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Buy One, Get One free? Benefits of Certain Antiretrovirals against Malaria

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Malaria is highly prevalent in many areas of the world where HIV-infected adults and children live, especially sub-Saharan Africa. Data have shown that when HIV and malaria are present in the same host, each enhances the pathogenicity of the other [1]. However, it has become apparent that the choice of antiretroviral therapy (ART) may influence the frequency of malaria infection.

Currently, the World Health Organization (WHO) recommends the use of combination antiretroviral therapy (ART) for HIV management, with 2 nucleoside reverse transcriptase inhibitors (NRTIs) and as first line, a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or, with second-line therapy, an HIV protease inhibitor (HIV PI), except for children under age 3 [2, 3]. Interestingly, both *in vitro* and *in vivo* data demonstrate that HIV protease inhibitors (HIV PIs) kill various life cycle stages of malaria parasites [4-8]. Recent clinical studies have evaluated whether these data translate reduction in clinical malaria. To date, there have been a handful of studies in areas of varying malaria transmission examining the impact of ART on malaria in children, pregnant women, and adults. This is important because age, pregnancy, and transmission intensity impact acquisition of naturally acquired immunity to malaria.

In children, studies have had significant results. In a study in a high transmission area of Uganda, children randomized to receive lopinavir-ritonavir or nevirapine ART had a lower risk of recurrent malaria after treatment with artemether-lumefantrine, the most commonly used treatment for uncomplicated malaria [9]. A subsequent pharmacokinetic and pharmacodynamic study in the same area found that, compared to HIV-uninfected children, both artemether and lumefantrine exposure was reduced in those on efavirenz and nevirapine ART, whereas lumefantrine exposure was increased in those on lopinavir-ritonavir ART. These changes translated into a significantly lower risk of recurrent malaria in those on lopinavir-ritonavir as compared with those on efavirenz ART [10]. Additionally, in a substudy conducted by the International Maternal Adolescent AIDS Clinical Trials (IMPAACT) network, lopinavir-ritonavir in combination with antimalarial treatment was associated with a lower risk of having a malaria-positive blood smear in an area of low to moderate transmission intensity [11].

For the adult population, studies have been less consistent. Two subanalyses of the multi-site OCTANE trial (A5208), in which HIV-infected women from malaria-endemic areas of

varying transmission intensity [12, 13] were randomized to treatment with either HIV PI lopinavir-ritonavir ART or NNRTI nevirapine ART failed to find significant differences in malaria incidence as clinical malaria [12], or simply blood smear or *P. falciparum* histidine-rich protein 2 antigen testing [13] between ART groups. Additionally, a single study in pregnant women in an area of high transmission intensity found no differences in placental malaria, as defined by placental thick smear or PCR, between women randomized to lopinavir-ritonavir or efavirenz ART [15].

In this issue of AIDS, Kasirye et al. [14] present data from an adult study encompassing an area of moderate to high transmission at the time of the study [16] that provides another important step in answering the question of whether ART regimen affects malaria in different populations. The authors compared clinical malaria incidence in HIV-infected Ugandan adults enrolled in the COSTOP trial, a trial originally designed to look at trimethoprim-sulfamethoxazole (TMP-SMX) effects in HIV-infected Ugandan adults with CD4 ≥ 250 cells/ μ l who were followed for up to 3.5 years. All patients received insecticide treated bednets at study initiation. Clinical malaria incidence, as defined by a positive smear occurring >28 days apart in the presence or history of fever was compared among patients who had received NNRTI-, PI-, or NRTI-only ART and results were analyzed taking TMP-SMX, enrollment site, and time on study into account. Of note, smears were obtained when patients were seen at scheduled visits (every month for the first 3 months and then every 3 months thereafter) or during intercurrent illness visits. Data were also stratified for a CD4 count $<$ or > 500 cells/ μ l, as malaria frequency and severity increases in those with a higher degree of immunodeficiency [1]. The authors found no impact of CD4 count in their stratified analysis, although the enrollment criteria for the parent study did specify a fair degree of immune competence to being with (CD4 ≥ 250 cells/ μ l), and CD4 of 500 is also rather high. Overall, after adjustments for treatment arm, site, and time since enrollment, malaria incidence was 1.6 (0.6-4.3) times *higher* in adults on an NNRTI ART, and 0.4 (0.2-1) times *lower* in adults on PI ART, as compared to those on NRTI ART ($p=0.05$). In addition, the authors noted a modest increase in the time to the first episode of clinical malaria after enrolment into the study [9].

As the authors acknowledge, this study was not originally designed to address the ART and malaria question, and there are problems such as differences among sample sizes for each group and differences in numbers from enrollment sites, which could have introduced significant biases. However, the parent study was carefully designed, and the large dataset of 2,154 participants and careful statistical analysis adds important information to this growing body of research. Admittedly, the authors' less strict definition of fever for defining clinical malaria could have led to overestimates in malaria incidence, and conversely, the infrequent (for a malaria study) follow-up could have led to underestimates in malaria incidence. However, for the latter, patients were encouraged to come for intercurrent illness visits to minimize this, and patients treated elsewhere were asked to bring records of positive malaria smears, with presumptive malaria episodes (i.e., negative smears) not counted in the analysis. Taking all these factors into account, however, this represents the first non-pediatric study to detect a reduced trend to clinical malaria in adults on HIV PI ART.

The study also provides an opportunity to highlight additional information gaps in the field, including a lack of studies in lower transmission areas, studies utilizing different antimalarials aside from artemether-lumefantrine, studies in areas where other non-falciparum species are prevalent (additional study of HIV PIs on nonfalciparum species would be welcome, given laboratory findings *anti-P.vivax* activity [17]), and a more thorough understanding of the mechanism of action of HIV PIs against the parasite. The study of other antimalarials-ART combinations is critical given the degree of drug-drug interactions which have been seen from existing studies, a call echoed by the WHO in the recent Guidelines for the Treatment of Malaria [18]. Study of other antimalarial-ART combinations will also help to clarify the relative contribution of direct versus indirect ART effects on the incidence of malaria. Whether the direct parasite killing that occurs is from hypothesized mechanisms of inhibition of the parasite's aspartyl proteases or interruption of glucose transporters [19, 20], or whether HIV PIs represent a new mechanism of action, remains to be seen. Indeed, new mechanisms for killing the malaria parasite will always be welcome with the parasite's astounding capability of developing resistance.

As more patients are started on antiretroviral therapy for HIV infection in malaria endemic areas, understanding HIV drug impact on malaria infection is important. Given the increased cost associated with HIV PIs [21], the potential additional “buy one, get one free” treatment for both malaria and HIV, may tip the scales in favor of these drugs in co-endemic settings [22]. For HIV-infected adults, pregnant women, and children who reside in malaria-endemic areas, this would be worth more than a bargain—it would be priceless.

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