



Supporting Online Material for
**Dual Infection with HIV and Malaria Fuels the Spread of Both Diseases
in Sub-Saharan Africa**

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This PDF file includes:

Materials and Methods
Figs. S1 and S2
Tables S1 to S6
References

HIV- malaria interaction model:

The model consists of twenty coupled nonlinear ordinary differential equations eighteen of which describe the host population (humans) and two dedicated to the vector population (female *Anopheles* mosquitoes). This system of equations is an extension of conventional systems in theoretical epidemiology (Anderson and May 1991). The theory assumes linear hazards for all processes, such as births, deaths and recoveries, except for the infection process which is a nonlinear quadratic term. The latter arises from the concept of “standard incidence” where the infection term of a sexually transmitted disease (or a vector borne disease) is proportional to the susceptible and infectious populations (Anderson and May 1991). Otherwise, the term depends on the transmission probability per contact, the new partner acquisition rate and the number of sexual contacts per person which does not scale with the population size.

The model calculates the size of the epidemiologic synergy between HIV-1 and malaria. The synergy is defined as the net effect of the presence of heightened viral load, enhanced susceptibility to malaria in HIV patients, reduction in sexual activity during malaria episodes and enhanced malaria mortality in advanced HIV patients. The complexity of the model is tied to the measured rates and parameters, and the formulation stresses the end-point of faithful representation of the interplay between the two diseases. We model only the sexually active population since it is the population where the epidemiologic overlap of the two diseases is of interest. We assume that the average vector-to-host density is constant throughout the epidemic, but include seasonal variations in mosquito population. We find generally that seasonality slightly moderates the impact of the interaction except in low or unstable malaria settings where fluctuations can make it harder for malaria to remain stable.

The model is in principle applicable in diverse malaria ecologies and HIV settings provided the relevant parameter values are chosen with possibly minor modifications in the model structure. Hence, the model is more general than the chosen parameter values delineated below which largely correspond to the results reported in the text.

The HIV and malaria infection status, the HIV stage of progression, and the sexual risk activity class divide the host population into compartments that delineate the dynamics:

$$\begin{aligned}
\frac{dS(i)}{dt} &= \mu N_0(i) + \nu I_0(i) - \mu S(i) - \Lambda_M^{V \rightarrow H} S(i) - \Lambda_{HIV}^{S(i)} S(i) \\
\frac{dI_0(i)}{dt} &= \Lambda_M^{V \rightarrow H} S(i) - \mu I_0(i) - \nu I_0(i) - \Lambda_{HIV}^{I_0(i)} I_0(i) \\
\frac{dY_1(i)}{dt} &= \Lambda_{HIV}^{S(i)} S(i) + \nu I_1(i) - \mu Y_1(i) - \omega_1 Y_1(i) - g_1 \Lambda_M^{V \rightarrow H} Y_1(i) \\
\frac{dI_1(i)}{dt} &= \Lambda_{HIV}^{I_0(i)} I_0(i) + g_1 \Lambda_M^{V \rightarrow H} Y_1(i) - \mu I_1(i) - \nu I_1(i) - \omega_1 I_1(i) \\
\frac{dY_2(i)}{dt} &= \omega_1 Y_1(i) + \nu I_{2a}(i) + \nu I_{2b}(i) - \mu Y_2(i) - \omega_2 Y_2(i) - g_2 \Lambda_M^{V \rightarrow H} Y_2(i) \\
\frac{dI_{2a}(i)}{dt} &= f_{HIV+} g_2 \Lambda_M^{V \rightarrow H} Y_2(i) + f_{HIV+} \omega_1 I_1(i) - \mu I_{2a}(i) - \nu I_{2a}(i) - \omega_2 I_{2a}(i) \\
\frac{dI_{2b}(i)}{dt} &= (1 - f_{HIV+}) g_2 \Lambda_M^{V \rightarrow H} Y_2(i) + (1 - f_{HIV+}) \omega_1 I_1(i) - \mu I_{2b}(i) - \nu I_{2b}(i) - \omega_2 I_{2b}(i) \\
\frac{dY_3(i)}{dt} &= \omega_2 Y_2(i) + \nu I_3(i) - \mu Y_3(i) - \omega_3 Y_3(i) - g_3 \Lambda_M^{V \rightarrow H} Y_3(i) \\
\frac{dI_3(i)}{dt} &= g_3 \Lambda_M^{V \rightarrow H} Y_3(i) + \omega_2 I_{2a}(i) + \omega_2 I_{2b}(i) - \mu I_3(i) - \nu I_3(i) - d \omega_3 I_3(i) \\
N(i) &= S(i) + \sum_{\alpha=1,2,3} Y_\alpha(i) + \sum_{\substack{\alpha=0,1,2,3 \\ a,b}} I_\alpha(i)
\end{aligned} \tag{1}$$

We use the notation that population variables are in capitalized Latin letters, dimensionless coefficients or factors in small Latin letters while dimensionful quantities (such as transition rates) are in Greek symbols. The index i stands for an i -sexual risk population where 1 represents the general population (low risk) while 2 represents the core group (high risk). The index α marks the stage of HIV pathogenesis; 0, 1, 2, and 3 which stand for no (infection), acute, chronic, and advanced HIV stages respectively. Here, $N(i)$ is the total population size of the i -risk group, $S(i)$ is the susceptible population, $I_\alpha(i)$ variables stand for malaria infected and infectious populations, while $Y_\alpha(i)$ represents the populations that are solely infected with HIV. The index $2a$ represents clinical malaria infection in HIV patients in their chronic stage while $2b$ represents non-clinical malaria infection in HIV patients also in their chronic stage. Clinical malaria is defined as the presence of fever and parasitaemia density greater than 2000/ μl (Kublin et al. 2005). The selection of the 2000 parasites/ μl cut-off is based on the distribution of parasite density in the study population (median was just under 2000/ μl).

The factor f_{HIV+} dictates the fraction of dually infected patients that develops clinical malaria, $N_0(i)$ is the initial total population size of the i -risk group, μ is the natural rate of removal from the sexually active class, ν is the gametocytes clearance

rate, and Λ 's denote the various forces of infection. The progression of HIV is described by ω_1 , the rate of progression from acute to chronic stage, ω_2 , the rate from chronic to advanced stage, and ω_3 , the rate of HIV disease mortality. The enhanced HIV mortality in dually infected patients who are in HIV advanced stage is dictated by the factor d . Finally, the parameters g_i govern the susceptibility enhancement to malaria per stage of HIV infection.

The vector population is described by

$$\begin{aligned}\frac{dV_S}{dt} &= \mu_V V - \mu_V V_S - \Lambda_M^{H \rightarrow V} V_S \\ \frac{dV_I}{dt} &= \Lambda_M^{H \rightarrow V} (t - \tau_{Incub}) V_S (t - \tau_{Incub}) e^{-\mu_V \tau_{Incub}} - \mu_V V_I\end{aligned}\quad (2)$$

where μ_V is the rate of mosquito mortality and τ_{Incub} denotes the incubation period that an infected mosquito needs to become infectious. The V , V_S , V_I are the total, susceptible, and infected vector populations respectively. The total mosquito population endures seasonal variations according to

$$V(t) = a[(1-b) + b\sin(2\pi t)] \quad (3)$$

where a is the amplitude and b is the relative size of the fluctuations in the population. They are derived using

$$a = \left(\frac{V}{\sum_{k=1,2} N(k)} \right)_{avg} \frac{2 \sum_{k=1,2} N(k)}{1 + 1/RatioV} \quad (4)$$

$$b = \frac{1}{2} \left(1 - \frac{1}{RatioV} \right) \quad (5)$$

Here, $(V / \sum_{k=1,2} N(k))_{avg}$ is the average vector density and $RatioV$ is the ratio of the maximum to minimum in the vector population.

As for the demographics of the host and vector populations, we assume for simplicity stationary population sizes in absence of disease mortality and seasonality

(Anderson and May 1991). The assumption facilitates the disentanglement of epidemiologic effects from demographic ones. Host susceptibles enter the sexually active population through the rate $\mu N_0(i)$ while the vector susceptibles enter through the rate $\mu_v V$. The natural rate of removal from the sexually active class is set at $\mu = 1/35$ corresponding to a sexually active lifespan of 35 years (the 15-49 years age group (UNAIDS/WHO 2004)). The value of the initial host population size depends on the community of interest. For example, in Kisumu district we have assumed a population size of 200,000 as the representative average adult population from 1980 to present in absence of HIV mortality (Law 1999; Morison et al. 2001; Law 2005; Law 2005). To be noted here that the system of equations can be transformed into an equivalent one in terms of population fractions and that most epidemiologic measures of interest, such as prevalence and incidence rate, are by definition per capita measures and hence independent of the total host population size $\sum_{k=1,2} N(t; k)$.

We define equilibrium in our model as endemic equilibrium (Anderson and May 1991), that is when the prevalence (and incidence) of the disease passes through the epidemic phase and reaches stable endemicity (constant prevalence for HIV and stable oscillations of constant magnitude for malaria). The model leads to equilibrium since new susceptibles for both risk groups enter the populations through the term $\mu N_0(i)$ at all times. The population is assumed demographically stable when HIV first enters the population. However, AIDS mortality decreases the population steadily till the epidemic reaches endemic stability where there is now equilibrium but at a lower population size. Since AIDS mortality affects the higher risk group more than the low risk group, the high risk group is smaller relative to the low risk one at equilibrium.

As an example, for the Kisumu calculation of Figure 1, the total sexually active population declined from 200,000 (11.3% of which in the high risk group) at the beginning of the run (year 1980) to 138655 at the end of the run (year 2010) of which 7169 (5.2%) are in the high risk group and 131486 (94.8%) are in the general population. At the endemic equilibrium attained around the year 2040, the total sexually active population is 108968 of which 6374 (5.8%) are in the high risk group and 102594 (94.2%) are in the general population.

