Artemisinin-Based Combination Therapies Are Efficacious and Safe for Treatment of Uncomplicated Malaria in HIV-Infected Ugandan Children

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Background. Artemisinin-based combination therapies (ACTs) are highly efficacious and safe, but data from human immunodeficiency virus (HIV)–infected children concurrently receiving antiretroviral therapy (ART) and ACTs are limited.

Methods. We evaluated 28-day outcomes following malaria treatment with artemether-lumefantrine (AL) or dihydroartemisinin-piperaquine (DP) in 2 cohorts of HIV-infected Ugandan children taking various ART regimens. In one cohort, children <6 years of age were randomized to lopinavir/ritonavir (LPV/r) or nonnucleoside reverse transcriptase inhibitor–based ART and treated with AL for uncomplicated malaria. In another cohort, children <12 months of age were started on nevirapine-based ART if they were eligible, and randomized to AL or DP for the treatment of their first and all subsequent uncomplicated malaria episodes.

Results. There were 773 and 165 treatments for malaria with AL and DP, respectively. Initial response to therapy was excellent, with 99% clearance of parasites and <1% risk of repeat therapy within 3 days. Recurrent parasitemia within 28 days was common following AL treatment. The risk of recurrent parasitemia was significantly lower among children taking LPV/r-based ART compared with children taking nevirapine-based ART following AL treatment (15.3% vs 35.5%, P = .009), and those treated with DP compared with AL (8.6% vs 36.2%, P < .001). Both ACT regimens were safe and well tolerated.

Conclusions. Treatment of uncomplicated malaria with AL or DP was efficacious and safe in HIV-infected children taking ART. However, there was a high risk of recurrent parasitemia following AL treatment, which was significantly lower in children taking LPV/r-based ART compared with nevirapine-based ART.

Keywords. ACTs; malaria; HIV; children; ART.

The majority of malaria-endemic countries now recommend artemisinin-based combination therapies (ACTs) for the treatment of uncomplicated falciparum malaria [1]. In sub-Saharan Africa, ACTs selected as first-line regimens include artemether-lumefantrine (AL) and artesunate-amodiaquine (AS-AQ). Dihydroartemisinin-piperaquine (DP), another ACT, was recently added to the World Health Organization (WHO) list of recommended drugs for the treatment of uncomplicated falciparum malaria and has been adopted as a second-line regimen in some African countries [2]. Numerous studies continue to demonstrate excellent efficacy and safety of AL, AS-AQ, and DP in Africa [3–11].

Although there is compelling evidence to support the use of ACTs for malaria treatment in the general population, data evaluating their efficacy and safety in human
immunodeficiency virus (HIV)–infected populations are limited. Some studies have shown equivalent antimalarial efficacy in HIV-infected and -uninfected persons [12–14], but others have reported lower efficacy in HIV-infected populations [15–17]. These studies were generally limited to adult populations that received non-ACT antimalarial treatment regimens that are no longer recommended, and did not account for the increasing use of daily trimethoprim-sulfamethoxazole prophylaxis or antiretroviral therapy (ART) among HIV-infected persons in Africa. Moreover, data evaluating the relative safety of ACTs in HIV-infected individuals are even more limited. There is emerging evidence of potential adverse and beneficial pharmacokinetic interactions between various ART regimens and ACTs [18–21].

Currently, WHO guidelines state that there is insufficient information to modify the general malaria treatment recommendations for HIV-infected patients, with the exception that those on zidovudine or efavirenz (EFV) should avoid AQ-containing regimens if possible [22]. The new WHO consolidated HIV treatment guidelines now recommend ART for all children <5 years of age [23]. Thus, it is critical to understand efficacy and safety of ACTs among HIV-infected children.

We evaluated efficacy and safety data of ACTs from 2 longitudinal clinic trials in cohorts of children living in a highly malaria-endemic area of eastern Uganda. In one trial (PROMOTE), HIV-infected children were randomized to either nonnucleoside reverse transcriptase inhibitor (NNRTI)–based or protease inhibitor–based ART, and all episodes of uncomplicated malaria were treated with AL. In the other trial (Tororo Child Cohort [TCC]), HIV-infected children were started on nevirapine (NVP)–based ART if they were eligible and randomized to either AL or DP for the treatment of their first and all subsequent episodes of uncomplicated malaria.

