Safety and Efficacy of Extended Cotrimoxazole Prophylaxis for the Prevention of Malaria in HIV-Exposed Ugandan Children: A Randomized Controlled Trial

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KEY FINDINGS

- **HIV-uninfected Ugandan children born to HIV-infected mothers, breastfed, and started at 6 weeks and continued on cotrimoxazole (cotrim) prophylaxis beyond breastfeeding until 4 years of age, experienced a 43% reduction in malaria incidence (IRR=0.57; 95% CI: 0.49-0.66; p<0.001) when compared to controls who stopped cotrim prophylaxis after the end of breastfeeding as recommended by WHO**
- **No significant differences in grade 3 or 4 adverse events, hospitalizations or deaths were found until age 5.**
- **No significant difference in malaria incidence in the year following discontinuation of Cotrim at age 2 or 4.**
- **However, malaria incidence increased significantly between 4 and 5 years of age in children who discontinued Cotrim at age 4.**

Conclusion: Continuing cotrimoxazole prophylaxis beyond the period recommended by WHO may be safe and efficacious in protecting HIV-exposed children living in malaria endemic areas.

METHODS

Location: **Tororo, Uganda**, with holoendemic malaria and very highantifolate resistance

Eligibility criteria: • age 6 weeks to 12 months, • documented HIV status of child and mother, • currently breastfeeding, • living within 30 km of study clinic, • agreeing to come to clinic for any fever or illness and to avoid taking medications outside the study protocol, • absence of medical condition requiring admission, • informed consent.

Enrolment by convenience sampling between August 2007 & April 2008:

- **203 HIV-exposed uninfected, 48 HIV-infected & 100 HIV-unexposed uninfected children**
- All participants received a **long-lasting insecticide-treated bednet** (ITN).
- **Daily cotrimoxazole prophylaxis** was prescribed to all HIV-exposed and HIV-infected enrolled children, following national guidelines.

Sequential randomizations of HIV-exposed uninfected children :

1. At end of breastfeeding, children who remained HIV-uninfected were randomized 1:1 to continue cotrim prophylaxis until 2 years of age or to discontinue prophylaxis immediately.
2. At 2 years of age, children who had continued Cotrim since the end of BF were re-randomized 1:1 to discontinue or continue Cotrim prophylaxis until 4 years of age.

Malaria was diagnosed by positive thick blood smear (regardless of parasite density) done upon documented tympanic temperature ≥38.0˚C or history of fever in the past 24 hours.

Treatment: • Children >4 months of age and >5 kg with uncomplicated malaria : **ACT**
• Children <4 months of age or <5 kg with uncomplicated malaria and children with severe or complicated malaria: **standard doses of quinine**.
• Children with Hbg <10 gm/dL: **ferrous sulfate** x 14 days + **antihelmintic therapy** as needed.

Follow-up: • Standard 28-day follow-up schedule for each malaria episode
• Standard WHO classification system for treatment outcomes
• New 28-day follow-up started in case of early or late clinical failure within 14d of treatment
• All children were followed up to 5 years of age

RESULTS

- 185 out of 203 enrolled HIV-exposed infants remained in follow-up up to first randomization
- 146 of 185 (79%) HIV-exposed children completed follow-up to age 5
- 40 of 48 (83%) HIV-infected children remained in follow-up to age 2, and 21 of 40 (44%) completed follow-up to age 5
- 88, 79, and 73 of the 100 HIV-unexposed children remained in follow-up to 2, 4 and 5 years of age, respectively

Table 1: Baseline characteristics of HIV-exposed children at 2nd randomization (age 2yrs)

