MAJOR ARTICLE

Artemether-Lumefantrine versus Dihydroartemisinin-Piperaquine for Falciparum Malaria: A Longitudinal, Randomized Trial in Young Ugandan Children

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(See the editorial commentary by Price and Douglas, on pages 1638–40.)

Background. Artemisinin-based combination therapies are now widely recommended as first-line treatment for uncomplicated malaria. However, which therapies are optimal is a matter of debate. We aimed to compare the short- and longer-term efficacy of 2 leading therapies in a cohort of young Ugandan children.

Methods. A total of 351 children aged 6 weeks to 12 months were enrolled and followed up for up to 1 year. Children who were at least 4 months of age, weighted at least 5 kg, and had been diagnosed as having their first episode of uncomplicated malaria were randomized to receive artemether-lumefantrine or dihydroartemisinin-piperaquine. The same treatment was given for all subsequent episodes of uncomplicated malaria. Recrudescent and new infections were distinguished by polymerase chain reaction genotyping. Outcomes included the risk of recurrent malaria after individual treatments and the incidence of malaria treatments for individual children after randomization.

Results. A total of 113 children were randomized to artemether-lumefantrine and 119 to dihydroartemisinin-piperaquine, resulting in 320 and 351 treatments for uncomplicated falciparum malaria, respectively. Artemether-lumefantrine was associated with a higher risk of recurrent malaria after 28 days (35% vs 11%; $P < .001$). When the duration of follow-up was extended, differences in the risk of recurrent malaria decreased such that the overall incidence of malaria treatments was similar for children randomized to artemether-lumefantrine, compared with those randomized to dihydroartemisinin-piperaquine (4.82 vs 4.61 treatments per person-year; $P = .63$). The risk of recurrent malaria due to recrudescent parasites was similarly low in both treatment arms.

Conclusions. Artemether-lumefantrine and dihydroartemisinin-piperaquine were both efficacious and had similar long-term effects on the risk of recurrent malaria.

Clinical trials registration. NCT00527800.

With increasing resistance to older drugs, nearly all African countries have recently adopted artemisinin-based combination therapies as first-line treatment for uncomplicated malaria. The World Health Organization currently recommends 4 artemisinin-based combination therapy regimens: artesunate-sulfadoxine-pyrimethamine, artesunate-mefloquine, artesunate-amodiaquine, and artemether-lumefantrine [1]. However, in Africa there are limitations to the first 3 regimens because of safety concerns and the emergence of drug resistance, especially in East Africa [2]. In contrast, artemether-lumefantrine has been highly efficacious and well tolerated, becoming the most widely adopted first-line regimen [1, 3]. Dihydroartemisinin-piperaquine, a newer artemisinin-based combination therapy, has shown excellent efficacy in multiple trials from Asia and Africa and is considered highly promising for global deployment [4–8]. Potential advantages of dihydroartemisinin-piperaquine include its simple once-a-day dosing and the longer half-life of piperaquine (3–4 weeks), compared with lume-

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fantrine (~4 days), which may lead to a longer posttreatment prophylactic effect [7–11].

There have been important gaps in clinical trials of artemisinin-based combination therapies. First, nearly all trials have studied individual episodes of malaria in patients followed up for a specified period after therapy, most commonly 28 days. However, important differences in drug efficacy may only be appreciated after longer durations of follow-up. Second, there is a paucity of data for artemisinin-based combination therapy efficacy in unique patient populations, such as very young children and patients exposed or infected with human immunodeficiency virus (HIV) [9]. In this trial, we compared the efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated malaria with use of a longitudinal study design in a cohort of children living in an area of very high malaria transmission intensity in Uganda. Our cohort included HIV-unexposed, HIV-exposed (HIV-uninfected infants born to HIV-infected mothers), and HIV-infected infants enrolled from 6 weeks to 12 months of age and followed up for up to 1 year.

