Cotrimoxazole and reduced infectious morbidity in HIV-exposed uninfected infants

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Background

Diarrhea and respiratory infections are among the leading causes of global morbidity and mortality in young children, with HIV-exposed infants at increased risk.

We have previously shown cotrimoxazole prophylaxis (CPT) to be associated with the following in HIV-exposed, uninfected infants in Malawi:

- Reduced severe infectious morbidity[1]
  [Hazard Ratio (HR) 0.36, 95% CI 0.23-0.58]
- Reduced mortality[1]
  (HR 0.48, 95% CI 0.25-0.93)
- Reduced risk of both clinical and asymptomatic malaria[2]
  [Risk Ratio 0.65, 95% Confidence Interval (CI) 0.49-0.86],

We now assess whether CPT has a similar association with all infant infectious morbidity, regardless of illness severity.

Study population

The BAN Study: Randomized trial in Lilongwe, Malawi (2004-2010) that used a 3x2 factorial design to assess the benefit and safety of ARVs given to HIV-infected mothers (ZDV+3TC+ either LPV/r, NFV) or their infants (daily NVP) to prevent breastmilk HIV transmission, compared with an enhanced control (single-dose NVP at delivery + 7 days ZDV/3TC). Mothers were also randomized to either receive or not receive a lipid-based nutrient supplement throughout breastfeeding.

Select BAN eligibility criteria

- Infant birthweight ≥2000 grams
- Maternal HIV infection with CD4 > 250 cells/µL
- Intend to breastfeed
- Maternal hemoglobin ≥7 g/dL
- No prior ARV use, including single-dose nevirapine (NVP)

Analysis eligibility criteria

- Infants who remained HIV-uninfected at 8 weeks of age

Cotrimoxazole provision

- Routine CPT (240 mg once daily) was provided to all infants in BAN beginning June 2006, in line with Malawi and WHO guidelines, from 6-36 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 June 2006 considered CPT-unexposed.

Table 1. Baseline characteristics of 1984 mother-infant pairs.

	Total*	
	N	(%)
Antiretroviral randomization		
Maternal antiretroviral	701	(35)
Infant nevirapine	739	(37)
Enhanced control*	544	(27)
Nutritional randomization		
No supplement	992	(50)
Received supplement	992	(50)
Mothers:		
Age (years)		
15-25	945	(48)
26-35	936	(47)
36-45	98	(5)
Education		
Primary school only	1286	(65)
More than primary school	696	(35)
Married		
No	151	(8)
Yes	1833	(92)
Parity		
0	245	(12)
≥1	1733	(88)
CD4+ count per mm3		
200-350	573	(29)
351-500	663	(33)
>500	748	(38)
Plasma viral load copies/ml		
≤ 1,000	204	(10)
1,001-10,000	586	(30)
> 10,000	1189	(60)
Hemoglobin (g/dl)		
< 11	1038	(52)
≥ 11	946	(48)
Infants:		
Sex		
Female	1022	(52)
Male	962	(48)
Birth weight (kg)		
<2.5	136	(7)
≥2.5	1844	(93)

*Maternal age and viral load are missing for 5 mothers, education missing for 2, and parity missing for 6 mothers.

**Mothers and infants randomized to enhanced control received single-dose nevirapine peripartum and zidovudine and lamivudine during labor and for 7 days post-partum.

Results

A total of 1984 infants contributed 1414 person-years (PY) of follow-up

- CPT-unexposed: 260 PY
- CPT-exposed: 1154 PY

CPT-exposed infants experienced 5.32 respiratory events and 2.87 diarrhea events per 100 person-weeks.

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 and a 41% relative reduction in diarrheal morbidity (respiratory HR 0.64, 95%CI 0.60-0.69; diarrheal HR 0.59, 95% CI 0.54-0.65).

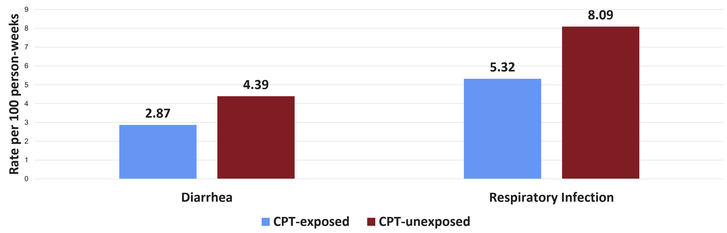
Adjustment for rainy season (Nov-Mar) and randomization arm resulted in similar findings.

Table 2. Hazard ratios for the association between cotrimoxazole prophylaxis (CPT) from 6-36 weeks of age and infant diarrhea or respiratory infection from 8-48 weeks of age.

	Unadjusted		Adjusted*	
	HR	(95% CI)	HR	(95% CI)
Outcome: Diarrhea				
Routine CPT vs no routine CPT	0.59	(0.54, 0.65)	0.59	(0.54, 0.65)
Outcome: Respiratory Infection				
Routine CPT vs no routine CPT	0.64	(0.60, 0.69)	0.65	(0.60, 0.69)

*Adjusted for rainy season (Nov-Mar) and BAN antiretroviral and nutrition randomization arm

Figure. Incidence of diarrhea and respiratory infection per 100 person-weeks, by cotrimoxazole prophylaxis (CPT) status



Analysis

A cohort study design was used.

Outcomes included all documented diarrhea or respiratory infection events occurring from 8-48 weeks of age; events occurring >2 weeks apart were treated as separate events.

Conditional gap-time proportional hazards models were used.

Conclusions

CPT was associated with a significant reduction in respiratory and diarrheal morbidity in HIV-exposed, uninfected infants.

Together with our previous findings of significant reductions in serious infant morbidity and mortality associated with cotrimoxazole prophylaxis in this cohort, our recent findings indicate that CPT may have an important role to play in reducing the leading global causes of morbidity and mortality in the growing population of HIV-exposed, uninfected infants in malaria-endemic resource-limited settings.

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[1]Kourtis AP, et al. Health Outcomes of HIV-Exposed Uninfected African Infants. AIDS. 2013; [2]Davis NL, et al. Impact of Daily Cotrimoxazole on Clinical Malaria and Asymptomatic Parasitemias in HIV-Exposed, Uninfected Infants. CID. 2015

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