MAJOR ARTICLE

Fosmidomycin-Clindamycin for the Treatment of *Plasmodium falciparum* Malaria

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It has been demonstrated that fosmidomycin has good tolerability and rapid onset of action, but late recrudescences preclude its use alone; in vitro, clindamycin has been shown to act synergistically with fosmidomycin against *Plasmodium falciparum*. We conducted a study in pediatric outpatients with *P. falciparum* malaria in Gabon to evaluate the efficacy and safety of an oral combination of fosmidomycin-clindamycin of 30 mg/kg and 10 mg/kg of body weight, respectively, every 12 h. Patients 7–14 years old were recruited in cohorts of 10. The first 10 patients were treated for 5 days. The duration of treatment was then incrementally shortened in intervals of 1 day if >85% of the patients in a cohort were cured by day 14. All dosing regimens were well tolerated, and no serious adverse events occurred. Asexual parasites and fever rapidly cleared in all patients. Cure ratios of 100% on day 14 were achieved with treatment durations of 5 (10/10 patients), 4 (10/10 patients), 3 (10/10 patients), and 2 days (10/10 patients); 1 day of treatment led to a cure ratio of 50% (5/10 patients). Fosmidomycin-clindamycin is safe and well tolerated, and short-course regimens achieved high efficacy in children with *P. falciparum* malaria. Fosmidomycin-clindamycin is a promising novel treatment option for malaria.

New drugs are urgently needed for the treatment of *Plasmodium falciparum* malaria in Africa to replace chloroquine, amodiaquine, and sulfadoxine-pyrimethamine, which are increasingly failing to cure patients with malaria. Serious morbidity and mortality is highest in African children because of the high risk for rapid disease progression, especially if first-line treatment fails.

Fosmidomycin is the first representative of a new class of antimalarial drugs that block the mevalonate-independent 1-deoxy-D-xylulose 5-phosphate pathway localized in the apicoplast of the malarial parasite *Plasmodium falciparum* [1, 2]. In adult patients from Gabon [3, 4] and Thailand [4], fosmidomycin has been shown to be well tolerated and to act rapidly, but late recrudescences preclude its use as monotherapy. Clindamycin emerged as a potential combination partner after the demonstration of synergistic inhibition of plasmodial growth in in vitro and animal studies [5]. We have previously shown that a 5-day regimen of fosmidomycin-clindamycin in children with asymptomatic *P. falciparum* infections was safe, well tolerated, and superior to both fosmidomycin alone and clindamycin alone with respect to rapid and complete parasite elimination [6]. Here we report the results of a clinical trial that was designed to identify the shortest efficacious and safe malaria treatment regimen of fosmidomycin-clindamycin for the treatment of African children with *P. falciparum* malaria.

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PATIENTS, MATERIALS, AND METHODS

Study area. The present study was conducted at the Albert Schweitzer Hospital in Lambaréné, Gabon. Lambaréné and its surrounding area are characterized by

high year-round transmission of *P. falciparum* and an entomological inoculation rate of ~50 infective bites/person/year [7, 8]. The study protocol was approved by the ethics committee of the International Foundation of the Albert Schweitzer Hospital in Lambaréné.

Study design. The present study was designed as an uncontrolled dose-reduction study, with consecutive recruitment of cohorts of 10 patients 7–14 years old. The first cohort was treated with fosmidomycin-clindamycin for 5 days. Once 10 patients were included in the cohort, we stopped the recruitment. The efficacy of the treatment was determined by use of predefined criteria of parasitological and clinical cure in the cohort by day 14. When >85% efficacy was achieved, a new cohort of 10 patients received a treatment regimen that was shortened by 1 day (equivalent to a reduction of 2 treatment doses). Recruitment was discontinued if the day-14 cure ratio was ≤85%. We included additional patients to compensate for patients who did not receive the full treatment course. The use of the >85% efficacy threshold in a cohort of 10 patients ensures that it can be estimated with 95% confidence that at least one-half of the patients in a population will be clinically and parasitologically cured by day 14 (95% confidence interval [CI] when 90% [9/10 patients] were cured by day 14, 55%–100%).