The HIV force of infection is decomposed into an HIV only infectious population and HIV-malaria coinfectious population. Accordingly, the force of infection felt by the susceptible population $S(i)$ is given by $\Lambda_{HIV}^{S(i)} = \Lambda_Y^{S(i)} + \Lambda_I^{S(i)}$ where

$$\Lambda_Y^{S(i)} = \rho_{S(i)} \sum_{\substack{j=1,2 \\ \alpha=1,2,3 \\ a,b}} z_{Y_\alpha(j) \rightarrow S(i)} \mathbf{G}(i, j) \frac{\rho_{Y_\alpha(j)} Y_\alpha(j)}{\rho_{S(j)} S(j) + \sum_{\beta=1,2,3} \rho_{Y_\beta(j)} Y_\beta(j) + \sum_{\substack{\beta=0,1,2,3 \\ a,b}} \rho_{I_\beta(j)} I_\beta(j)} \quad (6)$$

$$\Lambda_I^{S(i)} = \rho_{S(i)} \sum_{\substack{j=1,2 \\ \alpha=1,2,3 \\ a,b}} z_{I_\alpha(j) \rightarrow S(i)} \mathbf{G}(i, j) \frac{\rho_{I_\alpha(j)} I_\alpha(j)}{\rho_{S(j)} S(j) + \sum_{\beta=1,2,3} \rho_{Y_\beta(j)} Y_\beta(j) + \sum_{\substack{\beta=0,1,2,3 \\ a,b}} \rho_{I_\beta(j)} I_\beta(j)}$$

And that felt by the HIV susceptible but malaria infected population $I_0(i)$ is given by

$$\Lambda_Y^{I_0(i)} = \rho_{I_0(i)} \sum_{\substack{j=1,2 \\ \alpha=1,2,3 \\ a,b}} z_{Y_\alpha(j) \rightarrow I_0(i)} \mathbf{G}(i, j) \frac{\rho_{Y_\alpha(j)} Y_\alpha(j)}{\rho_{S(j)} S(j) + \sum_{\beta=1,2,3} \rho_{Y_\beta(j)} Y_\beta(j) + \sum_{\substack{\beta=0,1,2,3 \\ a,b}} \rho_{I_\beta(j)} I_\beta(j)} \quad (7)$$

$$\Lambda_I^{I_0(i)} = \rho_{I_0(i)} \sum_{\substack{j=1,2 \\ \alpha=1,2,3 \\ a,b}} z_{I_\alpha(j) \rightarrow I_0(i)} \mathbf{G}(i, j) \frac{\rho_{I_\alpha(j)} I_\alpha(j)}{\rho_{S(j)} S(j) + \sum_{\beta=1,2,3} \rho_{Y_\beta(j)} Y_\beta(j) + \sum_{\substack{\beta=0,1,2,3 \\ a,b}} \rho_{I_\beta(j)} I_\beta(j)}$$

In these expressions $\rho_{R_\alpha(i)}$ describes the new sexual partner acquisition rate for each $R_\alpha(i)$ host population variable. Accordingly, sexual activity is stratified by sexual risk classes, HIV stages and malaria disease states.

The mixing between the two risk groups is dictated by $\mathbf{G}(i, j)$ which is the sexual mixing matrix that provides the probability that an individual in risk group i would choose a partner in risk group j (Garnett and Anderson 1993). It is given by the expression

$$\mathbf{G}(i, j) = e \delta_{i,j} + (1-e) \frac{\rho_{S(j)} S(j) + \sum_{\beta=1,2,3} \rho_{Y_\beta(j)} Y_\beta(j) + \sum_{\substack{\beta=0,1,2,3 \\ a,b}} \rho_{I_\beta(j)} I_\beta(j)}{\sum_k \left(\rho_{S(k)} S(k) + \sum_{\beta=1,2,3} \rho_{Y_\beta(k)} Y_\beta(k) + \sum_{\substack{\beta=0,1,2,3 \\ a,b}} \rho_{I_\beta(k)} I_\beta(k) \right)} \quad (8)$$

Here, $\delta_{i,j}$ is the identity matrix and the parameter $e \in [0,1]$ measures the degree of assortativeness in the mixing. At the extreme $e = 0$, the mixing is fully homogenous while at the other extreme $e = 1$, the mixing is fully assortative as individuals choose partners only from within their risk group.

The parameters $z_{Q(j) \rightarrow X_\alpha(i)}$ stands for HIV transmission probability per partnership in a partnership between the susceptible population $X_\alpha(i)$ and the infected population $Q(j)$, and are expressed in terms of the transmission probability per coital act in this partnership ($p_{Q(j) \rightarrow X_\alpha(i)}$), the frequency of coital acts per HIV stage in this partnership ($n_{Q(j) \leftrightarrow X_\alpha(i)}$), and the duration (τ_p) of this partnership, using the binomial (Bernoulli) model

$$z_{Q(j) \rightarrow X_\alpha(i)} = 1 - \left(1 - p_{Q(j) \rightarrow X_\alpha(i)}\right)^{n_{Q(j) \leftrightarrow X_\alpha(i)} \tau_p} \quad (9)$$

Malaria morbidity, depending on malaria status as clinical versus non clinical, reduces the coital frequency $n_{Q(j) \leftrightarrow X_\alpha(i)}$ in the sexual partnerships that involve malaria patients. The magnitudes of these reductions are discussed in the subsection of HIV and malaria interaction parameters below. Note that the malaria infected but HIV susceptible population $I_0(i)$ is composed of clinical and non-clinical malaria subpopulations. Therefore the reduction in coital frequency in this group is assumed to be the average reduction in coital frequency in this population as a whole. That is, the fractional reduction in coital frequency is given by $f_{HIV-} r_{clin} + (1 - f_{HIV-}) r_{non-clin}$. Here, f_{HIV-} is the fraction of malaria infected but HIV susceptible persons that develop clinical malaria, and r_{clin} and $r_{non-clin}$ are the fractional reductions in coital frequency during malaria infection among clinical and non-clinical malaria persons respectively.

The above description highlights how HIV transmission depends on several parameters including the rate of partner change, the duration of partnership, the frequency of coital acts, and HIV transmission probability per coital act (Garnett and Anderson 1993; Anderson and Garnett 2000). The rates of partner change or the duration of partnership do not create the interaction between HIV and malaria. They merely drive the baseline HIV epidemic in absence of interaction. However, the transient raising of the viral load among established partnerships is what directly drives the interaction in our model by increasing the transmission probability per coital act according to the functional relationship between HIV-1 plasma viral load and HIV transmission probability per coital act (Quinn et al. 2000). In addition, malaria morbidity affects the interaction by decreasing the frequency of coital acts in partnerships involving malaria patients.

The malaria host to vector and vector to host forces of infection are given by

$$\Lambda_M^{V \rightarrow H} = \frac{V}{\sum_{k=1,2} N(k)} t^{V \rightarrow H} \theta \left(\frac{V_I}{V} \right) \quad (10)$$

$$\Lambda_M^{H \rightarrow V} = t^{H \rightarrow V} \theta \sum_{\substack{j=1,2 \\ \alpha=0,1,2,3 \\ a,b}} \frac{I_\alpha(j)}{\sum_{k=1,2} N(k)} \quad (11)$$

Here $V / \sum_{k=1,2} N(k)$ is the seasonally-varying vector per host density and θ is the female mosquito biting rate. The parasite transmission probabilities are $t^{V \rightarrow H}$ from vector to host, and $t^{H \rightarrow V}$ from host to vector. Both are defined according to the convention of Aron and May and Anderson and May (Aron and May 1982; Anderson and May 1991).

To be stressed here that the specific stratification in the model is done for purpose of realism in the representation of the measured data, and to reflect the biological mechanisms in action. In this manner we structured the model to divide the HIV infected population into three stages two of which (chronic and advanced) stratified according to how high or low the CD4 count. The impact of malaria on HIV viral load is dependent on the CD4 count (chronic with CD4 count > 300 cells/ μ l and advanced with CD4 count ≤ 300 cells/ μ l). Furthermore, we stratified the group of dually infected with chronic HIV into two groups: persons with clinical malaria defined as fever and parasitaemia density greater than 2000/ μ l (the group that shows the largest increase in viral load), and persons with non-clinical malaria. We have also built the model to allow for variations in the effect of malarial infection on sexual activity by setting different levels of sexual activity reduction depending on the status of the malaria episode (clinical versus non clinical).

The qualitative dynamics of our proposed nonlinear system is marked by three dynamical behaviors. The first is a threshold dynamics where the epidemic burns itself out if the number of secondary infections each index case causes (that is the reproductive number R_0 (Anderson and May 1991)) is less than one. If $R_0 > 1$, the transmission starts with an initial exponential spread as a branching process where each infection causes R_0 new infections, the growth of which is checked by the depletion of susceptibles leading to a peak in prevalence and incidence. Finally following the peak, saturation dynamics result in a stable equilibrium where there is an exact balance between the numbers of new infections and leaving infections as a consequence of disease and natural mortality as well as births. Extensive mathematical analysis of this type of deterministic epidemic models can be found in Anderson and May (Anderson and May 1991) and Diekmann and Heesterbeek (Diekmann and Heesterbeek 2000).

It is fitting here to describe the modeling landscape behind our model. Our approach, deterministic differential-equation model, belongs to one of two main approaches in theoretical epidemiology. An alternative approach is stochastic formalisms including compartmental or individual-based formulations that account for the randomness in diseases transmission. Since the infected population sizes are large for both diseases, it is reasonable to assume that population level effects described by these two distinct approaches will be similar. Furthermore, our model is based on the conventional theory to malaria modeling as pioneered by Ross and Macdonald (Macdonald 1957; Bailey 1982), and to HIV modeling as pioneered by Anderson and May (May and Anderson 1988; Anderson and May 1991). Within this genre of deterministic models, the main differences in treatments arise from the inclusion of various types of heterogeneity. Alternative schemes would include more heterogeneity such as explicit sexual behavior patterns, age dependence, spatial effects or diverse population susceptibilities. Our work is the first to model the epidemiological synergy between HIV and malaria and is constructed to include all effects that we deem relevant for the interaction at the population level.

Of particular relevance here is the issue of sexual behavior heterogeneity. The level of behavioral heterogeneity in our model was devised based on relevancy to the question we are addressing, the size of the epidemiologic synergy. We found that the magnitude of the synergy is predominantly sensitive to the interaction parameters and the baseline (no interaction) prevalence levels (implicitly hazard rates of infection), and to a much lesser extent to the parameters that drive these prevalence levels (please see sensitivity analyses below).

Sexual risk behavior is very complex and it is very difficult, if not virtually impossible, to precisely quantify it due to the multitude of facets of sexual behavior from partnership formation, to contact with sex workers, to heterogeneity in partner change rates, to assortative and age cohort mixing among other aspects (Table S3 conveys part of this complexity). Moreover, network structure plays a major role in HIV transmission (Watts and May 1992; Kretzschmar and Morris 1996; Ghani et al. 1997; Morris 1997). A person in a stable long partnership, who theoretically has very low risk behavior with no partner changes, can still be considered at high risk of infection only because she/he can be connected through her/his partner, or the partner of the partner, to a very high risk sexual network. Conversely a person, who is theoretically considered at high risk with frequent partnership changes, may still be at low risk of infection if his/her network is virtually closed with low risk of HIV penetration.

Despite this complexity, we found that the impact of this heterogeneity on specifically the epidemiologic synergy between HIV and malaria is largely determined by what these complex behavioral patterns entail in terms of HIV hazard rates of infection (forces of infection). It did not principally matter what behavioral mechanisms contributed to the hazard rate a person experiences, but what mattered is the actual value of the hazard rate. The hazard rate affects the dynamics through the competition among

hazards. For people experiencing a large hazard rate (that is in the high risk group), the impact of the synergy is limited since the increased hazard due to the heightened viral load is still small compared to the other hazards of infection and people are much more likely to acquire HIV by “usual ways” before they encounter an exposure due to malaria heightened viral load. On the other hand, people who are experiencing a small hazard of infection (that is in the low risk group), are more affected by the synergy since they are much less likely to acquire HIV before they encounter an exposure due to malaria. Furthermore, a small hazard rate imply a small baseline prevalence level and therefore it is more likely that excess transmissions will end up in susceptible persons as opposed to the case of large baseline prevalence level.

