast is associated with transmission of HIV through breast milk. In fact, asymptomatic subclinical mastitis could be responsible for up to 18-21% of all mother-to-child transmission or 50% of postnatal HIV transmission.[35] While sodium/potassium ratios are less susceptible to misclassification, breast milk samples were not available for these analyses.

This study was the first to consider whether maternal ART or infant NVP affects incidence of mastitis or breast inflammation for breastfeeding, HIV-infected women. We conclude that late mastitis may be more problematic for breast-feeding women taking ART and women whose infants are taking antiretroviral prophylaxis. In BAN, women initiated ART did so after delivery. As the standard of care shifts and women have access to lifelong ART beginning in pregnancy, most women will initiate treatment during pregnancy or be taking ART when they become pregnant. The effect of earlier initiation of ART during pregnancy

on incidence of mastitis will have to be monitored. The role of mastitis in this population is relevant, not just for the comfort and nutrition of nursing mothers and babies, but also as it relates to HIV transmission.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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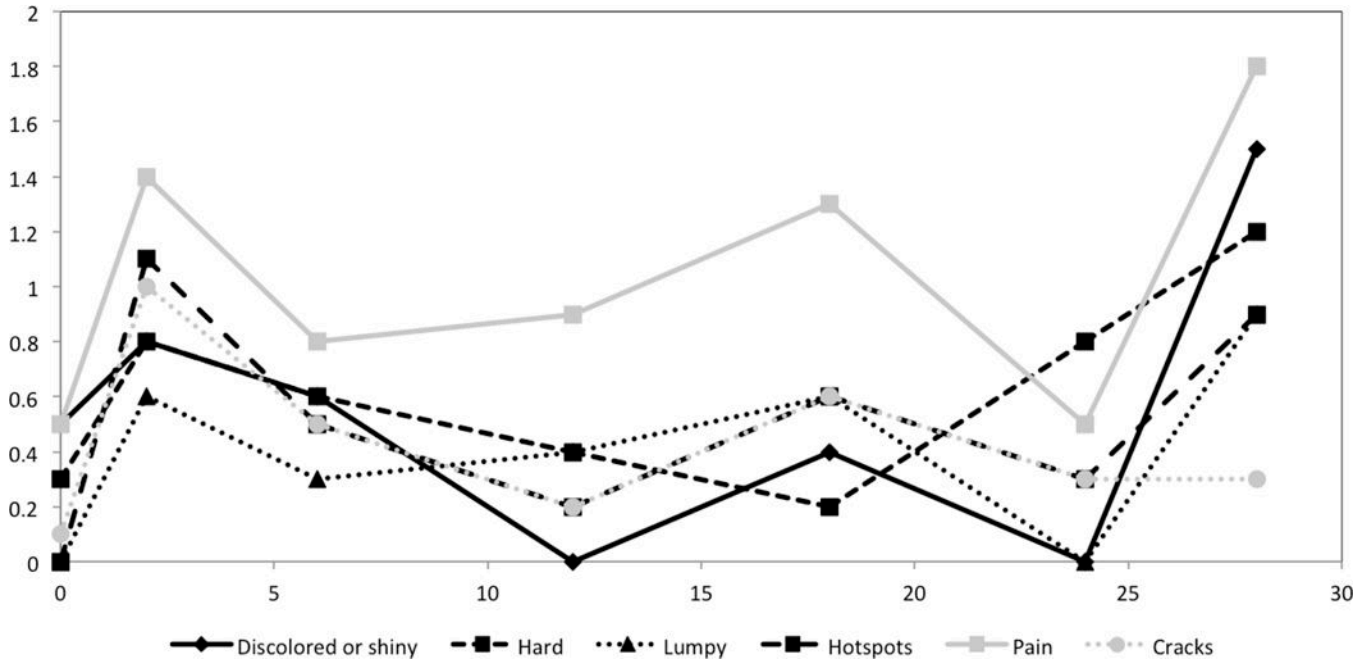

Figure 1.

Prevalence of symptoms of breast inflammation in the first 28 weeks after delivery among HIV-infected breastfeeding women in Lilongwe, Malawi

*Fewer than five women at any given visit presented with the following symptoms, which were not included in the above figure: Tender Lumps, Tender Axilla Nodes, Nipple Bleeding, Nipple Rash, Nipple Exudates, Breast Sores and Areola Sores