Enrollment of patients. The study took place from March 2002 to February 2003. Pediatric patients with uncomplicated *P. falciparum* malaria attending the outpatient pediatric department of the Albert Schweitzer Hospital in Lambaréné, Gabon, were admitted to the study if they met the following inclusion criteria: 7–14 years old; asexual parasitemia of 1000–100,000/μL and acute manifestation of malaria; body weight of 17.5–65.0 kg; ability to tolerate oral therapy; informed consent by the legal representative of the patient (if possible, the parents); oral agreement of the child, if appropriate; and residence in the study area for at least 4 weeks. The exclusion criteria were as follows: adequate antimalarial treatment within the previous 7 days; antibiotic treatment for a current infection; hemoglobin concentration <7 g/dL; hematocrit <25%; leukocyte count >15,000/μL; and mixed plasmodial infection, severe malaria, any other severe underlying disease, concomitant disease masking assessment of treatment response, inflammatory bowel disease, and any other disease causing fever.

Study drugs and administration. Fosmidomycin was formulated as capsules containing 150 mg of active substance. Clindamycin was supplied as 75-mg capsules. The drugs were administered orally in a 3:1 fixed ratio of 30 mg/kg of body weight of fosmidomycin and 10 mg/kg of body weight of clindamycin every 12 h. Each drug administration was supervised by at least 1 dedicated study physician. Patients who vomited or rejected the study drugs within 30 min received a second full dose. Vomiting or rejecting of the second dose led to withdrawal from the study and administration of a rescue treatment.

Study flow and procedures. Patients were seen by a study physician at 12-h intervals at each drug administration and until 2 consecutive blood smears remained free of asexual parasites; patients were seen again on days 7, 14, 21, and 28 and as otherwise indicated. On each visit during treatment and follow-up, a medical history was taken, vital signs were checked, tympanic temperature was measured, a thick blood smear was prepared from a fingerprick sample, and adverse events were documented. Venipunctures were performed on days 0, 2, 7, and 28, to monitor hemoglobin concentration, hematocrit, and differential white blood cell count as well as hepatic (alanine aminotransferase [ALT]) and renal (creatinine) function parameters. In addition, urine dipstick tests were done at the same time intervals. To distinguish recrudescent infections from reinfections, blood samples from day 0 and from the day of reappearance of asexual parasites were kept for polymerase chain reaction (PCR)–based genotyping analysis.

End points. The primary efficacy end point of this study was the day-14 cure ratio. Cure was defined as initial and sustained parasite and symptom clearance, with no increase in asexual parasitemia 48 h after initiation of treatment and absence of microscopically detectable asexual parasitemia within 120 h of the start of treatment until day 14. The primary safety end point was the incidence of adverse events after the start of treatment. Secondary end points were the parasite and fever clearance times and the PCR analysis–corrected day-28 cure ratio.

Laboratory methods. The dried thick blood smears were stained with 20% Giemsa solution (pH 7.2). Parasite species were identified by use of standard morphological characteristics, and parasitemia was quantified by use of the volumetric Lambaréné method (as described elsewhere [9, 10]) and expressed as number of parasites per microliter. *Msp1* and *msp2* genotyping was performed to distinguish recrudescences from new infections, comparing matched pairs of parasite isolates obtained on admission and on the day of reappearing asexual parasitemia [11, 12]. We classified a reappearing asexual parasitemia after initial clearance as reinfection if all electrophoretically separated PCR product bands detected on the day of reappearing asexual parasitemia were distinct in size from those detected on the day of admission.

Data management and statistical analysis. Data were captured by use of concise, specifically designed medical-record forms and were subsequently entered into an electronic database. Data were then validated by complete manual review. Statistical analysis of the data was performed by use of a commercial software package (Stata 8.2 for Mac OS X; StataCorp).

Cure ratios were calculated as the number of patients with clinical and parasitological cure by day 14 or 28 divided by the total number of evaluable patients (per protocol population). Mean asexual parasite clearance times were calculated and compared by use of a parametric proportional hazards model (Wei-

bull distribution). Fever clearance times were calculated as the time from the start of treatment to the first of 2 consecutive tympanic temperature measurements that remained <37.5°C. Differences in the fever clearance times between the cohorts of different treatment durations were evaluated by use of the Kruskal-Wallis rank test. Fisher's exact test was used to assess differences in categorical outcome variables between the cohorts. The safety analysis included abnormal laboratory data and adverse events from all patients who received at least 1 dose of the study drugs (intention-to-treat population). Differences in changes over time in the laboratory parameters across the cohorts of different treatment durations were assessed by use of repeated-measures analysis of variance, with Box's conservative ε correction for the repeated-measures variable (study day). The statistical significance level was set at 5%.

