Prevalence of Asymptomatic Parasitemia and Gametocytemia in HIV-Infected Children on Differing Antiretroviral Therapy

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Abstract. Laboratory data and prior pediatric reports indicate that HIV protease inhibitor (PI)-based antiretroviral therapy (ART) kills gametocytes and reduces rates of gametocytemia, but not asymptomatic parasitemia, in a high-malaria-transmission area. To determine whether ARV regimen impacts these rates in areas with less-intense malaria transmission, we compared asymptomatic parasitemia and gametocytemia rates in HIV-infected children by ARV regimen in Lillongwe, Malawi, an area of low-to-moderate transmission intensity. HIV PI lopinavir–ritonavir (LPV–rtv) ART– or non-nucleoside reverse transcriptase inhibitor nevirapine (NVP) ARV–treated children did not differ in the rates of polymerase chain reaction-detected asymptomatic parasitemia (relative risk [RR] 0.43 95% confidence interval [CI] [0.16, 1.18], P value 0.10) or microscopically detected gametocytemia with LPV–rtv ARV during symptomatic malaria (RR 0.48 95% CI [0.22, 1.04], P value 0.06). LPV–rtv ARV was not associated with reduced rates of asymptomatic parasitemia, or gametocytemia on days of symptomatic malaria episodes, in HIV-infected children. Larger studies should evaluate whether ARV impacts transmission.

INTRODUCTION

HIV and malaria occur co-endemically in sub-Saharan Africa.1 Laboratory data show that HIV protease inhibitors (PIs) kill various life cycle stages of malaria parasites.2–4 PIs are second-line World Health Organization (WHO)-recommended antiretroviral therapy (ART) for children above 3 years old and first-line ARV for those below 3 years.5 Clinical studies have shown that HIV-infected children on PI ART may have a modest reduction in clinical malaria episodes, and the effect may be partially attributed to pharmacokinetic interactions resulting in an increase in antimalarial drug levels.8–12 In addition, laboratory data1,5 and recent pediatric clinical studies indicate that HIV PI lopinavir–ritonavir (LPV–rtv) ARV, when compared with non-nucleoside reverse transcriptase inhibitor (NNRTI) ARV, is associated with reduced gametocytemia,11,13 but not asymptomatic parasitemia,13 rates in high malaria-transmission areas.

Because malaria transmission intensity influences malaria infection and intervention efficacy, we evaluated the malaria impact of different ARV regimens in HIV-infected children by measuring asymptomatic parasitemia and gametocytemia in an area of low-to-moderate transmission. We recently reported an association between increased time to recurrent positive malaria blood smears in LPV–rtv ARV–treated subjects compared with nevirapine (NVP) ARV–treated subjects, when accounting for an LPV–rtv and antimalarial treatment interaction, in an observational pediatric study.10 Herein, we measure and compare rates of asymptomatic parasitemia and gametocytemia in children receiving differing ARV regimens.

METHODS

Study design. The study was approved by site-specific institutional review boards; each child’s parent or legal guardian provided written informed consent.10 The study design was as previously described.10,14 The study was conducted at three sites with endemic-malaria transmission according to published data at the time, which included Kampala, Uganda; Lusaka, Zambia; and Lilongwe, Malawi; analysis was performed only on data from the Malawi site, however, because of low blood smear positivity rates at the other sites, as previously described.14 Briefly, subjects who enrolled in our study, P1068s, were HIV-infected children of age 2–36 months who qualified for treatment according to WHO criteria and were randomized to initiate PI- or NNRTI ARV in the larger HIV treatment study (P1060).10,14 Subjects received trimethoprim–sulfamethoxazole prophylaxis were given insecticide-treated bed nets, were breastfed, and lived within 30 km of the study site.10 Clinical illness (including malaria) was managed according to standard guidelines.10,16 Study visits occurred every 12 weeks and during intercurrent illness.10 Giemsa-stained thick smear and dried blood spots
Gametocytemia (during CCM visits) 0.48 (0.22, 1.04) 0.06
Gametocytemia (overall, or CCM + non-CCM visits) 0.67 (0.39, 1.17) 0.16

DISCUSSION

In an area of low-to-moderate transmission, LPV–rtv ARV was not associated with reduced rates of asymptomatic parasitemia, or gametocytemia with or without concurrent symptomatic malaria episodes, in HIV-infected children.

