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Efficacy and safety of three regimens for the prevention of malaria in young HIV-exposed Ugandan children: a randomized controlled trial

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Abstract

Objective—Trimethoprim-sulfamethoxazole (TS) prophylaxis is recommended for HIV-exposed infants until breastfeeding ends and HIV infection has been excluded. Extending prophylaxis with a focus on preventing malaria may be beneficial in high transmission areas. We investigated three regimens for the prevention of malaria in young HIV-exposed children.

Design—Open-label, randomized controlled trial.

Setting—Tororo, Uganda, a rural area with intense, year-round, malaria transmission.

Participants—200 infants aged 4-5 months enrolled and 186 randomized after cessation of breastfeeding and confirmed to be HIV uninfected (median 10 months of age).

Intervention—No chemoprevention, monthly sulfadoxine-pyrimethamine (SP), daily TS, or monthly dihydroartemisinin-piperaquine (DP) given from randomization to 24 months of age.

Main outcome measures—The primary outcome was the incidence of malaria during the intervention period. Secondary outcomes included the incidence of hospitalization, diarrheal illness, or respiratory tract infection; prevalence of anemia and asymptomatic parasitemia; measures of safety; and incidence of malaria over 1 year after the intervention was stopped.

Results—During the intervention, the incidence of malaria in the no chemoprevention group was 6.28 episodes per person-year at risk. Protective efficacy was 69% (95% CI, 53-80%, p<0.001) for DP, 49% (95% CI, 23-66%, p=0.001) for TS, and 9% for SP (95% CI, −35 to 38%, p=0.65). There

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were no significant differences in any secondary outcomes, with the exception of a lower prevalence of asymptomatic parasitemia in the DP arm.

Conclusions—Monthly chemoprevention with DP was safe and associated with a significant reduction in malaria in young HIV-exposed children.

Keywords

HIV-exposed uninfected infants; malaria chemoprevention; dihydroartemsinin piperaquine; trimethoprim sulfamethoxazole prophylaxis; sulfadoxine pyrimethamine

INTRODUCTION

Due to the success of prevention of mother-to-child transmission (PMTCT) interventions [1], HIV-exposed uninfected (HEU) children (HIV negative children born to HIV-infected mothers) are a growing population in Africa. Importantly, these children have been reported to have an increased risk of morbidity and mortality compared with children born to HIV-uninfected mothers [2-6]. This association is thought to be mediated through several factors, including impaired immunity[7-10], premature cessation of breastfeeding [11], and indirect factors such as increased parental mortality, exposure to maternal infections, and poverty.

Given the increased morbidity and mortality in HEU children and high rates of maternal to child transmission of HIV in the absence of PMTCT interventions, the World Health Organization (WHO) recommends placing HEU children on trimethoprim-sulfamethoxazole (TS) prophylaxis starting at 6 weeks of age [12]. This recommendation was initially made following studies in HIV-infected adults showing that TS effectively reduces morbidity by preventing opportunistic infections [13]. Subsequent studies showed that TS prophylaxis reduces morbidity in HIV-infected [14-16] and HEU children [11, 17, 18]. Current guidelines recommend discontinuation of TS prophylaxis in HEU children after the period of HIV exposure (i.e. after breastfeeding ends and HIV infection has been excluded) [12].

One of the principal benefits of TS prophylaxis in individuals living in Sub-Saharan Africa is the prevention of malaria. Several studies have shown a benefit of TS in preventing malaria in HIV-infected and uninfected children and adults [15, 19, 20]. Further, there is evidence of continued benefit of TS prophylaxis in immune reconstituted HIV-infected children and adults on antiretroviral therapy when administered beyond current guideline recommendations, largely through prevention of malaria [21, 22]. We previously showed that extending TS prophylaxis beyond breastfeeding cessation to 24 months of age was safe and resulted in 39% protective efficacy against malaria among HEU children living in a high malaria transmission setting [23]. In that study, TS did not have significant benefit against diarrhea or respiratory tract infections, two common infectious syndromes associated with HIV infection. We therefore asked whether we could improve upon the efficacy of daily TS in preventing malaria in HEU children beyond the period of HIV exposure by comparing it with two strategies of intermittent preventative therapy (IPT): monthly sulfadoxine pyrimethamine (SP), another antifolate medication used for prevention of malaria during pregnancy and in childhood [24-26], or monthly dihydroartemisinin-piperaquine (DP), a regimen with excellent treatment efficacy against malaria and a prolonged post-treatment

