Effect of nutritional status on response to treatment with artemisinin-based combination therapy in young Ugandan children with malaria

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The relationship between malnutrition and malaria in young children is under debate and no studies have been published evaluating the association between malnutrition and response to artemisinin-based combination therapies (ACTs). We evaluated the association between malnutrition and response to antimalarial therapy in Ugandan children treated with ACTs for repeated episodes of malaria.

Children aged 4 to 12 months diagnosed with uncomplicated malaria were randomized to dihydroartemisinin-piperaquine (DP) or artemether-lumefantrine (AL) and followed for up to 2 years. All HIV-exposed and HIV infected children received trimethoprim-sulfamethoxazole prophylaxis (TS). The primary exposure variables included height-for-age and weight-for-age z-scores. Outcomes included parasite clearance at day 2 and 3 and risk of recurrent parasitemia after 42 days of follow-up.

292 children were randomized to DP or AL, resulting in 2013 malaria treatments. Less than 1% of patients had a positive blood smear by day 3 (DP 0.2%, AL 0.6%, p=0.18). There was no significant association between height-for-age or weight-for-age z-scores and a positive blood smear 2 days following treatment. In children treated with DP not on TS, decreasing height-for-age z-scores <-1 were associated with a higher risk of recurrent parasitemia compared to height-for-age z-score > 0 (HR height-for-age z-score < -1 and ≥ -2 = 2.89, p=0.039; HR height-for-age z-score < -2 = 3.18, p=0.022).

DP and AL are effective antimalarial therapies in chronically malnourished children in a high transmission setting. However, children with mild to moderate chronic malnutrition not taking TS are at higher risk of recurrent parasitemia and may be considered a target for chemoprevention.
Malaria and malnutrition are major causes of morbidity and mortality in children in sub-Saharan Africa. Malaria, predominantly caused by *Plasmodium falciparum*, is estimated to cause 880,000 deaths each year, with the majority of deaths occurring in children under 5 years of age in sub-Saharan Africa (31). At the same time, malnutrition is a major public health problem in developing countries. Approximately one half of the 10.6 million children under 5 who die in low- and middle-income countries are malnourished (30). Common anthropometric indices used to assess the extent of malnutrition include height-for-age, a measurement for linear growth and an indicator of long-term growth deficits; weight-for-height, a measurement of body proportion and an indicator of acute growth disturbances; and weight-for-age, which represents a synthesis of linear growth and body proportion (5). In Africa, malnutrition is highly prevalent; 39%, 8%, and 28% of children under 5 are stunted (height for age z-score<-2), wasted (weight-for-height z-score<-2), or underweight (weight-for-age z-score<-2), respectively (20).

Although malaria and malnutrition frequently coexist (28), there have been few studies evaluating the effect of malnutrition on malaria, and results of such studies have been conflicting. Some studies have reported that children with evidence of malnutrition as characterized by either stunting, underweight, or wasting, have a higher risk of malaria, some have reported a lower risk, while others have reported no association (7, 9, 11, 12). However, in these studies, the anthropometric growth references, age ranges, transmission intensities, and definitions of malaria differed. To our knowledge, no studies have evaluated the effects of malnutrition on the risk of recurrent parasitemia.
Data are also lacking on the effect of malnutrition on response to antimalarial therapy (28).

Vulnerable populations, such as very young children, the HIV-infected and the malnourished are typically excluded from or under-represented in studies of antimalarial drug efficacy (2). The World Health Organization (WHO) currently recommends artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated *P. falciparum* malaria (28). Although WHO recognizes that malnutrition may affect the response to antimalarial therapy (28), there are no published studies examining the association between malnutrition and the response to antimalarial therapy with ACTs.

Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) are two of the most important ACTs for the treatment of uncomplicated *P. falciparum* malaria. AL is highly efficacious and well-tolerated, and has been recommended by WHO as first line treatment for malaria since 2004. DP is a newer ACT that has proven to be equivalent to or more effective than other ACT regimens in clinical trials (1, 3, 24, 32) and is now also recommended by WHO for use as a first line treatment for *P. falciparum* malaria (28). The potential advantages of DP over AL are convenient once-a-day dosing and a longer half-life (3-4 weeks) of the partner drug, piperaquine, compared with lumefantrine (~4 days), leading to a prolonged post-treatment prophylactic effect thus, reducing the risk of new infection. In this study, we evaluated the associations between measures of malnutrition and response to antimalarial therapy in a cohort of young Ugandan children treated with DP or AL for repeated episodes of uncomplicated *P. falciparum* malaria.
MATERIALS AND METHODS