Therefore, the diverse aspects of sexual behavior are all relevant to the size of the synergy only on how they affect the hazard rate of infection. Though they dictate the HIV baseline prevalence level, their impact on the epidemiologic synergy enters mainly through their contribution to the dynamics of competing hazards. We included in our model two risk groups, one representing exposure to a large hazard rate of infection, irrespective of the specific sexual risk behaviors that led to this high hazard, and the other representing a low risk group with a small hazard rate of infection. The epidemiologic synergy that we report provides an estimate of the average synergy over the studied population. Within the population however, the impact of the synergy can depend on the level of hazard rate in each group which in turn depends on the nature and level of sexual risk behavior.

Our finding that the impact of the synergy is largest among the low risk population is intriguing. In this regard at least, the dynamics of malaria in fueling HIV spread in the general population appears to be similar to that of herpes simplex virus type 2 (HSV-2). Orroth et al. suggested that HSV-2 role in HIV spread may increase as HIV spreads from the high risk group to the general population (Orroth et al. 2006). The similarity of this outcome for both malaria and HSV-2 suggests that this may be a general feature of the role of biological cofactors with repeated activations or chronic infection.

In our model we do not distinguish between males and females because the best data on HIV transmission probability per coital act (the Rakai study) indicates that there are no differences between HIV transmission probability per coital from male to female and from female to male (Gray et al. 2001; Wawer et al. 2005). The sources of the disparity in HIV spread among men and women appear to be due primarily to behavioral patterns such as age cohort mixing (young women with older men) (Gregson et al. 2002), as well as possibly because of the impact of cofactor sexually transmitted diseases (Glynn et al. 2001), or the role of male circumcision (Williams et al. 2006). Hence, to a large extent the differences between males and females seem to boil down to differences in sexual risk behavior which affects the synergy through the dynamics of competing hazards as discussed above.

We have restricted our dynamical model to the sexually active population, the population where the epidemiologic overlap is of interest, and we did not include child and elderly populations. There is little doubt that children play a dominant role in malaria transmissions (Githeko et al. 1992). Moreover, since children contribute relatively more to infection of the mosquito population than the sexually active age group, the excess malaria transmissions due to HIV in adults in a model that exclude children may overestimate the impact compared to a model that includes children. We effectively included the contribution of children to the transmission in the parameterization of the transmission among adults. As far as the impact of malaria on HIV is concerned, this simplification does not affect our results since we have shown below (sensitivity analyses) that the interaction is predominantly sensitive to baseline malaria prevalence among adults irrespective of the details of the transmissions that contributed to this prevalence.

As for the impact of HIV on malaria, this simplification may affect our predictions of the size of the synergy if the excess malaria transmissions in adults play a significant role in malaria dynamics. If however malaria prevalence level in Kisumu is at or not far from saturation, the increase in malaria transmissions from the dually infected patients would hardly increase the prevalence of parasitaemia. We found that malaria dynamics in Kisumu is not far from saturation. Despite the saturation, the presence of HIV changes malaria epidemiology and raises adult malaria prevalence primarily as a consequence of the enhanced susceptibility of HIV persons and not as a consequence of the excess malaria transmissions. This conclusion is based on the following:

First, in field studies, namely the Masaka cohort in Uganda (Whitworth et al. 2000) and the Thyolo cohort in Malawi (Kublin et al. 2005), both of which areas of intense malaria transmission, HIV has been observed to actually increase prevalence of parasitaemia among adults. Whitworth et al. have calculated the population attributable fraction (*PAR*) of adult malaria due to HIV in Masaka (an area of 8% HIV prevalence), and found it to be 4% (Whitworth et al. 2000). They also estimated that the *PAR* can be as high as 20% in an area of 30% HIV prevalence. We have also calculated the *PAR* in Thyolo (an area of 29% HIV prevalence (Kublin et al. 2005)) and found to be 14%. Therefore, the evidence from field studies does indicate that parasitaemia prevalence has increased. Clearly, this increase does not reflect increased transmissions from the dually infected, but reflects the poorer ability of HIV patients to clear parasitaemia challenges.

Second, we extended our model to include both children and elderly populations in the malaria dynamics but with simplified HIV dynamics (basically “freezing” HIV prevalence at the observed HIV prevalence level in Kisumu). This is our best attempt to investigate the impact of the inclusion of children and elderly in the dynamics short of a complete revamp of the model. We found that the inclusion of children and elderly has reduced our prediction of the number of excess malaria infections by 7%. The inclusion of these two populations has distributed the excess transmissions from the dually infected subjects over the different age groups. Since a large fraction of these excess transmission

ended up via vectors in the children population, their impact in increasing parasitaemia prevalence in this particular group is negligible since it is virtually at saturation. Nevertheless, the near saturation among the adult and elderly populations did not prevent them from acquiring higher levels of malaria prevalence, but mainly as a consequence of the “erosion” of acquired immunity with HIV infection. We conclude that the inclusion of children and elderly populations in our model can lead to a reduction in our estimates of the interaction-induced malaria excess prevalence but not by more than 10%.

Third, we calculated the *PAR* of malaria due to HIV in the Kisumu calculation of Figure 1 using our dynamical model as well as using the classical Levin formula (Levin 1953). Our model calculation yielded 10% and this value includes both the effects of enhanced susceptibility of HIV subjects to malaria as well the enhanced malaria transmissions from the dually infected. The Levin formula, which yielded a larger value of 12%, is an approximate expression that includes only the effect of HIV in increasing susceptibility to malaria. Interestingly, the combined effect of enhanced susceptibility and enhanced transmission in our model contributed less to the *PAR* than the effect of enhanced susceptibility alone in Levin formula. This is primarily due to the approximate nature of Levin formula as applied here which does not remove all confounding due to the assumed level of stratification (Greenland 1998). However, the comparable values of the two *PARs* suggest that the impact of enhanced malaria transmissions from the dually infected is much smaller than the impact of enhanced susceptibility of HIV patients to malaria. Most of the observed excess malaria infections occur because of the erosion of acquired immunity with HIV infection and not because of the enhanced transmission from the dually infected. Saturation of malaria transmission curtails the effect of enhanced transmission due to HIV.

Biological and behavioral input: Model parameters

We first provide a summary of the core assumptions of our model and then provide a detailed description and discussion of these assumptions and other parameters in the model. The core assumptions are: 1) a 2.45-fold increase in HIV-1 transmission probability with each one-log rise in viral load (Quinn et al. 2000). 2) HIV-1 transmission probability per coital act is 0.0107 in the acute, 0.0008 in the chronic, and 0.0042 in the advanced stage (Wawer et al. 2005). 3) HIV acute, chronic, and advanced stages last for 2.5 months (Wawer et al. 2005), 7.59 years (Morgan and Whitworth 2001; Morgan et al. 2002), and 2 years (Wawer et al. 2005) respectively. 4) Dual infection induces a 0.82 log increase in viral load in chronic HIV during clinical malaria and 0.08 log during non-clinical malaria, while it induces a 0.20 log increase in the advanced HIV stage (Kublin et al. 2005). Clinical malaria is defined as the presence of fever and parasitaemia density $\geq 2000/\mu\text{l}$ and malaria infection refers to any malaria parasitaemia and not simply to clinical disease. 5) The proportion of persons with malaria infection that develops clinical malaria is 16% for HIV negative (Whitworth et al. 2000), and 31% for HIV positive (Kublin et al. 2005). 6) HIV infection enhances susceptibility to malaria by a factor of 44% in the chronic stage and 103% in the advanced stage (Patnaik et al. 2005). 7) The

duration of heightened viral load equals that of malaria infectious period (gametocytaemia) at 42 days (Hoffman et al. 1999; Kublin et al. 2005). 8) An average 10% reduction in sexual activity due to malaria-induced morbidity in clinical malaria patients and a 3% reduction in persons with non-clinical malaria (Bruce-Chwatt 1963; Rogier et al. 1999; Snow et al. 2003). 9) Co-infection does not affect the rate of HIV disease progression as suggested by similar rates of progression in malarious and non-malarious areas (Morgan and Whitworth 2001). 10) There is limited evidence of an increase in susceptibility to HIV infection among malaria patients, so this variable has not been included (Xiao et al. 1998; Froebel et al. 2004). 11) Malaria infection does not affect HIV/AIDS mortality in areas of stable malaria (Whitworth et al. 2000; French et al. 2001; Quigley et al. 2005), while in areas of non-stable malaria, malaria enhances mortality in advanced HIV patients by a factor of 25% (Grimwade et al. 2004).

Vector entomological and malaria transmission parameters:

The parameters that describe the vector entomology and malaria transmission are tabulated in Table S1.

Table S1 The vector entomological and malaria transmission parameters used in the model

Parameter	Value
Daily survival rate (p_{vector}) for both <i>A. gambiae</i> and <i>A. funestus</i>	0.846 per day (Molineaux and Gramiccia 1980; Kiszewski et al. 2004)
Vector life expectancy ($\tau_{lifetime}$)	6 days (derived)
Vector mortality rate (μ_v)	0.167 per day (derived)
Human blood index (<i>HBI</i>)	0.946 (Molineaux and Gramiccia 1980; Kiszewski et al. 2004)
Duration between blood meals (<i>DBM</i>)	
<i>A. gambiae</i>	2 days (Molineaux and Gramiccia 1980)
<i>A. funestus</i>	3 days (Molineaux and Gramiccia 1980)
Mosquito biting rate (θ)	
<i>A. gambiae</i>	0.47 per day (derived)
<i>A. funestus</i>	0.33 per day (derived)

Parasite incubation period in vector (τ_{Incub})	16 days (Molineaux and Gramiccia 1980)
Average carrying capacity (C_{avg})	3.98 per day (Molineaux and Gramiccia 1980)
Average vector density ($\left(\frac{V}{\sum_{k=1,2} N(k)} \right)_{avg}$)	59.1 (derived)
Ratio of maximum to minimum vector population ($RatioV$)	2.0 (model fit)
Average Human biting rate (HBR_{avg})	23.8 per day (derived)
Duration of gametocytaemia (τ_{gamet})*	42 days (Boyd 1926; Kublin et al. 2005)
Recovery rate from malaria infectiousness (ν)	0.02 per day (derived)
The proportion of infectious bites on humans that produces a patent infection ($t^{V \rightarrow H}$) (Aron and May 1982; Bailey 1982; Anderson and May 1991)	0.026 (Bailey 1982)
Proportion of bites by susceptible vectors on infected people that produces a patent infection ($t^{H \rightarrow V}$) (Aron and May 1982; Anderson and May 1991)	0.495 (model fit)

The entomological quantities in Table S1 generally refer to those measured in Kisumu, Kenya and are roughly representative of those measured elsewhere. Entomological parameters in other malaria ecologies can be found in (Macdonald 1957; Molineaux and Gramiccia 1980; Bailey 1982; Killeen et al. 2000; Kiszewski et al. 2004).

The vector life expectancy ($\tau_{lifetime}$) is derived from the daily survival rate (p_{vector}) according to $\tau_{lifetime} = 1 / -\ln(p_{vector})$, while the vector mortality rate (μ_v) is given by $1 / \tau_{lifetime}$.

The vector biting rate (θ) is derived from the human blood index (HBI), which measures the number of bites on humans per mosquito bite, and the duration between blood meals (DBM) according to $\theta = HBI / DBM$. The value used in the model is the

* Assumed also to be equal to the duration of heightened viral load in HIV patients during malarial episodes.

average value for the biting rate of *A. gambiae* and *A. funestus* (Molineaux and Gramiccia 1980).

