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Effects of concurrent exposure to antiretrovirals and cotrimoxazole prophylaxis among HIV-exposed, uninfected infants

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Introduction

In settings where pneumonia, diarrhea, and malnutrition are major causes of infant mortality, breastfeeding for 12 months combined with antiretroviral (ARV) and cotrimoxazole preventive therapy (CPT) offers infants of HIV-infected mothers the greatest chance for HIV-free survival and is recommended by the World Health Organization [1]. Clinical trials showing the efficacy of ARV regimens for reduced risk of HIV transmission to breastfeeding infants and those showing the efficacy of CPT against opportunistic infections [2–4] have independently shown good overall safety. However, both maternal and infant antiretroviral and cotrimoxazole prophylaxis have been independently associated with reports of hematologic toxicities, including neutropenia and anemia [5–16]. These conditions, particularly severe anemia, are major causes of morbidity in Malawi and sub-Saharan Africa [17–20]. Given the similar hematologic side-effects for some antiretroviral agents and cotrimoxazole, it is important to evaluate the impact of their concurrent use among HIV-exposed, uninfected (HEU) infants.

We conducted a secondary analysis of data from the Breastfeeding, Antiretrovirals and Nutrition (BAN), a clinical trial of 2,369 mother-infant pairs randomized to 28 weeks of infant nevirapine, maternal ARVs, or neither for the prevention of HIV transmission during breastfeeding (www.ClinicalTrials.gov number NCT00164736) [21]. During the study, new guidelines were issued for the use of CPT in HEU infants. We used data from this randomized ARV design and mid-study implementation of CPT to evaluate the independent

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and concurrent effects of ARV and CPT on the risk of hematologic toxicities, including neutropenia, anemia, and elevated alanine transaminase (ALT) among HEU infants.

Methods

Study enrollment, design and procedures

Infants were enrolled in the BAN trial in Lilongwe, Malawi between March 2004 and January 2010. The BAN study design and primary findings have been reported elsewhere and indicate that the use of either maternal triple ARV prophylaxis or infant nevirapine for 28 weeks is effective in reducing HIV transmission during breastfeeding [21, 22].

From March 2004 to February 2009, the study screened 3,572 ARV-naive, HIV-infected pregnant women attending antenatal clinics in Lilongwe, Malawi, and enrolled 2,369 women who met antenatal and postnatal eligibility criteria. The antenatal criteria were age ≥ 14 years, no serious complications of pregnancy, no prior ARV use, CD4+ count ≥250 cells/μL (≥200 cells/μL before July 24, 2006), hemoglobin ≥ 7g/dL, plasma alanine aminotransferase (ALT) ≤2.5 times the upper limit of normal, and planning to breastfeed. The postnatal criteria were infant birth weight ≥2,000 g, no infant or maternal condition precluding study interventions, and the mother's acceptance of the perinatal antiretroviral regimen and treatment assignment within 36 hours of delivery.

All mothers in labor and their newborn infants received a single dose of oral nevirapine and 7 days of zidovudine, 300 mg, plus lamivudine, 150 mg twice-daily from the onset of labor for the mothers and zidovudine (2 mg per kilogram of body weight) and lamivudine (4 mg per kilogram) twice-daily for the infants. Mother-infant pairs who met eligibility criteria were randomly assigned to one of three ARV intervention arms to be initiated at birth and continued for 28 weeks or until breastfeeding cessation, if earlier: 1) infant nevirapine, 2) maternal triple-drug antiretroviral regimen, or 3) control (no mother or infant treatment). Using a standardized protocol derived from the WHO Breastfeeding Counseling Training Manual [23], all mothers were individually counseled to breastfeed exclusively for the first 24 weeks postpartum and then wean rapidly between 24 and 28 weeks. Due to overwhelming evidence of the benefit of the treatment arms, the Data Safety and Monitoring Board halted enrollment to the control arm after 668 mother-infant pairs had been assigned; participants in the control arm at that time were given the option of switching to the infant nevirapine or maternal ARV arms for the remainder of the 28-week intervention period.