Study Area and Population

This study was conducted in rural eastern Uganda in the district of Tororo. Malaria transmission in this area is holoendemic, occurring perennially and with an entomological inoculation rate (EIR) estimated to be 562 infective bites per person-year (21). Study participants were part of a clinical trial designed to compare the efficacy of two ACT regimens, AL and DP, for the treatment of uncomplicated malaria in very young children. The clinical trial was part of a larger cohort study. The study protocol was approved by the Uganda National Council of Science and Technology and the institutional review boards of Makerere University, the University of California San Francisco, the US Centers for Disease Control and Prevention, and the University of Washington.

A full description of the study design has been presented elsewhere (1). Briefly, convenience sampling was used to enroll 100 HIV-unexposed children (born to HIV-uninfected mothers), 48 HIV-infected children, and 203 HIV-exposed children (HIV-uninfected born to HIV-infected mothers) between August 2007 and April 2008. Eligibility criteria included the following: (1) age 6 weeks to 12 months, (2) documented HIV status of mother and child, (3) agreement to return to the study clinic for any febrile episode or other illness, (4) agreement to avoid medications administered outside of the study protocol, (5) residence within a 30 km radius of the study clinic, (6) currently breastfeeding if HIV-exposed, and (7) parent/guardian provision of informed consent. All mother-child pairs received two long-lasting insecticide treated bednets (ITNs), a safe water vessel, multivitamins, and condoms at the beginning of the study. All HIV-infected children received antiretroviral therapy (ART) consisting of nevirapine plus lamivudine...
plus zidovudine or stavudine, if eligible according to WHO criteria. All HIV-exposed children and HIV-infected children received daily trimethoprim-sulfamethoxazole (TS) prophylaxis. Following cessation of breastfeeding, HIV-exposed children who remained HIV-uninfected were randomized to continue or discontinue TS through 24 months of age. Children who were HIV-exposed and subsequently seroconverted continued TS prophylaxis.

**Malaria diagnosis and treatment**

Subjects were followed for all medical problems at a dedicated study clinic open 7 days a week. After hours care was available at the Tororo District Hospital, which provides service for the entire Tororo district area. Subjects who presented to the clinic with a fever (tympanic temperature $\geq 38.0^\circ C$) or reported history of fever in the past 24 hours provided blood obtained by finger prick for a thick blood smear. If the thick blood smear was positive, the patient was diagnosed with malaria regardless of parasite density. All episodes of malaria were classified as uncomplicated if the following criteria were met: fever ($>38.0^\circ C$ tympanic) or history of fever in the previous 24 hours; positive thick blood smear; and absence of complicated malaria (presence of severe malaria and parasitemia, danger signs and parasitemia, and/or parasite density $\geq 500,000/\mu l$).

At the first diagnosis of uncomplicated malaria, study participants 4 months of age or older and at least 5 kg in weight were randomized to open-label treatment with AL or DP and received the same antimalarial treatment regimen for all subsequent episodes of uncomplicated malaria. A nurse administered study drugs according to weight-based guidelines as follows: AL (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 DP (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 as 3
equally divided doses to the nearest one-quarter tablet. Each dose was given once (for DP) or
twice (for AL) a day over 3 days (days 0, 1 and 2). Patients were given a glass of milk or asked
to breast-feed after each dose of study medication to optimize drug absorption. The first daily
dose of study medication was administered in clinic and directly observed by a study nurse. Any
patient who vomited the medication within 30 minutes of administration was retreated with a
second dose.

**Malaria Follow-up and Outcome Classification**

Study participants diagnosed with malaria were asked to return to the clinic on days 1, 2, 3, 7,
14, 21, 28 or on any other day the parents thought the child was ill. Study participants who did
not return for a scheduled visit were visited at home and, if necessary, transported to the study
clinic. At these visits and on any unscheduled day when a fever was documented or reported in
the previous 24 hours, blood was obtained by finger prick for thick blood smears and filter paper
collection. Study participants were actively followed through day 28 and treatment outcomes
were classified according to the 2006 WHO treatment guidelines (29). Study participants who
took antimalarials outside of the protocol, were lost to follow up, or whose parent/guardian
withdrew consent were not assigned a treatment outcome. Recurrent episodes of malaria
recurring within 14 days of previous treatment were treated with quinine and recurrent episodes
occurring more than 14 days after therapy were treated as a new episode. After 28 days of active
follow-up, study participants were followed passively until their next episode of malaria or to the
end of the observation period. This study includes all episodes of malaria diagnosed from the
time of enrollment through August 2009.