prophylactic effect [27]. Children were randomized after the cessation of breastfeeding to one of these three chemoprevention strategies (daily TS, monthly SP, or monthly DP) or to no chemoprevention (discontinue TS prophylaxis) through 24 months of age, and then followed for an additional year after the intervention.

METHODS

Study design, site and population

We performed a randomized, controlled, open-label trial comparing the efficacy and safety of 3 regimens versus no therapy for the prevention of malaria in HEU children living in Tororo District, eastern Uganda, an area with intense year-round malaria transmission and an entomological inoculation rate estimated at 125 infectious bites per person-year in 2011-12[28].

Convenience sampling was used to enroll a cohort of 200 infants 4-5 months of age from the Tororo District Hospital Maternal and Child Health clinic between June 2010 and July 2011. Eligibility criteria included: 1) confirmed HIV positive status of biological mother; 2) confirmed negative HIV DNA PCR test of infant at time of enrollment; 3) infant actively breastfeeding at time of enrollment; 4) residency within 30 km of the study clinic with no intention of moving outside the study area; 5) agreement to come to the study clinic for any illness and to avoid medications outside the study protocol; 6) provision of informed consent by parent/guardian; 7) no history of allergy or sensitivity to any study drugs; 8) absence of active medical problem requiring in-patient evaluation or chronic medical conditions requiring frequent attention; 9) absence of clinically significant electrocardiogram abnormalities, family history of long QT syndrome, or current use of drugs that prolong the QT interval. Only one eligible child was enrolled per household, and at enrollment, all children were prescribed daily TS prophylaxis for the duration of breastfeeding as standard of care and each household was given 2 long lasting insecticide treated bednets (ITNs).

Study drugs and treatment allocation

Six weeks following cessation of breastfeeding, a DNA PCR test was done for each participant and those who remained HIV uninfected were randomized. A randomization list using permuted variable sized blocks of 4, 8, and 12 was computer generated by a member of the study not directly involved in patient care. Randomization was done using pre-made, consecutively numbered, sealed envelopes. Treatment allocation was performed by nurses not involved with patient care. Study drugs were dosed as: TS (Co-trimoxazole, *Kampala Pharmaceutical Industries*, Uganda) single dose once daily, SP (Kamsidar, *Kampala Pharmaceutical Industries*, Uganda) single dose each month, and DP (Duo-Cotexin, Holley-Cotec, Beijing, China) once daily for 3 consecutive days each month; each provided for administration at home according to weight-based guidelines. At the time of treatment allocation parents/guardians were given a 2 month supply of drugs and a diary with dates for dosing and check-offs to indicate administration. Parents/guardians were instructed to re-administer drugs if children vomited within 30 minutes of administration and to bring children to the clinic if they vomited again. During each visit to the study clinic parent/guardians were questioned about study drug use.