Mother-infant pairs were followed at 1, 2, 4, 6, 8, 12, 18, 21, 24, 28, 32, 36, 42, and 48 weeks post-partum, with the last pair completing follow-up in January, 2010. Infants who tested HIV positive were disenrolled and referred for care. A full blood count and ALT testing was done at birth, 2, 6, 12, 18, 24, 28, 36 and 48 weeks. Data capturing anthropometrics, vital signs, illnesses and hospitalizations since the last visit, current symptoms, and physical exam findings were collected at all follow-up visits. Participants were advised to return to the clinic between visits to receive treatment if the woman or child was ill. Medical care was provided according to the standard of care at the study clinics and participants were provided with insecticide-treated bed nets. Clinical and laboratory adverse events identified at regular study visits and interim sick visits were documented and graded

according to toxicity tables from the National Institute of Allergy and Infectious Diseases Division of AIDS, 2004 version [24] with modifications to the neutropenia definitions implemented May 10th, 2006 [21].

The BAN study was approved by the Malawi National Health Science Research Committee and institutional review boards at the University of North Carolina at Chapel Hill and the U.S. Centers for Disease Control and Prevention (CDC). All women provided written, informed consent for specimen storage and laboratory studies.

Exposures

The 852 babies randomized to infant nevirapine received a daily dose of nevirapine that increased according to age, ranging from 10 mg daily in the first 2 weeks to 30 mg daily for weeks 19 through 28. The 849 mothers on the maternal ARV arm received Combivir (twice daily) and either nevirapine (200 mg) once-daily for 14 days and twice-daily through week 28 (n=39), nelfinavir (1,250 mg) twice-daily through week 28 (n=146), or lopinavir (400 mg) plus ritonavir (100 mg) twice-daily through week 28 (n=664). These changes to the maternal antiretroviral regimen were made for reasons of safety, availability, and potency [21]. Data on ARV adherence were collected at five follow-up visits, and mothers reported taking all their antiretroviral doses a mean of 89% of the time and giving all infant antiretroviral doses 94% of the time.

In accordance with the Malawi Ministry of Health and Population Guidelines and WHO guidelines on CPT [25, 26], CPT was initiated in the BAN study for eligible women and infants on June 13, 2006. Cotrimoxazole was provided to all mothers with CD4<500 cells/μl (480 mg twice daily) and to all infants (240 mg once daily) beginning at their first study visit after 6 weeks of age and taken through 36 weeks of age or until weaning occurred and HIV infection was ruled out.

Outcomes

The outcomes studied in this analysis included severe forms of the following hematologic toxicities: anemia, neutropenia and elevated ALT. For each outcome, severe toxicity was defined as exceeding the cutpoint for grade 3 or higher on the 2014 version of the Division of AIDS toxicity tables [27]. Severe neutropenia was defined as <600 cells/mm^3. Severe anemia was defined as hemoglobin <8.5 g/dl for infants 56 days old or younger, and <9.5 g/dl for infants older than 56 days. Severe elevated ALT was defined as ≥ 5.0 times the upper limit of normal range. Additionally, hemoglobin concentrations, neutrophil counts and ALT concentrations from full blood counts taken at scheduled study visits were used to assess hematologic changes longitudinally.

Statistical methods

To examine the effects of CPT from 6 to 36 weeks postpartum, the 28-week postnatal antiretroviral intervention, and their interaction, this analysis was limited to HEU infants with at least one full blood count at the 6, 8, 12, 18, 21, 24, 28, 32, 36, 42, and 48 week post-partum study visits. This excluded 146 infants who were HIV-infected by 6 weeks of age, 17

HEU infants who died before 6 weeks of age and 200 infants lost to follow-up or with missing lab data. The final sample included 2006 infants.