**Anthropometric Measurements**

Anthropomorphic measurements were collected in accordance with internationally accepted
practices on the day malaria was diagnosed. Weight was taken using a spring scale for younger
children (up to approximately 1 year of age) or with a standing scale for older children (Seca,
Hamburg, Germany), both precise to the nearest 100 grams. Recumbent length measurements
were taken using a stadiometer for children up to approximately 1 year of age. After that age,
standing height measurements were taken. All length and height measurements were precise to
the nearest 1 centimeter. Age was calculated using the date of birth of the child.

**Laboratory Methods**

**Malaria Diagnosis:** Thick and thin blood smears were stained with 2% Giemsa for 30 minutes
and read by experienced laboratory technologists who were not involved in direct patient care.
Parasite densities were calculated by counting the number of asexual parasites per 200
leukocytes (or per 500 leukocytes, if the count is <10 asexual parasites/200 leukocytes),
assuming a leukocyte count of 8,000/µl. A blood smear was considered negative when the
examination of 100 high power fields did not reveal asexual parasites. Thin smears were used
for parasite species identification. For quality control, all slides were read by a second
microscopist and a third reviewer settled any discrepant readings. Microscopists were blinded to
the study participants’ treatment assignments.
Molecular Genotyping: Parasite species on the day malaria was diagnosed were determined using nested polymerase chain reaction as described elsewhere (26). For recurrent episodes of parasitemia, molecular genotyping was used to distinguish new infections from recrudescent infections. DNA was recovered from blood spots, and samples were genotyped in a step-wise fashion with use of six polymorphic markers as described elsewhere (13). For any of the six loci, if an allele was not shared between consecutive episodes of parasitemia, the episode was classified as a new infection. If at least one allele was shared at all six loci, the episode was classified as a recrudescence.

Statistical Analysis

All analyses included patients with uncomplicated falciparum malaria and were stratified according to the treatment arm (AL or DP). The primary exposure variables of interest were measures of malnutrition classified according to height-for-age, and weight-for-age z-scores, using the 2006 WHO child growth standards. Because the thresholds for classifying nutritional status have not been universally defined, for the purpose of this analysis, height-for-age (HAZ) and weight-for-age (WAZ) z-scores were divided into four categories with the following cut-offs; \( \geq 0, <0 \text{ and } \geq -1, < -1 \text{ and } \geq -2, \text{ and } < -2 \).

Associations were evaluated between measures of malnutrition and two treatment outcomes: 1) parasite clearance at day 2 and day 3 and 2) the risk of recurrent parasitemia. Parasite clearance was defined as the proportion of patients with a positive blood slide 2 or 3 days following initiation of therapy and comparisons made using generalized estimating equations with adjustment for repeated measures in the same patient by using exchangeable correlation,
binomial distribution, and robust standard errors. Recurrent parasitemia was defined as any early
treatment failure, a positive blood smear between 4 to 28 days of active follow-up, or malaria
diagnosed between days 29-42 of passive follow-up. The risk of recurrent parasitemia was
estimated using the Kaplan-Meier product limit formula with censoring for patients with
incomplete follow-up. The risk of recrudescence after adjustment by genotyping was not
evaluated because previously published data showed that this risk was less than 3% for both
treatment arms (1). Measures of association between categories of malnutrition and the risk of
recurrent parasitemia were made using Cox proportional hazards models, with inference adjusted
for repeated measures (14) in the same patient and adjustment for potential confounders,
including age, cumulative piperaquine or lumefantrine dose (provided over 3 days of dosing and
based on mg/kg of body weight), place of residence, breastfeeding status, and ART use. In addition,
Cox proportional hazard models were stratified by TS use because of the presence of significant
interaction.

Data were double entered in ACCESS (Microsoft Corporation, Redmond, WA). Statistical
analysis was performed using STATA, version 9.0 (Stata Corporation, College Station, TX). For
all analyses, a $P$ value (two-sided) of less than 0.05 was considered statistically significant.

