



Dual Infection with HIV and Malaria Fuels the Spread of Both Diseases in Sub-Saharan Africa

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pRNA, which suggests that 6S RNA can be used as a template for transcription in extract. Extract containing samples required heparin treatment to resolve specific complexes on native gels; therefore, 6S RNA–pRNA:core complexes were not observed. Gradient fractionation of a stationary phase extract after incubation with NTPs similarly demonstrated significant release of 6S RNA from Eo⁷⁰ (fig. S5).

The 6S RNA:Eo⁷⁰ complex is stable in vitro and accumulates to high levels in stationary phase, raising the question of how 6S RNA–RNAP interactions are disrupted when cells reinitiate growth. To test if RNA synthesis could mediate timely 6S RNA release, endogenous 6S RNA complexes were examined in extracts prepared from cells after dilution into rich medium (Fig. 3C). A 6S RNA complex with mobility suggesting it was 6S RNA–pRNA was detected in extracts from cells 2 to 30 min after dilution. Extracts were not incubated nor NTPs added; therefore, complexes represent those formed in vivo. Addition of an RNAP inhibitor (rifampicin) to the dilution medium prevented 6S RNA–pRNA complex formation, which demonstrated that its formation requires RNA synthesis. The presence of 6S RNA–pRNA complexes in cells after outgrowth signifies that Eo⁷⁰ uses 6S RNA as a template for RNA synthesis at this time, consistent with the hypothesis that 6S RNA release from Eo⁷⁰ could be mediated through this process.

We propose that 6S RNA–templated RNA synthesis occurs in response to the rapid increase in NTP pools upon outgrowth (26). In vitro RNA synthesis from 6S RNA required higher concentrations of NTPs (>50 μ M) than several tested DNA promoters (<1 μ M NTPs) (fig. S6), which suggests that transcription from 6S RNA is more sensitive to NTP concentration. Other factors also may affect the relative stability of 6S RNA:Eo⁷⁰ complexes or may prevent RNA synthesis from 6S RNA, as the 6S RNA–pRNA complex was observed only early after exit from stationary phase and did not persist through exponential growth.

In addition to freeing RNAP from 6S RNA inhibition, the RNA synthesis reaction likely results in decreased stability of 6S RNA. 6S RNA levels are decreased during outgrowth (fig. S7) and do not reach maximum levels until well after transition into stationary phase (7). Such decreased stability might be due to increased accessibility of 6S RNA to cellular nucleases on release from RNAP or could be through direct recognition of the 6S RNA–pRNA duplex. It also is tempting to consider whether the pRNA has a cellular function distinct from the role its synthesis has in 6S RNA release, especially because the template region within 6S RNA is more conserved than the rest of the RNA (8).

Control of 6S RNA levels and 6S RNA–Eo⁷⁰ interactions in direct response to NTP concentration create a regulatory circuit where

release from RNAP and control of stability of the sRNA inhibitor depend on the same features of the RNA required for its inhibitory nature. Precise positioning of 6S RNA in the active site of RNAP blocks DNA promoter binding but allows synthesis-mediated release of 6S RNA. The mechanism of 6S RNA inhibition appears to differ from FC* and B2 RNA, which do not exclude DNA binding within preinitiation complexes (4), which suggests their mechanism of release also will be distinct. However, a common theme for sRNA inhibitors of RNAP may be to exploit inherent properties and activities of the enzyme for its inhibition, as well as for its release from such regulation.

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Supporting Online Material

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Materials and Methods

Figs. S1 to S7
References

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Dual Infection with HIV and Malaria Fuels the Spread of Both Diseases in Sub-Saharan Africa

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Mounting evidence has revealed pathological interactions between HIV and malaria in dually infected patients, but the public health implications of the interplay have remained unclear. A transient almost one-log elevation in HIV viral load occurs during febrile malaria episodes; in addition, susceptibility to malaria is enhanced in HIV-infected patients. A mathematical model applied to a setting in Kenya with an adult population of roughly 200,000 estimated that, since 1980, the disease interaction may have been responsible for 8,500 excess HIV infections and 980,000 excess malaria episodes. Co-infection might also have facilitated the geographic expansion of malaria in areas where HIV prevalence is high. Hence, transient and repeated increases in HIV viral load resulting from recurrent co-infection with malaria may be an important factor in promoting the spread of HIV in sub-Saharan Africa.