METHODS

Study area and enrollment of cohort. The study was conducted in Tororo, an area of Eastern Uganda with a high malaria transmission intensity [10]. Convenience sampling was used to enroll a cohort of infants presenting to local antenatal clinics for routine care. Eligibility criteria included the following: (1) age of 6 weeks to 12 months, (2) documented HIV status of mother and child, (3) agreement to come to the study clinic for any illness and avoid medications administered outside the study protocol, (4) living within a 30-km radius of the study clinic, (5) absence of active medical problem requiring inpatient evaluation, (6) currently breast-feeding if HIV exposed, and (7) provision of informed consent. All study participants were given an insecticide-treated bed net at enrollment. Daily trimethoprim-sulfamethoxazole prophylaxis was given to all HIV-infected participants and HIV-exposed participants until completion of breast-feeding. HIV-infected participants were provided antiretroviral therapy according to national guidelines.

Follow-up of study participants. Study participants were followed up for all of their medical problems in a study clinic open 7 days a week free of charge. Parents or guardians were encouraged to bring their children to the study clinic or hospital any time the children were ill. Children presenting with new medical problems underwent standardized medical evaluation. Children who presented to the clinic with a documented fever (tympanic temperature ⩾38.0°C) or a history of fever in the previous 24 h had blood obtained by finger prick for a thick blood smear. If the thick blood smear result was positive, the patient was diagnosed as having malaria regardless of the par-

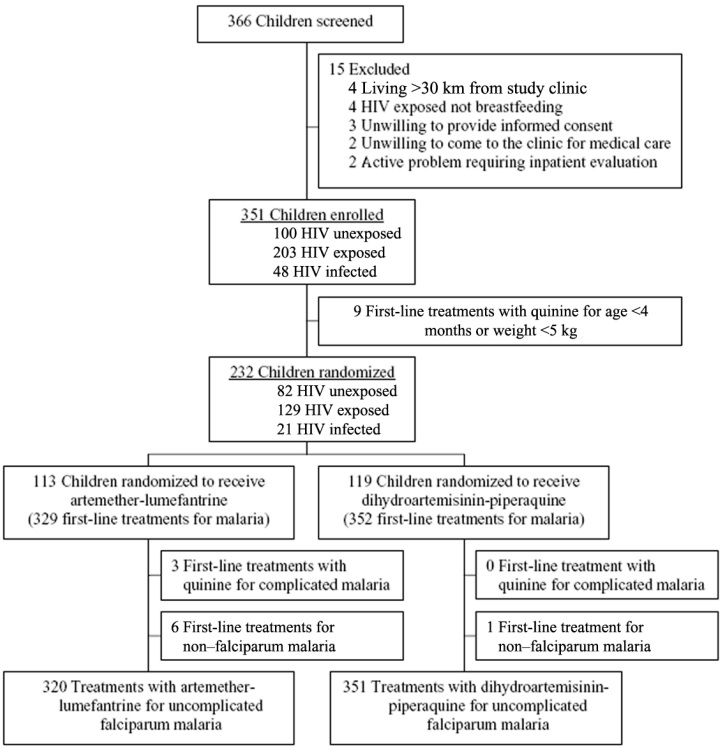

Figure 1. Trial profile. HIV, human immunodeficiency virus.

