HIV and helminths – not all worms created equal?

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Abstract

The disproportionate prevalence of human immunodeficiency virus (HIV) in sub-Saharan Africa, recognition of the T-helper (Th)1/Th2 immunological dichotomy, and geographical co-prevalence of helminths and HIV, led to the hypothesis that helminthiasis increases susceptibility to HIV. Recently-published data from Tanzania suggests infection with filariasis doubles an individual's risk of HIV acquisition.

Main text

By 2015, an estimated 25.5 million people in Sub-Saharan Africa were living with HIV, accounting for 71% of the global burden (http://www.unaids.org/en/resources/fact-sheet). The relationship between helminths and HIV has been studied extensively with conflicting reports on the effect of different helminth species. Kroidl et al recently published a carefully conducted observational study reporting an increased risk of HIV infection in *Wuchereria bancrofti* infected individuals residing in southwest Tanzania [1]. This observation is the first evidence supporting the hypothesis *W. bancrofti* infection plays a role in HIV acquisition.

Lymphatic filariasis (LF) is caused by the nematode species *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori* depending on geographic location.

Previous studies on *W. bancrofti* and HIV prevalence have shown no association with prevalence of LF infection, circulating filarial antigen (CFA) levels or response to anti filarial treatment [2-4]. However, in vitro experimentation using peripheral blood mononuclear cells (PBMC) from patients with filarial infections showed that cells from persons with *W. bancrofti* infections exhibited enhanced susceptibility to HIV-1 infection compared to cells from individuals without filariasis [5].

Kroidl et al [1] present data from the Surveillance of Lymphatic Filariasis (SOLF) cohort-study, a prospective observational study in which they were able to determine the incidence of HIV infection in individuals with or without lymphatic filariasis. Five annual surveys were performed where blood, urine, stool and sputum were collected together with data on sociodemographic and behavioural factors.

Circulating filarial antigen (CFA) testing was performed on 2699 stored serum samples. Individuals underwent contemporaneous HIV testing. The overall prevalence of lymphatic filariasis infection was 26% (691 / 2673). Individuals found to be HIV positive at enrolment and children under the age of fourteen were excluded from analysis leaving 1055 individuals with 2626 person years of observation for the final analysis. HIV seroconversion events were identified in 44 participants >14 years of age.

HIV incidence was 0.80 cases per 100 person-years in those without lymphatic filariasis compared with 1.91 cases per 100 person-years in those with lymphatic filariasis. When adjusted for sex, age and socioeconomic status this suggests a 2.17 times increased risk of HIV infection in individuals infected with *W. bancrofti* compared with uninfected participants [adjusted incidence rate ratio (aIRR) 2.17, 95% confidence interval (CI) 1.08–4.37, p=0.0300]. Adolescents and young adults (aged 14-24) seemed to be unusually affected by *W. bancrofti* co-infection, (risk ratio 3.16, 95% CI 0.53 – 2.17, p=0.075), but this sub-group experienced only seven HIV infections, so the finding must be interpreted with caution.

Multiple binomial regression models were constructed, each including lymphatic filariasis and age plus one potential confounding risk factor associated with HIV infection. Having a HIV positive partner, having more than one sex partner and being divorced or separated had significant association with HIV incidence but lymphatic filariasis remained a stable risk factor throughout. No data is available on the existence of concomitant sexually transmitted infections – a key risk factor for HIV acquisition.. However, the fact that the effect estimate changed very little when relevant behavioural risk factors were included in the model provides reassurance.

No significant effect on HIV incidence was seen for individuals who had ever experienced haematuria or ever had *Schistosoma haematobium* (measured by microscopic examination of urine) but it is not clear that the timing of these exposures coincided with HIV exposure within the cohort. Similarly, no association was observed for any intestinal nematode (*Trichuris*, *Ascaris* or hookworm on Kato Katz examination of stool). Why then should lymphatic filariasis have a unique effect? Perhaps this systemic helminth infection, with constantly circulating microfilariae, compared with intestinal infections (albeit with transient larval migration in some species), more potently induces immune changes such as increased expression of HIV co-receptors CCR5 and CXCR4 on T cells, or Th2-mediated suppression of the Th1 biased antiviral immune responses, and hence HIV acquisition [6].

Like lymphatic filariasis, the systemic helminth infection *Schistosoma mansoni* is recognized to have profound immunomodulatory effects in humans: *S. mansoni* might therefore be expected to have a similar effect. Some epidemiological studies have described an association between *S. mansoni* and HIV infection prevalence. However, a recent prospective matched case–control study examining HIV incidence performed in endemic communities around Lake Victoria found that *S. mansoni* infection was not associated with HIV acquisition [7]. In macaque studies, *S. mansoni* infection enhanced simian HIV acquisition by

rectal challenge but not by intravenous inoculation, suggesting that physical lesions in the mucosa play a key role in HIV acquisition for schistosomiasis [8].

In keeping with this, *S. haematobium* is recognized as a cause of mucosal damage to the female genital tract and these lesions are hypothesized to increase HIV susceptibility. *S. haematobium* infection in women has been identified as associated with HIV infection in observational studies performed in Zimbabwe and Mozambique [9,10]; having *S. haematobium* or living in a highly endemic area appeared to increase the risk of HIV infection approximately 3 fold. To date there are no published prospective or interventional trials examining this key hypothesis, or demonstrating a benefit of schistosomiasis control for HIV incidence.

Kroidl et al suggest that infection with *W. bancrofti* more than doubles the risk of HIV acquisition and that this must prompt consideration of interventional trials evaluating the effect of antifilarial treatment on HIV incidence. Such studies would need detailed ethical consideration. Planning would need to take into account recent changes in HIV prevention policy which encourage HIV test-and-treat, especially for high HIV-risk populations. These policies may substantially reduce HIV incidence. But, as an extension of Kroidl's suggestion, it would certainly be of interest to include an investigation of HIV incidence into large-scale implementation trials comparing the effectiveness of mass drug administration with current, microfilaricidal regimens (such as ivermectin and albendazole) with new strategies including macrofilaricidal agents (such as doxycycline) which are expected to reduce the filarial burden more rapidly. As well, nested studies could explore effects on immunological parameters hypothesised to mediate effects of filariasis on HIV acquisition. Ultimately, control of lymphatic filariaisis is necessary to public health in its own right, and must be pursued.

References

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