RESULTS

Treatment and follow-up. In total, 52 patients were enrolled in the study and received at least 1 treatment dose. Enrollment in the study was stopped after the inclusion of 10 patients in the cohort receiving the 1-day regimen. The number of patients included in the cohorts with treatment durations of 5, 4, 3, 2, and 1 day of fosmidomycin-clindamycin is detailed in table 1.

Figure 1 also summarizes the flow of patients through the trial. A total of 50 patients were evaluable for the primary and the secondary efficacy end points (day-14 and -28 cure ratios, respectively). The first patient of this study, a 10-year-old boy (5-day regimen cohort), vomited the first treatment dose and the replacement dose within 30 min and was thus excluded. He was then successfully treated with the rescue treatment of sulfadoxine-pyrimethamine (dose of 25 mg/kg and 1.25 mg/kg, respectively). Another male patient, 7 years old, who was in the 4-day regimen cohort was excluded after inadvertent overdosing on day 1 and received rescue treatment with sulfadoxine-pyrimethamine (same dose). No losses to follow-up occurred.

Baseline characteristics. Table 1 details the baseline characteristics of patients receiving treatment regimens with durations between 1 and 5 days. Baseline parameters were similar among the cohorts, except for median plasma ALT concentrations ($P = .018$).

Efficacy. The results describing the parasitological and clinical response to treatment with fosmidomycin-clindamycin are summarized in table 2. Treatment with fosmidomycin-clindamycin for 5, 4, 3, and 2 days led to mean asexual parasite clearance times (PCT) of 41, 38, 39, and 35 h, respectively. Treatment with fosmidomycin-clindamycin for 1 day (2 doses) was characterized by a prolonged PCT of 63 h ($P < .001$). Fosmidomycin-clindamycin led to prompt fever clearance, with a combined median fever clearance time of 46 h and no significant differences among the cohorts of different treatment durations ($P = .84$). By day 7, all evaluable patients were clinically and parasitologically cured.

By day 14, all evaluable patients who received fosmidomycin-clindamycin for 5, 4, 3, and 2 days were clinically and parasitologically cured (10/10 patients in each cohort) (table 2). In contrast, only 5 of the 10 patients in the 1-day regimen cohort (2 doses) remained free of asexual parasites until day 14. PCR analysis showed that all of these asexual parasite reappearances in the 1-day regimen cohort were due to recrudescent infections.

By day 28, treatment regimens of 5, 4, and 3 days led to high cure ratios of, respectively, 100% (95% CI, 69%–100%) (10/10 patients), 100% (95% CI, 69%–100%) (10/10 patients), and 90% (95% CI, 55%–100%) (9/10 patients). However, treatment regimens of fosmidomycin-clindamycin with durations of 2 days or 1 day were less efficacious in completely eliminating asexual parasites, as evidenced by the accumulating number of recrudescent infections that occurred until day 28, leading to day-28 cure ratios of 70% (95% CI, 35%–93%) (7/10 patients) for 2 days of treatment and only 10% (95% CI, 0%–45%) (1/10 patients) for 1 day of treatment (for the comparison of treatments with durations of $\geqslant$3 days to $\leqslant$2 days, $P < .001$). In total, there were 3 patients with asymptomatic asexual parasite reappearances detected by day 28 that were classified as new infections, 1 patient each in the cohorts receiving fosmidomycin-clindamycin for 4, 3, and 2 days. All of the patients with parasitological treatment failure in the 1-day regimen cohort presented with signs and symptoms suggestive of malaria at the time of detection of asexual parasite reappearance; however, only 2 of the 3 patients with parasitological failure in the 2-day regimen cohort also had clinical failure, and the only patient with parasitological failure in the 3-day regimen cohort was symptom free.

Treatment with fosmidomycin-clindamycin was associated with a high cumulative gametocyte carrier rate (gametocytes detected during at least 1 follow-up visit) of 80% (41/51 patients), with no detectable differences among the cohorts of different treatment durations ($P = 1.0$). The analysis did not change when patients with gametocytes on admission were excluded. In addition, no evidence was found for a gametocytocidal effect of the drug combination in terms of sustained clearance of gametocytes in patients with gametocytes at baseline, with only 2 of 12 patients remaining free of sexual stage parasites during follow-up.

Safety and tolerability. Treatment with fosmidomycin-clindamycin was safe, and no serious adverse events occurred. In total, 64 clinical adverse events were documented: 58 mild and 6 moderate adverse events, of which 26 and 3, respectively, were judged to be either possibly or probably related to the study drugs. The majority of adverse events were reported during the treatment phase and shortly after until day 7 (51/64 events; 80%) (table 3). The most frequent adverse events oc-

Table 1. Baseline characteristics of pediatric patients with *Plasmodium falciparum* malaria.

