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MAJOR ARTICLE

Co-trimoxazole Prophylaxis, Asymptomatic Malaria Parasitemia, and Infectious Morbidity in Human Immunodeficiency Virus–Exposed, Uninfected Infants in Malawi: The BAN Study

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Background. Human immunodeficiency virus (HIV)–exposed infants are disproportionately at risk of morbidity and mortality compared with their HIV-unexposed counterparts. The role of co-trimoxazole preventive therapy (CPT) in reducing leading causes of infectious morbidity is unclear.

Methods. We used data from the Breastfeeding, Antiretrovirals and Nutrition (BAN) clinical trial (conducted 2004–2010, Malawi) to assess the association of (1) CPT and (2) asymptomatic malaria parasitemia with respiratory and diarrheal morbidity in infants. In June 2006, all HIV-exposed infants in BAN began receiving CPT (240 mg) from 6 to 36 weeks of age, or until weaning occurred and HIV infection was ruled out. All HIV-exposed, uninfected infants (HEIs) at 8 weeks of age (n = 1984) were included when CPT was the exposure. A subset of HEIs (n = 471) were tested for malarial parasitemia using dried blood spots from 12, 24, and 36 weeks of age. Cox proportional hazards models for recurrent gap-time data were used to examine the association of time-varying exposures on morbidity.

Results. CPT was associated with a 36% reduction in respiratory morbidity (hazard ratio [HR], 0.64 [95% confidence interval {CI}, .60–.69]) and a 41% reduction in diarrheal morbidity (HR, 0.59 [95% CI, .54–.65]). Having asymptomatic malaria parasitemia was associated with a 40% increase in respiratory morbidity (HR, 1.40 [95% CI, 1.13–1.74]) and a 50% increase in diarrheal morbidity (HR, 1.50 [95% CI, 1.09–2.06]), after adjusting for CPT.

Conclusions. CPT may have an important role to play in reducing the leading global causes of morbidity and mortality in the growing population of HEIs in malaria-endemic resource-limited settings.

Keywords. co-trimoxazole; HIV; infant; infectious morbidity; malaria.

Diarrhea, respiratory infections, and malaria are among the leading causes of morbidity and mortality in children <5 years of age worldwide [1]. Human immunodeficiency virus (HIV)–exposed infants are disproportionately at risk of morbidity and mortality compared with their HIV-unexposed counterparts [2, 3]. HIV prevalence in pregnant women has been as high as 35% in some sub-Saharan Africa settings [4]. When adhering to antenatal, intrapartum, and postnatal World Health Organization (WHO) antiretroviral treatment recommendations, approximately 98% of HIV-infected mothers will not transmit HIV to their infants [5]. Therefore, the population of HIV-exposed, uninfected infants (HEIs) is growing as antiretroviral (ARV) programs roll out.

Effective interventions for preventing and treating diarrhea and respiratory infections exist [6–9]. However, ensuring timely access to proven life-saving interventions remains challenging [10]. Co-trimoxazole is a combined broad-spectrum antibiotic used to prevent and treat certain infections, including *Pneumocystis jirovecii* pneumonia, respiratory tract, and other infections. Co-trimoxazole also has antimalarial activity. To ensure that infants who do become HIV infected receive timely co-trimoxazole preventive therapy (CPT) to prevent often fatal opportunistic infections, WHO recommends that all HIV-exposed infants begin CPT between 4 and 6 weeks of age and continue CPT until complete cessation of breastfeeding and exclusion of HIV infection [11]. However, there has been conflicting evidence regarding the benefits of giving daily CPT to the growing population of HEIs. No difference

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in the rate of survival was observed in a recent randomized controlled trial that randomized HEIs to receive either CPT or a placebo from 2 to 4 weeks of age until 15 months of age in Botswana [12]. However, we have shown that CPT protected HEIs against severe (grade 3 or 4) infant morbidity and mortality in the Breastfeeding, Antiretrovirals, and Nutrition (BAN) study in Malawi [13]. We have also shown that CPT protected HEI against asymptomatic malaria parasitemias, defined as polymerase chain reaction (PCR)–positive samples collected at non-ill routine visits, potentially reducing not only infant morbidity but also malaria transmission [14]. For this analysis, we explored (1) whether CPT protects HEI from 2 of the leading causes of childhood morbidity and mortality—respiratory and diarrheal infections—in a setting of high malaria endemicity and regardless of severity grade; and (2) whether presence of asymptomatic malaria parasitemia was associated with increased risk of respiratory and diarrheal infections.