RESULTS

Of the 351 participants enrolled in the study, 292 (83%) were diagnosed with at least one episode
of uncomplicated malaria and randomized to therapy. Of these, 145 were randomized to DP and
147 were randomized to AL, resulting in 981 and 1032 treatments for uncomplicated $P. falciparum$ malaria, respectively, that were included in this study (Figure 1).
Demographic and anthropomorphic baseline characteristics of all episodes of uncomplicated falciparum malaria stratified by treatment are presented in Table 1. At the time of treatment, 90% of study participants resided in a rural area, approximately one-third of all participants were breastfeeding, 30% were taking TS prophylaxis, 8.5% were HIV infected and 92% of these were taking ARTs. Forty-three percent of the study participants had an HAZ z-score <-2 and 13% had a WAZ z-score of <-2, consistent with rates reported across Uganda (15).

Effect of nutritional status on parasite clearance for AL and DP. The proportion of patients with a positive blood smear two days following initiation of therapy was lower in patients treated with DP compared to those treated with AL (5.0% vs. 10.0%, p<0.001). There were very few patients with a positive blood smear three days following the initiation of therapy in either the DP or AL treatment arms (0.2% vs. 0.6%, p=0.18). There was no significant association between HAZ and WAZ scores and a positive blood smear two days following treatment with DP or AL (Table 2).

Effect of nutritional status on risk of recurrent parasitemia. The overall risk of recurrent parasitemia after 42 days of follow-up was higher in study participants treated with AL compared to those treated with DP (54%; 95% CI 51-57% vs 29%; 95% CI 27 - 32%). During model fitting, concomitant use of TS prophylaxis was associated with a significantly lower risk of recurrent parasitemia (HR =0.57, p=0.001 and HR=0.66, p=0.002 for patients receiving DP and AL, respectively) and there was significant interaction between TS use and associations...
between measures of malnutrition and the risk of recurrent parasitemia. Therefore, each model was stratified by TS use.

In study participants not on TS prophylaxis treated with DP, the risk of recurrent parasitemia after 42 days of follow-up increased as HAZ score decreased (log rank test p=0.03, Figure 2). After controlling for age, place of residence, breastfeeding status, cumulative dose of piperaquine received, and ART use, a decreasing HAZ score was independently associated with a higher risk of recurrent parasitemia (Table 3). However, statistical significance was reached only when comparing HAZ scores < -1 with those ≥ 0. There were no significant associations between HAZ scores and the risk of recurrent parasitemia among patients treated with DP and taking TS prophylaxis (Table 3). Similarly, there were no significant associations between WAZ scores and the risk of recurrent parasitemia among patients treated with DP, regardless of whether or not the patient was taking TS prophylaxis (Table 3).

In study participants not on TS prophylaxis treated with AL, the unadjusted risk of recurrent parasitemia after 42 days of follow-up increased as HAZ scores decreased (log rank test p=0.05, Figure 2). After controlling for age, place of residence, breastfeeding status, cumulative dose of lumefantrine received, and ART use, a decreasing HAZ score was independently associated with a higher risk of recurrent parasitemia, although statistical significance was not achieved. There were no significant associations between HAZ scores and the risk of recurrent parasitemia among patients taking TS prophylaxis and treated with AL (Table 4). As with DP, the WAZ score was not associated with recurrent parasitemia in those not taking TS prophylaxis. In study
participants taking TS prophylaxis, there was an association of WAZ scores and recurrent parasitemia. However, this was only significant when comparing those with the lowest (<-2) and highest WAZ score (<0 and ≥ -1) to a WAZ score ≥ 0 (Table 4).