Category, parameter	Duration of treatment				
	5 days (n = 11)	4 days (n = 11)	3 days (n = 10)	2 days (n = 10)	1 day (n = 10)
Dosing					
Dose of fosmidomycin, mean (SD), mg/kg	32.5 (1.4)	31.9 (1.4)	32.9 (2.8)	31.3 (1.7)	31.6 (1.5)
Dose of clindamycin, mean (SD), mg/kg	11.0 (1.0)	10.0 (1.3)	10.9 (1.1)	10.3 (0.8)	96 (0.5)
Dosing interval, median (range), h	11.9 (9.2–14.9)	11.9 (10.0–13.8)	11.8 (9.7–16.0)	11.7 (10.0–13.7)	12.2 (10.0–15.0)
Characteristics					
Age, median (range), years	9 (7–12)	11 (7–14)	9 (7–13)	9 (7–13)	9 (7–12)
Sex, male:female	5:6	4:7	5:5	2:8	3:7
Weight, median (IQR), kg	28 (13)	29 (15)	27 (10)	26 (17)	25 (9)
Systolic blood pressure, mean (SD), mm Hg	98 (10)	99 (12)	90 (9)	97 (13)	99 (9)
Diastolic blood pressure, mean (SD), mm Hg	62 (8)	61 (12)	53 (5)	62 (7)	62 (10)
Pulse, mean (SD), beats/min	99 (18)	96 (22)	102 (17)	98 (21)	96 (12)
Tympanic temperature, median (IQR), °C	37.3 (1.4)	37.2 (3.2)	38.0 (2.4)	36.7 (0.9)	36.3 (1.0)
Parasitologic results					
Density of asexual *P. falciparum,* median (range), parasites/μL	16,650 (3600–97,600)	30,300 (1100–91,200)	39,000 (1020–100,000)	34,900 (1100–100,000)	16,500 (4200–73,500)
Gametocyte carrier, proportion	6/11	3/11	1/10	1/10	2/10
Hematologic results					
Hemoglobin concentration, mean (SD), g/dL	10.0 (1.1)	11.1 (1.3)	10.3 (1.4)	10.9 (2.0)	10.2 (1.2)
Hematocrit, mean (SD), %	32 (3)	37 (5)	32 (4)	33 (5)	32 (5)
Leukocyte count, mean (SD), 10^9 cells/L	7.2 (2.0)	5.6 (1.4)	7.2 (2.7)	6.5 (2.3)	7.8 (1.6)
Thrombocyte count, median (IQR), 10^9 cells/L	190 (77)	206 (79)	137 (73)	139 (61)	222 (97)
Clinical chemistry					
Plasma ALT concentration, median (IQR), U/L	35 (45)	8 (9)	22 (22)	36 (25)	24 (3)
Plasma creatinine concentration, median (IQR), μmol/L	52 (27)	54 (14)	50 (16)	47 (29)	62 (9)

NOTE. ALT, alanine aminotransferase; IQR, interquartile range.