Descriptive analyses included calculation of frequencies and medians for all exposures, outcomes and covariables. Categorical proportions were compared using chi-square tests and continuous variables were assessed using the Kruskal–Wallis test. To describe and illustrate the toxicity burdens suffered by the different groups, Cox proportional hazards models, one per outcome, were used to assess the hazards of severe hematologic toxicities by time-dependent CPT status, ARV arm and their interaction, and did not include other covariates. The extended Kaplan-Meier method, as described by Snapinn, et al [28], was used to visualize the hazards assessed in the Cox models. Per the study protocol, infant follow-up was censored at death, maternal death, or loss to follow-up.

Linear mixed models were used to evaluate the effects of the time-dependent CPT exposure, ARV arm, and their interaction on continuous longitudinal measurements of hemoglobin, neutrophils, and ALT. To determine whether the medication effects varied with infant age, interactions between week of age and CPT exposure were evaluated and significant interaction terms were retained. Mixed models used an autoregressive covariance structure with a random effect for subject, and were adjusted for randomization to the maternal nutritional supplement arm, infant gender, birthweight, infant hematologic values measured at birth (neutrophil counts, hemoglobin and ALT concentrations), maternal factors measured at birth (CD4 count, body mass index and hemoglobin concentration) and rainy season (defined as November through March). In analyses considering time-varying CPT exposure, infants were considered exposed from the first visit at or later than 6 weeks postnatal until 48 weeks, meaning CPT status will vary only for individuals actively in follow up when CPT was implemented. Study arm is modeled as an intent-to-treat variable. A sensitivity analysis was conducted, cutting off follow up for all participants at the discontinuation of the control group (March 27, 2008). Extended Kaplan Meier plots were created using R 3.3.2; all other analyses were performed using SAS 9.4.

Results

Among the 2,006 HEU infants, 553 were enrolled before and 1,453 after study implementation of the new CPT guidelines (Table 1). There was a small, but significant difference in median maternal BMI, with higher values in the group enrolled after CPT implementation; there were no other differences in maternal characteristics or infant sex and birthweight according to either CPT implementation or ARV treatment arm (Table 1). Prevalence of all three severe hematologic toxicities (anemia, neutropenia and elevated ALT) was low at baseline.

Over the course of follow up from 6 to 48 weeks of age, 10.5% of infants had at least one episode of severe anemia; by comparison, 3.5% and 0.8%, respectively had severe neutropenia and elevated ALT.

Initial episodes of severe anemia were less frequent for infants exposed to CPT than for those not exposed to CPT, especially after 24 weeks of age (Figure 1a), and CPT was

associated with a decreased hazard of severe anemia (HR: 0.65, 95% CI: 0.48 – 0.88) (Table 2). Compared to the control arm, the infant nevirapine arm had a significantly lower hazard of severe anemia (HR: 0.68, 95% CI: 0.48 – 0.96) (Table 2). Most initial episodes of severe anemia occurred later in follow up (Figure 1c).

Cox proportional hazards models showed CPT exposure was associated with an increased hazard of severe neutropenia (HR: 1.97, 95% confidence interval (CI): 1.01 – 3.86) (Table 2). Unlike severe anemia, most initial episodes of severe neutropenia during follow up occurred by 18 weeks of age (Figure 1b), regardless of CPT exposure. ARV treatment arm was not significantly associated with severe neutropenia (Table 2; figure 1d).

Neither CPT exposure nor ARV treatment arm assignment was associated with severe elevated ALT (Table 2). Models were also run with interaction terms between CPT exposure and weeks of age and between CPT exposure and ARV treatment arm for all of the outcomes studied, but none of the interactions tested showed statistical significance (data not shown).