METHODS

An observational cohort study was conducted using data and specimens from the BAN study. Details of the BAN study have been reported previously [15]. In brief, the BAN study was conducted in Lilongwe, Malawi, from 2004 to 2010, to assess the benefit and safety of maternal or infant ARVs to prevent HIV transmission during breastfeeding. HIV-positive pregnant women were recruited at antenatal clinics and randomized after delivery via a factorial design to receive, or not receive, a lipid-based nutrient supplement throughout breastfeeding and to receive 1 of the following postpartum prevention of mother-to-child HIV transmission regimens: (1) 28 weeks of maternal triple ARVs; (2) 28 weeks of daily infant nevirapine (NVP); or (3) no further ARVs postpartum (enhanced control). All mothers and infants received 1 dose of NVP at delivery or birth and 7 days of postpartum zidovudine and lamivudine. Mothers were counseled to exclusively breastfeed for 24 weeks and wean from 24 to 28 weeks postpartum. Mothers with $CD4^+$ T-cell count >200–250 cells/μL and infants weighing at least 2000 g at birth were enrolled in the BAN study. Ethical approval for the BAN study 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 US Centers for Disease Control and Prevention.

All infants enrolled in BAN who remained HIV uninfected at 8 weeks of age (n = 1984) were included in analyses of CPT and both diarrheal and respiratory morbidity. Infants who became HIV infected after 8 weeks of age were censored at the time of their last HIV-negative test. Infant HIV status was determined by Roche Amplicor 1.5 DNA PCR (Roche Molecular Systems, Pleasanton, California) at 2, 12, 28, and 48 weeks. PCR-positive results were confirmed by testing an additional blood specimen. The window of infection was then narrowed by testing infant dried blood spot specimens collected at 4, 6, 8, 18, 24, 32, and 36 weeks.

Analyses of asymptomatic malaria parasitemias and infectious morbidity included a subset of infants (n = 471) who remained HIV uninfected through 48 weeks of age and were tested for asymptomatic parasitemias using stored dried blood spots from 12, 24, and 36 weeks of age. Selection of infants for malaria parasitemia testing has been previously described [14]. In brief, infants were chosen based on birthdate to mitigate the impact of calendar time on malaria prevalence. In addition, only specimens collected during peak malaria season (October–April) were used to increase the likelihood of detecting asymptomatic parasitemias.

Molecular analysis to determine asymptomatic malaria parasitemias was conducted using real-time PCR to detect the single-copy gene *Plasmodium falciparum* lactate dehydrogenase *(pfldh)* as previously described [16]. Samples testing positive for malaria parasites by 2 previously described real-time PCR assays were considered positive [17]. Samples positive with only 1 assay were considered indeterminate and not used in analyses. Asymptomatic malaria infection was treated as a dichotomous time-varying variable (detectable vs undetectable parasitemia).

All HIV-exposed infants began receiving CPT as part of the BAN study on 13 June 2006, in accordance with WHO and Malawi Ministry of Health guidelines. CPT (240 mg once daily) was initiated at 6 weeks of age and continued through 36 weeks of age or until weaning occurred and HIV infection was ruled out. CPT was treated as a time-varying exposure, with infants attending BAN study visits prior to 13 June 2006 considered CPT unexposed and infants attending BAN study visits after 13 June 2006 considered CPT exposed.

Infants with a documented case of diarrhea or respiratory infection, regardless of severity grade, from 8 to 48 weeks of age on any 1 of the following routine study visit forms were considered to have the outcome of interest: infant's physical examination form, infant symptom form, and the infant's concomitant medication log. Diarrhea or respiratory events occurring >2 weeks apart were treated as separate events. In analyses of asymptomatic parasitemias and infectious morbidity, only diarrhea or respiratory events occurring from 12 to 48 weeks were used to ensure that the outcome did not occur prior to the first sample tested. To estimate associations, asymptomatic parasitemia was defined using the most recent sample collected before the morbidity outcome.