The average vector density $\left(V / \sum_{k=1,2} N(k) \right)_{avg}$ in Kisumu, Kenya is derived from the measured average value of the vectorial capacity (C). The latter is defined by Garrett-Jones (Garrett-Jones 1964) as

$$C = \left(\frac{V}{N} \right) \theta^2 \frac{(p_{vector})^{\tau_{lifetime}}}{-\ln(p_{vector})} \quad (12)$$

The *RatioV* is determined by fitting the model to malaria prevalence seasonal fluctuations.

The human biting rate is calculated using its definition as

$$HBR = \frac{V}{\sum_{k=1,2} N(k)} \theta. \quad (13)$$

The daily recovery rate from malarial infection (ν) is derived from the duration of gametocytaemia according to $\nu = 1/\tau_{gamet}$.

We calculated the malaria parasite transmission probability from host to vector ($t^{H \rightarrow V}$) using Macdonald's stability index *MSI* (Macdonald 1957) as parameterized by Anderson and May (Anderson and May 1991)

$$t^{H \rightarrow V} = \frac{\mu_V MSI}{\theta}$$

Here we used $MSI = 3.9$ (Garrett-Jones and Shidrawi 1969) and $\theta = 0.47$ (Molineaux and Gramiccia 1980) as determined in the Garki project for *A. gambiae*, and $\tau_{lifetime} = 1/\mu_V$ as an average of three field studies: 11.26 (Gillies and Wilkes 1965), 15.4 (Garrett-Jones and Shidrawi 1969), 8.0 (Garrett-Jones and Grab 1964) days.

As for malaria prevalence level in Kisumu, Kenya in Figure 1 of the article, we were unable to obtain a time series for this measure despite repeated efforts and therefore used the adult prevalence level and degree of seasonality as reported for one year in the

seminal Garki project (Molineaux and Gramiccia 1980). We corroborated the Garki measurement in Kisumu indirectly with recent measurements that include high prevalence exceeding 60% among children aged 10-14 (Bloland et al. 1999), the age distribution of prevalence (Molineaux and Gramiccia 1980; Omumbo et al. 1998), and observed parasitaemia prevalence of about 50% over two seasons among a sample of mainly adults (Kurtis et al. 2001). It has been also reported that malaria prevalence in pregnant women in Kisumu has the value of 90% (Guyatt and Snow 2001). We are not confident however of the proper interpretation of this value since it seems excessively high.

Noteworthy here is that the 35-40% malaria prevalence used here is the prevalence of any malaria parasitaemia irrespective of clinical disease. Parasitaemia levels are much larger than clinical malaria levels and only a small fraction of this prevalence is actually due to clinical malaria (about 15% of malaria parasitaemia in HIV negative subjects are clinical (Whitworth et al. 2000)). Furthermore, malaria transmission in Kisumu is extremely high and re-infection is an almost daily occurrence. The entomological inoculation rate in this area exceeds 300 infectious bites per person per year (Beier et al. 1994).

We also calculated the sporozoite rate (malaria vector prevalence) in Kisumu using our model and found it to be 2.0%. This value accords well with actual field measurements of the sporozoite rate for *Plasmodium falciparum* in *Anopheles gambiae* and *Anopheles Funestus* vectors (Krafsur 1977; Krafsur and Garrett-Jones 1977; Adungo et al. 1991; Wanji et al. 2003; Cuamba et al. 2006)

HIV transmission parameters:

The parameters that describe HIV transmission are tabulated in Table S2.

Table S2 The HIV transmission parameters used in the model

Parameter	Value
HIV transmission probability per coital act per stage of HIV infection:	
Acute stage (p_{Y_1})	0.0107 (Wawer et al. 2005)
Chronic stage (p_{Y_2})	0.0008 (Wawer et al. 2005)
Advanced stage (p_{Y_3})	0.0042 (Wawer et al. 2005)
Duration of each of HIV stages:	

Acute stage (η_1)	2.5 months (Wawer et al. 2005)
Chronic stage (η_2)	7.59 years (Morgan and Whitworth 2001; Morgan et al. 2002)
Advanced stage (η_3)	2.0 years (Wawer et al. 2005)
HIV progression rates:	
Acute to chronic stage (ω_1)	4.80 per year (derived)
Chronic to advanced (ω_2)	0.13 per year (derived)
Advanced to death [†] (ω_3)	0.50 per year (derived)
Average frequency of coital acts:	
Acute stage (n_{y_1})	10.6 per month (Wawer et al. 2005)
Chronic stage (n_{y_2})	11.0 per month (Wawer et al. 2005)
Advanced stage (n_{y_3})	7.1 per month (Wawer et al. 2005)
Fraction of the core (high risk) group in the population (f_{core})	11.3% (derived)
The new sexual partner acquisition rate	
General population (low risk) ($\rho_{general}$)	0.93 partners per year (model fit)
Core group (high risk) (ρ_{core})	$10 \times \rho_{general}$ partners per year (representative value)
Average population (ρ_{avg})	1.88 partners per year (derived)
Degree of assortativeness (e)	0.1 (model fit)
Average duration of sexual partnership	6 months (representative value)

The HIV transmission probabilities per coital act are extracted from the measurements of Wawer *et al.* (Wawer et al. 2005) by collapsing the sub-strata in their

[†] The HIV-related mortality rate.

three-tier classification of incident, prevalent, and late stages into the three HIV stages: acute, chronic, and advanced, and by a reanalysis of the data using the binomial (Bernoulli) model (Gray et al. 2001) for the partnership transmission probability. Hence, the partition into acute, chronic and advanced stages is adopted to represent the measurements of HIV transmission probability per stage of infection according to Wawer et al. Note that this last study is a population-based cohort study in rural Uganda (Rakai) that provides the HIV transmission probability per coital act per stage of infection and is distinct from the Quinn et al study that provides the quantitative relationship between HIV viral load and HIV transmission probability per coital act (Quinn et al. 2000). Yet, both studies are based on the Rakai cohort.

There is compelling evidence that suggests an epidemiologic synergy between HIV and sexually transmitted diseases (STDs) (Wasserheit 1992; Fleming and Wasserheit 1999). Bacterial STDs in particular, which are prevalent in the high risk group but with limited presence in the general population, may play a role in increasing HIV transmission probability per coital act among the high risk group (Orroth et al. 2003; Korenromp et al. 2005). HSV-2 can also induce a biological cofactor in HIV transmission probability (Corey et al. 2004), but it affects both the high risk group and the general population because of its high prevalence in both groups (Orroth et al. 2006). The values of the STD-induced cofactors are still far from being well-established because of the many difficulties inherent in their measurements (Korenromp et al. 2001).

In principle, we can include an STD cofactor in our model as a multiplicative factor of the HIV transmission probabilities in each risk group. However, the impact of such cofactor is already effectively included in the model through the model parameterization. The partnership transmission probability in presence of such cofactor is given by $\rho \times (1 - (1 - \Omega p)^{n \times \tau_p})$ where ρ is the partner change rate, p is the transmission probability per coital act, Ω is the STD-induced cofactor, τ_p is the duration of partnership and n is the frequency of coital act. Since Ωp is small for HIV and since $\tau_p n$ is not large considering the short duration of the average partnership (here 6 months), then the partnership transmission probability in presence of such cofactor is given approximately by $\rho \Omega p n \tau_p$. The effect of the cofactor can be absorbed by the behavioral parameters of ρ , τ_p or n . Therefore, the presence of an STD cofactor is already effectively included in the model when we fit HIV prevalence level by varying the partner change rate ρ .

The durations of the acute and advanced stages have been chosen according to the measured coital probability classification in Wawer *et al.* (Wawer et al. 2005), while that for the chronic stage has been determined from the measured median time from seroconversion to death in sub-Saharan Africa (Morgan and Whitworth 2001; Morgan et al. 2002) minus the time spent in the acute and advanced stages. The rates of HIV

progression from one stage to the next are derived from the durations of each stage according to $\omega_i = 1/\eta_i$.

To be remarked here that since we defined the advanced stage according to that used by Wawer et al as the last two years of HIV patients before death, our definition encompasses both AIDS and over one year before the development of AIDS since the median survival from developing AIDS to death in a sub-Saharan African setting was measured to be 9.2 months (Morgan et al. 2002). Note also that the median CD4 count at the onset of AIDS in a sub-Saharan Africa setting is 126 cells/ μ l (Morgan et al. 2002), and that “the median survival (95% CI) of 73 HIV infected participants who had at least one CD4 count of less than 200 cells $\times 10^6/l$ was 17.1 (11.1, 22.0) months” (Morgan et al. 2000). Therefore, assuming an advanced stage starting at CD4 count of 300 cells/ μ l in Kublin et al (Kublin et al. 2005) seems to be a reasonable assumption.

Furthermore, we combine many sources of data into our mathematical model ranging for example from data for HIV transmission probability per coital act per HIV stage (Wawer et al. 2005), natural history of HIV and distribution from onset of infection to death in sub-Saharan Africa in absence of treatment (Morgan and Whitworth 2001; Morgan et al. 2002), and impact of malaria on HIV viral load and impact of HIV on increasing susceptibility to malaria both stratified by CD4 count (French et al. 2001; Kublin et al. 2005; Patnaik et al. 2005). These sources of data do not necessarily use identical definitions for the HIV advanced stage. This is typically due to limitations in study design or the statistical power of the studies. However, all sources of data used agree that the average HIV advanced stage, according to our definition, is roughly the last two years of the life of HIV patients. In addition, the various biological mechanisms that these studies explore in the advanced stage are all manifestations of the same underlying phenomenon which is the onset of the rapid but gradual decline in the immune system of HIV patients. This decline expresses itself in different forms whether it is a gradual increase in transmission probability per coital act, gradual increase in viral load, gradual decline in CD4 count, gradual decline in sexual activity, or substantial increase in susceptibility to malaria and opportunistic infections. To assess the impact of different definitions for the HIV advanced stage, we have done a sensitivity analysis by allowing this stage to vary within six months at the expense of the chronic stage (see next section). The result of the analysis shows clearly how the impact of such changes is limited particularly for the impact of malaria on HIV. This is not surprising since the bulk of the impact of malaria on HIV occurs in the HIV chronic stage which is much longer in duration than the advanced stage.

Table S3 Key sex behavior measures in Kisumu, Kenya.