In Africa, an estimated 40 million people are infected with HIV, resulting in an annual mortality of over 3 million (1), whereas over 500 million clinical *Plasmodium falciparum* infections occur every year with more than a million malaria-associated deaths (2). There is considerable geographic overlap between the two diseases, particularly in sub-

Saharan Africa (3), and growing evidence of an interactive pathology (4–10). HIV has been shown to increase the risk of malaria infection and the development of clinical malaria, with the greatest impact in immune-suppressed persons (4, 6, 8–10). Conversely, malaria has been shown to induce HIV-1 replication in vitro (11) and in vivo (5, 7). A biological explanation for

these interactions lies in the cellular-based immune responses to HIV and malaria (11–13).

There is a functional relationship between HIV-1 plasma viral load and transmission probability per coital act, in which a logarithmic increase in viral load is associated with a 2.45-fold increase in transmission probability (14). Investigations of HIV-1 transmission probability per stage of infection indicate that the acute stage of HIV infection, during which the viral load peaks at a two-log excess over the chronic stage, plays a pivotal role in transmission (15, 16). This amplification seems to be responsible for as much as half of the infections, at least in the early stages of the epidemic (16, 17). A prospective study of dual infection with HIV and malaria has confirmed and extended earlier findings (4–6, 8–10) that, first, co-infection leads to a near one-log increase in viral load in chronic-stage HIV-infected patients during febrile malaria episodes (7) and, second, HIV infection substantially increases susceptibility to malaria infection (9). These findings have highlighted the need for a robust quantitative assessment of the population-level implications of the immune-mediated interaction of the two diseases (18).

Thus, we asked the question: does recurrent malaria promote HIV transmission because of a concomitant elevation of viremia during febrile periods? In the absence of field studies that directly measure the effect of malaria on HIV spread, we attempted to answer this question by synthesizing recent quantitative biological findings into a mathematical model that estimates the impact of HIV and malaria on one another (19). The core assumptions of our model are shown in Table 1. The duration of the heightened viral load and the impact of co-infection on sexual activity are not adequately characterized parameters. The supporting online material details the bases of our parameter choices and quantifies the impact of the uncertainty in the assumed parameters by means of univariate and multivariate sensitivity analyses (19). These analyses indicate a significant role for dual infection in fueling the spread of both diseases in sub-Saharan Africa

We examined the impact of the synergy in Kisumu, Kenya, a setting with high HIV and malaria prevalences. Malaria prevalence refers here to any malaria parasitaemia rather than to clinical disease alone. In the presence of interaction between the two diseases, the HIV

epidemic peak is 8% higher whereas the malaria peak is 13% larger than the levels in a scenario where there is no interaction (Fig. 1). The excess prevalence, which is the baseline prevalence subtracted from the prevalence after the inclusion of the interaction, is 2.1% for HIV and 5.1% for malaria, respectively. In

the Kisumu district [with an adult human population $\approx$ 200,000 (19)], the interaction in the absence of malaria intervention may account for a cumulative 8,500 excess HIV infections and 980,000 excess malaria episodes since 1980. Furthermore, for the period from 1990 through 2005, a duration marked by an

Table 1. The core assumptions of our HIV/malaria interaction model.

Assumption	Parameter value	Sources
Rate ratio increase in HIV coital transmission probability per one-log (base 10) rise in viral load	2.45	(14)
Logarithmic increase in HIV viral load level during malaria infection		
Acute stage	0.0	Assumption
Chronic stage with clinical malaria	0.82	(7)
Chronic stage with nonclinical malaria	0.08	(7)
Advanced stage	0.20	(7)
Susceptibility enhancement to malaria infection in HIV-infected persons		
Acute stage	0%	Assumption
Chronic stage	44%	(9, 19)
Advanced stage	103%	(9, 19)
Duration of heightened viral load during malaria episodes	42 days	(5, 7, 19)
Fractional reduction in sexual activity during malarial infection		
Clinical malaria	10%	(19, 25, 26)
Nonclinical malaria	3%	(7, 19)
Fraction of malaria-infected patients developing clinical malaria		
HIV-negative	16%	(10)
HIV-positive	31%	(7)
Enhanced HIV mortality in dually infected patients		
Areas of stable malaria	0%	(4, 10, 27)
Areas of nonstable malaria	25%	(19, 28, 29)