Linear mixed models, used to analyze the longitudinal effects of CPT exposure on continuous hematologic outcomes, showed that CPT exposure was associated with increases in mean concentration of hemoglobin compared to infants not exposed to CPT, and that this association was modified by both ARV treatment and infant age. The significant interactions in this model mean the beta coefficients presented for this model in Table 3 represent changes in mean hemoglobin concentration compared to CPT-unexposed infants in the control arm at 12 weeks of age. They indicate that the observed association of CPT with mean hemoglobin was greater for infants in the control arm and for older infants. Using the mixed model coefficients, mean hemoglobin concentration was 0.18 g/dL (95% CI: 0.03, 0.33) higher for those exposed to CPT in the control group at 12 weeks of age (Table 3). Mean hemoglobin concentration was higher in the maternal ARV and infant nevirapine arms compared to the control arm when not exposed to CPT (increases of 0.25 g/dL and 0.18 g/dL, respectively at 12 weeks of age), but these effects of ARV treatment were diminished when exposed to CPT (decreases of 0.22 g/dL and 0.24 g/dL for maternal ARV and infant nevirapine arms, respectively) due to the significant interaction terms.

CPT exposure was associated with a 191.8 cells/mm^3 decrease in mean neutrophil count (95% CI: −303.1, −80.6) in the control arm at 12 weeks of age, however this decrease was reduced by 7.8 cells/mm^3 for each additional week of age due to a significant interaction term. There was no significant interaction between CPT and study arm in the model with neutrophil count as the dependent variable.

CPT exposure was not associated with ALT levels (increase of 0.53 IU/L, 95% CI: −0.68, 1.74) (Table 3).

Results of the sensitivity analysis where follow up was cut off at the discontinuation of the control group yielded similar results to the main analysis (data not shown).

Discussion

In this cohort of breastfed HEU infants followed until 48 weeks of life, severe anemia was relatively common, while severe neutropenia was rare. There was a significant decrease in severe anemia and a significant increase in severe neutropenia associated with CPT. Longitudinal mixed models showed corresponding increases in hemoglobin levels and decreases in neutrophil counts associated with CPT exposure. Associations between CPT and hemoglobin levels increased with age but were reduced by exposure to ARV (either maternal ARV or infant nevirapine). The reduction in neutrophil count associated with CPT exposure lessened with age.

A previous study on the effects of CPT on hematologic outcomes in HEU infants in Botswana showed that severe anemia and neutropenia were rare among HEU infants and there was no association between CPT and either outcome [29]. Our research confirms the low frequency of severe neutropenia in HEU infants, while the difference in frequency of severe anemia may be attributable to the different population studied. The BAN study took place in a region where malaria, a cause of anemia [30], is prevalent and all infants breastfed, while the previous study took place in a non-malarial region of Botswana and very few infants receiving CPT were breastfed. Nearly 50% of HEU infants in another study in Uganda and Zimbabwe (HPTN-046) who were taking CPT developed severe anemia and/or neutropenia [31]. However, that analysis focused on the effects of ARVs in the studied population, and did not present results for severe anemia and severe neutropenia separately; also, because all subjects were also exposed to CPT, the effects of each on the outcomes could not be determined.

While there is evidence from studies in adults that the combination of CPT and zidovudine-containing ARV treatment may cause hematologic toxicities [32], our analysis shows that for HEU infants in areas of high malarial prevalence, it is possible that CPT may reduce the occurrence of severe anemia. In a separate analysis of data from the BAN trial, it was shown that CPT was associated with a reduction in sub-clinical malaria, although it had no effect on clinical malaria [33]. Thus, CPT may cause a reduction in malaria-related anemia separate from the drug's direct effects on blood hemoglobin. Severe anemia in sub-Saharan Africa is associated with adverse clinical outcomes, including death [19, 34, 35], and the results of this analysis suggest that in populations with a high malaria prevalence, CPT has the potential to reduce the frequency of these outcomes among HIV-exposed infants.

