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Malaria and HIV: a silent alliance

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HIV and malaria are leading causes of morbidity in sub-Saharan Africa. Recently, Abu-Raddad and colleagues explored the synergy between these diseases through a mathematical model that included all documented interactions. It emerges from the model parameter inputs that concomitant infection of both HIV and malaria fuels the spread of both diseases. For the first time, it is shown that, according to the model, transient but repeatedly elevated HIV viral loads due to recurrent co-infections, such as malaria, can also influence and increase HIV prevalence. Probably, these results are conservative and the true impact of the interaction could be even more important.

HIV–malaria overlap and interaction

The distribution of HIV and malaria in tropical regions overlaps, particularly in Eastern and Southern Africa, so that any interaction between both diseases, even a small one, could be of great public health importance. This has been a cause for concern since the 1980s, although early studies and reviews discarded any major interaction [1]. A second series of studies, however, began to clarify the nature and the scale of HIV-malaria interaction and this has been extensively reviewed for both non-pregnant and pregnant adults [2,3] (Table 1). A review of the pathophysiological mechanisms has identified the cellular-based immune responses to both HIV and malaria as the biological explanation of the interaction [4]. Recently, Abu-Raddad and colleagues [5] explored the synergy between HIV and malaria through a mathematical model that included all documented interactions at population level. Their conclusion is that concomitant infections of both HIV and malaria might fuel the spread of both diseases in sub-Saharan Africa.

Direct epidemiological evidence?

Investigators have speculated that because HIV immune suppression increases the risk of malaria infection, the reservoir of *Plasmodium* parasites in humans would also increase its transmission [6,7]. Also, as malaria infection provokes a transient increase in the viral load in HIV-infected individuals, and high HIV viral loads have been associated with a higher risk of HIV transmission, malaria could increase HIV transmission [8,9]. Innovative epidemiologic studies are needed to understand how malaria interacts with HIV at population level. An impact of HIV on malaria transmission is suggested by the fact that families living in the same household as an HIV-infected individual have higher rates of malaria among HIV-negative children than do families without an HIV-infected individual [10]. Apart from this observation, there is currently no firm evidence that HIV modifies malaria transmission or that malaria modifies HIV transmission [11]. This is probably due to the fact that HIV and malaria coexist in regions where the health surveillance systems are poorly developed. Furthermore, any future investigation on this topic should consider that the use of insecticide-treated bed nets and cotrimoxazole prophylaxis drastically reduces the incidence of malaria in HIV-infected people [12].

Insights from modeling

Mathematical modeling, similar to that used by Abu-Raddad and colleagues [5] offers an alternative

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Table 1. An overview of malaria-HIV biological interactions[a,b]

Impact HIV on malaria	Impact HIV and malaria co-infection	Impact malaria on HIV
↑ Parasitemia	↓ Hb in children	↓ Internal validity rapid HIV test
↑ Clinical malaria	↓ Hb in adults	↑ Viral load: transient
↑ Antimalarial drug use	↑ Hospital admission	↓ CD4: transient
↑ Severity	↑ Mortality	? HIV transmission
↑ Treatment failure		? Progression to AIDS
? Transmission		
Pregnancy related		
- IPT with SP or CQ less efficacious	↓ Birth weight	? Mother to child transmission
- All gravidae at risk	↑ Infant mortality	
	↓ Hb	

[a]Abbreviations: IPT, intermittent preventive treatment; Hb, Hemoglobin; MTCT, mother to child transmission.
[b]Symbols: ↓ Decreased, ↑ Increased, ? Unknown.

approach and can be applied to different malaria and HIV settings, provided the relevant parameters are included. According to the model, the largest epidemiological impact occurs when the prevalence of one disease, HIV or malaria, is very high while the other is low and near its endemic threshold. Previously, another model that assessed the impact of HIV-1 on malaria in Sub-Saharan Africa estimated that the HIV-1 epidemic contributed to observed increases of malaria in the 1990s in areas of unstable malaria transmission, such as Southern Africa [13].

If one of the diseases is just below its threshold while the other is at endemic equilibrium, the interaction lowers the threshold of the one near its threshold, which allows it to reach endemic stability. For example, unstable malaria in an area of high HIV prevalence would evolve towards stability and its burden at population level would increase. Paradoxically, a higher infection burden at the population level would, because of the development of semi-immunity, lead to a lower clinical malaria disease incidence in adults.

According to the model, when the prevalence of both diseases is very high, the direct epidemiological impact of the interaction seems less drastic. Indeed, when the model is applied to Kisumu, Kenya, where HIV and malaria prevalence are high, the interaction between the diseases increased the HIV epidemic peak by 8%, whereas it enlarged the malaria peak by 13%. The fraction of HIV infections attributable to malaria was estimated at 4.8%, whereas that of malaria promoted by HIV was estimated at 9.9%. The 9.9% estimate is similar to what is actually observed in rural Uganda [14] and is supported by observations from Malawi that showed that, where malaria is common, malaria infection and disease were less strongly associated with HIV-associated immune suppression than were other opportunistic infections [15].