Study Procedures

Participants received all of their medical care at a designated study clinic open every day. Children who presented with a documented fever (tympanic temperature ≥ 38.0°C) or history of fever in the previous 24 hours had blood obtained by finger prick for a thick blood smear. If the smear was positive, the patient was diagnosed with malaria and a complete blood count (CBC) and thin blood smear for parasite speciation were performed. Episodes of uncomplicated malaria were treated with artemether-lumefantrine (AL). AL was administered twice a day for 3 days, with the first dose each day directly observed in the clinic and the second administered at home. Episodes of complicated malaria (severe malaria or danger signs) [29] or treatment failures occurring within 14 days of prior therapy were treated with quinine. Routine evaluations, including thick blood smears and assessment of adherence with ITNs and study drugs, were done monthly. CBC, glucose, and alanine aminotransferase (ALT) levels were assessed every 4 months. HIV DNA PCR tests were done every 60 days during breastfeeding, at 6 weeks following cessation of breastfeeding and at 18 months of age. Adverse events were assessed and graded according to severity (mild, moderate, severe, life-threatening) using standardized criteria at every clinic visit. Diagnosis of incident episodes of non-malarial illnesses, including diarrheal illnesses and respiratory tract infections, were based on a pre-specified list of diagnostic criteria developed by the study team. Medications with antimalarial activity were avoided for the treatment of non-malarial illnesses when possible. Antihelminthics, iron sulfate, and vitamin A were prescribed following Integrated Management of Childhood Illness guidelines.

Chemoprevention was stopped at 24 months of age and study participants were followed-up 1 additional year until they reached 36 months of age. Study participants were prematurely withdrawn from the study for: 1) documented HIV infection by DNA PCR (these children were referred to an appropriate HIV care center), 2) movement out of the study area, 3) failure to be seen in the study clinic for > 60 consecutive days, 4) withdrawal of informed consent, or 5) inability to comply with the study schedule and procedures.

Laboratory procedures

Thick and thin blood smears were stained with 2% Giemsa for 30 minutes. Parasite density was estimated by counting the number of asexual parasites per 200 white blood cells and assuming a white blood cell count of 8,000 per μL. A smear was deemed negative if no parasites were seen in 100 high powered fields. Microscopy quality control included re-reading all blood smears and resolution of any discrepancies by a third microscopist. Piperaquine (PQ) drug levels were measured from capillary blood collected on filter paper on the day malaria was diagnosed among study participants randomized to monthly DP, as previously described [30].

Statistical analysis

The study was designed to test the hypotheses that chemoprevention will lower the incidence of malaria compared to no chemoprevention, and that the optimal chemoprevention regimen will be DP. We assumed that the incidence of malaria would be 1.85 episodes per person year with TS based on a prior cohort study in the same area [23], and thus that we would need to enroll 50 participants in each arm to detect a reduction in the

incidence of malaria in either the monthly SP or DP arms (two-sided significance level = 0.05) compared to the daily TS arm of 48% or greater with 80% power at 95% significance (two-sided), allowing for 10% loss to follow-up.

Data were double-entered and verified in Microsoft Access and statistical analyses performed using Stata, version 12 (Stata-Corp). All analyses used an intention-to-treat approach for participants who were randomized to therapy. The primary outcome was the incidence of malaria, defined as the number of incident episodes per time at risk, during the period the intervention was given. Treatments within 14 days of a prior episode were not considered incident events. Time at risk was from the day following the initiation of study drugs to the last day of observation, minus 14 days after each treatment for malaria. Secondary outcomes included the incidence of complicated malaria, hospitalizations, diarrheal illnesses, respiratory tract infections, and serious adverse events or adverse events of moderate or greater severity (grade 3-4); the prevalence of moderate-severe anemia (hemoglobin < 8 gm/dL) at the time of each episode of malaria and upon routine testing every 4 months and the prevalence of parasitemia and gametocytemia seen in monthly routine blood smears. To assess the impact of chemoprevention on the development of naturally acquired immunity, the incidence of malaria, complicated malaria, and hospitalizations were compared after the intervention was stopped, between 24-36 months of age.

Incidence outcomes were compared using a negative binomial regression model, and prevalence outcomes and measure of compliance with ITNs at the time of monthly assessments were compared using generalized estimating equations with adjustment for repeated measures. For all analyses, only the assigned treatment arm was included as a covariate, with the exception of a multivariate analysis performed for the primary outcome of malaria incidence, which also included age at randomization and incidence of malaria prior to randomization, covariates thought to be potential independent risk factors for malaria. Measures of association were expressed as protective efficacy (PE = 1 minus the incident rate ratio or prevalence ratio) during the intervention and incident rate ratios after the intervention was stopped. A p value < 0.05 was considered statistically significant.