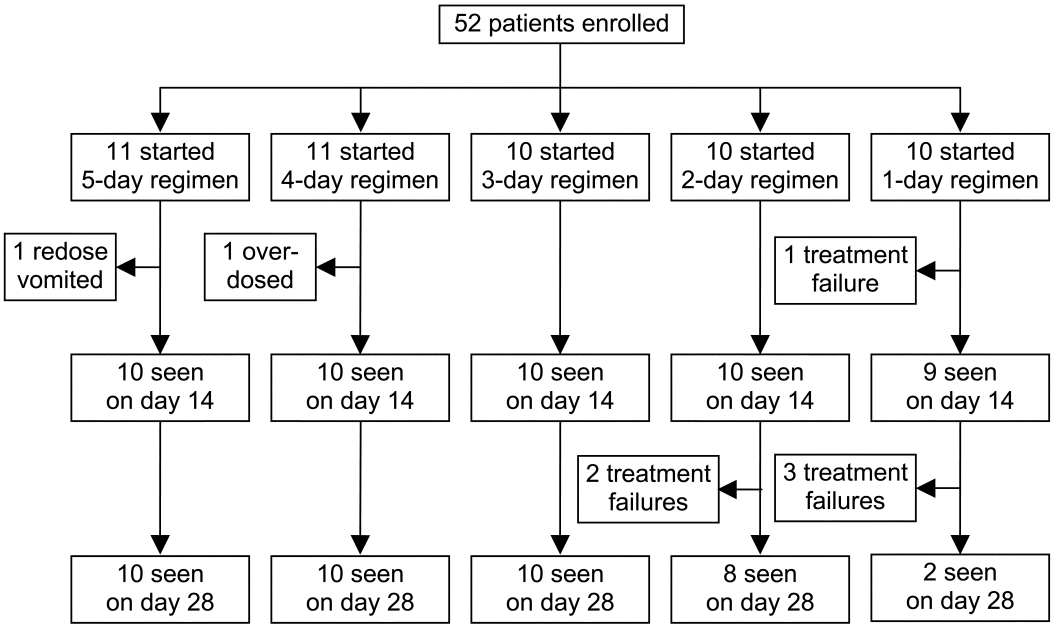

Figure 1. Trial profile

curring before day 7 were gastrointestinal events (29 events, all mild), mostly loose stools (13 events) and abdominal pain (9 events). There was no difference in the distribution of gastrointestinal adverse events among the cohorts of different treatment durations.

The evolution of laboratory parameters is summarized in table 4. No significant differences among the cohorts were observed for mean hemoglobin concentrations ($P = .33$), mean leukocyte counts ($P = .22$), and mean plasma creatinine concentrations ($P = .25$). Differences among the cohorts could not be evaluated for median plasma ALT concentrations, due to significant differences in admission values. Significant changes within cohorts over time were observed for mean hemoglobin concentrations and mean leukocyte counts, with initial decreases from day 0 to day 2 of 1.0 g/dL and 1.0×10^9 cells/L ($P < .001$), respectively, and subsequent recoveries until day 28. No significant changes were observed in median plasma ALT and median plasma creatinine concentrations.

DISCUSSION

The present study confirms previous results from laboratory investigations [5] and initial clinical studies of asymptomatic *P. falciparum* infection [6] indicating a synergistic action of fosmidomycin-clindamycin against *P. falciparum*. Starting with the demonstration of the efficacy of a 5-day regimen of fosmidomycin-clindamycin, we could successfully establish the efficacy of incrementally shortened regimens down to a 2-day regimen, which was still 100% efficacious by day 14.

The day-28 cure ratio is a conservative estimate for complete elimination of asexual parasites from the body and, thus, for the efficacy of an antimalarial drug. In particular, the 3-day regimen led to a high day-28 cure ratio of 90% (9/10 patients) in patients 7–14 years old. African children of this age group bear a major burden of the worldwide morbidity from malaria [13].

Monotherapy of fosmidomycin is not sufficient to completely cure patients [4]. Regimens of clindamycin alone achieve

Table 2. Efficacy of fosmidomycin-clindamycin for the treatment of pediatric patients with *Plasmodium falciparum* malaria.

	Duration of treatment				
Category	5 days ($n = 10$)	4 days ($n = 10$)	3 days ($n = 10$)	2 days ($n = 10$)	1 day ($n = 10$)
Day-14 cure ratio	10/10 (100 [69–100])	10/10 (100 [69–100])	10/10 (100 [69–100])	10/10 (100 [69–100])	5/10 (50 [19–81])
Day-28 cure ratio	10/10 (100 [69–100])	10/10 (100 [69–100])	9/10 (90 [55–100])	7/10 (70 [35–93])	1/10 (10 [0–45])
Asexual parasite clearance times, mean (95% CI), h	41 (33–49)	38 (32–49)	39 (28–42)	35 (25–58)	63 (43–88)

NOTE. Data are proportion (% [95% confidence interval {CI}]) of patients who were cured, unless otherwise noted.

Table 3. No. of adverse events up to day 7, in pediatric patients with *Plasmodium falciparum* malaria treated with fosmidomycin-clindamycin.

