Commentary: Malaria and HIV transmission: old meets new in a deadly partnership or an opportunity for healthcare synergism?

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In this issue of the International Journal of Epidemiology, Cuadros et al.1 provide intriguing population-level evidence supporting another potential risk factor for HIV transmission among individuals living in areas endemic for Plasmodium falciparum. With a considerable geographical overlap between these two entities (Figures 1 and 2) and substantial global prevalence, it is not surprising that pathogenic and sociological interactions would complicate the prevention, care and treatment of each infection individually.

It has now been well established that HIV infection results in a higher incidence2–4 and more severe manifestations5,6 of malaria, particularly for patients who are significantly immunosuppressed. Dually infected children in particular have been shown to have more severe anaemia and increased mortality in Kenya.7 Furthermore, the diagnosis and management of co-infected individuals are complicated for multiple reasons.8 For example, in endemic regions, individuals with fever are often misdiagnosed as having malaria instead of an opportunistic infection and vice versa.6 Additionally, malaria treatment failure is more common for HIV-infected adults especially those with more advanced disease.4,9,10

Correspondingly, other studies have shown that AIDS progression can be accelerated by concomitant malaria infection primarily through an increase in HIV viral load (VL); however, additional mechanisms have been proposed. The earliest report of this phenomenon found that malaria antigen induced expression of cytokines that enhance HIV replication, activated long-terminal repeat-directed viral transcription and increased immune activation of T cells in vitro.11 Subsequently, data from two clinical cohorts revealed that individuals with acute P. falciparum infection had significantly higher HIV plasma VL than individuals without evidence of infection, and the increase in VL was greatest when the CD4 count was >300 cells/μL.12,13 On average, plasma VL decreased in the 5–8 weeks after malaria treatment in these same patients. In a separate study, Pisell et al.14 were able to demonstrate an increase in cellular HIV replication related to cytokine-induced macrophage and lymphocyte activation. Since HIV plasma VL is a principal predictor of HIV transmission among discordant sexual partners,15,16 these findings provided the basis for considering malaria as a risk factor for horizontal sexual transmission. It was also suggested that vertical HIV transmission might be more likely to occur for HIV-infected pregnant women.17 Pregnant women with placental P. falciparum in Malawi were found to have a 1.7-fold increase in geometric mean peripheral plasma HIV VL and a 2.0-fold increase for placental plasma HIV VL compared with HIV-infected pregnant women without P. falciparum after adjusting for other covariates.

A close examination of the biological factors underlying HIV transmission reveals plausibility for an increased risk of HIV acquisition for individuals living in a region endemic with P. falciparum. As described above, since malaria increases the HIV plasma VL, the donor has an increased risk of transmitting HIV during periods of co-infection. It is estimated that for areas with high rates of P. falciparum, the number of infectious bites per year for an individual can be as high as 1000 and a single infection can last on average 6 months.18–20 Using mathematical modelling of data from an adult population of roughly 200 000 in Kisumu, Kenya, Abu-Raddad et al.21 were able to demonstrate that transient but repeated elevated HIV VL associated with recurrent co-infections with malaria could have increased the cumulative HIV prevalence by 8500 infections during the period from 1980 to 2005. Independent of HIV VL, there are other factors related to malaria infection functioning in the recipient that may play a role in HIV...
Figure 1  Geographical distribution of *P. falciparum* malaria in Africa by country. The data are the model-based geostatistical point estimates of the annual mean *P. falciparum* PR2–10 for 2007 within the stable spatial limits of *P. falciparum* malaria transmission, displayed as a continuum of yellow to red from 0–100% (see map legend). The rest of the land area was defined as unstable risk (medium grey areas, where *P. falciparum* API < 0.1 per 1000 pa) or no risk (light grey, where *P. falciparum* API = 0 per 1000 pa). *Plasmodium falciparum* API refers to the *P. falciparum* annual parasite incidence. Adapted from Hay et al. (A world malaria map: Plasmodium falciparum Endemicity in 2007. PLoS Med 2009;6:e1000048.)