METHODS

Study Setting and Participants

Both studies were conducted in Tororo district, Uganda, a largely rural area with high malaria transmission intensity and an estimated entomological inoculation rate of 591 infective bites per person-year [24]. Details of both studies have been published previously [21, 25–30]. In brief, the PROMOTE study (ClinicalTrials.gov, NCT00978068) included 184 HIV-infected children aged 2 months to <6 years enrolled between October 2009 and October 2011 who were either ART naive and eligible for ART or already receiving ART with viral suppression.

Part of the PROMOTE cohort results have been published elsewhere [21]. In this article, however, we had additional follow-up data of 287 uncomplicated malaria episodes. In addition, we made comparisons of risk of recurrent parasitemia using NVP-based ART group as a baseline, in contrast to the earlier published data where the combined NNRTI-based ART group was used as a baseline. Furthermore, adverse events included in this current data were only assessed for during malaria follow-up as opposed to the entire study duration in the earlier published data.

The TCC study included 48 HIV-infected children aged 6 weeks to 12 months enrolled between August 2007 and April 2008 who were ART naïve and an additional 9 children who were HIV exposed (HIV-uninfected children born to HIV-infected mothers) and seroconverted during follow-up.

Study Participant Follow-up

Participants in both studies were given a long-lasting insecticide-treated bed net and trimethoprim-sulfamethoxazole prophylaxis at enrollment and were followed up for all their medical care at a dedicated study clinic open 7 days a week. Parents/guardians were encouraged to bring their children to the clinic whenever they were sick, and after-hours care was provided at Tororo District Hospital. Children who presented with new medical problems underwent standardized medical evaluation. Medications with antimalarial activity were avoided for the treatment of nonmalarial illnesses when possible.

In the PROMOTE study, participants were randomized at enrollment to receive either a protease inhibitor (lopinavir/ritonavir [LPV/r]) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) or an NNRTI (NVP for children <3 years of age; EFV for children ≥3 years) plus 2 NRTIs. For NRTIs, children received lamivudine plus zidovudine, with stavudine or abacavir replacing zidovudine for children with anemia. In the TCC study, all participants were ART naïve at enrollment and those meeting standard WHO criteria during follow-up received NVP plus 2 NRTIs using the same approach as the PROMOTE study.

Malaria Diagnosis, Treatment, and Follow-up

Children who presented with a documented fever ( tympanic temperature ≥38.0°C) or history of fever in the previous 24 hours had blood obtained by finger-prick for a thick blood smear. If the smear was positive, the patient was diagnosed with malaria. In the PROMOTE study, patients with uncomplicated malaria were treated with AL. In the TCC study, patients were randomized to receive AL or DP at the time of their first episode of uncomplicated malaria, and they then received the same treatment for all subsequent episodes. In both studies, antimalarials were administered by a study nurse according to weight-based guidelines. Artemether-lumefantrine (tablets of 20 mg of artemether and 120 mg of lumefantrine; Coartem, Novartis), was administered as 1 (5–14 kg) or 2 (15–24 kg) tablets given twice daily for 3 days. Dihydroartemisinin-piperaquine (tablets of 40 mg of dihydroartemisinin and 320 mg of piperaquine; Duocotexin, Holley Pharm) was given as a total dose of 6.4 mg/kg and 51.2 mg/kg of dihydroartemisinin and...
piperaquine, respectively, given in 3 equally divided daily doses to
the nearest quarter-tablet. Patients were given a glass of milk or
asked to breastfeed after each dose of antimalarial medication
and observed for 30 minutes with the dose repeated if vomiting
occurred. For patients treated with AL, the second daily dose was
given at home by the parent or guardian. Patients with compli-
cated malaria were treated with quinine. Patients were instructed
to return for follow-up evaluation on days 1, 2, 3, 7, 14, 21, and
28. In the PROMOTE study, complete blood count and alanine
aminotransferase (ALT) level were assessed on days 0 and 28. In
the TCC study, hemoglobin measurements were assessed on days
0 and 28. Standardized treatment outcomes after 28 days were
classified according to WHO guidelines [31].