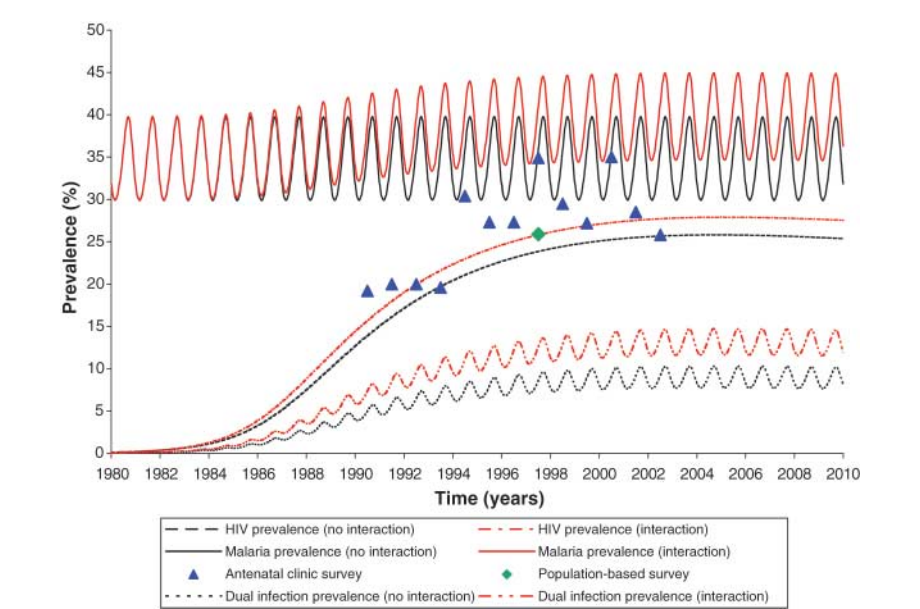


Fig. 1. The time course of HIV and malaria interaction in Kisumu, Kenya. HIV and malaria prevalences in Kisumu as compared with the baseline predictions in the absence of interaction are shown. The measured prevalences were extracted from several studies (19).

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average HIV prevalence of roughly 25%, the fraction of HIV infections attributable to malaria is 4.8% whereas that of malaria promoted by HIV is 9.9%. The latter estimate accords well with a derived estimate from rural Uganda (10). We estimate that an HIV prevalence that reached 24% in 1995 would have needed two additional years to reach this level in the absence of synergy with malaria.

We proceed to describe the interaction in diverse settings with different HIV and malaria prevalence levels. We characterized the synergy at the endemic equilibrium of both diseases

and used the average sexual partner acquisition rate (ρ_{avg}) in the population as a proxy for HIV baseline prevalence level and Macdonald's stability index (MSI) (20) as a proxy for that of malaria (19). Once we incorporated the interaction between the two diseases in the diverse settings described in Fig. 2, A and B, we derived the excess prevalences (Fig. 2, C and D). It is evident how the interplay, though dependent on baseline measures, can considerably increase HIV and malaria prevalences. The largest increase occurs when one baseline measure is very high while the other is very

low and near its endemic threshold. For example, a setting with 1.0% malaria but 37.8% HIV at baseline prevalence transforms into a setting of 9.2% malaria and a barely changed value of 38.5% HIV. When both prevalences are very high, the impact of the interaction is minimal. For HIV, there are two "endemic thresholds" arising for each of the two sexual risk groups assumed in our model. The first threshold is when sexual transmission becomes sustainable in the high-risk group, whereas the other threshold is when the transmission becomes sustainable in the general population (low-risk group) once the partner change rate is high enough to support sustainable transmission, even in the absence of mixing with the high-risk group.