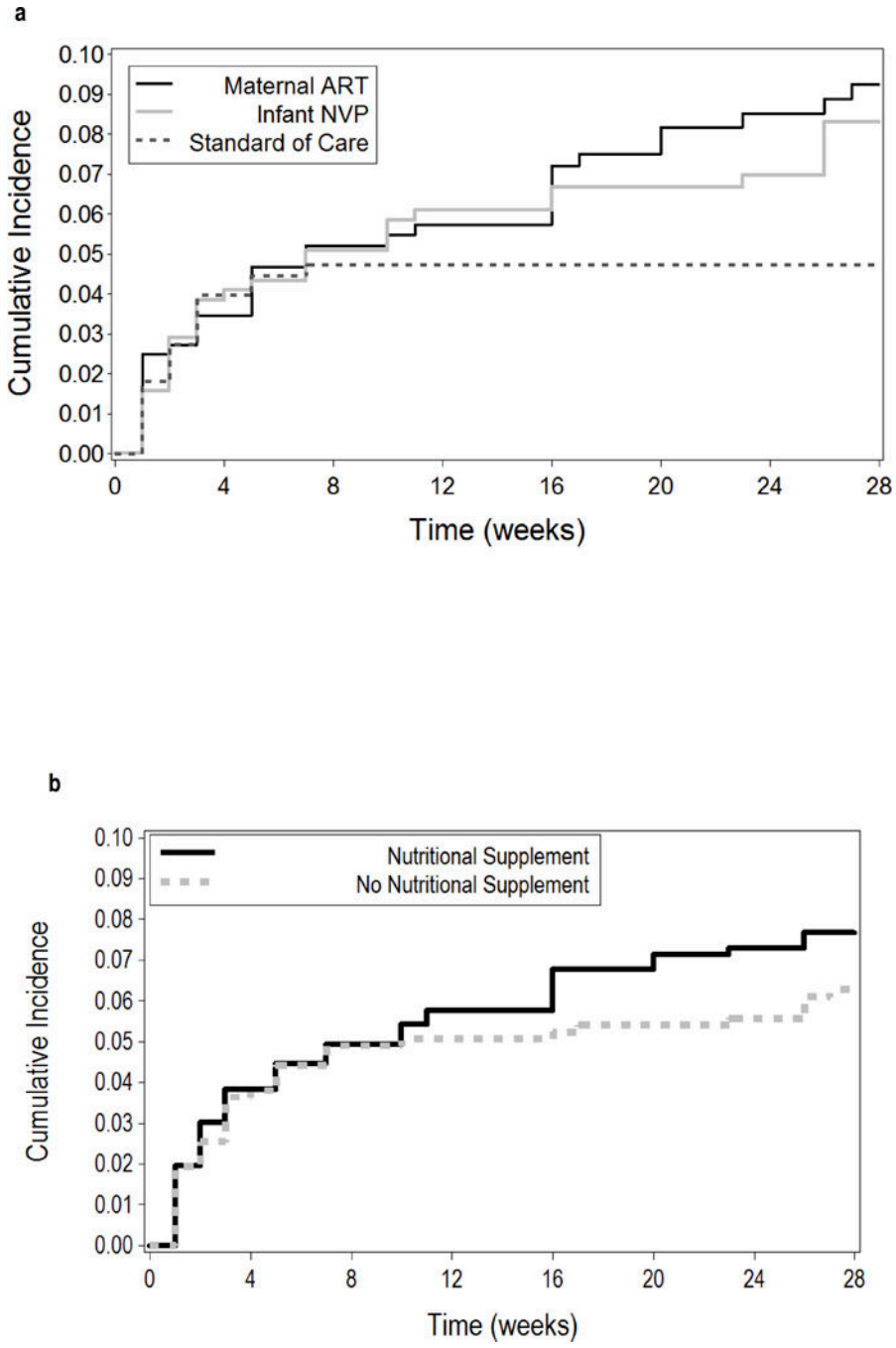

Figure 2.

Cumulative incidence estimates for mastitis or breast inflammation, comparing 2a) maternal ART, infant NVP and standard of care and 2b) nutritional supplement versus no nutritional supplement

Table 1

Characteristics for 1472 women participating in the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study in Lilongwe, Malawi (2004-2007)[1]

	Overall n=1472		**Maternal ART n=487**		**Infant NVP n=492**		**Standard of Care n=493**	
Median (IQR)								
Age	25	(22, 29)	26	(22, 29)	25	(22, 29)	26	(22, 29)
Baseline Maternal CD4	443	(328, 590)	443	(326, 571)	440	(328, 600)	446	(333, 589)
HIV RNA Viral Load (log10)[3]	4.2	(3.7, 4.7)	4.3	(3.8, 4.7)	4.2	(3.7, 4.7)	4.2	(3.6, 3.7)
Number (%)								
Primary Education or More	1298	(88%)	429	(88%)	433	(88%)	436	(88%)
Primiparous	180	(12%)	54	(11%)	71	(14%)	55	(11%)
Married	1350	(92%)	451	(93%)	450	(91%)	449	(91%)
Breastfeeding to at least 24 weeks	1154	(78%)	375	(77%)	395	(80%)	384	(78%)
HIV Transmission to Infant[2]	74	(5%)	23	(5%)	15	(3%)	36	(7%)
Mastitis Occurrences—count								
1	102	(7%)	38	(8%)	40	(8%)	24	(5%)
2+	9	(1%)	3	(1%)	4	(1%)	2	(1%)
Included in the treatment analysis[4]	**1317**	**(90%)**	**436**	**(90%)**	**444**	**(90%)**	**437**	**(89%)**
Followed-up for 28 weeks	1123	(85%)	366	(84%)	382	(86%)	375	(86%)