**DISCUSSION**

This is the first longitudinal study assessing the effect of malnutrition on the post-treatment prophylactic effect of ACTs; thus, no direct comparisons to previous studies can be made. We evaluated patients prospectively, taking advantage of a comprehensive clinic infrastructure which provided assurance that all episodes of malaria were captured and followed and compliance with the treatment regimen was high. Compared to other studies which evaluated this vulnerable patient population, our sample size of over 2000 malarial episodes is one of the largest published. In addition, this study utilized the new 2006 WHO growth standards which provide a more accurate tool for monitoring growth differences as they evaluate growth patterns from healthy breast-fed children from around the world (6). Our results indicate that in a high transmission setting, both AL and DP are efficacious antimalarial regimens for treatment of *P. falciparum* malaria in children under three years of age, regardless of nutritional status. Parasite clearance overall was excellent, with more than 99% of study participants clearing all primary parasites by day three. Recrudescence could not be directly evaluated as an outcome of this study due to low numbers (less than 3%), though the lack of recrudescence is further support of the efficacy of these two drug regimens. Compared to children treated with DP, children treated with AL were at higher risk of recurrent parasitemia after 42 days of follow up. Children with signs of mild to moderate chronic malnutrition not taking TS prophylaxis were at higher risk of recurrent parasitemia. However, this was only significant in the DP group.
Although there are no published studies evaluating the relationship of malnutrition and recurrent parasitemia, a few studies have assessed the association between malnutrition and malaria risk. In a cross-sectional study in Kenya of 1862 children under 36 months of age, stunted children were more likely to have more parasitemia (OR=1.98) and clinical malaria (OR=2.65) than non-stunted children (11). Likewise, a prospective cohort study of 487 children under 5 in the Gambia found that stunted children were at a higher risk of malaria (RR=1.35) than non-stunted children (7). Contrary to our findings, a prospective cohort study of 136 children 4 months to 10 years of age in Papua New Guinea found the incidence rate of malaria (of any type, as well as \textit{P. falciparum} alone) increased with increasing HAZ (12), indicating that lower HAZ was protective against an attack of clinical malaria. Two longitudinal studies, one in Senegal in children 12 months to 5 years of age and the other in Burkina Faso in children 10 months to 10 years of age, found that stunting and being underweight were not associated with an increased risk of \textit{P. falciparum} malaria (9, 19). There may be several explanations for the conflicting findings. The study conducted in Kenya was conducted in children of a similar age range to the children in the Tororo study, while the studies conducted in Papua New Guinea and Burkina Faso were conducted in older children. Moreover, the study in Kenya was conducted in an area of high transmission (60 to 300 infective bites per person per year) whereas the studies which found compromised nutritional status to be protective or to have no effect on malaria risk were conducted in areas where malaria transmission occurred seasonally with lower transmission rates than in Kenya as well as in the Tororo district in Uganda. Both the differences in age and transmission intensity may lead to differences in acquired immunity and thus differences in malaria risk.
The mechanism behind the increased risk of recurrent parasitemia in children with signs of mild to moderate chronic malnutrition is unclear, but is likely due in part to the impact of chronic malnutrition on the immune system. Chronic malnutrition and accompanying micronutrient deficiencies (e.g., zinc, magnesium, iron, selenium, and vitamin A) can lead to immune dysfunction and increased infection in children by impairing both the innate and adaptive immune system, affecting thymic activity and cytokine production; impairing T cell response and macrophage activation; and disrupting IgA and IgG antibody response (4, 25). Results from the few studies evaluating the relationship between malnutrition and immune response in children with malaria have been conflicting. A cross-sectional study in preschool-aged children conducted in Senegal found that IgG antibody levels were significantly lower in stunted children compared to controls, regardless of differences in parasite density (10). In contrast, a study of children through 10 years of age conducted in Papua New Guinea found an increase in cytokine production in response to stimulation by specific antimalarial antigens in undernourished (stunted and wasted) children and a decrease in antibody response in wasted children (12).

Future studies evaluating the effect of malnutrition on immune response are warranted. In addition to altering immune function, malnutrition may have an impact on the pharmacokinetics of antimalarial treatment. Total body water has been shown to be increased in malnourished children, leading to a greater volume of distribution of drugs, which in turn would result in lower blood concentrations of drug. In addition, malnutrition is associated with intestinal malabsorption and villous atrophy of the jejunal mucosa which can impair drug absorption (22). The few pharmacokinetic studies conducted in children have indicated that because of differences in drug metabolism and elimination, children may be receiving suboptimal doses of
antimalarial drugs (23, 27). Additional analysis of data from a subset of this patient population, including complete pharmacokinetic profiles, is currently underway.

Interestingly, the association of increased risk of recurrent parasitemia with decreasing HAZ was evident only for children not taking TS prophylaxis. TS is an antifolate which has been associated with reduced morbidity and mortality in HIV-infected children and adults. TS also has antimalarial properties. Though TS has been used to treat *P. falciparum* malaria in the past, its effectiveness as an antimalarial treatment is limited (8), and it is no longer considered acceptable as a first-line therapy. However, TS has been shown to reduce the incidence of malaria even in areas of high parasite resistance to antifolates (16-18). Perhaps the chronic use of TS, a moderately effective antimalarial when used alone, acts synergistically with the administration of a relatively more potent artemisinin-based treatment to override the deleterious effect of chronic malnutrition on the immune system. TS is easy to administer, with treatment once a day or thrice weekly for prophylaxis, is widely available, and relatively inexpensive. The results from this study indicate that children with mild to moderate signs of chronic malnutrition at risk for malaria may benefit from TS prophylaxis.