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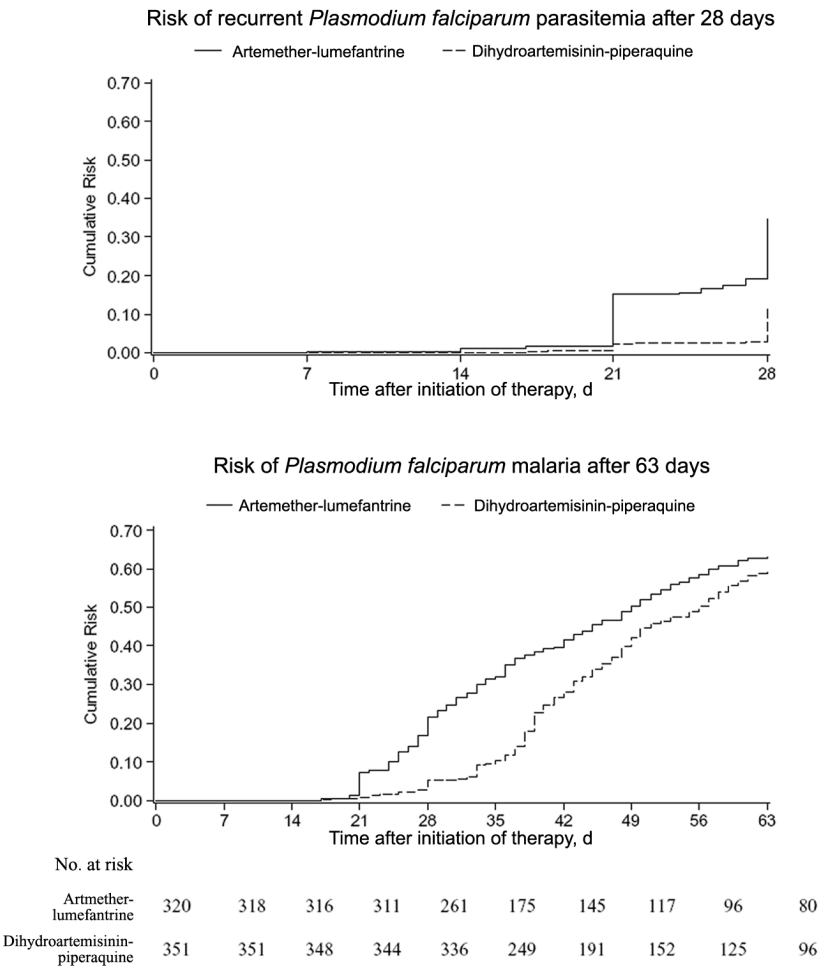

Figure 2. Cumulative risks of recurrent parasitemia and recurrent malaria stratified by treatment group using the Kaplan-Meier product limit formula.

asite density. Monthly routine assessments were performed in the study clinic to ensure adherence with the study protocol. Study participants were withdrawn from the study for (1) movement outside the study area, (2) inability to be located for >60 consecutive days, (3) withdrawal of informed consent, (4) inability to adhere to the study schedule and procedures, or (5) inability to tolerate study drugs.

Treatment allocation and study drug administration. Study participants aged ⩾4 months and weighing ⩾5 kg were randomly assigned to receive either open-label artemether-lumefantrine or dihydroartemisinin-piperaquine at the time that their first episode of uncomplicated malaria was diagnosed. A randomization list was computer generated by an off-site investigator. Sequentially numbered, sealed envelopes containing the treatment group assignments were prepared from the randomization list. The study nurse assigned treatment numbers sequentially and allocated treatment by opening the envelope corresponding to the treatment number. Study participants received the same treatment regimen for all subsequent episodes of uncomplicated malaria.

A nurse administered study drugs according to weight-based guidelines for fractions of tablets as follows: artemether-lumefantrine (tablets of 20 mg of artemether and 120 mg of lumefantrine; Coartem; Novartis), administered as 1 (5–14 kg) or 2 (15–24 kg) tablets given twice daily for 3 days; and dihydroartemisinin-piperaquine (tablets of 40 mg of dihydroartemisinin and 320 mg of piperaquine; Duocotecxin; Holley Pharm), targeting a total dose of 6.4 and 51.2 mg/kg of dihydroartemisinin and piperaquine, respectively, given in 3 equally divided daily doses to the nearest one-quarter tablet. Patients were given a glass of milk or asked to breast-feed after each dose of study medication. The first daily dose of study drugs was directly observed at the study clinic. After each dose, children were observed for 30 min, and the dose was readministered if vomiting occurred. For patients randomized to receive artemether-lumefantrine, parents or guardians were in-

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Table 1. Baseline Characteristics of All Episodes of Uncomplicated Falciparum Malaria Treated with Study Drugs