This analysis did show an increase in severe neutropenia and a corresponding reduction in neutrophil counts associated with CPT. However, the effect on neutrophil count lessened with age, and the frequency of severe neutropenia was low even for those exposed to CPT. We did not find any association between CPT exposure and elevated ALT.

There was no overall difference in severe anemia or severe neutropenia according to ARV treatment arm, although those infants receiving daily nevirapine did have a lower estimated hazard of severe anemia compared with the control arm. Likewise, in longitudinal mixed models, both maternal ARV and infant nevirapine were associated with higher levels of hemoglobin in the absence of cotrimoxazole[36].

This study instructed mothers to wean rapidly after 28 weeks, and self-reported adherence to the breastfeeding schedule was high. Median breastfeeding duration was 169 days, and did not vary by study arm. Median breastfeeding duration was 172 days for infants born before CPT implementation and 169 days for those born after (Kruskal-Wallis Test p-value < 0.001). Current guidelines for HIV-infected women on ART recommend breastfeeding until 12– 24 months [36]. HIV-uninfected mothers in Malawi generally continue breastfeeding until about 24 months, which means that the infants will continue to be exposed to ARVs and CPT. The reassuring findings of this study related to drug toxicities, combined with results from BAN and other studies showing increased morbidity and mortality in HIV-exposed infants after early weaning suggest that the benefits of continued breastfeeding should outweigh concerns related to these exposures.

While a randomized controlled trial would be ideal to evaluate the hematologic effects of CPT in HEU infants in areas of high malaria prevalence, this is not possible or ethical following the release and implementation of CPT guidelines from the WHO and Malawi Ministry of Health. Thus, our analysis took advantage of the unplanned experiment caused by the BAN study's implementation of CPT in June 2006 by treating CPT as a time-varying exposure. To account for secular trends in participants' environments and health that may have confounded the association between CPT and the studied outcomes, longitudinal mixed models included factors indicative of maternal and infant health before entry into the analysis cohort at 6 weeks of age, along with variables to account for seasonal changes. Despite our ability to control for these factors, there may have been changes over time in participants' health unrelated to CPT that we could not account for.

Changes in the study protocol over time may have affected results. An increase in the minimum CD4+ cell count for enrollment eligibility, from <200 to <250, 6 months after CPT implementation and changes to the maternal ARV regimen over time [21] may have led to the inclusion of healthier individuals later in the study, and changes in study population health unrelated to CPT. These changes should be at least partially addressed by the factors adjusted for in longitudinal mixed models, which included maternal CD4+ cell count. If changes to the maternal ARV regimen improved outcomes at around the same time as CPT implementation and inflated the observed positive associations between CPT and hemoglobin levels, this effect should show up in the maternal ARV arm. Instead, in linear mixed models, the positive association between CPT and hemoglobin levels was reduced in the maternal ARV arm compared to the control arm, and associations between CPT and other outcomes did not differ according to study arm (Table 3). Likewise, the similarity of the results of the sensitivity analysis to the main analysis indicate that the observed effect of CPT was not due to the shift, later in the study, of participants to the two intervention arms. Rates of analysis-specific exclusions were non-differential with respect to CPT implementation, so we do not have reason to expect bias to results. Most of the 146 HIV-related exclusions were due to in-utero infection (n=119); post-natal pre-6 week visit infections (n=27) were more likely in the control group. If these excluded infants were more likely to suffer adverse study outcomes due to poor health, this could bias results related to the two ARV arms towards significant associations, but the number involved is small and any effect is unlikely to be large. Exclusions due to LTFU and infant deaths before the 6

week visit were non-differential by study arm. The results of this analysis may only apply to populations similar to the one studied.

The findings of this analysis further support the use of daily CPT among HEU infants, especially in areas of high malaria prevalence. There has been concern about the potential for the combined use of CPT and ARV treatment to cause hematologic toxicities. While our data suggest that CPT may increase the hazard of severe neutropenia, the overall prevalence of this outcome remained low. The reduction in severe anemia associated with CPT is an additional benefit for HEU infants at increased risk for adverse health outcomes and mortality.