Limitations of this study should be considered. First, we may have not controlled for all potential confounders that may be involved in the complex relationship between malnutrition and malaria. Second, we made multiple comparisons evaluating the relationship between malnutrition and the risk of recurrent parasitemia, which could potentially lead to spurious findings. Only by comparing the lowest levels of malnutrition to the baseline group was statistical significance achieved. Finally, the mechanisms underlying the differences in risk of
recurrent parasitemia in children with mild to moderate chronic malnutrition could not be elucidated.

Conclusion: AL and DP are effective antimalarial therapies for clearing primary infection in chronically malnourished young children in a high transmission setting. However, young children with signs of mild to moderate chronic malnutrition not taking TS prophylaxis are at increased risk of recurrent parasitemia. Further studies are warranted to evaluate if this risk is mediated by altered drug metabolism in chronically malnourished children or through differences in immune response. Children with chronic malnutrition should be targeted for malaria prevention strategies such as provision of bednets or chemoprevention integrated with nutrition-based interventions.

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The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.
REFERENCES


FIGURE LEGENDS

Figure 1. Trial Profile.

Figure 2. Cumulative risks of recurrent parasitemia stratified by HAZ following treatment with AL or DP using the Kaplan-Meier product limit formula.

HAZ Score 0 = HAZ score ≥ 0
HAZ score 1 = HAZ score <0 and ≥ -1
HAZ score 2 = HAZ score <-1 and ≥ -2
HAZ score 3 = HAZ score <-2
<table>
<thead>
<tr>
<th>Age category</th>
<th>DP</th>
<th>AL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in months, mean (SD)</td>
<td>18.2 (6.3)</td>
<td>18.4 (6.3)</td>
</tr>
<tr>
<td>Age ≤ 12 months, n (%)</td>
<td>197 (20%)</td>
<td>198 (19%)</td>
</tr>
<tr>
<td>Age &gt; 12 months ≤ 18 months, n (%)</td>
<td>278 (28%)</td>
<td>286 (28%)</td>
</tr>
<tr>
<td>Age &gt; 18 months ≤ 24 months, n (%)</td>
<td>298 (30%)</td>
<td>330 (32%)</td>
</tr>
<tr>
<td>Age &gt; 24 months, n (%)</td>
<td>208 (21%)</td>
<td>218 (21%)</td>
</tr>
<tr>
<td>Rural (v. urban) residence, n (%)</td>
<td>869 (89%)</td>
<td>950 (92%)</td>
</tr>
<tr>
<td>Breastfeeding, n (%)</td>
<td>334 (34%)</td>
<td>314 (30%)</td>
</tr>
<tr>
<td>HIV-infected, n (%)</td>
<td>71 (7.2%)</td>
<td>101 (9.8%)</td>
</tr>
<tr>
<td>Taking TS prophylaxis, n (%)</td>
<td>276 (28%)</td>
<td>333 (32%)</td>
</tr>
<tr>
<td>Taking ARTs, n (%)</td>
<td>64 (6.5%)</td>
<td>94 (9.1%)</td>
</tr>
<tr>
<td>Cumulative piperaquine dose (mg), mean (SD)</td>
<td>57.8 (8.1)</td>
<td>-</td>
</tr>
<tr>
<td>Cumulative lumfantrine dose (mg), mean (SD)</td>
<td>-</td>
<td>149.0 (27.3)</td>
</tr>
<tr>
<td>HAZ score ≥ 0, n (%)</td>
<td>50 (5.0%)</td>
<td>57 (5.5%)</td>
</tr>
<tr>
<td>HAZ score &lt;0 and ≥ -1, n (%)</td>
<td>176 (18%)</td>
<td>208 (20%)</td>
</tr>
<tr>
<td>HAZ score &lt;-1 and ≥ -2, n (%)</td>
<td>290 (30%)</td>
<td>376 (36%)</td>
</tr>
<tr>
<td>HAZ score &lt;-2, n (%)</td>
<td>465 (47%)</td>
<td>391 (38%)</td>
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<td>WAZ score ≥ 0, n (%)</td>
<td>229 (23%)</td>
<td>319 (31%)</td>
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<tr>
<td>WAZ score &lt;0 and ≥ -1, n (%)</td>
<td>318 (32%)</td>
<td>362 (35%)</td>
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<tr>
<td>WAZ score &lt;-1 and ≥ -2, n (%)</td>
<td>260 (27%)</td>
<td>256 (25%)</td>
</tr>
<tr>
<td>WAZ score &lt;-2, n (%)</td>
<td>174 (18%)</td>
<td>95 (9.0%)</td>
</tr>
</tbody>
</table>
Table 2. Associations between measures of malnutrition and parasite clearance at day 2 following therapy with DP or AL.