Ethics statement

Ethical approval was obtained from the Uganda National Council for Science and Technology, the Makerere University School of Medicine Research and Ethics Committee, and the University of California, San Francisco Committee on Human Research.

RESULTS

Trial profile and baseline characteristics

We screened 205 children and 200 were enrolled (Figure). Of enrolled children, 14 (7.0%) were excluded before randomization, including 7 who became infected with HIV. The 186 enrolled children were randomized to one of the four treatment arms at a median age of 10 months: 46 to no chemoprevention, 46 to monthly SP, 47 to daily TS, and 47 to monthly DP. Baseline characteristics were similar across treatment arms (Table 1). Prior to

randomization, the incidence of malaria was lower in children subsequently randomized to all three treatment arms compared to children randomized to no chemoprevention, although these differences were not statistically significant (Table 1). Among the 186 infants who were randomized, 174 (95.5%) and 171 (91.9%) were followed-up to 24 months and 36 months of age, respectively (Figure). At monthly assessments 96.8% reported sleeping under an ITN the prior evening, without significant differences between the study arms (p=0.31).

Protective efficacy of chemoprevention regimens against malaria

From the time of randomization to 24 months of age, the incidence of malaria in the no chemoprevention group was 6.28 episodes per person year (Table 2). After adjusting for age at randomization and incidence of malaria prior to randomization, monthly DP had the greatest protective efficacy (PE) against malaria (PE=69%, 95% CI, 53-80% p<0.001), followed by daily TS (PE=49%, 95% CI, 23-66%, p=0.001). Monthly SP did not have significant PE compared to the no chemoprevention group (PE=9%, 95% CI, −35-38%, p=0.65). In comparison to daily TS, monthly DP was associated with a marginally significant protective efficacy (PE = 39%, 95% CI 0-62%, P=0.05). In all 4 arms the incidence of malaria increased with age and the protective efficacies in the daily TS and monthly DP arms were greater for children 16 months or younger compared to those 17-24 months of age (Table 2, Supplemental Figure).

The proportion of assigned doses of study medications administered at home based on diaries completed by the primary care givers were 93% for SP, 99% for TS, and 96% for DP. To further explore adherence among study participants randomized to monthly DP, PQ blood concentrations were measured at the time of each episode of malaria. Among 82 episodes, 81 samples were available for analysis. For 3 episodes PQ levels were > 100 ng/mL and the primary caregivers reported giving the DP within the prior 24 hours, suggesting the coincidental onset of malaria just before the scheduled time for monthly DP dosing. For the remaining 78 samples PQ levels were below the level of detection (< 10 ng/mL) on the day malaria was diagnosed in 53% of episodes, suggesting that a complete dose of DP was not administered in the previous month [31, 32]. Thus, despite caregiver reports to the contrary, our results suggest frequent non-adherence with study dosing schedules.

Protective efficacy of chemoprevention regimens against secondary outcomes

Overall, complicated malaria was uncommon. Of a total of 620 treatments for malaria during the intervention period, 18 (2.9%) were for complicated malaria; 10 for severe malaria (9 severe anemia and 1 respiratory distress) and 8 for danger signs (6 single convulsions and 2 persistent vomiting). There were no significant differences in the incidence of complicated malaria, hospitalization, diarrheal illnesses, respiratory tract infections or the prevalence of moderate to severe anemia or gametocytemia between the treatment arms (Table 3). Monthly DP was significantly protective against asymptomatic parasitemia compared to the no chemoprevention arm (PE= 88%, 95% CI, 48-91%, p=0.001). Daily TS and monthly SP were not significantly protective against asymptomatic parasitemia (Table 3).

The incidence of malaria was 9.08 episodes per person year at risk among children 24-36 months of age who had not received chemoprevention (Table 3). Following the cessation of the interventions, the incidence of malaria was 6.75, 8.13, and 6.78 episodes per person year for children who had been on monthly SP, daily TS and monthly DP, respectively. There were no significant differences in these incidences, although there were trends towards a lower incidence in children randomized to SP or DP. Similarly, there were no significant differences in the incidence of complicated malaria or hospitalizations between the treatment arms in the year after the interventions were stopped, although there were trends towards a lower incidence in children randomized to DP (Table 3).

