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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.

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