<table>
<thead>
<tr>
<th>HAZ Score</th>
<th>Treatment with DP</th>
<th>WAZ Score</th>
<th>Treatment with AL</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Proportion with</td>
<td>Odds Ratio (95% CI)</td>
<td>Proportion with</td>
</tr>
<tr>
<td></td>
<td>Positive Blood</td>
<td>p-value</td>
<td>Positive Blood</td>
</tr>
<tr>
<td></td>
<td>Smear (%)</td>
<td></td>
<td>Smear (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAZ ≥ 0 (n=50)</td>
<td>8.0%</td>
<td>1.00 (ref)</td>
<td>6.1%</td>
</tr>
<tr>
<td>HAZ &lt;0 and z -1 (n=176)</td>
<td>5.1%</td>
<td>0.62 (0.21-1.83)</td>
<td>6.0%</td>
</tr>
<tr>
<td>HAZ &lt;1 and z -2 (n=290)</td>
<td>4.1%</td>
<td>0.50 (0.15-1.64)</td>
<td>3.9%</td>
</tr>
<tr>
<td>HAZ &lt;2 (n=465)</td>
<td>5.2%</td>
<td>0.64 (0.22-1.80)</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAZ ≥ 0 (n=57)</td>
<td>5.3%</td>
<td>1.00 (ref)</td>
<td>8.5%</td>
</tr>
<tr>
<td>HAZ &lt;0 and z -1 (n=208)</td>
<td>13%</td>
<td>4.19 (1.08-16.20)</td>
<td>12%</td>
</tr>
<tr>
<td>HAZ &lt;1 and z -2 (n=376)</td>
<td>7.5%</td>
<td>2.42 (0.64-9.20)</td>
<td>11%</td>
</tr>
<tr>
<td>HAZ &lt;2 (n=391)</td>
<td>13%</td>
<td>4.70 (1.25-17.64)</td>
<td>14%</td>
</tr>
</tbody>
</table>

1 Adjusted for repeated measures in same patient
Table 3. Associations between measures of malnutrition and recurrent parasitemia following therapy with DP after 42 days of follow-up.

<table>
<thead>
<tr>
<th>Measure of Malnutrition</th>
<th>Not on TS Hazard Ratio(^1) (95% CI)</th>
<th>p-value</th>
<th>Cumulative Risk of Recurrent Parasitemia(^2)</th>
<th>On TS Hazard Ratio(^1) (95% CI)</th>
<th>p-value</th>
<th>Cumulative Risk of Recurrent Parasitemia(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height-for-Age Z-scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAZ ≥ 0</td>
<td>1.00</td>
<td>-</td>
<td>13%</td>
<td>1.00</td>
<td>-</td>
<td>22%</td>
</tr>
<tr>
<td>HAZ ≥ -1 - &lt; 0</td>
<td>2.35 (0.85-6.48)</td>
<td>0.099</td>
<td>28%</td>
<td>1.15 (0.46-2.91)</td>
<td>0.765</td>
<td>23%</td>
</tr>
<tr>
<td>HAZ ≥ -2 - &lt; -1</td>
<td>2.89 (1.06-7.89)</td>
<td>0.039</td>
<td>33%</td>
<td>0.58 (0.20-1.68)</td>
<td>0.319</td>
<td>12%</td>
</tr>
<tr>
<td>HAZ &lt; -2</td>
<td>3.18 (1.18-8.56)</td>
<td>0.022</td>
<td>36%</td>
<td>1.01 (0.30-3.40)</td>
<td>0.993</td>
<td>23%</td>
</tr>
<tr>
<td>Weight-for-Age Z-scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAZ ≥ 0</td>
<td>1.00</td>
<td>-</td>
<td>36%</td>
<td>1.00</td>
<td>-</td>
<td>17%</td>
</tr>
<tr>
<td>WAZ ≥ -1 - &lt; 0</td>
<td>0.65 (0.37-1.15)</td>
<td>0.137</td>
<td>27%</td>
<td>1.46 (0.83-2.58)</td>
<td>0.192</td>
<td>24%</td>
</tr>
<tr>
<td>WAZ ≥ -2 - &lt; -1</td>
<td>0.86 (0.45-1.62)</td>
<td>0.636</td>
<td>35%</td>
<td>1.05 (0.46-2.37)</td>
<td>0.908</td>
<td>21%</td>
</tr>
<tr>
<td>WAZ &lt; -2</td>
<td>1.01 (0.54-1.89)</td>
<td>0.969</td>
<td>35%</td>
<td>1.13 (0.33-3.89)</td>
<td>0.844</td>
<td>15%</td>
</tr>
</tbody>
</table>