A change-in-estimate approach was used to assess for confounding. Potential confounding variables consisted of rainy season (November to March), BAN randomization arm, and co-trimoxazole status (for association between asymptomatic parasitemias and both diarrheal and respiratory morbidity). Potential confounders that did not change the point estimate by >10% were dropped to create a more parsimonious model. Cox proportional hazards models for recurrent gap-time data with

robust variance estimators [18] were used to estimate associations between (1) CPT and diarrheal or respiratory morbidity from 8 to 48 weeks of age, and (2) asymptomatic parasitemias and diarrheal or respiratory morbidity from 12 to 48 weeks of age, allowing for repeated events of diarrhea or respiratory infection. All data analyses were conducted using SAS version 9.3 software (SAS Institute, Cary, North Carolina).

RESULTS

A total of 1984 infants contributed 1414 person-years (PY) of follow-up to analyses of CPT and infectious morbidity (CPT unexposed: 260 PY, CPT exposed: 1154 PY). The median infant birth weight was 3.0 kg (interquartile range [IQR], 2.7–3.3). Most mothers were married (92%) and reported at least 1 previous live birth (88%) (Table 1). Fifty percent of mother–infant pairs were randomized to receive a maternal lipid-rich nutrient supplement. Overall, 35% of mother–infant pairs were randomized to the maternal ARV arm, 37% to the infant NVP arm, and 27% to the enhanced control arm of the BAN study. Mothers had a median baseline $CD4^+$ count of 440 cells/μL (IQR, 332–582 cells/μL) and 60% had a baseline plasma HIV RNA load >10 000 copies/mL of blood. The median maternal age was 26 years (IQR, 23–29 years).

CPT-exposed infants experienced 5.32 respiratory events and 2.87 diarrhea events per 100 person-weeks between 8 and 48 weeks of age. The incidence rate of respiratory and diarrheal morbidity among CPT-unexposed infants was 8.09 and 4.39 per 100 person-weeks, respectively. CPT was associated with a 36% relative reduction in respiratory morbidity (hazard ratio [HR], 0.64 [95% confidence interval {CI}, .60–.69]) and a 41% relative reduction in diarrheal morbidity (HR, 0.59 [95% CI, .54–.65]). Adjustment for rainy season and randomization arm resulted in similar findings (respiratory HR, 0.65 [95% CI, .60–.69]; diarrheal HR, 0.59 [95% CI, .54–.65]) (Table 2).

A total of 676 dried blood spots from 471 infants were tested for asymptomatic malaria parasitemias at 12, 24, and 36 weeks of age (230 specimens at 12 weeks, 231 at 24 weeks, and 215 at 36 weeks). As previously reported, a total of 61 (9%) specimens had detectable parasitemias during peak malaria season [14]. Specifically, 12 (5%) infants experienced asymptomatic malaria infection at 12 weeks of age, 44 (19%) at 24 weeks, and 5 (2%) at 36 weeks of age. A greater proportion of infants with detectable parasitemias had at least 1 episode of diarrhea and respiratory infection between 12 and 23 weeks of age, 24 and 35 weeks of age, and 36 and 48 weeks of age, compared with infants with no detectable parasitemias (Figure 1). Having asymptomatic parasitemias was associated with a 50% relative increase in diarrheal morbidity (HR, 1.50 [95% CI, 1.09–2.06]) and a 40% relative increase in respiratory morbidity (HR, 1.40 [95% CI, 1.13–1.74]) after adjusting for CPT status, rainy season (November–March), and BAN antiretroviral and nutrition randomization arms (Table 3).