Laboratory Methods
Thick and thin Giemsa-stained blood smears were used for
estimating parasite density and to determine the parasite spe-
cies, respectively. Parasite densities were calculated as the num-
ber of asexual parasites per 200 leukocytes (or per 500
leukocytes, if the count was <10 asexual parasites/200 leuko-
cytes), assuming a leukocyte count of 8000/μL. A blood smear
was considered negative when the examination of 100 high-
power fields did not reveal asexual parasites. For quality control,
all slides were read by a second reader, and a third reader settled
any discrepancies.

Statistical Methods
Data were double entered into Access databases and analyzed
using Stata version 12 (Stata Corp, College Station, Texas). Risk of recurrent parasitemia within 28 days of initiation of
therapy was estimated using the Kaplan-Meier product limit
formula, and comparisons were made using the Cox propor-
tional hazards model, controlling for age and with adjustment
for repeated measures in the same patient. Associations between
ART regimen and the risk of adverse events within 28 days of
initiation of therapy with AL from the PROMOTE study were
estimated using generalized estimating equations controlling for
age and with adjustment for repeated measures in the same
patient using exchangeable correlation and robust standard
errors. \( P < .05 \) was considered statistically significant.

Ethical Approval
In both studies, informed consent was obtained from at least 1
parent or legal guardian of each participant at enrollment. Both
studies were approved by the Uganda National Council of Sci-
ence and Technology, the Makerere University School of Med-
iceine Research Ethics Committee, and the University of
California, San Francisco Committee for Human Research.
The TCC study was also approved by the institutional review
boards of the University of Washington and the Centers for
Disease Control and Prevention.

RESULTS
Study Profiles and Characteristics of Study Participants
A total of 184 HIV-infected children were enrolled in the
PROMOTE study, of whom 123 (66.8%) were diagnosed with
at least 1 episode of malaria. A total of 57 HIV-infected children
were included in the TCC study, of whom 43 (75.4%) were diag-
nosed with at least 1 episode of malaria (Figure 1). Characteristics
of study participants at enrollment and during follow-up for

Figure 1. Study profile. Abbreviations: AL, artemether-lumefantrine; DP, dihydroartemisinin-piperaquine; HIV, human immunodeficiency virus; TCC, Tororo
Child Cohort.
both studies are presented in Table 1. Compared to those in the TCC study, participants in the PROMOTE study were older at enrollment (mean age, 3.4 vs 0.6 years, \( P < .001 \)). In the PROMOTE study, a total of 581 treatments were given for malaria, of which 572 were uncomplicated episodes treated with AL and 9 were complicated episodes treated with quinine (6 episodes with danger signs and 3 episodes with severe anemia). In the TCC study, a total of 581 treatments were given for malaria, of which 572 were uncomplicated episodes treated with AL and 9 were complicated episodes treated with quinine (6 episodes with danger signs and 3 episodes with severe anemia). There were no deaths due to malaria in either study.

Characteristics of Malaria Episodes Treated With ACTs
In both studies, >93% of episodes of uncomplicated malaria were due to *Plasmodium falciparum*. Compared with the TCC study, episodes of malaria in the PROMOTE study occurred in older children (mean age, 4.4 vs 2.6 years; \( P < .001 \)) and with lower geometric mean parasite densities (7792 vs 12 144 asexual parasites/\( \mu L \); \( P = .005 \)). All of the episodes in the PROMOTE study occurred in children taking ART, with 43.5%, 38.6%, and 17.8% on LPV/r, NVP, or EFV-based regimen, respectively. In the TCC study, 94.5% of episodes occurred in children taking ART, with all receiving NVP-based regimens (Table 2).

### Efficacy Outcomes Following Treatment With ACTs
Combining results for the PROMOTE and TCC studies, initial response to therapy was excellent, with >97% of patients with fever clearance and 99% with parasite clearance by day 3 after initiation of therapy (Table 3). Only 4 early treatment failures were seen during the first 3 days of follow-up (all in the PROMOTE study): 2 patients developed danger signs, 1 patient had a low parasite density of 320 asexual parasites/\( \mu L \) on day 0 that increased to 640 on day 2, and 1 patient had a very high parasite density of 419 360 asexual parasites/\( \mu L \) on day 0 with persistent fever and parasitemia on day 3.