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A.P.K., C.S.C., C.vd.H., and D.J.J. designed the trial. C.S.C., D.K., G.T., M.C.H. and M.G.H. collected data. A.C.E., A.F. and C.C.K. analyzed data. A.C.E., A.P.K., C.C.K., J.B.W., C.vd.H., and D.J.J. interpreted data. A.C.E. wrote the manuscript. All authors reviewed versions of the report and contributed to the intellectual content of the article.

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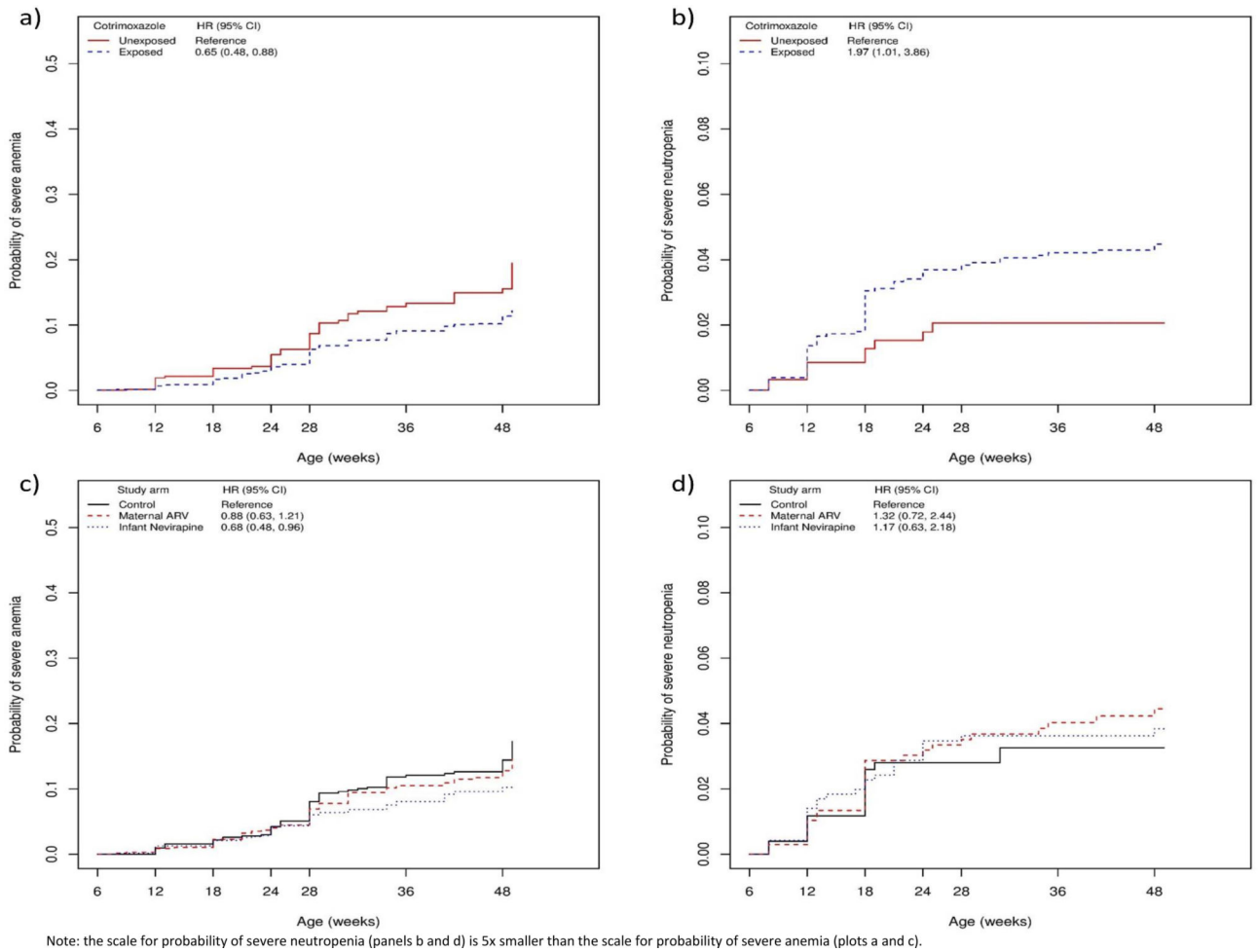