Furthermore, if one of the diseases is at endemic equilibrium while the other is just below its threshold, the interaction can lower the threshold of the second disease, thereby allowing this disease to reach endemic stability. This effect can be seen in Fig. 3, where the interaction has lowered the endemicity threshold for malaria from $\text{MSI} = 1.353$ to 1.270 (a 6% reduction). A myriad of factors, however, affect malaria ecology, so lowering the threshold does not necessarily expand the distribution of malaria. Nevertheless, in areas that can support malaria with a small change in the entomological or transmission parameters, the interaction can drive unstable malaria prevalence toward stability. Though not evident in the figure because of the small absolute change, the interaction has also lowered the HIV endemicity threshold (the threshold of sustainability in the high-risk group) by 6% from $\rho_{\text{avg}} = 0.456$ to $\rho_{\text{avg}} = 0.430$ partners per year (corresponding to $\rho_{\text{high-risk}} = 2.261$ to $\rho_{\text{high-risk}} = 2.132$ partners per year).

The rapid increase in excess prevalence in Figs. 2, C and D, and 3 just above the threshold implies that settings with high HIV (or malaria) endemicity but with low or unstable malaria (or HIV) prevalence are particularly at risk for this interaction. Given that, in areas of unstable malaria endemicity, a larger part of the malaria burden is in adults in whom HIV is concentrated, the high HIV prevalence, for example in

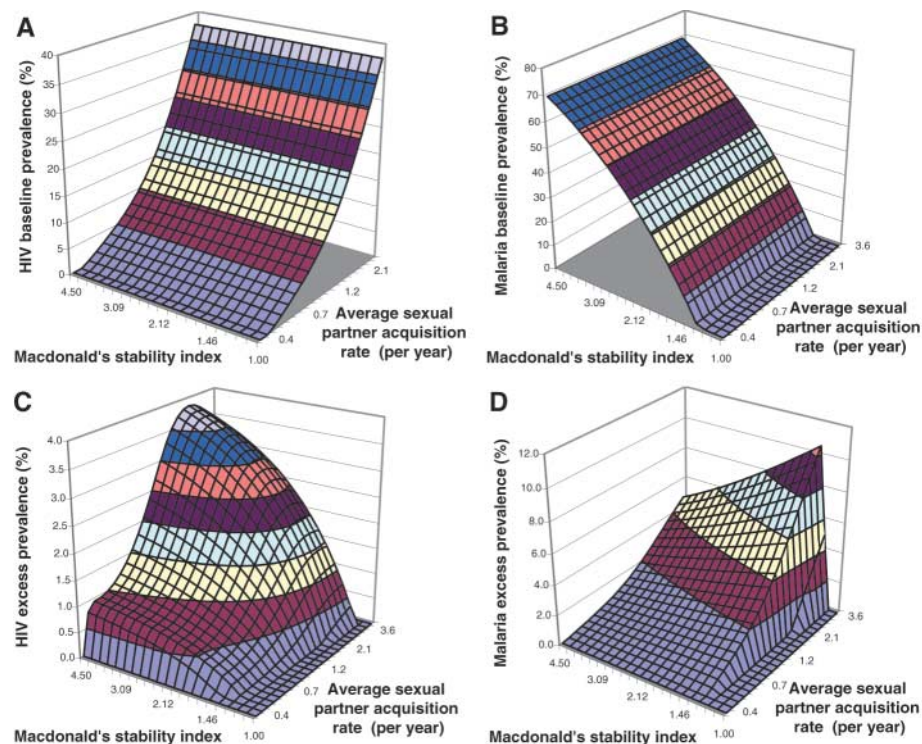


Fig. 2. Excess HIV and malaria prevalences in a wide range of settings. The equilibrium prevalences of HIV (A) and malaria (B) in the absence of interaction are shown as functions of ρ_{avg} and MSI. Both parameters increase geometrically to capture a wide spectrum corresponding to a change in baseline adult HIV prevalence from 0 to 50% and baseline adult malaria prevalence from 0 to 70%. (C) and (D) display the corresponding excess HIV and malaria prevalences. Excess prevalence is defined as no-interaction prevalence subtracted from the prevalence in the presence of interaction. Colored gradients correspond to the units in the Y axis.