Characteristics	Treatment arm	
	Artemether-lumefantrine (n = 320)	Dihydroartemisinin-piperaquine (n = 351)
Age, mean months ± SD	11.7 ± 3.3	11.9 ± 3.6
Age, months		
4–8	70 (22)	76 (22)
9–11	106 (33)	107 (30)
12–20	144 (45)	168 (48)
Temperature, mean °C ± SD	38.6 ± 1.1	38.4 ± 1.0
Parasite density, geometric mean cells/μL (IQR)	18,534 (8160–74,277)	14,164 (4720–60,800)
Gametocytes present	26 (8.1)	30 (8.6)
Hemoglobin, mean g/dL ± SD	9.8 ± 1.5	9.9 ± 1.5
Receiving trimethoprim-sulfamethoxazole prophylaxis	124 (39)	127 (36)
HIV exposed[a]	145 (45)	162 (46)
HIV infected	38 (12)	26 (7.4)
Receiving antiretrovirals	33 (10)	18 (5.1)

NOTE. Data are no (%) of patients, unless otherwise indicated. HIV, human immunodeficiency virus; IQR, interquartile range; SD, standard deviation.

[a] HIV-uninfected children born to HIV-infected mothers.

structed to give the second daily dose at home. Patients aged <4 months or weighing <5 kg and patients with severe malaria or danger signs were treated with standard doses of quinine (unsupervised for 7 days).

Malaria follow-up and outcome classification. Participants diagnosed as having malaria were asked to return on days 1, 2, 3, 7, 14, 21, and 28 and any other day they felt ill. Blood was obtained by finger prick for thick blood smears and storage on filter paper on all follow-up days, except day 1. Treatment outcomes were classified according to World Health Organization guidelines as early treatment failure (complicated malaria or failure to adequately respond to therapy on days 0–3), late clinical failure (complicated malaria or fever and parasitemia on days 4–28), late parasitological failure (asymptomatic parasitemia on days 7–28), and adequate clinical and parasitological response (absence of parasitemia on day 28, without previously meeting criteria for treatment failure) [1]. Patients with treatment failure within 14 days were treated with quinine. Malaria diagnosed >14 days after a previous episode was treated with study drugs. Patients were not assigned a treatment outcome in the event of (1) use of antimalarials outside the study protocol, (2) loss to follow-up, or (3) withdrawal of informed consent. At each follow-up visit, study clinicians assessed patients for adverse events according to standardized criteria based on World Health Organization and National Institutes of Health guidelines.

Laboratory procedures. Thick smears were stained with 2% Giemsa for 30 min. Parasite density was estimated by counting the number of asexual parasites per 200 white blood cells and calculating parasites per microliter, assuming a white blood cell count of 8000 cells/μL. A smear result was judged to be negative if no parasites were seen after review of 100 high-powered fields. Final microscopy results were based on a rigorous quality control system with re-reading of all blood smears by a second microscopist and resolution of any discrepancies by a third microscopist. Hemoglobin measurements were made using a portable spectrophotometer (HemoCue; Ängelholm) on day 0 and day 28 or the day of recurrent malaria.

Parasite species on the day malaria was diagnosed were determined using nested polymerase chain reaction as described elsewhere [11]. For recurrent episodes of parasitemia, molecular genotyping was used to distinguish new from recrudescent infections. DNA was isolated from blood spots, and samples were genotyped in a step-wise fashion with use of 6 polymorphic markers as described elsewhere [12]. If, for any of the 6 loci, an allele was not shared between consecutive episodes of parasitemia, the episode was classified as a new infection. If at least 1 allele was shared at all 6 loci, the episode was classified as a recrudescence.