Our previous study indicated that the reduced frequency of recurrent positive blood smears was only observed when accounting for a drug interaction between LPV–rtv ARV and the antimalarial (artemether–lumefantrine). In this report, however, we did not detect differences in asymptomatic parasitemia. Direct PI ARV killing of malaria parasites may not be significant, or our study may be underpowered, both because of the small size of the study and decreased likelihood of finding younger children with asymptomatic parasitemia in an area of low-to-moderate transmission. Indeed, the majority of infections being new rather than recrudescent may also reflect sampling which was performed mostly every 3 months, with the exception of intermittent illness visits.

As expected, gametocytemia during CCM was more commonly detected when compared with non-CCM episodes. We compared the gametocyte prevalence overall between children on LPV–rtv ARV or NVP ARV but did not detect any significant difference between the groups when comparing overall (CCM and non-CCM) episodes. However, when

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<tr>
<th>Table 1</th>
<th>Summary of rates of asymptomatic parasitemia and gametocytemia for children on lopinavir–ritonavir antiretroviral therapy</th>
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<tbody>
<tr>
<td><strong>RR</strong></td>
<td><strong>Confidence interval</strong></td>
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<tr>
<td>Asymptomatic parasitemia</td>
<td>0.43 (0.16, 1.18)</td>
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<tr>
<td>Gametocytemia (overall, or CCM + non-CCM visits)</td>
<td>0.67 (0.39, 1.17)</td>
</tr>
<tr>
<td>Gametocytemia (non-CCM visits)</td>
<td>1.01 (0.33, 3.07)</td>
</tr>
<tr>
<td>Gametocytemia (during CCM visits)</td>
<td>0.48 (0.22, 1.04)</td>
</tr>
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*Adjusted for gender, age at enrollment, baseline CD4, and time from enrollment in the parent study to the time of enrollment in the P1068s. The indicator of PI-based ARV was based on having enrolled on the substudy while receiving PI-based ARV; two subjects had switched to PI-based ARV from their randomized treatment before entry into the substudy. ARV = antiretroviral therapy; CCM = confirmed clinical malaria; PI = protease inhibitor.
limiting gametocytemia analysis to CCM visits, a significant difference was not appreciated.

A larger, randomized previous pediatric study that was conducted in an area of high-intensity malaria transmission also found that PIs were also not associated with reduced asymptomatic parasitemia in HIV-infected children, despite the study reporting fewer cases of recurrent clinical malaria with LPV–rtv ARV when compared with NNRTI ARV in an area of high malaria transmission intensity. This finding was partially attributed to a pharmacokinetic interaction between the ritonavir component of LPV–rtv and the antimalarial drugs, resulting in a prolonged period of lumefantrine detection, which is consistent with our prior publication. Moreover, analysis revealed no difference in gametocyte prevalence for children receiving LPV–rtv ARV compared with NNRTI ARV. However, when evaluating gametocytemia difference on the day of malaria diagnosis, they also found that it was much more likely that a child was gametocytemic on the day of malaria diagnosis, and within this analysis, LPV–rtv ARV was associated with significantly lower risk of gametocytemia. The data we report herein parallel some of these findings, except that gametocytemia on the day of CCM in LPV–rtv ARV compared with NVP ARV–treated children was not significantly different (P = 0.06). Part of this difference may be due to our study comparing children on LPV–rtv ARV with those on NVP ARV, whereas the prior study compared children on NNRTI ARV (either NVP or efavirenz, EFV) to those on LPV–rtv. This is of note as EFV has been shown to reduce antimalarial exposure much more significantly than NVP. PI kills malaria gametocyte and transmission forms at clinically relevant levels through an unclear mechanism. Clinical trials from adult and pregnant women have shown little or no PI effect on clinical malaria, but pediatric data suggest that reduction of clinical malaria occurs with PI ARV, possibly because of direct parasite killing or pharmacokinetic effects. Our data suggest that HIV PI–based ARV did not reduce the asexual parasite pool because we found no difference in asymptomatic parasitemia rates. Lack of significant difference in gametocytemia rates between ARV groups similarly suggests a lack of PI-gametocytocidal effect.

A limitation of our study is our small sample size. Moreover, we were not able to assess gametocytemia differences at time points post treatment to account for residual drug interaction effects, although similar previous assessments resulted in no significant differences.

A combination of interventions will likely eradicate malaria. Further studies are needed to evaluate whether PI ARV reduces gametocytemia and impacts transmission.

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