Fig. 3. Interaction impact on shifting endemicity thresholds. (A) HIV prevalence in the absence of interaction, in its presence, and in excess prevalence as a function of ρ_{avg} in a setting of 30% malaria baseline prevalence. (B) Malaria prevalence in the absence of interaction, in its presence, and in excess prevalence as a function of MSI in a setting of 25% HIV baseline prevalence. Excess prevalence is a manifestation of the shift in the epidemic curves for each of the diseases to below threshold after interaction.

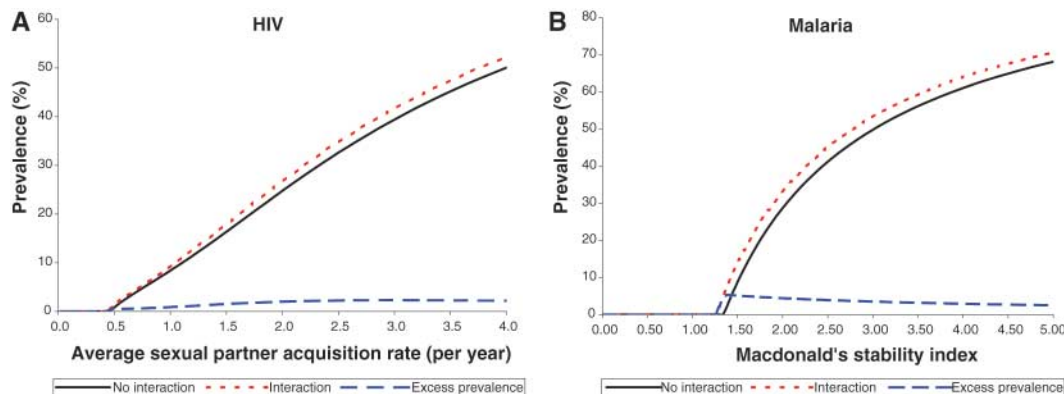
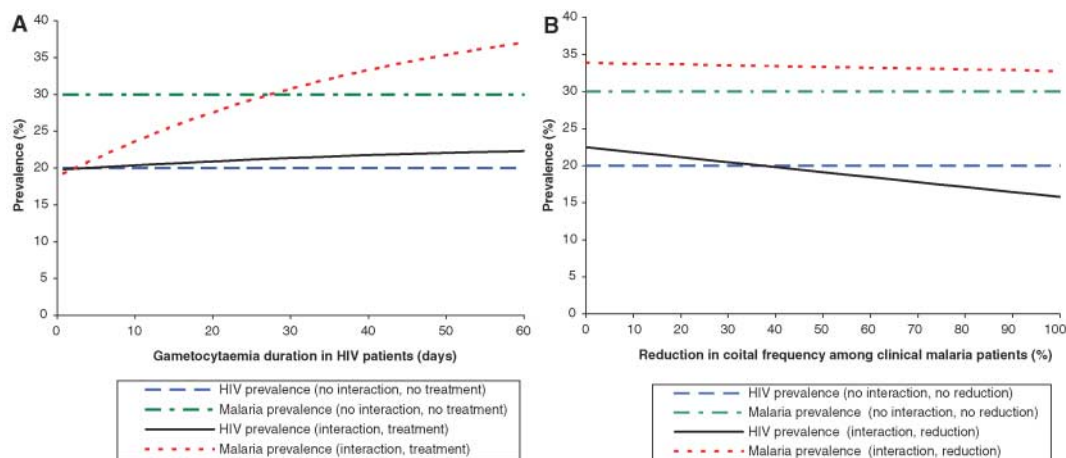


Fig. 4. Impact of potential interventions and the sensitivity of predictions to key assumptions about the parameters of the interaction. **(A)** Impact of malaria treatment on dually infected patients as expressed in HIV and malaria prevalences in the presence of interaction and treatment as compared with the baseline with no interaction and no treatment. The intervention reduces excess prevalence for both diseases, but its impact is stronger on malaria. **(B)** Impact of reducing sexual activity during clinical malaria and HIV dual infection as expressed in HIV and malaria prevalences in the presence of interaction and activity reduction as compared to the baseline with no interaction and no reduction. The intervention reduces excess prevalence for both diseases but its impact is more substantial to the HIV epidemic.