	Duration of treatment				
Adverse event	5 days (n = 11)	4 days (n = 11)	3 days (n = 10)	2 days (n = 10)	1 day (n = 10)
Loose stool	3	2	3	1	4
Abdominal pain	2	1	4	1	1
Headache	3	1	…	1	…
Diarrhea	2	1	…	1	…
Fatigue	1	1	1	…	1
Fever	2	1	…	1	…
Anorexia	…	…	2	…	…
Nausea	1	1	…	…	…
Scabies	…	1	…	1	…
Schistosomiasis	2	…	…	…	…
Anemia	1	…	…	…	…
Coughing	1	…	…	…	…
Sore throat	…	1	…	…	…
Vomiting	…	…	…	…	1
Total	18	10	10	6	7

acceptable cure ratios in the treatment of uncomplicated *P. falciparum* malaria, but the onset of action is too slow to be used in nonimmune patients [3, 4, 14, 15]; additionally, clindamycin alone has to be administered for at least 4–7 days, a requirement thought to be related to (1) its short plasma half-life [15] and (2) the pharmacodynamic relationship between limited parasite killing rates (effect per parasite replication cycle) and the resultant requirement to attain peaks of plasma drug concentration for a sufficient number of parasite cycles [16]. The present study clearly demonstrates that coadministration of fosmidomycin-clindamycin leads to a substantial reduction in the duration of treatment required for radical cure, likely because the synergistic action leads to an increased parasite killing rate. The combination of fosmidomycin-clindamycin benefits from fosmidomycin's rapid action in terms of fast malarial symptom and parasite clearance rates [3, 4, 6] and has a clear advantage over clindamycin alone, which cannot be recommended as monotherapy because of its slow onset of action [15].

The present study validates antimalarial drug combinations that target the apicoplast of *P. falciparum*. The rapid antimalarial action of fosmidomycin is thought to be related to the direct inhibition of an essential metabolic pathway of *P. falciparum,* which is located inside the plastid organelle [1]. In contrast, clindamycin inhibits the replication of the apicoplast by binding to a subunit of the apicoplast's ribosomal complex, an effect that might lead to delayed killing of parasites [17].

A short-course regimen of fosmidomycin-clindamycin—ideally a 3-day regimen—fulfils many criteria for an antimalarial first-line treatment option in endemic countries. Most importantly, it is safe and well tolerated; leads to rapid clinical improvement and sustained parasite clearance; has independent and novel mechanisms of action, with no potential cross-resistance to antimalarial drugs currently in use; and is characterized by short plasma half-lives [18, 19], which reduce the selection pressure for drug-resistant parasite strains through prolonged subtherapeutic plasma levels [20, 21].

Fosmidomycin-clindamycin has only a few potential disadvantages. One is the 12-h dosing regimen, which, in the interest of compliance, may be more difficult to achieve than a 24-h dosing regimen outside a clinical trial setting. Another shortcoming is the observed induction of sexual stage parasites. Treat-

Table 4. Evolution of laboratory hematological and biochemical parameters, in pediatric patients treated with fosmidomycin-clindamycin for uncomplicated *Plasmodium falciparum* malaria.

	Study days				
Parameter	Day 0	Day 2	Day 7	Day 28	P
Hemoglobin concentration, mean (SD), g/dL	10.5 (1.5)	9.5 (1.4)	9.8 (1.4)	11.4 (1.0)	<.001
Leukocyte count, mean (SD), 10^9/L	6.8 (2.1)	5.8 (1.5)	6.9 (1.7)	7.0 (2.1)	<.001
Plasma ALT concentration, median (IQR), U/L	24 (22)	26 (20)	28 (14)	17 (14)	.38
Plasma creatinine concentration, mean (IQR), μmol/L	54 (15)	52 (14)	54 (17)	54 (15)	.44

NOTE. Data from all patients are pooled. ALT, alanine aminotransferase; IQR, interquartile range.

ment with fosmidomycin-clindamycin, as with fosmidomycin alone [3], exhibits gametocyte-induction kinetics similar to that with treatment with sulfadoxine-pyrimethamine [22], which could facilitate the transmission of drug-resistant parasite strains.

The present study has demonstrated that fosmidomycin-clindamycin is safe and well tolerated. It is associated with few and mild gastrointestinal side effects, which are all self-limiting. However, loose stools and diarrhea can also arise after treatment with other antimalarial drugs [23–25]. Whether fosmidomycin-clindamycin can trigger rare but severe side effects remains to be seen.

In conclusion, fosmidomycin-clindamycin is safe, well tolerated, and highly efficacious for the treatment of uncomplicated *P. falciparum* malaria in African children >6 years old. A short-course regimen of fosmidomycin-clindamycin emerges as a promising novel antimalarial treatment option for Africa. Future studies should simultaneously focus on the consolidation of the estimate of efficacy of the 3-day regimen and on the systematic evaluation of a 3-day regimen in younger pediatric patients, who have less parasite-specific immunity and, hence, are at higher risk for treatment failure.

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