Statistical analysis. The study was powered to test the hypothesis that the risk of recurrent parasitemia (unadjusted by genotyping) after 28 days of follow-up would be lower for dihydroartemisinin-piperaquine, compared with artemether-lumefantrine. We estimated that the incidence of malaria would be 0.62 and 3.04 episodes of malaria per person-year among those receiving and not receiving trimethoprim-sulfamethoxazole prophylaxis, respectively. On the basis of these estimates, after 1 year of data accrual, we expected to have 205 treatments

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Table 2. World Health Organization Treatment Outcome after 28 Days of Follow-up

Treatment outcome	Treatment arm, no (%) of patients	
	Artemether-lumefantrine (n = 320)	Dihydroartemisinin-piperaquine (n = 351)
No treatment outcome		
All	5 (1.6)	6 (1.7)
Other antimalarial use	2	1
Lost to follow-up	2	5
Complicated malaria on day 0	1	0
Recurrent malaria caused by non-falciparum species	1 (0.3)	0 (0)
Early treatment failure	0 (0)	0 (0)
Late clinical failure[a]	45 (14.1)	13 (3.7)
Late parasitological failure[a]	64 (20.0)	26 (7.4)
All failure		
Overall	109 (34.1)	39 (11.1)
Recrudescence	3	1
New infection	105	38
Genotyping unsuccessful	1	0
Adequate clinical and parasitological response	205 (64.1)	306 (87.2)

[a] All late clinical failures and late parasitological failures were genotyped to distinguish recrudescence from new infections.

in each treatment arm. We further estimated that the risk of recurrent parasitemia after 28 days would be 50% in the artemether-lumefantrine arm. Given these estimates and assuming 90% of patients treated with study drugs would complete 28-day follow-up, we would have 80% power (2-sided type 1 error of .05) to detect a ⩾15% risk difference between the treatment groups.

Data were double-entered in Epi-Info, and statistical analysis was performed using Stata statistical software, version 10 (StataCorp). Efficacy and safety data were evaluated using an intention-to-treat analysis, including all patients with falciparum malaria who were randomized to study drug therapy. Primary efficacy outcomes included 28-day risk for recurrent falciparum parasitemia (early treatment failure, late clinical failure, or late parasitological failure) both unadjusted and adjusted by genotyping to distinguish recrudescence and new infection. Secondary outcomes included 63-day risk of recurrent falciparum malaria (unadjusted and adjusted by genotyping), incidence of malaria after randomization, rates of fever and parasite clearance, and measures of safety and tolerability. Risks of treatment failure were estimated using the Kaplan-Meier product limit formula. Data were censored for patients who did not complete follow-up or were reinfected with non-falciparum species and for new *Plasmodium falciparum* infections on the basis of outcomes adjusted by genotyping. Pairwise comparisons of treatment efficacy for individual episodes of malaria were made using a Cox proportional hazards model with adjustment for repeated measures in the same patient. Comparisons for the incidence of malaria treatments were made using a negative binomial regression model with exposure reflected by the time at risk after the first treatment with study drug and adjustment for age at the time of randomization. $P < .05$ was considered to be statistically significant.

RESULTS

Trial profile. A total of 366 children were screened, 351 of whom were enrolled in the study from August 2007 through April 2008 (Figure 1). Study participants were followed up through July 2008. A total of 26 study participants (7%) were withdrawn from the study because of movement outside the study area (n = 14), death due to nonmalaria illnesses (n = 8), inability to be located for >60 consecutive days (n = 1), withdrawal of informed consent (n = 1), inability to adhere to study schedule and procedures (n = 1), and inability to tolerate study drugs (n = 1). In monthly surveys of parents or guardians, children were reported to have slept under an insecticide-treated bed net the prior evening 98% of the time (1256 of 1278 monthly surveys).

Of the 351 participants enrolled in the study, 119 were never diagnosed as having malaria and 232 were randomized to receive therapy. Randomized children experienced 3 episodes of complicated malaria that were treated with quinine, 7 episodes of malaria due to *Plasmodium ovale,* and 671 episodes of uncomplicated falciparum malaria that were treated with study drugs (Figure 1).