Sex acts and partnerships	
Median age at first sexual intercourse	
Men	16.9 years (Ferry et al. 2001)
Women	16.5 years (Ferry et al. 2001)
Median age at first marriage	
Men	25.5 years (Ferry et al. 2001)
Women	19.6 years (Ferry et al. 2001)
Median interval between first sex and first marriage	
Men	8.8 years (Ferry et al. 2001)
Women	3.0 years (Ferry et al. 2001)
Proportion of women who had their sexual debut before age 15	27.4% (Ferry et al. 2001)
Average number of partners at time of interview	1.18 (Lagarde et al. 2001)
Proportion reported more than one partner (spousal or non-spousal but excluding sex workers) in the past 12 months among the sexually active population	
Men	33.5% (Lagarde et al. 2001)
Women	5.9% (Lagarde et al. 2001)
Proportion reported a non-spousal partner in the past 12 months among the sexually active population	
Men	48.2% (Lagarde et al. 2001)
Women	21.1% (Lagarde et al. 2001)
Proportion of people with non-spousal partnerships > 1 (excluding contact with sex workers) in the past 12 months	

Men	19.5% (Ferry et al. 2001)
Women	4.1% (Ferry et al. 2001)
Mean number of non-spousal partners (excluding contact with sex workers) among those who declared having at least one non-spousal partner	
Men	1.67 per year (Lagarde et al. 2001)
Women	1.23 per year (Lagarde et al. 2001)
Median duration of non-spousal partnerships	
Men	10 months (Ferry et al. 2001)
Women	12 months (Ferry et al. 2001)
The average number of non-spousal partnerships (excluding contact with sex workers) for males	701 per 1000 men-year (Ferry et al. 2001)
Total number of coital acts of men with non-spousal partners (excluding contact with sex workers)	5363 per 1000 men-year (Ferry et al. 2001)
Median lifetime number of partners	
Men	5 (Ferry et al. 2001)
Women	2 (Ferry et al. 2001)
Condom use with non-spousal partners	
Men	23.3% (Lagarde et al. 2001)
Women	20.6% (Lagarde et al. 2001)
Proportion of married men in polygamous union	12.3% (Lagarde et al. 2001)
Proportion of those who exchanged sex for money in the past 12 months among those who reported non-spousal partnerships	
Men	19.6% (Ferry et al. 2001)
Women	40.0% (Ferry et al. 2001)

Concurrency	
Concurrency Index (k) (Kretzschmar and Morris 1996; Lagarde et al. 2001)	0.44 (Lagarde et al. 2001)
Individual Indicator of Concurrency (iic) (Lagarde et al. 2001)	
Men	0.14 (Lagarde et al. 2001)
Women	-0.21 (Lagarde et al. 2001)
Mean duration of overlap in partnerships during the past 12 months	
Men	117 days (Lagarde et al. 2001)
Women	10 days (Lagarde et al. 2001)
Proportion of men who had more than one partnership ongoing at the time of interview	24.1% (Ferry et al. 2001)
Of the men who reported more than two non-spousal partners in the past 12 months, the proportion of their partners who did not have any other partners is	48.0% (Ferry et al. 2001)
Female sex workers and their contacts	
Proportion of men who had contact with female sex workers (FSW) in the past 12 months	3% (Morison et al. 2001)
The average number of male client contacts with sex workers	960 per 1000 men-year (Ferry et al. 2001; Morison et al. 2001)
The number of female sex workers per 1000 men aged 15-49 years	19.5 per 1000 men (Morison et al. 2001)
Median years as female sex worker	1 year (Morison et al. 2001)
Median number of clients in past week for FSW	1 per week (Morison et al. 2001)
Current steady partners (not clients) of FSW	
Median number of steady partners	2 (Morison et al. 2001)
Median number of coitus	4 per four weeks (Morison et al. 2001)

Table S3 shows some of the risk behavior measures in Kisumu, Kenya. These values are representative of those found in sub-Saharan Africa. Indeed, the multi-centre study has established that overall the levels of risk behavior are comparable across four sub-Saharan cities despite the contrasting HIV prevalence levels (Buve et al. 2001; Buve et al. 2001; Ferry et al. 2001; Lagarde et al. 2001; Morison et al. 2001). We use some of these measures in the derivation of the sexual behavior parameters in our model. The table also illustrates how complex it is to quantify sexual risk behavior considering the different sexual behavior measures and the multitude of facets of human sexuality.

The fraction of people who are in the core (high risk) versus the general population (low risk) group is taken as the average of the following quantities: 1) proportion of men (33.5%) and of women (5.9%) who reported more than one partner (spousal or non-spousal but excluding sex workers) in the past 12 months among the sexually active population (Lagarde et al. 2001), 2) the proportion of men (19.5%) and of women (4.1%) with more than one non-spousal partnership (excluding contact with sex workers) in the past 12 months (Ferry et al. 2001), 3) the proportion of men (3%) who had contact with female sex workers in the past 12 months (Morison et al. 2001), and 4) the number of female sex workers per man aged 15-49 years (1.95%) (Ferry et al. 2001; Morison et al. 2001). Hence we arrive at 11.3% as the representative average value for the fraction of the core group in the population for both males and females. This estimate is reasonable considering that the high risk group is a minority in the population. Furthermore, this value leads to the good fit seen for HIV prevalence in Figure 1 of the main text. Increasing the fraction of the core group substantially would lead to faster growth of HIV prevalence than is seen in the data while a substantially lower fraction would lead to a slower rise than is seen.

We assume for simplicity that the new sexual partner acquisition rate is independent of HIV or malaria infection status but depends only on the risk group status (core group versus the general population). However, the frequency of coital acts does vary depending on HIV stage of progression as measured by Wawer *et al.* (Wawer et al. 2005) and included in Table S2. Furthermore, the frequency of coital acts is reduced with malaria morbidity in a manner that depends on malaria status (discussion in the next subsection).

For the new sexual partner acquisition rate among the general population, we use the representative value of 0.93 partner changes per year based on the model fit and motivated by the following measures: 1) the mean number of non-spousal partners (excluding contact with sex workers) of 1.67 for men and of 1.23 for women during the last 12 months (Lagarde et al. 2001), 2) the average number of non-spousal partnerships (excluding contact with sex workers) for men of 701 per 1000 men-year (Ferry et al. 2001), and 3) the average number of male client contacts with sex workers of 960 per 1000 men-year (Ferry et al. 2001; Morison et al. 2001). As for the new sexual partner

acquisition rate among the core group, we assume a fixed rate of ten fold that of the general population as a reasonable value for the differences in risk behavior. Hence, the average partner change rate in the population is given by

$$\rho_{avg} = \rho_{general} (1 - f_{core}) + \rho_{core} f_{core} \quad (14)$$

which has the value of 1.88 partners per year in the Kisumu calculation.

There are no measurements of the assortativeness in the mixing between the risk groups in Kisumu. However, the behavior measures in Table S3, such as the mixing with female sex workers, suggest a limited degree of assortativeness relative to homogenous mixing. Therefore motivated by the model fit, we adopted a value of $e = 0.1$ for the assortativeness parameter.

We have chosen the representative value of 6 months for the average duration of sexual partnerships at the coital frequency levels described in Table S2. The estimate reflects the mid-range value between the long duration and high coital frequency of spousal and non-spousal partnerships excluding contacts with sex workers (median non-spousal is 11 months in Kisumu) (Ferry et al. 2001), and the variable but generally short duration and low coital frequency partnerships with sex workers (Morison et al. 2001). The estimate also reflects the comparable number of non-spousal partnerships excluding contacts with sex workers (701 per 1000 men per year in Kisumu) (Ferry et al. 2001) and the number of contacts with sex workers (960 per 1000 men per year in Kisumu) (Ferry et al. 2001; Morison et al. 2001).

We have explored in the model variations in partnership duration per risk group but found that such variations have little impact on the size of the epidemiologic synergy. Just as the other facets of sexual behavior heterogeneity discussed at the end of the previous section, the impact of such variability is tied to the dynamics of competition among hazards. Note that Kisumu sexual behavior data (Table S3) suggests that a large fraction of sexual partnerships in the population lasts for less than a year (Ferry et al. 2001; Lagarde et al. 2001; Morison et al. 2001). Moreover, AIDS morbidity and mortality prevents the duration of HIV discordant partnerships from lasting for longer than few years at the maximum (Morgan et al. 2000; Morgan et al. 2002).

Since it is very challenging to measure and to quantify concretely what constitutes a risk behavior considering the complexity of human sexuality, the ultimate validity of our choices of the sexual behavior parameters rests on their ability to describe HIV dynamics and to fit the observed prevalence levels.

As for the measured HIV prevalence level in Kisumu, Kenya, there is one notable population level survey, that of the multi-centre study, for the duration of June 1997 to

March 1998 for the 15-49 years age group (Buve et al. 2001). There are also antenatal clinic surveillance data provided by UNAIDS for the period of 1990 to 2002 (WHO/AFRO 2002). The value of these data lies in providing HIV trends since they do not necessarily reflect the HIV population prevalence level during this time period (UNAIDS/WHO 2003). We include these data points in Figure 1 and use them to fit the trend while we use the only available population survey to fit the level in the year 1997-1998 for the sexually active population (Buve et al. 2001).

HIV and malaria interaction parameters:

The parameters that delineate the interaction between HIV and malaria are tabulated in Table S4.

Table S4 The HIV and malaria interaction parameters used in the model

Parameter	Value
Logarithmic increase in HIV viral load level during malaria infection	
Acute stage ($LogInc_{I_1}$)	0.0 (assumption)
Chronic stage with clinical malaria ($LogInc_{I_{2a}}$)	0.82 (Kublin et al. 2005)
Chronic stage with no clinical malaria ($LogInc_{I_{2b}}$)	0.08 (Kublin et al. 2005)
Advanced stage ($LogInc_{I_3}$)	0.20 (Kublin et al. 2005)
Rate ratio increase in HIV coital transmission probability per one-log (base 10) rise in viral load	2.45 (Quinn et al. 2000)
Susceptibility enhancement to malaria infection in HIV infected persons	
Acute stage ($g_1 - 1$)	0% (assumption)
Chronic stage with clinical malaria ($g_2 - 1$)	44% (Patnaik et al. 2005)
Advanced stage ($g_3 - 1$)	103% (Patnaik et al. 2005)

Duration of heightened viral load during malaria episodes (τ_{gamet}) [‡]	42 days (Boyd 1926; Kublin et al. 2005)
Fractional reduction in coital frequency during malarial infection	
Clinical malaria (r_{clin})	10% (assumption)
Non-clinical malaria ($r_{non-clin}$)	3% (assumption)
Fraction of malaria patients developing clinical malaria	
HIV negative (f_{HIV-})	16% (Whitworth et al. 2000)
HIV positive (f_{HIV+})	31% (Kublin et al. 2005)
Enhanced HIV mortality in dually infected patients who are in HIV advanced stage ($d-1$)	
Areas of stable malaria	0% (Whitworth et al. 2000; French et al. 2001; Quigley et al. 2005)
Areas of non-stable malaria	25% (representative value (Grimwade et al. 2004; Cohen et al. 2005))

For the coinfecting population, the HIV transmission probability per coital act is increased due to the transient increase in plasma viral load where the enhancement depends on the logarithmic (base 10) incremental change in the viral load according to $p_{I_i} = p_Y 2.45^{\text{LogInc}_i}$. The 2.45 factor is the rate ratio increase in transmission probability with each one-log increment in viral load (Quinn et al. 2000). Though the quantitative functional relationship between HIV viral load and transmission probability per coital act has been measured by only one study (Quinn et al. 2000), the strong relationship between HIV viral load and transmission probability per coital act is well established as indicated by the evidence that higher viral load, such as during HIV acute stage, implies higher transmission probability (Jacquez et al. 1994; Lee et al. 1996; Operskalski et al. 1997; Ragni et al. 1998; Pedraza et al. 1999; Pope and Haase 2003; Pilcher et al. 2004; Cohen and Pilcher 2005).