Other factors to consider

First, in a district of 200 000 adults, during a 25-year period, this 'relatively low' impact represents 8500 additional HIV infections, and almost one million additional malaria episodes.

Second, the studies used in the mathematical model reported a transient increase in viral load in patients successfully treated for malaria. Successfully treated patients become aparasitemic and afebrile within days, but their heightened viral loads persist for much longer [6]. With no or inefficacious treatment, it is reasonable to assume that the duration of heightened viral load and increased prevalence of parasitemia due to HIV immune suppression would be extended. This is a reasonable assumption because the immune activation as a result of malaria would persist if parasites were not eliminated. Moreover, HIV immune suppression has been identified as an independent risk factor for treatment failure [16] and a higher parasite load has been reported in co-infected patients [14]. Both observations indicate that parasites are more likely to persist in this group of patients.

Third, when both diseases reach an epidemic equilibrium, even if the direct epidemiological impact is minimal, interaction will occur frequently; viremia would increase in HIV patient as a result of malaria infection and parasite load would also be higher in immune suppressed co-infected patients. Therefore, co-infection is likely to produce a higher circulating biomass and a higher biodiversity of both species. If the probability of a *de novo* emergence of a resistant mutation is distributed evenly among all parasites and all viruses, then an increment of the parasite and viral biomass due to HIV–malaria interaction could favour the emergence of new resistant strains [17] that would be selected by antimalarials and/or antiretrovirals use. Finally, malaria infection leads to a strong CD4 activation [18]. The selective infection of the antigen-specific memory CD4 cells by HIV leads to the loss of these cells [19]. Therefore, HIV patients could loose the *de novo* activated, malaria-specific CD4 cells during each malaria attack because they are more susceptible to HIV and they could progress more rapidly to end-stage HIV disease [11,20]. This element was not considered in the mathematical model by Abu-Raddad and colleagues [5] because there is no empirical evidence on it. Their model did not include the higher parasite load in symptomatic co-infected patients. Neither did it incorporate other possible effects attributable to malaria and HIV-1 co-infection such as anemia, the impact on genetic diversity and consequently the spread of drug resistance [21]. In areas of high-intensity transmission, such as in Kisumu, Kenya, the indirect effects might be more important than malaria cases and deaths *per se*. Furthermore, pregnancy, a vulnerable period for malaria morbidity and mortality and HIV transmission was not considered [3]. Therefore, the actual impact of the interaction, in the absence of any control intervention, might be more important than anticipated. It should be noted, however, that the impact of malaria on

HIV transmission depends largely on parameters for which we lack consistent data such as the duration and level of heightened viral load [2,22] and the malaria-morbidity effect on sexual behavior.

There is compelling evidence that suggests an epidemiologic synergy between HIV and sexually transmitted infections (STIs) [23,24]. For the first time, Abu-Raddad and colleagues [5] have incorporated in a model the transient, although repeated, elevated HIV viral loads due to malaria. They estimated, as previously suggested [7], the possible impact of how a recurrent co-infection, other than STIs, could also influence and increase HIV prevalence. This might be one of the factors that contributes to the high 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 at an individual level and favor its spread at the population level.

The need for integrated health services for the early and effective treatment and prevention of malaria in HIV-infected persons is obvious. HIV-malaria co-infection is common in sub-Saharan Africa and shares a similar clinical presentation, similar sites, health staff involved, and services to be provided, resourced and coordinated. VCTs should, for example, include malaria intervention of insecticide-treated bed net distributions. Furthermore, cotrimoxazole as prophylaxis for opportunistic infections has good antimalarial properties and might be beneficial at an earlier stage of HIV infection than currently recommended.

Unfortunately, the link between the current prevention and control programs for HIV and malaria is weak, despite several common features and goals and the existence of similar financing mechanisms such as the Global Fund for AIDS, tuberculosis and malaria (GFATM).

Concluding remarks

Abu-Raddad and colleagues [5] suggest that dual infection with HIV and malaria might fuel the spread of both diseases and, as outlined above, the actual impact might be even larger than they suggest. Intervention studies and modeling techniques are needed to quantify the impact, and the efficacy and effectiveness of disease control interventions that target both diseases simultaneously. Effective prevention and management of HIV and malaria, and probably of other highly prevalent diseases, will contribute to reduce their burden. More concerted actions and a comprehensive disease-control strategy addressing malaria and HIV are urgently required. All those involved in control activities for malaria and HIV (policy makers, health staff, and researchers) should approach the control of these two diseases in a more integrated way.

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