CHARACTERISTICS	HIV-EXPOSED CHILDREN (N=91) Second randomization		Comparison cohorts	
	Daily Cotrim continued from age 2 to 4 (n=45)	Daily Cotrim stopped at age 2 (n=46)	HIV-UNEXPOSED children not on Cotrim (n=88)	HIV-INFECTED children on daily Cotrim since HIV diagnosis (n=48)
Female gender, n (%)	24 (53%)	18 (39%)	36 (41%)	25 (52%)
Median age at study enrollment in months (IQR[1])	3.0 (2.3-5.2)	3.3 (2.2-5.6)	5.4 (3.4-7.5)	5.6 (2.8-8.5)
Median age at breastfeeding end in months (IQR)	7.5 (6.0-10.6)	7.2 (6.4-8.9)	21.1 (18.3-23.2)	17.0 (9.6-20.8)
Median age at first randomization in months (IQR)	10.1 (8.2-13.1)	9.6 (8.5-11.2)	N/A	N/A
Time on Cotrim before 2nd randomization (CPY[2])	74.8	75.9	0	72.8
Percent time using an insecticide-treated bed net	97%	98%	98%	99%
Residing in Tororo town, n (%)	12 (27%)	7 (15%)	18 (20%)	13 (27%)
Malaria incidence per person-year before 2nd randomization (95% CI)	1.93[3] (1.63-2.27)	2.87 (2.50-3.27)	4.68 (4.32-5.05)	2.01[3] (1.69-2.37)
Randomization for treatment of uncomplicated malaria: Artemether-lumefantrine (%)	15 (33%)	24 (52%)	39 (44%)	19 (40%)
Dihydroartemisinin-piperaquine (%)	16 (36%)	17 (37%)	46 (52%)	16 (33%)
Not randomized (%)	14 (31%)	5 (11%)	3 (3%)	13 (27%)

[1] IQR: Interquartile range; [2] CPY: Cumulative person-years

- No difference in baseline characteristics except for malaria incidence
- Adherence to Cotrim prophylaxis and ITNs was >97%

Table 2: Comparative safety outcomes among HIV-exposed children randomized to discontinue or continue cotrimoxazole (Cotrim) prophylaxis through age 4

Safety outcome	Discontinued Cotrim prophylaxis (177 PYAR[1])	Continued Cotrim prophylaxis (188 PYAR[1])	IRR (95% CI)	p-value
All grade 3-4 AEs (incidence per PYAR)	215 (1.216)	111 (0.592)	0.51 (0.36-0.72)	<0.001
Individual Grade 3-4 AEs[2] (Incidence / PYAR[1]):				
Elevated temperature	133 (0.752)	48 (0.256)	0.35 (0.24-0.51)	<0.001
Anemia	67 (0.379)	51 (0.272)	0.69 (0.34-1.40)	0.31
Neutropenia	10 (0.057)	9 (0.048)	0.85 (0.34-2.15)	0.73
Thrombocytopenia	5 (0.028)	2 (0.011)	0.36 (0.06-2.33)	0.28
All serious adverse events (incidence PYAR[1])	33 (0.187)	31 (0.165)	0.91 (0.42-1.98)	0.81
Hospitalizations (incidence PYAR[1])	25 (0.141)	30 (0.160)	1.35 (0.57-3.16)	0.50

[1] PYAR = persons-years at risk ; [2] Only includes children with at least 5 total events

- No significant differences in adverse events or safety outcomes among HIV-exposed children randomized to stop or continue Cotrim at any age
- 13 deaths occurred in total, 7 of them among HIV-exposed children with no difference among groups on or off Cotrim. No death was attributed to Cotrim administration.

Table 3: Incidence of any malaria among HIV-exposed , HIV-unexposed and HIV-infected children according to Cotrim randomizations and age ranges

HIV status	Age range	N	Cotrimoxazole prophylaxis status	Episodes	PY*	Incidence per PY	IRR† (95% CI)	p-value
HIV-exposed	Enrollment–end of BF	203	On Cotrim since age 6 wks	142	105.5	1.35		
HIV-infected	*Enrollment–2 years of age*	*48*	On Cotrim since age 6 wks	*142*	*73.5*	*1.93*	*N/A*	
HIV-unexposed	*Enrollment–2 years of age*	*100*	*Not on Cotrim*	*674*	*145.7*	*4.63*		
HIV-exposed	End of BF – 2 years of age	87	Cotrim stopped after BF	400	86.9	4.60	Reference	-
		98	On Cotrim until age 2	305	104.1	2.93	0.66 (0.52-0.82)	<0.001
HIV-exposed	>2–4 years of age	80	Cotrim stopped after BF	900	151.2	5.95	Reference	-
		46	Cotrim stopped at age 2	503	89.9	5.60	0.96 (0.78-1.17)	0.69
		45	On Cotrim until age 4	243	83.4	2.91	0.53 (0.43-0.67)	<0.001
HIV-infected	>2–4 years of age	*40*	*On Cotrim since HIV Dx*	*166*	*62.4*	*2.66*	*0.47 (0.37-0.60)*	*<0.001*
HIV-unexposed		*88*	*Not on Cotrim*	*959*	*164.8*	*5.82*	*0.99 (0.84-1.17)*	*0.91*
HIV-exposed	>4–5 years of age	71	Cotrim stopped after BF	371	69.7	5.32	Reference	-
		36	Cotrim stopped at age 2	204	42.4	4.81	0.93 (0.73-1.18)	0.54
		45	Cotrim stopped at age 4	167	36.2	4.61	0.92 (0.71-1.20)	0.55
HIV-infected	>4–5 years of age	*21*	*On Cotrim since HIV Dx*	*59*	*22.8*	*2.59*	*0.55 (0.42-0.69)*	*<0.001*
HIV-unexposed		*79*	*Not on Cotrim*	*383*	*76.8*	*4.99*	*0.97 (0.79-1.18)*	*0.74*