South Africa, can intensify and possibly stabilize malaria endemicity.

Korenromp *et al.* have assessed the impact of HIV on malaria in sub-Saharan Africa and indicated that the overall impact is limited because of differences in geographic distributions and age patterns between the two diseases, although the effect in the presence of geographic overlap can be locally considerable and is substantial in areas of high HIV with unstable malaria as we predict (21). In some parts of Africa, the geographic overlap may increase if HIV continues to spread from urban centers to rural areas. Our analysis indicates that the impact on malaria is at its maximum when the number of advanced HIV cases reaches its zenith shortly after the HIV epidemic peaks (Fig. 1), a trajectory akin to that of tuberculosis (22). Nonetheless, the malaria peak lags behind that of HIV at most by 1 year, in contrast to that of tuberculosis, which lags by 7 years (23).

Our model can be expanded to accommodate general intervention measures such as provision of condoms and insecticide-treated bednets, but here we have focused on measures that target the interaction in co-infected persons. Thus, we have specifically modeled the effect of malaria treatment of HIV-infected patients, assuming either that such treatment shortens the period of heightened HIV viral load or that prophylaxis prevents malaria infection from being established in HIV-infected patients in the first place (8). We varied the malaria infectious period (gametocytaemia) from 0 to 60 days in HIV-infected patients (Fig. 4A) and observed a steady decline in excess HIV prevalence as we cut back the duration of malaria episode. However, the outcome showed that malaria treatment is more effective in reducing malaria prevalence than it is at reducing the prevalence of HIV. Shortening gametocytaemia to less than 27 days eliminates all HIV-induced malaria prevalence.

We also tested the impact of a loss of sexual activity during malaria episodes among clinical malaria-infected patients (Fig. 4B). The impact on HIV is considerable, but it is minimal on malaria. A 36% reduction in activity can remove all excess HIV prevalence. Avoidance of sex during, and for 8 weeks after, malarial fever would considerably diminish HIV spread, but this degree of intervention is probably impractical to implement despite key successes in behavioral interventions such as in Uganda (24). A more-effective approach may be an emphasis on treatment of malaria and protection against mosquitoes for HIV-infected persons. Thus, linking health services for HIV and malaria would be advantageous. The combination of cotrimoxazole prophylaxis, antiretroviral therapy, and insecticide-impregnated bednets can reduce the incidence of malaria by 95% in HIV-infected persons (8).

Our model shows that transient but repeated elevated HIV viral loads associated with recurrent co-infections, such as malaria, can amplify HIV prevalence. This finding suggests one more independent explanatory variable for the high HIV incidence and rapid spread of HIV infection in sub-Saharan Africa. Diseases that are not sexually transmitted can thus affect the natural history of HIV and impact the process of infection spread. Our work highlights the need for field studies that better characterize the parameters of the interaction and explore the impact of intervention measures. However, such studies must account for the ethical considerations posed by the recent findings of Mermin *et al.* (8) that there are effective interventions to reduce the incidence of malaria in HIV-infected persons. Finally, we emphasize the need for more-concerted health services for early and effective treatment and prevention of malaria in HIV-infected persons.

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Supporting Online Material

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Materials and Methods

Figs. S1 and S2

Tables S1 to S6

References

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ERRATUM

Post date 2 February 2007

Reports: "Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa" by L. J. Abu-Raddad *et al.* (8 Dec. 2006, p. 1603). The first sentence of the paper, "In Africa, an estimated 40 million people are infected with HIV resulting in an annual mortality of over three million (1), while over 500 million clinical *Plasmodium falciparum* infections occur every year with more than a million malaria-associated deaths..." is incorrect. These numbers refer to worldwide numbers for both infections, not just in Africa. The number of HIV infected persons in Africa is approximately 25 million, and the number of malaria infections is roughly 350 million.