Table 1. Baseline Characteristics of 1984 Mother–Infant Pairs

	Total[a]	
Characteristic	No.	(%)
Antiretroviral randomization		
Maternal antiretroviral	701	(35)
Infant nevirapine	739	(37)
Enhanced control[b]	544	(27)
Nutritional randomization		
Received supplement	992	(50)
Mothers		
Age, y		
15–25	945	(48)
26–35	936	(47)
36–45	98	(5)
Primary school only	1286	(65)
Married	1833	(92)
Parity ≥1	1733	(88)
$CD4^+$ count, cells/μL		
200–350	573	(29)
351–500	663	(33)
>500	748	(38)
Plasma viral load, copies/mL		
≤1000	204	(10)
1001–10 000	586	(30)
>10 000	1189	(60)
Hemoglobin <11 g/dL	1038	(52)
Infants		
Female	1022	(52)
Birth weight <2.5 kg	136	(7)

[a]Maternal age and baseline viral load are missing for 5 mothers, education is missing for 2 mothers, and parity is missing for 6 mothers.

[b]Mothers and infants randomized to the enhanced control arm received single-dose nevirapine peripartum plus twice-daily zidovudine and lamivudine during labor and for 7 days postpartum.

DISCUSSION

CPT was associated with a significant reduction in respiratory and diarrheal morbidity in HEIs. In contrast, asymptomatic malaria infection was associated with a significant increase in respiratory and diarrheal morbidity, after adjusting for CPT

Table 2. Hazard Ratios[a] for the Association Between Co-trimoxazole Preventive Therapy From 6 to 36 Weeks of age and Infant Diarrhea or Respiratory Infection From 8 to 48 Weeks of Age

	Unadjusted		Adjusted	
Outcome	HR	(95% CI)	HR	(95% CI)
Diarrhea				
Routine CPT vs no routine CPT	0.59	(.54–.65)	0.59	(.54–.65)
Respiratory infection				
Routine CPT vs no routine CPT	0.64	(.60–.69)	0.65	(.60–.69)

Abbreviations: CI, confidence interval; CPT, co-trimoxazole preventive therapy; HR, hazard ratio.

[a]Adjusted for rainy season (November–March) and Breastfeeding, Antiretrovirals and Nutrition study antiretroviral and nutrition randomization arm.

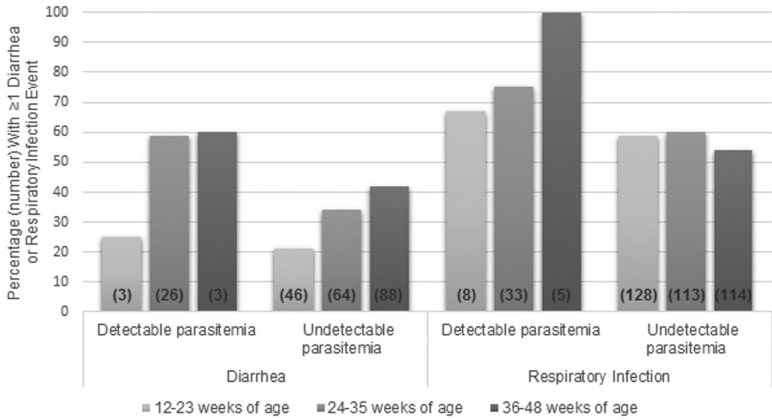

Figure 1. Percentage and number of human immunodeficiency virus–exposed, uninfected infants with ≥1 diarrhea or respiratory infection event, by malaria parasitemia status and weeks of age.

status. This adds to our previous findings of CPT being associated with reduced risk of both clinical and asymptomatic malaria [14], as well as severe infectious morbidity and mortality in HEIs in Malawi [13].

Similar incidence of diarrhea and pneumonia was seen among HIV-exposed, uninfected children in Uganda randomized to either discontinue co-trimoxazole after complete cessation of breastfeeding or to continue co-trimoxazole until 2 years of age [19]. However, only outcomes occurring after cessation of breastfeeding were assessed; as younger infants suffer generally higher rates and more severe morbidity (and mortality) of infections, the effects of any intervention need to be examined in each age group specifically.

The association between asymptomatic malarial infection and increasing infant morbidity from other causes has biological plausibility. It is possible that asymptomatic malaria infection may make infants more susceptible to other infections by increasing immune activation, decreasing effective immune responsiveness, or by predisposing to anemia and increase metabolic demands. Notably, helminthic infections are known to compromise vaccine responses and shift immunity to Th2-type response that can impair the control of replication of viral and other infections [20], suggesting that prevention of parasitic infections, including malaria, in childhood needs to be a global health priority. Of interest, and concurrent with our findings, an association between malaria parasitemia and *Salmonella* septicemia was previously noted in young children residing in a malaria-endemic area [21].