\(^1\) Adjusted for age, residence, cumulative piperaquine dose, breastfeeding status, ART status (on TS only), and for repeated measures in same patient

\(^2\) Unadjusted
Table 4. Associations between measures of malnutrition and recurrent parasitemia following therapy with AL after 42 days of follow-up.

<table>
<thead>
<tr>
<th>Measure of Malnutrition</th>
<th>Not on TS Hazard Ratio &lt;sup&gt;1&lt;/sup&gt; (95% CI)</th>
<th>p-value</th>
<th>Cumulative Risk of Recurrent Parasitemia&lt;sup&gt;2&lt;/sup&gt;</th>
<th>On TS Hazard Ratio &lt;sup&gt;1&lt;/sup&gt; (95% CI)</th>
<th>p-value</th>
<th>Cumulative Risk of Recurrent Parasitemia&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height-for-Age Z-scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAZ ≥ 0</td>
<td>1.00</td>
<td>-</td>
<td>37%</td>
<td>1.00</td>
<td>-</td>
<td>50%</td>
</tr>
<tr>
<td>HAZ ≥ -1 - &lt; 0</td>
<td>1.55 (0.76-3.17)</td>
<td>0.232</td>
<td>55%</td>
<td>1.15 (0.69-1.90)</td>
<td>0.588</td>
<td>61%</td>
</tr>
<tr>
<td>HAZ ≥ -2 - &lt; -1</td>
<td>1.68 (0.77-3.66)</td>
<td>0.194</td>
<td>58%</td>
<td>0.62 (0.33-1.17)</td>
<td>0.143</td>
<td>37%</td>
</tr>
<tr>
<td>HAZ &lt; -2</td>
<td>1.98 (0.93-4.22)</td>
<td>0.077</td>
<td>64%</td>
<td>0.71 (0.41-1.22)</td>
<td>0.209</td>
<td>39%</td>
</tr>
</tbody>
</table>

| Weight-for-Age Z-scores |                                           |         |                                               |                                 |         |                                               |
| WAZ ≥ 0                 | 1.00                                      | -       | 59%                                          | 1.00                           | -       | 47%                                          |
| WAZ ≥ -1 - < 0          | 0.97 (0.69-1.34)                          | 0.837   | 54%                                          | 1.62 (1.03-2.54)               | 0.038   | 48%                                          |
| WAZ ≥ -2 - < -1         | 1.47 (0.89-2.43)                          | 0.131   | 69%                                          | 1.61 (0.82-3.13)               | 0.164   | 35%                                          |
| WAZ < -2                | 0.94 (0.43-2.06)                          | 0.873   | 44%                                          | 3.60 (1.26-10.27)              | 0.017   | 46%                                          |

<sup>1</sup> Adjusted for age, residence, cumulative piperaquine dose, breastfeeding status, ART status (on TS only), and for repeated measures in same patient

<sup>2</sup> Unadjusted
Figure 1.

351 Children enrolled August 2007 – April 2008 with follow-up through August 2009
100 HIV-unexposed, 203 HIV-exposed, 48 HIV-infected

292 children with at least one episode of uncomplicated malaria randomized to study drugs

145 children randomized to dihydroartemisinin-piperaquine
50 HIV-unexposed, 80 HIV-exposed, 15 HIV-infected
995 total treatments for malaria

14 treatments for non-falciparum malaria

981 treatments for uncomplicated falciparum malaria

147 children randomized to artemether-lumefantrine
42 HIV-unexposed, 88 HIV-exposed, 17 HIV-infected
1071 total treatments for malaria

8 treatments with quinine for complicated malaria

26 treatments for non-falciparum malaria

5 treatments with quinine for treatment failure within 14 days

1032 treatments for uncomplicated falciparum malaria
Figure 2.

p-value = 0.03

p-value = 0.05