Figure 1.

Extended Kaplan-Meier curves for the probabilities of severe anemia and severe neutropenia, as defined in the 2014 version of the Division of AIDS toxicity tables, according to time-varying cotrimoxazole (CPT) exposure status (panels a and b) and according to antiretroviral study arm (panels c and d) over follow up of HIV-exposed, uninfected infants in the Breastfeeding, Antiretrovirals and Nutrition (BAN) study in Malawi from 6 to 48 weeks of age (2004–2010).

Table 1

Baseline Characteristics of 2,006 HIV-uninfected infants (at the 6-week post birth visit)* in the Breastfeeding, Antiretrovirals and Nutrition (BAN) Study, Malawi, 2004–2010, according to baseline visit timing relative to cotrimoxazole prophylaxis (CPT) guideline implementation (June, 2006) and antiretroviral (ARV) treatment arm assignment.

	CPT guideline implementation					ARV treatment arm					
	Before (n=553)		After (n=1453)		p**	Control (n=548)		Infant nevirapine (n=748)		Maternal ARV (n=710)		p**
Maternal and infant characteristics												
Male (%)	290	(52.4)	740	(50.9)	0.54	286	(52.2)	379	(50.7)	365	(51.4)	0.86
Birthweight, kg †	3.0	(2.7, 3.3)	3.0	(2.7, 3.3)	0.53	3.0	(2.7, 3.3)	3.0	(2.7, 3.3)	3.0	(2.7, 3.3)	0.98
Maternal hemoglobin, g/dL †	10.8	(10.0, 11.6)	10.9	(10.1, 11.7)	0.10	10.9	(10.0, 11.7)	10.8	(10.0, 11.7)	10.9	(10.1, 11.7)	0.40
Maternal CD4, cells/μL †	440	(333, 595)	442	(333, 578)	0.83	445	(342, 578)	440	(331, 591)	440	(331, 571)	0.53
Maternal BMI, †	22.7	(21.2, 24.3)	23.3	(21.7, 25.6)	<0.001	23.2	(21.5, 25.4)	23.2	(21.6, 25.1)	22.9	(21.4, 25.4)	0.50
Outcomes												
Neutrophil count, 10^3 cells/μL †	1.5	(1.1, 2.1)	1.6	(1.2, 2.2)	0.52	1.6	(1.2, 2.3)	1.6	(1.2, 2.2)	1.5	(1.2, 2.1)	0.41
Severe neutropenia (%) ‡	9	(1.8)	13	(1.0)	0.16	8	(1.6)	8	(1.1)	6	(0.9)	0.56
Hemoglobin, g/dL †	10.8	(9.9, 11.7)	11	(10.2, 11.9)	0.01	11	(10.2, 12.0)	10.9	(9.9, 11.7)	11.1	(10.3, 11.9)	<0.001
Severe anemia (%) ‡	6	(1.2)	1	(0.1)	0.002	2	(0.4)	3	(0.4)	2	(0.3)	1.00
Alanine aminotransferase, IU/L †	15	(11, 19)	13	(10, 18)	<0.001	14	(10, 19)	13	(10, 18)	14	(10, 18)	0.83
Severe elevated ALT (%) ‡	0	(0.0)	1	(0.1)	1.00	0	(0.0)	0	(0.0)	1	(0.2)	0.62

*The 116 infants missing the 6 week post birth visit contributed data on characteristics measured at birth (sex, birthweight and maternal characteristics).