Safety outcomes

Among those assigned to study drugs, there were 144 grade 3 or 4 adverse events, but only 8 (5.6%) were classified as possibly related to study drugs (3 for TS and 5 for DP, Table 4). The incidence of grade 3 or 4 adverse events, anemia and elevated temperature were significantly lower in the DP arm compared to the control arm. The incidence of grade 3 or 4 anemia was significantly lower in the TS arm compared to the control arm (p=0.009). There were no significant differences in the incidence of serious adverse events between the treatment arms (Table 4).

DISCUSSION

We evaluated the efficacy and safety of 3 different malaria chemoprevention strategies given to HEU children beyond the period of HIV exposure when TS prophylaxis is normally discontinued: continuation of daily TS; monthly SP; or monthly DP. Despite the use of ITNs, the incidence of malaria in those discontinuing TS was remarkably high, at more than 6 episodes per person-year at risk from randomization to 24 months of age, and more than 9 episodes per person-year at risk from 24-36 months of age. Monthly SP provided no significant protection against malaria. Continuation of daily TS prophylaxis reduced the incidence of malaria by 49%. Monthly DP was the most effective regimen, reducing the incidence of malaria by 69% and the prevalence of asymptomatic parasitemia by 88%. None of the regimens provided significant protection against diarrheal illnesses or respiratory tract infections. All three regimens were safe and there were no differences in the incidence of malaria between the treatment arms after the intervention was stopped.

Current WHO guidelines recommend discontinuation of TS prophylaxis in HEU children after breastfeeding cessation, assuming that the main benefit of prophylaxis is prevention of opportunistic infections, such as *Pneumocystis* pneumonia, if a child is infected with HIV [12]. Several studies have shown that a major benefit of TS prophylaxis in sub-Saharan Africa is prevention of malaria [15, 19, 20], and that this benefit extends beyond immune reconstitution in HIV-infected children and adults on antiretroviral therapy [21, 22]. We previously showed that extending TS prophylaxis in HEU children beyond the period of HIV exposure was safe and modestly efficacious at preventing malaria [23]. In the present study, daily TS again provided modest benefit against malaria, without significant benefit against diarrheal or respiratory tract infections, suggesting that the main benefit in extending TS prophylaxis in HEU children in this setting is the prevention of uncomplicated malaria.

The other intensive antifolate regimen studied, monthly SP, offered no significant protection against malaria, which may not be surprising given the high prevalence of mutations in *P. falciparum* target genes associated with antifolate resistance in Uganda [23, 33]. Monthly DP was the most protective against malaria and asymptomatic parasitemia. Importantly, the true protective efficacies of all 3 studied regimens may have been underestimated, as treatments were not directly observed, and measurements of PQ blood levels suggested frequent noncompliance with chemoprevention regimens. Overall, our results were not surprising given recent studies showing excellent protective efficacy of monthly DP in African children [34, 35], including a parallel study showing 58% protective efficacy of DP compared to no chemoprevention in HIV-unexposed children in Tororo [30].

We were also interested in the subsequent impact of chemoprevention after cessation of study drugs, given concerns that chemoprevention might delay the acquisition of antimalarial immunity, leading to a rebound in the incidence of malaria after the intervention is stopped [36, 37]. Interestingly, recent studies of IPT have not been associated with a rebound in the incidence of malaria [25], with one study showing a sustained reduction in the incidence of malaria in the year after the intervention was stopped, suggesting that IPT could actually enhance the development of naturally acquired immunity [38]. In the present study, in the year following the discontinuation of study drugs, the incidence of malaria was similar in children randomized to the 3 chemopreventive regimens and in children who had not received prior chemoprevention, suggesting that, in this high transmission setting, the use of chemopreventive regimens with a range of protective efficacies did not negatively impact the development of antimalarial immunity. Further, there were trends towards lower incidences of malaria, complicated malaria, and all cause hospital admissions after cessation of chemoprevention in children randomized to monthly DP, suggesting a more rapid acquisition of immunity in those children.