Figure 2  HIV prevalence in Africa by country. Adapted from the UNAIDS and WHO 2007 report on the AIDS Epidemic.
transmission. Increased levels of immune activation during malaria infection\textsuperscript{11,14} could result in greater CCR5 expression\textsuperscript{22,23} thereby increasing cellular susceptibility to HIV infection. The malaria pigment, haemoglobin, has also been shown to enhance transfer of HIV from immature monocyte-derived dendritic cells (DCs) to CD4 T cells by provoking DC maturation.\textsuperscript{24}

Both malaria and HIV have had profound genetic associations identified with their receptor and co-receptor, respectively.\textsuperscript{25} Discovered in 1950, the Duffy antigen receptor for chemokines (DARC) found on red blood cells binds to \textit{Plasmodium vivax} and \textit{Plasmodium knowlesi}, permitting invasion of erythrocytes by these malaria parasites. However, due to a mutation in the promoter region of the DARC gene, this antigen is not expressed on the surface of erythrocytes for some individuals homozygous for the trait (Duffy null) thus rendering them resistant to infection.\textsuperscript{26} It is hypothesized that an ancient, virulent malaria species that also bound to DARC, selected for this mutation so highly that it became relatively fixed in the vast majority of West and Central Africans.\textsuperscript{27} In a similar fashion, the co-receptor for HIV attachment and entry, CCR5, has a naturally occurring deletion in the coding region referred to as ‘\textasciitilde A-32’. When individuals are homozygous for this deletion, there is no expression of CCR5 on the surface of T cells, causing near-complete resistance to HIV infection.\textsuperscript{28} This deletion is present in 5–14% of Europeans and may have become enriched in this population during the Black Plague due to a similar pathogen-protective effect.\textsuperscript{29} Since DARC binds various cytokines and HIV,\textsuperscript{30} the absence of the Duffy antigen has also been associated with benign ethnic neutropenia,\textsuperscript{31} increased HIV transmission\textsuperscript{32} and AIDS survival\textsuperscript{33} in certain populations. Yet the findings associated with HIV transmission risk have not been reproduced in other settings,\textsuperscript{34,35} and it is unclear how this association would be relevant in East African populations where \textit{P. vivax} is rare and the Duffy null phenotype less common. The study described herein is the first to show an actual epidemiological relationship between malaria and risk of HIV infection beyond sociological predisposing factors. Using databases from the Demographic and Health Survey for HIV and the Malaria Atlas Project for \textit{P. falciparum}, these investigators were able to assess the geographical overlap of these two diseases in Kenya, Tanzania and Malawi. In a multivariate model which adjusted for measured social and biological factors, the \textit{P. falciparum} parasite rate (PR) was found to be a significant risk factor for HIV infection. Using empirical quartiles of \textit{P. falciparum} PR, individuals living in areas with a high \textit{P. falciparum} PR (>0.42) were twice as likely to be infected with HIV as individuals living in areas with a low \textit{P. falciparum} PR (<0.10). Their findings demonstrate that malaria may account for nearly 27% of incidental HIV infections in areas with a \textit{P. falciparum} PR >0.1 which was similar to the effect on HIV infection attributed to herpes simplex virus type 2.

Despite a very thorough evaluation and adjustment for the multitude of social and biological risk factors associated with both diseases, there are likely unmeasured confounders which could result in non-causal associations. As reported in this study, individuals living in areas with a high \textit{P. falciparum} PR were more likely to have a lower wealth index and education level. With a high correlation between these factors, it becomes challenging to control for these covariates in an analysis of HIV infection rates. For example, although condom use is infrequent in the regions studied (author communication), a higher education level could be associated with other important HIV prevention measures. As mentioned by Cuadros et al.,\textsuperscript{1} chronic helminthic and other parasitic infections may also be more common in high \textit{P. falciparum} PR areas thereby increasing levels of immune activation and HIV transmission risk. Additionally, both infections can be transmitted via blood transfusions and although this would likely contribute only a small fraction to overall prevalence, it is worth considering blood donor screening for malaria in endemic areas.\textsuperscript{36–38} Regardless of causality, this relationship is still significant for targeting intervention efforts wherever these two diseases overlap.

Ultimately, the interactions between HIV and malaria operate in a multitude of directions. This article further highlights the tremendous need to address each of these epidemics with strong individual initiatives. Beyond an individual approach, it will be necessary to identify sound strategies that can combine these separate efforts in order to create the most effective and sustainable programmes, particularly for sub-Saharan Africa. These programmes should be innovative combinations of validated interventions such as bed nets and condom distribution, mosquito eradication and education for HIV prevention, malaria treatment and antiretroviral therapy scale-up. Some policies have been established to address these diseases in a more unified fashion as outlined by the World Health Organization in 2005\textsuperscript{39} and the common funding mechanism developed by the Global Fund to Fight AIDS, Malaria and Tuberculosis. However, it has become apparent that this dilemma will require new synergies and a greater concerted enterprise in order to have a significant impact. This study provides strong evidence that should motivate policy-makers to support more resource sharing and cooperation between existing malaria and HIV prevention efforts.

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