**P-values based on Kruskal-Wallis test for continuous variables. P-values for categorical variables based on Pearson's chi-square test or Fisher's exact test when there are cells with counts < 5.

†Median (interquartile range).

‡Severe hematologic outcomes were defined as those grade 3 and higher according to the 2014 version of the National Institute of Allergy and Infections Diseases Division of AIDS toxicity tables. Severe neutropenia was defined as <600 cells/mm^3. Severe anemia was defined as hemoglobin <8.5 g/dl for infants 56 days old or younger, and <9.5 g/dl for infants older than 56 days. Severe elevated ALT was defined as ≥ 5.0 times the upper limit of normal range.

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Table 2

Hazard ratio estimates for associations of cotrimoxazole (CPT) exposure and ARV treatment arm with hematologic toxicities in the Breastfeeding, Antiretrovirals and Nutrition (BAN) study, Malawi 2004–2010, Cox proportional hazards models

Outcome*	Cotrimoxazole exposure		ARV treatment arm		
			Infant nevirapine	Maternal ARV	p†
	HR (95% CI)	p†	HR (95% CI)	HR (95% CI)	
Severe neutropenia	1.97 (1.01 – 3.86)	0.05	1.17 (0.63 – 2.18)	1.32 (0.72 – 2.44)	0.67
Severe anemia	0.65 (0.48 – 0.88)	0.01	0.68 (0.48 – 0.96)	0.88 (0.63 – 1.21)	0.08
Severe elevated ALT	3.63 (0.48 – 27.6)	0.21	0.84 (0.28 – 2.51)	0.51 (0.14 – 1.8)	0.56

*Severe hematologic outcomes were defined as those grade 3 and higher according to the 2014 version of the Division of AIDS toxicity tables. Severe neutropenia was defined as <600 cells/mm^3. Severe anemia was defined as hemoglobin <8.5 g/dl for infants 56 days old or younger, and <9.5 g/dl for infants older than 56 days. Severe elevated ALT was defined as ≥ 5.0 times the upper limit of normal range.

†P-value for the joint test of the effect of the exposure on hazards of the outcome

CI: Confidence interval

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Table 3

Random effects models of effects of cotrimoxazole (CPT) exposure and antiretroviral (ARV) treatment arm on infant hematologic concentrations from the first post 6-week study visit to 48 weeks of age in the Breastfeeding, Antiretrovirals and Nutrition (BAN) study, 2004–2010

	β coefficients for main effects					β coefficients for interaction terms		
	Intercept	**CPT**	**AGE†**	**Maternal ARV**	**Infant nevirapine**	**AGE*CPT**	**CPT × maternal ARV**	**CPT × infant netvirapine**
Outcome								
Hemoglobin‡, g/dL	10.16	0.18*	−0.01*	0.25*	0.18*	0.01*	−0.22*	−0.24*
Neutrophils§, cells/mm^3	1952.9	−191.8*	20.9*	−61.0	−16.7	7.8*	−164.5	−90.5
ALT‖, IU/L	15.64	0.53	0.14*	−1.24	−1.56*	0.08	−1.65	−2.40

*p-value for β coefficient estimate is significant at α=0.05

†Age is centered at 12 weeks, the date of most subjects' first measurement where it was possible to be CPT exposed

‡Intercept and main effects are from a model with interactions CPT exposure and both age and ARV treatment arm

§Intercept, main effects and age*CPT interaction estimate are from a model with an interaction between age and CPT exposure

‖Intercept and main effects are from a model with no interaction terms

All models adjusted for birth measurements of both maternal (maternal BMI, maternal CD4, maternal hemoglobin) and infant characteristics (sex, birthweight, white blood cell count, hemoglobin, neutrophils, and ALT) and rainy season