In conclusion, we found that, in an area of high malaria endemicity, continuing daily TS or starting monthly DP in HEU children from the time of breastfeeding cessation through 24 months of age had significant protective efficacy against malaria in comparison to the current standard of care, discontinuation of TS prophylaxis. Monthly DP had the greatest protective efficacy, was safe, and was not associated with rebound in malaria morbidity in the 1 year following the intervention. Given the rising number of HEU children living in malaria endemic settings, our results argue strongly for continued malaria prophylaxis beyond the period of HIV exposure. Additional studies are needed to evaluate optimal chemoprevention strategies in breastfeeding children in the era of Option B+, as well as strategies to optimize treatment compliance and maintain surveillance for potential selection of drug-resistant parasites.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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MRK, DVH, PR, TDC, JA, and GD conceived and designed the study. VB, JK, SK, FM, MKM, AK, and BO supervised the enrolment and follow-up of patients. VB, JK, PJ, and GD assisted with verification, analysis, and interpretation of the data. MK drafted the original version of the manuscript. FA and LH were responsible for measurements of piperaquine drug levels. All authors participated in the writing of the manuscript, and read and approved the final manuscript.

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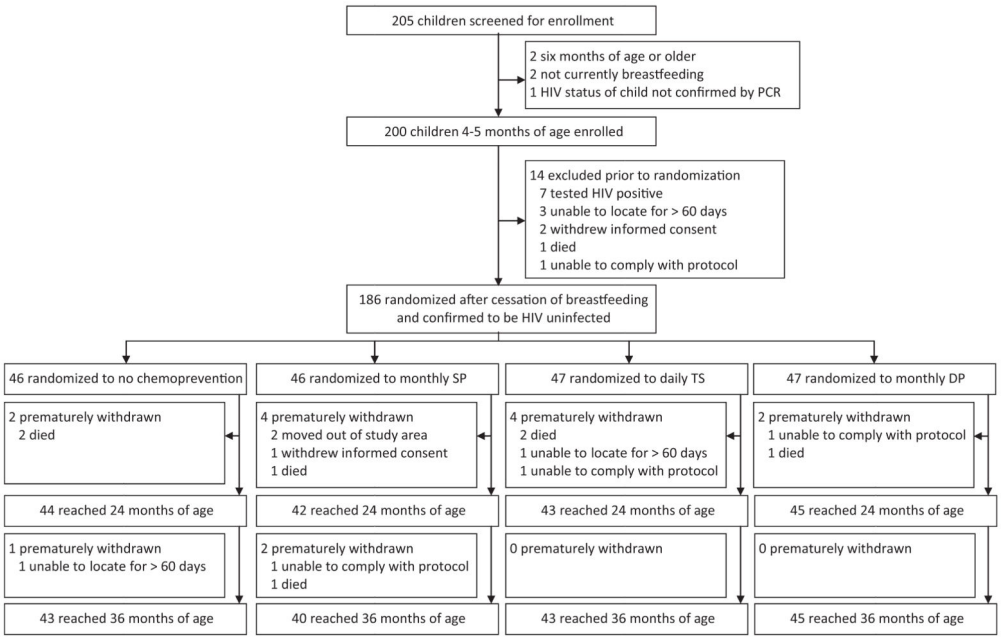

Figure.
Trial Profile.