In the PROMOTE study, the cumulative risk of recurrent parasitemia after 28 days of follow-up was 29.7% among children treated with AL. In the TCC study, the cumulative risk...
of recurrent parasitemia was significantly lower among children randomized to DP compared with AL (8.6% vs 36.2%; \(P < .001\)). In the PROMOTE study, the choice of ART regimen was associated with the risk of recurrent parasitemia after 28 days of follow-up among children treated with AL (Table 4). Compared with children taking an NVP-based regimen, those taking a LPV/r-based regimen had a significantly lower risk of recurrent parasitemia (15.3% vs 35.5%; \(P = .009\)). Children taking an EFV-based regimen had a trend toward a high risk of recurrent parasitemia compared with those taking NVP-based regimen (52.5% vs 35.5%; \(P = .06\)).

Safety and Tolerability Following Treatment With ACTs

Overall, ACTs were safe and well tolerated in both studies (Table 5). Most adverse events were mild to moderate and either unrelated to study drugs (cough) or commonly associated with malaria (diarrhea, anorexia, vomiting, and malaise). In the TCC study, there were no grade 3–4 adverse events and there was no statistically significant difference in the risk of clinical adverse events between patients treated with AL and DP (Table 5). In the PROMOTE study, among 572 treatments with AL there were 59 grade 3–4 adverse events; all were laboratory abnormalities (52 neutropenia, 3 anemia, 2 thrombocytopenia, and 2 elevated ALT level).

In the PROMOTE study, the risk of most adverse events did not differ significantly between children receiving different ART regimens (Table 6). However, EFV-based ART was associated with a significantly reduced risk of neutropenia compared with NVP-based ART (risk ratio [RR], 0.55; 95% confidence interval [CI], .32–.94; \(P = .03\)). In addition, those receiving LPV/r-based ART had an 84% reduction in the risk of elevated ALT after malaria treatment compared with those receiving NVP-based ART (RR, 0.16; 95% CI, .06–.43; \(P < .001\)).

**DISCUSSION**

Treatment of uncomplicated malaria with AL and DP was efficacious and safe in HIV-infected children taking LPV/r or NVP or EFV-based ART. Overall, there was >99% parasite clearance by day 3 in children treated for malaria. In a new era of HIV treatment where nearly all children diagnosed with HIV receive ART, our results add assurance that ACTs can be used to treat uncomplicated falciparum malaria.
In this study that we conducted in a high malaria transmission setting, recurrent parasitemia during 28 days of follow-up was common. Treatment with AL was associated with a higher risk of recurrent parasitemia within 28 days compared to treatment with DP in children taking NVP-based ART. A higher risk of recurrent parasitemia was associated with a lower risk of elevated ALT and EFV-based ART [21]. Of the NNRTIs, EFV remains preferred for uncomplicated malaria.

Table 5. Safety Outcomes Over 28 Days Following Treatment With Artemisinin-Based Combination Therapies

<table>
<thead>
<tr>
<th>Selected Adverse Events of Any Severity</th>
<th>PROMOTE AL (n = 572)</th>
<th>TCC DP (n = 165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>247 (43.2%)</td>
<td>74 (36.8%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>50 (8.7%)</td>
<td>23 (11.4%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>45 (7.9%)</td>
<td>4 (2.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>39 (6.8%)</td>
<td>18 (9.0%)</td>
</tr>
<tr>
<td>Malaise</td>
<td>35 (6.1%)</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>156/515 (30.3%)</td>
<td>NA NA</td>
</tr>
<tr>
<td>Anemia</td>
<td>29/522 (5.6%)</td>
<td>NA NA</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22/522 (4.2%)</td>
<td>NA NA</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>32/488 (6.6%)</td>
<td>NA NA</td>
</tr>
</tbody>
</table>

Elevated ALT 1.0 (reference) . . . 0.34 (.09–1.36) .13 0.16 (.06–.43) <.001
Thrombocytopenia 1.0 (reference) . . . 1.99 (1.14–3.46) .07 1.07 (0.57–2.01) .90
Anemia 1.0 (reference) . . . 1.59 (0.92–2.72) .14 1.00 (0.57–1.77) .99
Neutropenia 1.0 (reference) . . . 0.76 (0.50–1.19) .26 0.35 (0.20–0.63) .003
Vomiting 1.0 (reference) . . . 1.01 (0.86–1.18) .89 0.98 (0.79–1.22) .89
Malaise 1.0 (reference) . . . 0.83 (0.60–1.16) .34 1.08 (0.69–1.72) .70
Anorexia 1.0 (reference) . . . 2.30 (1.25–4.21) .006 1.00 (0.54–1.87) .99
Cough 1.0 (reference) . . . 1.13 (0.81–1.59) .48 1.03 (0.78–1.36) .85
Diarrhea 1.0 (reference) . . . 1.03 (0.42–2.53) .95 1.03 (0.53–1.99) .94

Data are presented as No. (%).