[‡] Assumed to be equal to the duration of gametocytaemia (τ_{gamet}).

The magnitudes for the heightened viral load in coinfecting patients are adopted from Kublin et al study (Kublin et al. 2005) and tabulated in Table S4. Prior to this last publication, the role of malaria in inducing the seven fold increase in viral load was first reported by Hoffman et al in a larger sample of 47 patients (Hoffman et al. 1999). The Kublin et al work completed this picture of the changes in viral load by measuring the viral load prior to malaria and by extending the follow-up post malaria. To be noted here both observations of the heightened viral load were no surprise considering that the massive outpouring of TNF- α and other proinflammatory cytokines in response to malaria infection and the activation of CD-4 cells, generate ideal conditions for HIV replication (Rowland-Jones and Lohman 2002). Indeed, the biological basis for viral activation and replication following activation of T cells by exposure to malaria antigens has already been established by several studies (Xiao et al. 1998; Freitag et al. 2001; Pisell et al. 2002; Froebel et al. 2004). In particular it has been observed that in vitro HIV replication was increased ten-fold to 100-fold in peripheral blood mononuclear cells exposed to malaria antigens or malaria pigments, mediated by enhanced expression of the cytokine tumour necrosis factor (Xiao et al. 1998; Rowland-Jones and Lohman 2002).

The susceptibility enhancement of HIV patients to malaria is incorporated from a reanalysis of the Patnaik et al data (Patnaik et al. 2005). This is done by regrouping the HIV positive patients into high and low CD4 count groups, instead of the three-tier analysis in Patnaik et al, with the HIV negative population being the reference group. In this manner we are consistent with the two tier CD4 classification in Kublin et al (Kublin et al. 2005), and the parameter definitions in our model (g_i). However, as opposed to the CD4 300 cells/ μ l dichotomization in Kublin et al, we have dichotomized at the CD4 400 cells/ μ l level since this is the point at which we observed a biological shift between the two susceptibility enhancement regimes of moderate increase in susceptibility versus a large increase in susceptibility. A dichotomization at CD4 300 cells/ μ l, which has been also done but not reported here, would entail a spurious increase in the number of malaria infections attributed to HIV and therefore was rejected for the purpose of being faithful to the biological transition seen at CD4 400 cells/ μ l. Table S5 displays the results of the reanalysis.

Table S5 A reanalysis to transform the CD4 three tier Patnaik *et al.* data (Patnaik et al. 2005) into a two-tier high and low CD4 classification dichotomized at CD4 400 cells/ μ l with the HIV negative population as the reference group

Exposure category	N	%
HIV-negative	119	39
CD4 \geq 400	78	26
CD4 < 400	106	35
Total	303	100

Number of Episodes	Baseline CD4 count	Incidence Rate (per 1000 person days)	Hazard Ratio	
			Unadjusted	Adjusted*
137		IR (95% CI)	HR (95% CI)	HR (95% CI)
Overall incidence of parasitaemia throughout the study period	HIV-negative	2.3 (1.8-3.1)	1.00	1.00
	HIV+ \geq 400	3.3 (2.4-4.6)	1.45 (0.95-2.20)	1.44 (0.94-2.20)
	HIV+ < 400	5.1 (4.1-6.3)	2.08 (1.47-2.93)	2.03 (1.44-2.86)

Cox proportional hazards models adjusted for: * Gender, age, marital status.

Please note that the different stratification of malaria episodes by CD4 count between Kublin et al and Patnaik et al is for the purpose of improving the statistical power and significance of the study for the effect of interest. Specifically, the CD4 300 cells/ μ l dichotomization in Kublin et al was done to improve the statistical power for the viral load measurements, while the conventional three-level stratification of CD4 was possible in Patnaik et al.

To be stressed here that the evidence of HIV increasing susceptibility to malaria is well established by several studies that observed similar enhancements as in Patnaik et al work in both magnitude and nature (Whitworth et al. 2000; French et al. 2001; Patnaik et al. 2005; Kanya et al. 2006; Mermin et al. 2006). There are also many studies that observed these enhancements in specific groups particularly HIV positive pregnant women where malaria has been shown to be more frequent and with higher parasite density (Steketee et al. 1996; Steketee et al. 1996; Leroy et al. 1998; Parise et al. 1998; Verhoeff et al. 1999; Shulman et al. 2001; van Eijk et al. 2001; van Eijk et al. 2003).

The Kublin et al cohort study excludes stage 4 AIDS patients (Kublin et al. 2005; Patnaik et al. 2005). Inclusion of these patients may only increase the impact of HIV on malaria that we predict, as a result of the compromised immune system. Thus, by excluding stage 4 patients, Kublin et al demonstrate that co-infection with malaria is of concern even in earlier stages of HIV disease. Yet, as stated in the previous paragraph, prior studies (Whitworth et al. 2000; French et al. 2001) have witnessed similar magnitudes of the malaria enhancements in HIV patients as in Patnaik et al thereby affirming the Patnaik et al findings. As for the impact of malaria on HIV, the stage 4 patients experience substantial reduction in sexual activity due to their morbidity and so

are unlikely to have as dramatic an impact on HIV infectious spread as those subjects included in our analysis.

It bears noting that we are assuming for simplicity the independence (in absence of interaction) of the individual risks of acquiring malaria and HIV infections within the sexually active population. There may be though variations in the individual vulnerabilities due to socio-economic factors, living conditions, and of course pregnancy status.

The estimates for the duration of malaria infectious period and the duration of heightened viral load in HIV patients are comparable in magnitude. The former, which depends on the strain of the parasite and the age of the infected, is estimated at about 50 days (Boyd 1926) while the latter is estimated to be in the range of five to eight weeks (see next paragraph) (Hoffman et al. 1999; Kublin et al. 2005). Moreover, these two durations overlap and may be biologically identical since both are manifestations of the immune reaction against malaria in HIV patients. Therefore, we assume for simplicity that these two durations are equal and simultaneous at six weeks.

We arrived at the six weeks estimate for the following considerations based on the two studies that assessed this effect (Hoffman et al. 1999; Kublin et al. 2005): first, Hoffman et al measured the viral load every week for four weeks. For those followed for four weeks, the median viral load started at 19.1×10^4 copies per mL at enrolment followed by 18.1×10^4 copies per mL (week 1), 13.5×10^4 copies per mL (week 2), and 12.0×10^4 copies per mL (week 4) compared to a baseline of 2.24×10^4 copies per mL in the non-malaria patients. Therefore relative to baseline, the log increase in viral load was at 0.93 at enrolment and went down to 0.73 at week four; not a very substantial reduction. Added to this is that the median duration between the onset of illness and presentation was 3 days (range 1-14 days) (Hoffman et al. 1999). Hence, within the fifth week after infection the viral load was still at a 0.72 log increase, and in fact by this time only 16 out of 27 patients had any decline in RNA concentrations (Hoffman et al. 1999). In the Kublin et al cohort, the relevant population for the enhanced HIV transmission considering its high elevated viral load, the group with fever and parasitaemia density $> 2000/\mu\text{l}$ and $\text{CD4} > 300 \text{ cells}/\mu\text{l}$, still had 7.5×10^4 copies per mL after 8-9 weeks post malaria compared to a baseline of 3.8×10^4 copies per mL (0.30 log increase) (Kublin et al. 2005).

A second consideration is malaria treatment. Virtually all of the subjects in these studies were treated successfully for malaria and became a parasitaemic and afebrile within days but their heightened viral loads persisted for much longer durations. It is reasonable to hypothesize that with treatment failure or no treatment, the duration of heightened viral load is lengthened. This is reasonable since the immune activation as a result of malaria would persist in the absence of elimination of the parasites. Considering

that there is no universal effective treatment of malaria in the population at large, this issue points to a longer duration of heightened viral load.

It has been suggested that the enhanced HIV transmission in dually infected subjects may be undermined by the reduction in sexual activity due to malaria morbidity (WHO 2004; Whitworth and Hewitt 2005). Yet, there are no studies that measured directly the impact of malaria infection on sexual activity. In light of the fact that malaria induced morbidity in adults in areas of stable malaria lasts for a median of less than four days (Bruce-Chwatt 1963; Rogier et al. 1999; Snow et al. 2003), while the heightened viral load lasts for about 42 days (Hoffman et al. 1999; Kublin et al. 2005), it is reasonable to assume that malaria reduces sexual activity in clinical malaria subjects, through a reduction in the coital frequency within the partnership, by 10%. This may be an overestimate of this effect since daily surveillance of adult malaria morbidity reported a mean duration of 2.6 days in an asylum in Nigeria (Bruce-Chwatt 1963), while another surveillance in Senegal reported a mean duration of 0.86 days (Rogier et al. 1999). These are the best detailed measurements of malaria morbidity in adults (Snow et al. 2003).

As we indicated above, the assumed duration of 42 days for the heightened viral load reflects measurements in people who have been effectively treated for malaria (Hoffman et al. 1999; Kublin et al. 2005). If this duration proves to be longer for non-treated patients, this would further reduce the effect of reduction in sexual activity since the duration of malaria morbidity relative to the duration of heightened viral load, would become smaller.

As for the timing of malaria morbidity and HIV heightened viral, the heightened viral load may lag that of malaria morbidity instead of coinciding with it since the heightened viral load is a direct consequence of immune activation following malaria infection rather than a consequence of malaria infection per se. The heightened viral load of almost one log was measured a median of 3 days following the onset of symptoms (range 1-14 days) (Hoffman et al. 1999). Note also that the heightened viral load declines gradually and slowly. At enrolment in the Hoffman et al. study, the viral load log increase was measured to be 0.93 while four weeks later it was at 0.73.

Malaria morbidity can impact sexual activity through a reduction in coital frequency as well as a reduction in the partner change rate, but with the absence of data it is not clear how the reduction in sexual activity can be decomposed in terms of these two components. The best remedy to quantify this effect is actual measurement of the reduction in sexual activity during dual infection. Our rationale based on malaria morbidity provides only a rough estimate for this effect. It is also possible that the effect of sexual activity reduction may be minimal. For the majority of adults in stable malaria areas, malaria morbidity is a mild disease and though it is an inconvenience it may not reduce sexual activity. Malaria morbidity may lead people to spend more time with their sexual partners thereby increasing sexual activity during dual infection. With all the

above considerations, our assumption of blanket 10% reduction in sexual activity for those with clinical malaria, expressed in terms of reduction in coital frequency, is a reasonable estimate for this effect.

In account of the fact that non-clinical malaria patients may also experience fever considering our definition of clinical malaria as presence of fever and parasitaemia density greater than 2000/ μl , we also assume a 3% reduction in coital frequency among non-clinical malaria persons. This last assumption reflects the observation that 8 out of 29 non-clinical malaria patients had fever and the observation that morbidity was associated with the presence of fever (Kublin et al. 2005).

Note that the sexual activity reduction induced by malaria morbidity affects all malaria subjects irrespective of their HIV status though in a manner that depends on malaria status which in turn depends indirectly on HIV status. Changes in the sexual behavior of the HIV infected affect HIV transmission while that of HIV uninfected affect HIV acquisition. It is also biologically plausible that this latter effect may be compensated for by increased susceptibility to HIV acquisition in malaria patients following immune activation against the parasite. In absence of prospective cohort studies that measure all of these effects, the precise role of these mechanisms in the dynamics remains not certain.