Table 1
Baseline characteristics of study participants randomized to the intervention

Characteristic	Intervention arm			
	Control (n=46)	Monthly SP (n=46)	Daily TS (n=47)	Monthly DP (n=47)
At the time of enrollment				
Age in months, mean (SD)	4.8 (0.7)	4.7 (0.7)	4.8 (0.8)	4.7 (0.8)
Female gender, n (%)	22 (47.8%)	21 (45.7%)	27 (57.5%)	25 (53.2%)
Slept under any bednet prior night, n (%)	27 (58.7%)	27 (58.7%)	26 (55.3%)	29 (61.7%)
Slept under ITN prior night, n (%)	22 (47.8%)	24 (52.2%)	19 (40.4%)	22 (46.8%)
Taking TS prophylaxis, n (%)	5 (10.9%)	7 (15.2%)	5 (10.6%)	9 (19.2%)
Stunted[1], n (%)	6 (13.0%)	7 (15.2%)	6 (12.8%)	7 (14.9%)
Wasted[2], n (%)	0	4 (8.7%)	1 (2.1%)	4 (8.5%)
Hemoglobin (gm/dL), mean (SD)	10.1 (1.2)	10.0 (1.4)	10.1 (1.1)	10.0 (1.5)
Positive thick blood smear, n (%)	8 (17.4%)	4 (8.7%)	8 (17.0%)	6 (12.8%)
At the time of randomization				
Age in months, median (range)	10.0 (6.0-18.0)	9.3 (6.5-18.8)	11.6 (6.2-18.7)	10.3 (6.5-20.0)
Duration of follow-up in months, median (range)	5.7 (1.9-13.4)	5.1 (2.0-14.8)	6.1 (1.8-14.7)	5.2 (1.8-15.9)
Incidence of malaria per PYAR[3] (95% CI)	2.12 (1.57-2.80)	1.51 (1.05-2.10)	1.63 (1.18-2.20)	1.82 (1.32-2.44)

[1] Length-for-age Z-score < −2

[2] Weight-for-age Z-score < −2

[3] Person-year at risk from date of enrollment to date of randomization

Table 2

Protective efficacy against incident episodes of malaria stratified by age

Treatment arm	Randomization to 24 months of age					Randomization to 16 months of age			17 to 24 months of age		
	Number of cases	PYAR[1]	Incidence per PYAR[1]	PE[2] (95% CI)	p value	Incidence per PYAR[1]	PE[2] (95% CI)	p value	Incidence per PYAR[1]	PE[2] (95% CI)	p value
Control	240	38.2	6.28	reference	-	5.42	reference	-	7.04	reference	-
Monthly SP	182	40.4	4.50	9% (−35 to 38)	0.65	3.72	2% (−64 to 42)	0.93	5.22	14% (−29 to 43)	0.47
Daily TS	116	40.6	2.86	49% (23 to 66)	0.001	1.70	63% (34 to 79)	0.001	3.79	42% (12 to 62)	0.01
Monthly DP	82	44.7	1.83	69% (53 to 80)	<0.001	0.90	84% (69 to 92)	<0.001	2.67	61% (39 to 75)	<0.001

[1] PYAR = person-year at risk

[2] PE = protective efficacy adjusted for age at randomization and incidence of malaria prior to randomization

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Table 3
Comparative effectiveness against secondary outcomes