Treatment efficacy for uncomplicated falciparum malaria. The baseline characteristics of all episodes of uncomplicated

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Table 3. Comparative Outcomes for Treatment of Uncomplicated *Plasmodium falciparum* Malaria

Outcome	Risk of infection (95% CI), %		HR[a] (95% CI)	*P*
	Artemether-lumefantrine arm	Dihydroartemisinin-piperaquine arm		
28-Day risk of recurrent parasitemia unadjusted by genotyping[b]	35 (30–40)	11 (8.4–15)	3.45 (2.21–5.39)	<.001
28-Day risk of recurrent parasitemia adjusted by genotyping[c]	1.0 (0.3–3.2)	0.3 (0.1–2.1)	3.64 (0.41–32.3)	.24
63-Day risk of recurrent malaria unadjusted by genotyping[b]	63 (57–69)	60 (54–66)	1.38 (1.06–1.80)	.02
63-Day risk of recurrent malaria adjusted by genotyping[c]	1.6 (0.5–5.4)	4.2 (2.1–8.4)	0.49 (0.12–2.05)	.33

NOTE. CI, confidence interval; HR, hazard ratio.

[a] The HR was adjusted for repeated measures in the same patient.

[b] Episodes with no outcomes and recurrent parasitemia or malaria caused by non-falciparum species were censored.

[c] Episodes with no outcomes and recurrent parasitemia or malaria caused by non-falciparum species and new *Plasmodium falciparum* infections were censored.

falciparum malaria treated with study drugs are presented in Table 1. At the time of treatment, 54% of the study participants were aged <1 year, 46% were HIV exposed, 10% were HIV infected, 37% were receiving trimethoprim-sulfamethoxazole prophylaxis, and 8% were receiving antiretrovirals. No statistically significant differences were found in the baseline characteristics between the treatment arms.

Treatment outcomes after 28 days of follow-up are presented in Table 2. Initial response to therapy was excellent, with no early treatment failures. Recurrent parasitemia within 28 days was relatively common in the artemether-lumefantrine treatment arm, with 105 of 320 episodes classified as late clinical failure or late parasitological failure, resulting in a cumulative risk of failure of 35%. In the dihydroartemisinin-piperaquine treatment arm, 39 of 351 episodes were classified as a late clinical failure or late parasitological failure, resulting in a cumulative risk of recurrent parasitemia of 11% (Figure 2 and Table 3). Compared with dihydroartemisinin-piperaquine, artemether-lumefantrine was associated with >3 times the hazard of recurrent parasitemia within 28 days after treatment (hazard ratio, 3.45; 95% confidence interval, 2.21–5.39; Table 3). Results were similar after controlling for age, use of trimethoprim-sulfamethoxazole prophylaxis, and use of antiretrovirals (data not shown). For both treatment arms, nearly all failures were attributable to new infections rather than recrudescences. Considering only recrudescences, the risks of failure were 1.0% with artemether-lumefantrine and 0.3% with dihydroartemisinin-piperaquine ($P = .24$).

When follow-up was extended to 63 days, the risk of recurrent malaria was 63% in the artemether-lumefantrine treatment arm and 60% in the dihydroartemisinin-piperaquine treatment arm (hazard ratio, 1.38; 95% confidence interval, 1.06–1.80; Table 3 and Figure 2). Results were similar after controlling for age, use of trimethoprim-sulfamethoxazole prophylaxis, and use of antiretrovirals (data not shown). Extending follow-up from 28 to 63 days identified 1 additional recrudescence in the artemether-lumefantrine treatment arm and 7 additional recrudescences in the dihydroartemisinin-piperaquine treatment arm. The cumulative risk of recurrent malaria due to recrudescent parasites after 63 days was 1.6% in the artemether-lumefantrine treatment arm and 4.2% in the dihydroartemisinin-piperaquine arm ($P = .33$). The median time to recrudescence with symptomatic malaria was 28 days (range, 21–50 days) in the artemether-lumefantrine arm and 42 days (range, 33–51 days) in the dihydroartemisinin-piperaquine arm. Interestingly, all recrudescences in the artemether-lumefantrine arm occurred in different study participants, whereas in the dihydroartemisinin-piperaquine treatment arm, 3 recrudescences occurred consecutively in the same patient and 2 occurred consecutively in another patient. We also measured the incidence of recurrent malaria, considering all episodes after randomization. Study participants randomized to the artemether-lumefantrine treatment arm had a nonsignificant 5% (95% confidence interval, −13% to 26%; $P = .63$) increase in the incidence of malaria treatments, compared with study participants randomized to the dihydroartemisinin-piperaquine treatment arm (4.82 vs 4.61 treatments per person-year).

