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1 **HIV and helminths – not all worms created equal?**

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9

10 **Abstract**

11

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

18

19

20 **Main text**

21

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

31

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

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

41

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

48

49 Circulating filarial antigen (CFA) testing was performed on 2699 stored serum  
50 samples. Individuals underwent contemporaneous HIV testing. The overall  
51 prevalence of lymphatic filariasis infection was 26% (691 / 2673). Individuals  
52 found to be HIV positive at enrolment and children under the age of fourteen  
53 were excluded from analysis leaving 1055 individuals with 2626 person years of  
54 observation for the final analysis. HIV seroconversion events were identified in  
55 44 participants >14 years of age.

56

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

67

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

77

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

90

91 Like lymphatic filariasis, the systemic helminth infection *Schistosoma mansoni* is  
92 recognized to have profound immunomodulatory effects in humans: *S. mansoni*  
93 might therefore be expected to have a similar effect. Some epidemiological  
94 studies have described an association between *S. mansoni* and HIV infection  
95 prevalence. However, a recent prospective matched case-control study  
96 examining HIV incidence performed in endemic communities around Lake  
97 Victoria found that *S. mansoni* infection was not associated with HIV acquisition  
98 [7]. In macaque studies, *S. mansoni* infection enhanced simian HIV acquisition by

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

101

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

111

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

128

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130

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132

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