Treatment arm	Number of cases	PYAR	Incidence per PYAR	PE (95% CI)	p value
Complicated malaria					
Control	5	47.3	0.106	reference	-
Monthly SP	8	47.2	0.170	−57% (−417 to 52)	0.46
Daily TS	3	44.9	0.067	37% (−181 to 86)	0.55
Monthly DP	2	47.8	0.042	61% (−110 to 93)	0.27
All-cause hospital admissions					
Control	10	47.3	0.211	reference	-
Monthly SP	17	47.2	0.360	−60% (−342 to 42)	0.36
Daily TS	8	44.9	0.178	21% (−147 to 75)	0.69
Monthly DP	6	47.8	0.126	46% (−81 to 84)	0.32
Diarrheal illnesses					
Control	101	47.3	2.13	reference	-
Monthly SP	82	47.2	1.74	21% (−20 to 47)	0.27
Daily TS	98	44.9	2.18	−2% (−53 to 32)	0.91
Monthly DP	77	47.8	1.61	25% (−13 to 51)	0.17
Respiratory tract infections					
Control	146	47.3	3.08	reference	-
Monthly SP	144	47.2	3.05	6% (−33 to 33)	0.73
Daily TS	158	44.9	3.52	−8% (−52 to 23)	0.65
Monthly DP	170	47.8	3.56	−11 (−57 to 21)	0.53
Incident episodes of malaria after intervention stopped (24 to 36 months of age)					
Control	294	32.4	9.08	reference	-
Monthly SP	219	32.5	6.75	0.83 (0.55-1.24)	0.36
Daily TS	266	32.7	8.13	1.06 (0.71-1.59)	0.77
Monthly DP	243	35.8	6.78	0.78 (0.52-1.16)	0.22
Complicated malaria after intervention stopped (24 to 36 months of age)					
Control	7	43.6	0.161	reference	-
Monthly SP	6	40.9	0.147	1.00 (0.16-6.26)	0.99
Daily TS	5	43.0	0.116	0.73 (0.12-4.66)	0.74
Monthly DP	2	45.1	0.044	0.28 (0.03-2.35)	0.24
All cause hospital admissions after intervention stopped (24 to 36 months of age)					
Control	20	43.6	0.459	reference	-

Treatment arm	Number of cases	PYAR	Incidence per PYAR	PE (95% CI)	p value
Monthly SP	13	40.9	0.318	0.99 (0.18-5.58)	0.99
Daily TS	8	43.0	0.186	0.41 (0.07-2.40)	0.32
Monthly DP	4	45.1	0.089	0.20 (0.03-1.29)	0.09
Prevalence of moderate-severe anemia (Hb < 8 gm/dL)					
Control		42/362 (11.6%)		reference	-
Monthly SP		46/347 (13.3%)		−11% (−128 to 46)	0.77
Daily TS		22/285 (7.7%)		7% (−100 to 57)	0.86
Monthly DP		25/282 (8.9%)		27% (−62 to 67)	0.44
Prevalence of asymptomatic parasitemia					
Control		37/228 (16.2%)		reference	-
Monthly SP		23/228 (10.1%)		41% (−17 to 70)	0.13
Daily TS		22/282 (7.8%)		46% (−8 to 72)	0.08
Monthly DP		12/369 (3.3%)		88% (48 to 91)	0.001
Prevalence of gametocytemia					
Control		10/228 (4.4%)		reference	-
Monthly SP		3/228 (1.3%)		67% (−84 to 94)	0.21
Daily TS		4/282 (1.4%)		61% (−44 to 89)	0.16
Monthly DP		6/369 (1.6%)		61% (−41 to 89)	0.15

PYAR = person-year at risk. PE = protective efficacy. SP = sulfadoxine-pyrimethamine. TS = trimethoprim-sulfamethoxazole. DP = dihydroartemisinin-piperaquine.

Table 4

Comparative safety outcomes

Characteristic	Number of events (incidence per PYAR[1]) by treatment arm			
	Control	Monthly SP	Daily TS	Monthly DP
All grade 3-4 adverse events	62 (1.214)	77 (1.478)	32 (0.659)	35 (0.678)[3]
Individual grade 3-4 adverse events[2]				
Anemia	36 (0.705)	32 (0.631)	10 (0.206)[4]	15 (0.291)[3]
Elevated temperature	22 (0.431)	27 (0.532)	10 (0.206)	9 (0.174)[3]
Thrombocytopenia	0	6 (0.118)	0	3 (0.058)
Elevated aspartate aminotransferase	2 (0.039)	1 (0.020)	2 (0.041)	2 (0.039)
Malnutrition	1 (0.020)	1 (0.020)	1 (0.021)	2 (0.039)
Grade 3-4 events possibly related to study drugs	N/A	0	3 (0.062)	5 (0.097)
All serious adverse events	21 (0.411)	23 (0.453)	16 (0.330)	10 (0.194)

[1] PYAR = person-year at risk

[2] Only includes those with at least 5 total events

[3] p-value< 0.05 compared to control group

[4] p-value< 0.01 compared to control group