Secondary outcomes. Little difference was found in secondary outcomes between the 2 treatment arms (Table 4). Treatment with dihydroartemisinin-piperaquine was associated with a significantly lower risk of fever on day 1, compared with artemether-lumefantrine; however, by day 2, the risk of fever was equally low in both treatment arms. Both treatment arms were associated with rapid parasite clearance. The new appearance of gametocytes after treatment was uncommon, with a trend toward a higher risk in the dihydroartemisinin-piperaquine arm (2.5% vs 0.3%, $P = .07$). Hemoglobin recovery was also similar among the treatment arms. Both treatments appeared to be safe and well tolerated. No significant differences were found in the risk of any adverse events reported (Table 4). A total of 4 serious adverse events were reported (1 in the artemether-lumefantrine arm and 3 in the dihydroartemisinin-piperaquine arm). All these events were due to the development

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Table 4. Secondary Outcomes

Outcome	Treatment arm: Artemether-lumefantrine (n = 320)	Treatment arm: Dihydroartemisinin-piperaquine (n = 351)	P
Fever clearance[a]			
Fever present on day 1	163 (51)	138 (39)	.01
Fever present on day 2	17 (5.3)	13 (3.7)	.30
Fever present on day 3	12 (3.8)	9 (2.6)	.37
Parasite clearance			
Positive blood smear on day 2	22 (6.9)	12 (3.4)	.09
Positive blood smear on day 3	0 (0)	1 (0.3)	.52
Appearance of gametocytes[b]			
Gametocytes present on day 2	1 (0.3)	4 (1.3)	.25
Gametocytes present on day 3	0 (0)	3 (0.9)	.25
Gametocytes present on days 4–14	0 (0)	3 (0.9)	.25
Gametocytes present on days 15–28	0 (0)	1 (0.3)	.52
Hemoglobin recovery,[c] mean g/dL ± SD	0.56 ± 1.58	0.62 ± 1.68	.41
Adverse events on days 1–28			
Cough	153 (48)	177 (50)	.51
Diarrhea	86 (27)	79 (23)	.20
Vomiting	20 (6.3)	23 (6.6)	.65
Anorexia	0 (0)	3 (0.9)	.25
Weakness	0 (0)	1 (0.3)	.55
Pruritus	0 (0)	0 (0)	>.99
Any severe adverse event	1 (0.3)	3 (0.85)	.56

NOTE. Data are no (%) of patients, unless otherwise indicated. SD, standard deviation.

[a] Subjective fever during the previous 24 h or temperature ⩾38.0°C.

[b] Patients with gametocytes present on day 0 were not included.

[c] Change in hemoglobin level from day 0 to day 28 or day of clinical failure.

of severe anemia (hemoglobin level, <5 g/dL) during follow-up.

DISCUSSION

In this longitudinal randomized clinical trial, artemether-lumefantrine and dihydroartemisinin-piperaquine were both highly efficacious for the treatment of uncomplicated falciparum malaria in a cohort of young HIV-infected and HIV-uninfected children. As shown in previous studies, artemether-lumefantrine was associated with a markedly higher risk of new infection, compared with dihydroartemisinin-piperaquine, when follow-up was limited to 28 days [4, 7]. However, this difference was much lower when follow-up was extended to 63 days. During the full observation period after randomization, the incidence of malaria was equally high in both treatment arms. Both artemether-lumefantrine and dihydroartemisinin-piperaquine were safe and well tolerated, and they were equally effective when considering secondary outcomes.