Abbreviations: AL, artemether-lumefantrine; DP, dihydroartemisinin-piperaquine; NA, not applicable; TCC, Tororo Child Cohort.

In HIV-infected children randomized to different ART regimens, LPV/r-based ART was associated with a lower risk of elevated ALT and EFV-based ART was associated with a lower risk of neutropenia, compared to DP.

Table 6. Associations Between Antiretroviral Therapy Regimen and Risk of Adverse Events Following Treatment With Artemether-Lumefantrine in the PROMOTE Study

<table>
<thead>
<tr>
<th>Selected Adverse Events of Any Severity</th>
<th>NVP-Based ART RR (95% CI)* P Value</th>
<th>EFV-Based ART RR (95% CI)* P Value</th>
<th>LPV/r-Based ART RR (95% CI)* P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough</td>
<td>1.0 (reference) . . .</td>
<td>1.13 (0.81–1.59) .48</td>
<td>1.03 (0.78–1.36) .85</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.0 (reference) . . .</td>
<td>1.03 (0.42–2.53) .95</td>
<td>1.03 (0.53–1.99) .94</td>
</tr>
<tr>
<td>Anorexia</td>
<td>1.0 (reference) . . .</td>
<td>1.20 (0.47–3.07) .70</td>
<td>1.50 (0.87–2.59) .14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.0 (reference) . . .</td>
<td>0.92 (0.38–2.18) .84</td>
<td>0.42 (0.15–1.14) .09</td>
</tr>
<tr>
<td>Malaise</td>
<td>1.0 (reference) . . .</td>
<td>1.69 (0.77–3.71) .19</td>
<td>1.00 (0.43–2.32) .99</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.0 (reference) . . .</td>
<td>0.55 (0.32–0.94) .03</td>
<td>0.83 (0.60–1.16) .29</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.0 (reference) . . .</td>
<td>1.88 (0.63–5.63) .26</td>
<td>1.24 (0.54–2.87) .61</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1.0 (reference) . . .</td>
<td>1.98 (0.52–7.50) .32</td>
<td>0.40 (0.13–1.18) .10</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>1.0 (reference) . . .</td>
<td>0.34 (0.09–1.36) .13</td>
<td>0.16 (0.06–.43) &lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RR, risk ratio.

* Controlling for age and repeated measures in the same study participant.
with NVP-based ART. Nevirapine is known to cause liver toxicity [40]; we saw 32 adverse events due to elevated ALT levels in NVP-treated children, but only 2 were of grade 3–4 severity.

Our study had some limitations. Genotyping was not done for all episodes of recurrent parasitemia, limiting our ability to differentiate new infections from treatment failure due to recrudescence. However, genotyping of the first 107 episodes of recurrent parasitemia in the PROMOTE cohort demonstrated that all recurrent infections were new, suggesting that recrudescence after therapy was very uncommon [21]. In the PROMOTE cohort, children who were randomized to NNRTI-based ART received EFV-based ART if they were 3 years or older and NVP-based ART if they were <3 years of age. This could have confounded our findings, although age was controlled for in the analysis. Finally, laboratory adverse events were not assessed in the TCC cohort.

In summary, both AL and DP were safe and efficacious among HIV-infected children on LPV/r-based or NVP- or EFV-based ART. In high transmission settings where AL is used as first-line treatment, LPV/r-based ART has a significant advantage over NVP or EFV, being associated with a lower risk of recurrent parasitemia. DP used to treat children receiving an NVP-based ART regimen was associated with the lowest rates of recurrent parasitemia, due to the longer posttreatment prophylactic effect of DP compared with AL. Drug interaction studies between DP and ART will help inform its optimal use in HIV-infected patients.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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