[1] Data are median(interquartile range) or number(%). Abbreviations: antiretroviral therapy (ART), nevirapine (NVP), human immunodeficiency virus (HIV), ribonucleic acid (RNA)

[2] Infants with inconclusive HIV test excluded.

[3] Baseline plasma HIV viral load RNA log10 copies/mL

[4] Mother-infant pairs were included in the treatment analysis if they delivered after July 14, 2007, when data collection from the breast exam ceased; had mastitis at delivery; or did not have any visits after ranodmizaiton to characterize infant breastfeeding status

Table 2

Risk differences (%) and 95% confidence limits of mastitis or breast inflammation while breastfeeding by treatment group and nutritional supplement group among women enrolled in the BAN study [1]

Weeks After Delivery		4		12		18		24		28	
Treatment Group	Maternal ART	−0.5	(−3.9, 2.9)	1.0	(−2.0, 4.0)	2.8	(−0.5, 6.0)	3.8	(0.3, 7.2)	4.5	(0.9, 8.1)
	Infant NVP	0.1	(−3.0, 3.2)	1.4	(−1.6, 4.3)	1.9	(−1.1, 5.0)	2.3	(−0.8, 5.3)	3.6	(0.3, 6.9)
	Standard of Care	0.0	(Reference)	0.0	(Reference)	0.0	(Reference)	0.0	(Reference)	0.0	(Reference)
Nutritional Supplement	Yes	−0.0	(−2.3, 2.3)	0.7	(−1.9, 3.3)	1.5	(−1.4, 4.3)	1.9	(−1.0, 4.9)	1.5	(−1.7, 4.7)
	No	0.0	(Reference)	0.0	(Reference)	0.0	(Reference)	0.0	(Reference)	0.0	(Reference)

[1] Risk differences were estimated by contrasting cumulative incidence estimates by group. Confidence intervals were estimated using the bootstrap. Mastitis or breast inflammation while breastfeeding includes women who had a diagnosis of mastitis or breast inflammation or, who, upon examination, had breasts that were discolored or shiny, hard, tight, lumpy, hot, bleeding/bloody, painful during the exam, or that had tender axilla nodes, cracks, a rash, exudate, or open or oozing sores on breast or areola.

Table 3

Sub-distribution hazard ratios of mastitis or breast inflammation while breastfeeding, by treatment group and nutritional supplement group[1]

		Early Mastitis (weeks 0 – 4) Hazard Ratios (95% CI)	Late Mastitis (weeks 5-28) Hazard Ratios (95% CI)
Primary Analysis: Mastitis or breast inflammation[2]			
Treatment Group	Maternal ART	0.9 (0.4, 1.8)	6.7 (2.0, 22.6)
	Infant NVP	1.0 (0.5, 1.9)	5.1 (1.5, 17. 5)
	Standard of Care	1.0 (Reference)	1.0 (Reference)
Nutritional Supplement	Yes	1.0 (0.6, 1.8)	1.5 (0.8, 2.8)
	No	1.0 (Reference)	1.0 (Reference)
Sensitivity Analyses: Severe Mastitis[3]			
Treatment Group	Maternal ART	0.8 (0.3, 1.8)	8.0 (1.8, 35.0)
	Infant NVP	0.9 (0.4, 2.0)	7.7 (1.8, 33.3)
	Standard of Care	1.0 (Reference)	1.0 (Reference)
Nutritional Supplement	Yes	1.1 (0.6, 2.3)	1.5 (0.7, 2.9)
	No	1.0 (Reference)	1.0 (Reference)

[1]This cohort consisted of 1317 women enrolled in the BAN study between April 2004-July 7, 2007. To estimate the effect of treatment assignment on mastitis, sub-distribution hazard ratios were estimated and an interaction term between treatment group and time (0-4 weeks vs 5-28 weeks) was included.

[2]Mastitis or breast inflammation while breastfeeding includes women who had severe mastitis or breast infection or had any of the following breast problems: discolored or shiny, hard, lumpy, hot, painful, tight breasts, tender axilla nodes, cracks, blood, rash, exudate, open or oozing sores on breast or areola.

[3]Severe mastitis is defined as breasts that, upon exam, had tender axilla nodes or were discolored or shiny, hard, lumpy, hot or painful during exam.