Artemisinin-based combination therapies have recently been widely adopted for the treatment of uncomplicated malaria in Africa. Indeed, 24 countries in Africa have now adopted artemether-lumefantrine as recommended first-line therapy, making this the most widely recommended treatment on the continent [13]. Several studies have documented excellent efficacy and safety of artemether-lumefantrine in Uganda and other East African countries [3, 14, 15]. However, artemether-lumefantrine has some limitations, including twice-daily dosing and frequent subsequent infections after therapy in high-transmission locations [4, 16]. Dihydroartemisinin-piperaquine is another fixed-dose artemisinin-based combination therapy that is being increasingly used in Southeast Asia and is part of the national treatment recommendations in Cambodia and Vietnam [17]. This drug benefits from simple once-a-day dosing and an extended period of posttreatment prophylaxis because of the long half-life of piperaquine. There have been 4 published studies documenting the excellent efficacy and safety of dihydroartemisinin-piperaquine in Africa [4, 5, 7, 8]. However, these studies were limited to individual episodes of disease with follow-up of only 28–42 days.

To our knowledge, this study is the first to compare artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated falciparum malaria with use of a

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longitudinal study design. After 28 days of follow-up, patients treated with artemether-lumefantrine had a much higher risk of recurrent parasitemia due to new infections, compared with dihydroartemisinin-piperaquine. However, when follow-up was extended to 63 days, the cumulative risks of recurrent malaria converged, such that there was only a small difference between the 2 drugs. Interestingly, a similar convergence in cumulative risks was seen in a recent study from Apac, Uganda, another area with high transmission intensity [4]. In contrast, in Kanungu, Uganda, a region with much lower transmission intensity, the risk difference between artemether-lumefantrine and dihydroartemisinin-piperaquine increased when extending follow-up from 28 to 42 days [7]. These results suggest that the better posttreatment prophylactic effect of dihydroartemisinin-piperaquine may be short-lived in areas of high transmission intensity, because of the overwhelming risk of recurrent malaria. In contrast, in areas of moderate malaria transmission intensity, the posttreatment prophylactic benefit of dihydroartemisinin-piperaquine may be sustained.

With slowly eliminated drugs, the benefit of longer posttreatment prophylaxis must be balanced against the potential harm of an increased risk for the selection of resistant parasites [18]. Modeling studies have suggested that the spread of antimalarial drug resistance is primarily driven by a "window of selection" after therapy, and the duration of this window is increased for drugs with longer terminal elimination half-lives [19]. The artemisinin drugs have short terminal elimination half-lives and are thus less likely to select for resistance [19]. Lumefantrine, the partner drug in artemether-lumefantrine, has an estimated terminal elimination half-life of 96 h and a modeled window of selection 3–5 weeks after therapy [19]. In contrast, piperaquine, the partner drug in dihydroartemisinin-piperaquine, has an estimated terminal elimination half-life of 28 days and a much larger window for the selection of drug resistance after therapy [17]. Interestingly, 7 of the 8 recrudescences in the dihydroartemisinin-piperaquine arm occurred after 28 days of follow-up, compared with only 1 of 4 in the artemether-lumefantrine arm. Thus, it cannot be ruled out that prolonged piperaquine drug levels delayed but did not prevent the emergence of recrudescent parasites with diminished sensitivity to the drug.

In summary, considering long-term outcomes, artemether-lumefantrine and dihydroartemisinin-piperaquine were both efficacious and safe for the treatment of uncomplicated falciparum malaria in a cohort of young Ugandan children. However, the incidence of malaria was high even in those receiving effective treatment and using insecticide-treated bed nets, with most children experiencing recurrences within 63 days after treatment, highlighting the need for improved malaria control efforts in high transmission areas of Africa.

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Potential conflicts of interest. All authors: no conflicts.

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