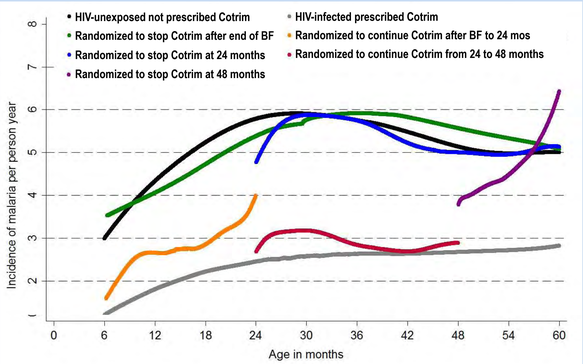
*PY = persons-years ; †IRR = Incidence Rate Ratio

- **HIV-exposed children who continued Cotrim prophylaxis to age 4 had a 47% lower risk of malaria when compared to children who stopped Cotrim at age 2 or to children who stopped Cotrim after the end of breastfeeding**
- **Cotrim provided a 55% protective efficacy against complicated malaria**
- **Cotrim provided a 43% overall protective efficacy againts malaria from first randomization after breastfeeding cessation to age 4**
- **No statistically significant differences in malaria incidence in the year following discontinuation of Cotrim prophylaxis among children who stopped at age 2 or 4**

CONCLUSIONS

- **Continuing cotrimoxazole prophylaxis beyond the period of HIV exposure until age 4 was safe and provided a 43% protective efficacy against malaria in an area characterized by very high malaria transmission intensity and anti-folate plasmodium resistance**
- **Extending cotrimoxazole prophylaxis to age 4 may be followed by rebound malaria incidence, possibly due to delaying the development of natural anti-malarial immunity**

Fig. 1: Malaria incidence in relation to age between 6 and 60 months among HIV unexposed, HIV-infected, and HIV-exposed children randomized to continue Cotrim at end of breastfeeding and 2 years of age



- **Malaria incidence was similar among HIV-unexposed children who never received Cotrim prophylaxis and HIV-exposed children who discontinued Cotrim at breastfeeding cessation**
- **Malaria incidence between 48 and 60 months of age was stable or decreasing for HIV-exposed children who discontinued Cotrim at end of breastfeeding or age 2, but rose for HIV-exposed children who stopped Cotrim at age 4**

Table 4: Risk of malaria with increasing age in relation to exposure to HIV and Cotrim prophylaxis

COTRIMOXAZOLE EXPOSURE GROUP	AGE RANGE	or* (95% ci)	P-value
HIV-unexposed never on Cotrim	30-60 months	0.84 (0.78-0.90)	<0.001
HIV-exposed - Cotrim stopped after breastfeeding	30-60 months	0.86 (0.79-0.93)	<0.001
HIV-exposed - Cotrim stopped at 24 months	30-60 months	0.86 (0.78-0.94)	0.001
HIV-infected - Always on Cotrim	30-60 months	1.08 (0.83-1.39)	0.57
HIV-exposed - Cotrim stopped at 48 months	48-60 months	1.78 (1.19-2.66)	0.005

- **Significant and consistent association between increasing age and decreasing risk of malaria from 30-60 months of age in HIV-exposed children who stopped Cotrim after breastfeeding or age 2**
- **Increasing age was associated with an increased risk of malaria between 48-60 months of age in HIV-exposed children who stopped Cotrim at age 4**