The fraction of malaria infected but HIV negative persons who develop clinical malaria (f_{HIV-}) is taken as the average of the estimates for those coming for routine (11%) or interim (22%) visits in a population based cohort in rural Uganda (Whitworth et al. 2000). The fraction of malaria infected but HIV positive persons who develop clinical malaria (f_{HIV+}) is substantially larger than that in HIV negative persons since HIV infection changes the natural history of malaria in coinfecting patients (Whitworth et al. 2000; Francesconi et al. 2001). The fraction can also depend on malaria endemicity level since endemicity level drives the level of acquired malaria immunity (Baird 1995). We have adopted the value of 31% for this fraction as measured in Kublin *et al.* population based cohort in rural Malawi (Kublin et al. 2005). We made this choice, rather than the 17% for the routine and 29% for the interim in (Whitworth et al. 2000), since our model is primarily based on the parameters estimated for this cohort and for consistency with the definition for clinical malaria. However, we have used the estimates of the Uganda cohort for HIV positive persons to assess the sensitivity of our results to this parameter (next section).

Lastly on this issue, there are no available measurements of the fractions of malaria infected persons that develop clinical malaria in unstable malaria areas though it is likely that these fractions are higher than the fractions in stable malaria areas due to the lower level of acquired immunity (Baird 1995). Therefore, we have elected to use the same values for these fractions in all areas of malaria endemicity though this choice may underestimate the impact of the synergy in unstable malaria areas.

The effect of HIV on adult malaria mortality depends on the level of malaria endemicity. No increase has been found in all-case mortality in HIV infected adults in areas of stable malaria (Whitworth et al. 2000; French et al. 2001; Quigley et al. 2005). Meanwhile, Grimwade *et al.* (Grimwade et al. 2004), though not Cohen *et al.* (Cohen et al. 2005), found a substantial increase in malaria mortality in an area of unstable malaria. It is likely that this discrepancy in the findings reflects the different levels of residual immunity in stable versus unstable malaria areas, and the manner in which this immunity develops. The first evidence of accrued immunity to be seen is protection from severe complicated disease and death. Then with increasing immunity there develops a reduction in febrile illness, then reduced parasite density and finally reduced frequency of parasitaemia. HIV immuno-suppression appears to erode away some of whatever malaria immunity has been acquired. Therefore in stable malaria ecologies, HIV patients have an increased susceptibility to malaria infection, higher parasite densities and more febrile illness. However they do not appear to have more severe and complicated disease, nor to die more frequently, presumably because they always retain some of their immunity (Whitworth et al. 2000; French et al. 2001; Quigley et al. 2005). However in unstable malaria ecologies, HIV patients have an increased frequency of severe and complicated disease and of death (Grimwade et al. 2004; Cohen et al. 2005). They do not have an increased frequency of infection or higher parasite densities because they have not acquired any immunity to these aspects of malaria infection. Indeed our finding that the interaction could drive unstable malaria towards stability, might actually result in benefit in terms of reducing mortality from malaria, even at the expense of more infection.

In view of this evidence, we assume that malaria infection does not affect HIV/AIDS mortality in stable malaria areas (Whitworth et al. 2000; French et al. 2001; Quigley et al. 2005) while it enhances mortality in advanced HIV patients by a factor of 25% in non-stable malaria areas (Grimwade et al. 2004). Since this effect can potentially have considerable impact on the epidemiological synergy between the two diseases in stable malaria areas, we have discussed its impact in the sensitivity analysis (see next section) by a factor in the range of 0 to a maximum of 20% despite the lack of evidence to support its existence in these areas.

More on the parameters of the main text figures:

The parameters used to generate the figures of the main text are delineated above. In addition, we have modified the values of the following parameters to set different malaria and HIV baseline prevalence levels in different settings:

In Figure 2, we used a parasite incubation period in vector of $\tau_{Incub} = 21$ days. The vector biting rate (θ) is varying with the Macdonald's stability index (MSI) according to

$$\theta = \frac{\mu_v MSI}{t^{H \rightarrow V}} .$$

In Figure 3a, we used $\tau_{incub} = 20$ and $MSI = 1.669$ (corresponding to $\theta = 0.57$ per day). In Figure 3b, $\tau_{incub} = 20$, $\theta = \frac{\mu_V MSI}{t^{H \rightarrow V}}$ and $\rho_{general} = 1.00$ (corresponding to $\rho_{avg} = 2.02$).

In Figure 4, we used $\tau_{incub} = 20$, $MSI = 1.669$ (corresponding to $\theta = 0.57$ per day), and $\rho_{general} = 0.852$ (corresponding to $\rho_{avg} = 1.72$).

Sensitivity and uncertainty analyses on the parameter estimates and its impact on the conclusions:

In this section we incorporate a sensitivity analysis to determine first which parameters in the model play dominant roles in the size of the epidemiologic synergy. Second, we examine the impact on the predictions of the uncertainty in the measured values of the key parameters. Third, we assess the robustness of the predicted considerable impact of the interaction to changes in the key assumptions of the model.

Key parameters in the model:

We have examined the sensitivity of our predictions to the various parameters in the model by calculating the sensitivity matrix (whose elements are the sensitivity functions) according to Bailey's sensitivity theory (Bailey 1982). We find that the magnitude of the epidemiologic synergy between HIV and malaria is primarily sensitive to the interaction parameters including level and duration of heightened viral load, enhancement in susceptibility to malaria in HIV patients, fraction of dually infected that develops clinical malaria, reduction in sexual activity during malaria episodes and enhanced malaria mortality in advanced HIV patients. Moreover, the strength of the rate ratio increase in HIV coital transmission probability per one-log rise in viral load and the length of the HIV chronic stage, where the heightened viral load is especially acute, strongly influence the interaction.

Furthermore, we find that the magnitude of the synergy principally depends *directly* on the baseline prevalence levels of the two diseases and *indirectly* on the nature of the sexual behavior or malaria ecology in the community that dictates these prevalence levels. A proper quantitative characterization of the two disease prevalences and their overlap is a key determinant in predicting the ramifications of the interaction. Therefore, baseline prevalence levels can be used as proxies of the indirect impact of HIV and malaria baseline transmission parameters. In setting prevalence levels to the measured values, we can effectively characterize the epidemiologic synergy between the two diseases as the following two examples illustrate

- 1) A setting with an HIV baseline prevalence of 25%, malaria baseline prevalence of 35%, average sexual partner acquisition rate of 2.02 per year, and the Wawer *et al.* measured HIV coital transmission probabilities (Wawer et al. 2005), has similar HIV excess prevalence of 2.26% (versus 2.26%) and malaria excess prevalence of 4.31% (versus 4.30%) as a setting with the same baseline HIV and malaria prevalence levels, but with an average partner acquisition rate of 1.85 per year and a 10% overall increase in the HIV coital transmission probabilities.
- 2) A setting with an HIV baseline prevalence of 25%, malaria baseline prevalence of 35%, Macdonald's stability index of 2.0 and vector to host density of 59.10, has similar HIV excess prevalence of 2.26% (versus 2.25%) and malaria excess prevalence of 4.31% (versus 4.21%) as a setting with the same baseline HIV and malaria prevalence levels but with a Macdonald's stability index of 2.2 and a vector to host density of 50.87.

To sum up, the size of the epidemiologic synergy depends predominantly on the baseline HIV and malaria prevalences and the parameters that directly influence the interaction. Other parameters that are crucial in dictating baseline prevalence levels, such as the sexual partner acquisition rates or vector to host density, are critical only as they drive the prevalence levels but otherwise do not considerably affect the size of the synergy.

Impact of uncertainty in the measured values of the key parameters using univariate sensitivity and uncertainty analyses:

Having identified the key parameters that influence the epidemiologic synergy, we proceed to examine the impact of uncertainty in the measured values of these parameters on our predictions. We do so by varying these parameters according to the confidence intervals of their point estimates, or if not available, according to evidence-based or plausible ranges. We use the Kisumu calculation as an illustrative example where at the epidemic peak the HIV excess prevalence is found to be 2.1% and that of malaria to be 5.1%.

- 1) We varied the logarithmic level of HIV heightened viral-load during clinical malaria in HIV chronic-stage patients in the range of 0.55 to 1.10 with the point estimate at 0.82 (Kublin et al. 2005). Accordingly, the HIV excess prevalence varied in the range of 1.3 to 3.1% and that of malaria in the range of 4.9 to 5.2%.
- 2) We varied the duration of heightened viral load (implicitly the duration of gametocytaemia in HIV patients) in the range of 5 to 8 weeks with the point estimate at six weeks (Hoffman et al. 1999; Kublin et al. 2005). Accordingly, the HIV excess prevalence varied in the range of 1.8 to 2.5% and that of malaria in

- the range of 3.0 to 5.2%. Figure 4a in the article implicitly provides a further sensitivity analysis to this parameter in the range of 0 to 60 days.
- 3) We varied the rate of change of coital transmission probability per log of viral load in the range of 1.85 to 3.26 with the point estimate at 2.45 (Quinn et al. 2000). Accordingly, the HIV excess prevalence varied in the range of 0.9 to 3.5% and that of malaria in the range of 4.9 to 5.3%.
 - 4) We varied the fraction of dually infected persons who develop clinical malaria in the range of 17 (Whitworth et al. 2000) to 31% (Kublin et al. 2005). The point estimate is at 31% representing the results of the Malawi cohort study. Accordingly, the HIV excess prevalence varied in the range of 1.5 to 2.1% and that of malaria in the range of 5.0 to 5.1%.
 - 5) We varied the susceptibility enhancement to malaria in HIV infected persons in the range of -6 to 120% in chronic HIV persons and in the range of 44 to 186% in HIV advanced patients (Patnaik et al. 2005). The point estimates are 44% and 103% respectively. Accordingly, the HIV excess prevalence varied in the range of 1.5 to 2.7% and that of malaria in the range of 0.2 to 9.6%.
 - 6) We varied the reduction in sexual activity due to malaria morbidity among clinical malaria patients in the range of 15 down to 5%. The point estimate is at 10%. This is a plausible range motivated by the measured duration of adult malaria morbidity (Bruce-Chwatt 1963; Rogier et al. 1999; Snow et al. 2003). Accordingly, the HIV excess prevalence varied in the range of 1.7 to 2.5% and that of malaria in the range of 5.0 to 5.1%. Figure 4b in the article implicitly provides a further sensitivity analysis to this parameter in the range of 100 down to 0% reduction in risk behavior among clinical malaria patients.
 - 7) We varied the fractional increase in mortality hazard rate in HIV advanced dually infected patients in the range of 20 down to 0%. The point estimate is at 0%. Accordingly, the HIV excess prevalence varied in the range of 0.8 to 2.1% and that of malaria in the range of 4.8 to 5.1. Clearly, enhanced malaria mortality can substantially affect the epidemiologic synergy as expressed by the HIV excess prevalence though this is much less true for HIV excess incidence. Malaria mortality affects the synergy mainly by prematurely killing dually infected patients thereby reducing their contribution to the overall prevalence.
 - 8) We varied the duration of the advanced stage at the expense of the chronic stage in the range of 1 year and six months to 2 years and six months with the point estimate at 2 years. Accordingly, the chronic stage was increased by six months and decreased by six months respectively, and the average partner change rate has been modified to generate the fit for the HIV baseline prevalence level. The HIV

excess prevalence varied in the range of 2.1 to 2.1% and that of malaria in the range of 4.7 to 5.5%. Note that the impact of this uncertainty is very limited on HIV excess prevalence though it has modest impact on malaria excess prevalence as longer duration for the advanced stage implies higher incidence of malaria due to the higher susceptibility of advanced HIV patients to malaria.