Table 3. Hazard Ratios[a] for the Association Between Asymptomatic Malaria at 12, 24, and 36 Weeks of Infant Age and Infant Diarrhea or Respiratory Infection From 12 to 48 Weeks of Age

	Unadjusted		Adjusted	
Outcome	HR	(95% CI)	HR	(95% CI)
Diarrhea				
Asymptomatic parasitemias vs no parasitemias	1.93	(1.45–2.57)	1.50	(1.09–2.06)
Respiratory infection				
Asymptomatic parasitemias vs no parasitemias	1.59	(1.31–1.94)	1.40	(1.13–1.74)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Adjusted for co-trimoxazole status, rainy season (November–March) and Breastfeeding, Antiretrovirals and Nutrition study antiretroviral and nutrition randomization arm.

In Botswana, similar mortality was seen between HIV-exposed, uninfected children randomized to receive CPT and those randomized to placebo from 14 to 34 days of life until age 15 months [12]. In contrast, we previously found lower mortality among infants who received CPT in BAN compared with infants who did not [13]. There are several potential reasons for the difference in findings. First, CPT was not randomized in BAN, creating the potential for confounding by unmeasured variables (eg, bed net or artemisinin combination therapy use). Second, unlike Malawi, Botswana is not a malaria-endemic country. Third, Botswana has a lower overall infant mortality rate than Malawi. In addition, pneumococcal and rotavirus vaccines were introduced into the national immunization schedule in Botswana in 2012, resulting in significant declines in hospitalizations and death due to gastroenteritis [22] and, potentially, respiratory infection. Pneumococcal and rotavirus vaccines are not part of the immunization schedule in Malawi. A similar randomized controlled trial of co-trimoxazole prophylaxis in breastfed HEIs is planned in South Africa [23]. However, only 10% of the South African population lives in malaria-endemic areas [24], potentially limiting the generalizability of findings to resource-limited malaria-endemic countries.

Our study has some limitations. Misclassification of CPT exposure or infectious morbidity status may have occurred. CPT status was based on calendar time. However, a prior random review of pharmacy records in the BAN study indicated good adherence to CPT guidelines [25]. Diarrhea and respiratory events were determined by retrospective review of clinical forms, including concomitant medication logs. Patient symptoms, as well as medications prescribed for diarrhea and

respiratory infection, are not always unique to these conditions. Therefore, some outcome misclassification may have occurred. However, our definition of outcome represents clinical practice in resource-limited settings where laboratory capacity to confirm diagnoses may be limited. Unmeasured variables that could affect the incidence of respiratory or diarrheal morbidity over the included time period could also have confounded our results. Selection bias may have occurred if infants tested or not tested for asymptomatic malaria parasitemia differed by unmeasured variables, such as multiple antibiotic use. However, infants did not differ by measured baseline covariates collected in BAN [14]. Testing results for asymptomatic parasitemia were only available for the 12-, 24-, and 36-week study visits, requiring reliance on prior study visits to define this exposure for many morbidity outcomes. This may have led to some misclassification of exposure.

We have shown CPT to be associated with reduced infectious morbidity and reduced asymptomatic and clinical malaria in HIV-exposed, uninfected infants in a malaria-endemic setting. In addition, our finding that asymptomatic malarial infection is associated with increased infectious morbidity from other causes in infants suggests another possible mechanism by which CPT may decrease infectious morbidity and improve the health of infants in malaria-endemic settings. This builds on previous work that demonstrated reduced mortality in HEIs in this population. CPT may have an important role to play in reducing the leading global causes of morbidity and mortality in the growing population of HEIs in malaria-endemic, resource-limited settings. Randomized controlled trials to directly study the effects of CPT in improving infant and young child health in malaria-endemic, resource-limited settings are needed to inform policy and practice.

Notes

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Disclaimer. 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 (CDC).

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