Table S6 summarizes the results of these univariate sensitivity analyses.

Table S6 Summary of the univariate sensitivity and uncertainty analyses for the key parameters in the model.

Parameter to be varied	Range of variation in parameter	Range of variation in HIV excess prevalence	Range of variation in malaria excess prevalence
Level of HIV heightened viral-load during clinical malaria in HIV chronic-stage patients	0.55 to 1.10	1.3% to 3.1%	4.9% to 5.2%
Duration of heightened viral load in dually infected patients	5 to 8 weeks	1.8% to 2.5%	3.0% to 5.2%
Rate ratio increase in HIV coital transmission probability per one-log (base 10) rise in viral load	1.85 to 3.26	0.9% to 3.5%	4.9 to 5.3%
Fraction of dually infected persons who develop clinical malaria	17% to 31%	1.5% to 2.1%	5.0% to 5.1%
Susceptibility enhancement to malaria infection in HIV infected persons	-6% to 120% (chronic HIV) 44% to 186% (advanced HIV)	1.5% to 2.7%	0.2% to 9.6%
Reduction in sexual activity during dual infection among clinical malaria patients	15% down to 5%	1.7% to 2.5%	5.0% to 5.1%

Fractional increase in mortality hazard rate in advanced dually infected patients	20% down to 0%	0.8% to 2.1%	4.8% to 5.1%
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Impact of uncertainty in the measured values of the key parameters using multivariate sensitivity and uncertainty analyses:

In addition to the univariate sensitivity and uncertainty analyses, we have also performed multivariate analyses to examine the impact of uncertainty in the combination of parameter values. We have done so for the Kisumu calculation by using the ranges of the parameters specified above in the univariate analyses, and by sampling from these ranges using the uniform distribution. The analyses were achieved using 1000 runs of the model for two scenarios: first without the inclusion of enhanced malaria mortality and second with the inclusion of enhanced malaria mortality in HIV subjects according to the uncertainty range specified in the univariate analysis.

- 1) Without the inclusion of malaria enhanced mortality in HIV subjects, the HIV excess prevalence varied in the range of 1.1 to 3.1% with a mean of 2.1%, and that of malaria in the range of 3.5 to 8.8% with a mean of 6.1%. Figure S1 shows the outcome of the Kisumu run with these uncertainties.
- 2) With the inclusion of malaria enhanced mortality in HIV subjects, the HIV excess prevalence varied in the range of 0.4 to 2.4% with a mean of 1.4%, and that of malaria in the range of 3.1 to 8.5% with a mean of 5.8%. Figure S2 shows the outcome of the Kisumu run with these uncertainties.

The uncertainty would have been substantially smaller if we would have used distributions that allocate more weight to the point estimate values such as normal or triangular distributions as opposed to the flat uniform distribution. To be stressed here that current evidence indicates no enhanced malaria mortality in HIV subjects in stable malaria areas (Whitworth et al. 2000; French et al. 2001; Quigley et al. 2005). Furthermore, though enhanced malaria mortality can substantially affect the epidemiologic synergy as expressed by HIV excess prevalence, it has limited impact on excess HIV incidence attributed to malaria. Malaria mortality affects the synergy mainly by prematurely killing dually infected patients thereby reducing their contribution to the overall prevalence.

Robustness of the predicted considerable impact of the interaction:

We have identified in the previous two subsections the sensitivity of our model to the various model parameters and quantified the effect of uncertainty in the key ones. Considering the concrete evidence for the heightened viral load and enhanced susceptibility to malaria, our calculations establish a considerable population-level epidemiological synergy between HIV and malaria though the lack of precise assessment for the duration of heightened viral load and malaria-morbidity effect on sexual behavior prevents us from precisely quantifying the magnitude of the synergy.

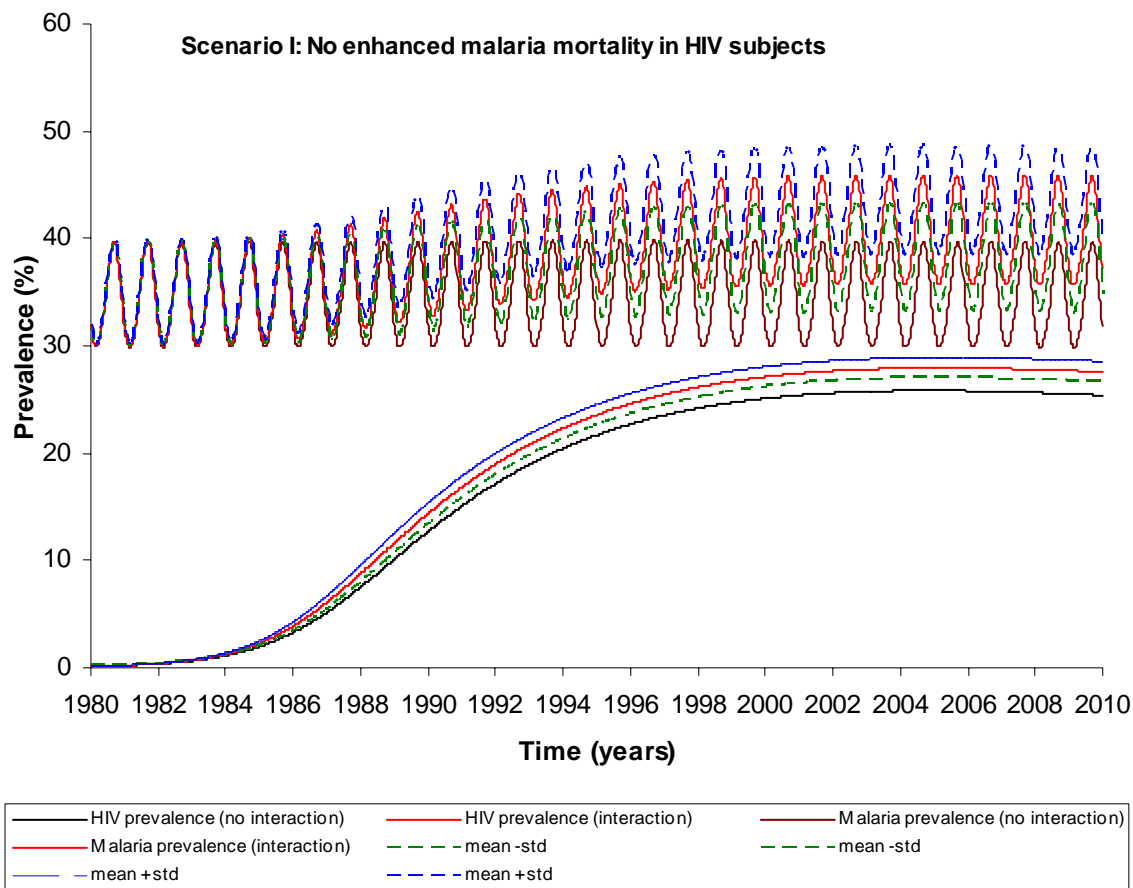


Figure S1 Scenario I: The outcome of the multivariate sensitivity and uncertainty analysis without the inclusion of malaria enhanced mortality in the Kisumu calculation.

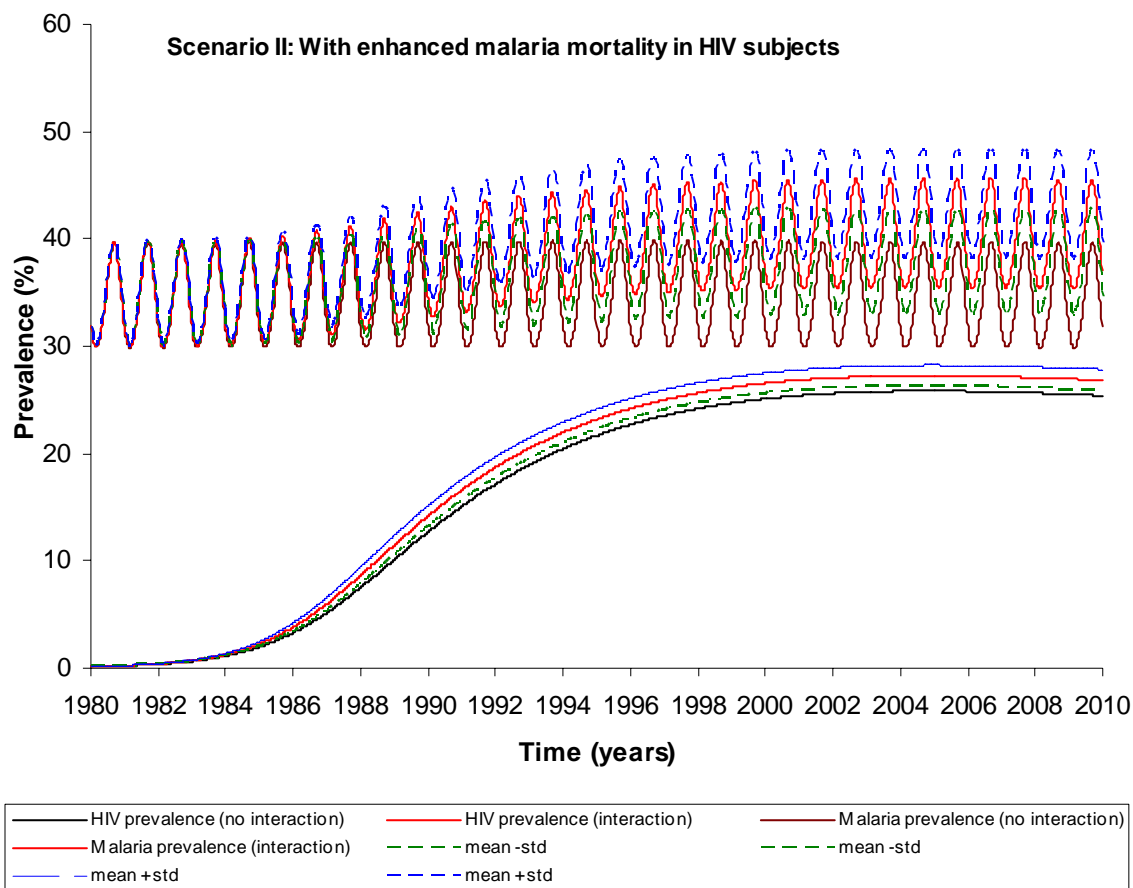


Figure S2 Scenario II: The outcome of the multivariate sensitivity and uncertainty analysis with the inclusion of malaria enhanced mortality in the Kisumu calculation.

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