



## Perspective

## Impacts of neglected tropical disease on incidence and progression of HIV/AIDS, tuberculosis, and malaria: scientific links



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## SUMMARY

The neglected tropical diseases (NTDs) are the most common infections of humans in Sub-Saharan Africa. Virtually all of the population living below the World Bank poverty figure is affected by one or more NTDs. New evidence indicates a high degree of geographic overlap between the highest-prevalence NTDs (soil-transmitted helminths, schistosomiasis, onchocerciasis, lymphatic filariasis, and trachoma) and malaria and HIV, exhibiting a high degree of co-infection. Recent research suggests that NTDs can affect HIV and AIDS, tuberculosis (TB), and malaria disease progression. A combination of immunological, epidemiological, and clinical factors can contribute to these interactions and add to a worsening prognosis for people affected by HIV/AIDS, TB, and malaria. Together these results point to the impacts of the highest-prevalence NTDs on the health outcomes of malaria, HIV/AIDS, and TB and present new opportunities to design innovative public health interventions and strategies for these 'big three' diseases. This analysis describes the current findings of research and what research is still needed to strengthen the knowledge base of the impacts NTDs have on the big three.

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## 1. Introduction

The Millennium Development Goals were established in the year 2000 to combat various dimensions of extreme poverty, including the sixth goal: "to combat HIV/AIDS, malaria, and other diseases." Since that time, new financing and delivery mechanisms for disease control have been introduced through the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), as well as the US President's Malaria Initiative (PMI) and the President's Emergency Plan for AIDS Relief (PEPFAR). To date, approximately USD \$32 billion has been committed to the Global Fund,<sup>1</sup> USD \$3 billion to PMI,<sup>2</sup> and USD \$45 billion to PEPFAR.<sup>3</sup> Many billions of additional funding has made a huge difference in the lives of the world's poorest people. However, millions of people are still affected by these diseases, especially in the most remote and marginalized populations. Evidence suggests that co-infections between HIV, malaria, and TB exacerbate the individual diseases. Indeed, this is the reason that funding for the 'big three' is linked.<sup>4,5</sup> New research also suggests the highest-prevalence NTDs (soil transmitted helminths, schistosomiasis, onchocerciasis, lymphatic filariasis, and trachoma) result in increased

susceptibility to and worsen the disease course for people infected with one or more of HIV, TB, and malaria. This paper summarizes the new evidence on how NTDs impact the progression and severity of HIV/AIDS, TB, and malaria infections, and outlines priorities for future research.

## 2. Geographic overlap

Over the past several years, detailed mapping of NTDs has confirmed previous modeling based on statistical and spatial analyses,<sup>6</sup> and has demonstrated large degrees of geographical overlap between multiple NTDs and HIV and malaria.<sup>7</sup> For example, Sub-Saharan Africa has not only the world's highest incidence of HIV but also has more than 100 million people infected with soil-transmitted helminth infections and approximately 200 million people with schistosomiasis.<sup>8</sup> The geographical overlap is particularly prominent between urogenital schistosomiasis caused by *Schistosoma haematobium* and HIV and AIDS in the large southern and east African countries of Kenya, Mozambique, South Africa, Tanzania, Zambia, and Zimbabwe, and to some extent, Cameroon in West Africa.<sup>9</sup> Additionally, one-quarter of all schoolchildren in Sub-Saharan Africa are simultaneously at risk for both hookworm and malaria.<sup>6</sup> This pattern has also been noted between malaria and schistosomiasis.<sup>10</sup>

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### 3. Evidence on clinical links between NTDs and HIV

New research is beginning to suggest increased susceptibility and enhanced progression of HIV disease as a result of several helminthic, bacterial, and protozoan NTD co-infections. Soil-transmitted helminth infections have had a contributing, albeit largely hidden, impact on the AIDS epidemic.<sup>6,10–12</sup> In a study in Ethiopia, helminth co-infection was associated with increased T-cell activation; subsequent anti-helminthic treatment appeared to reduce the degree of T-cell activation, leading to a significant increase in absolute CD4 cell counts (192 vs. 279 cells/mm<sup>3</sup>).<sup>13</sup> A systematic review of treatment of HIV-1 and helminthic co-infections found reductions in viral load following deworming, ranging from 0.17 log<sub>10</sub> to 2.10 log<sub>10</sub> copies/ml drop in plasma.<sup>11</sup> In addition, studies on the treatment of schistosomiasis and lymphatic filariasis in HIV-infected individuals have demonstrated a 0.39 log<sub>10</sub> and 0.77 log<sub>10</sub> reduction in viral load, respectively, noting that a 1.0 log<sub>10</sub> viral load reduction corresponds to a halving of transmission risk and a 2-year delay in the development of AIDS.<sup>12,14</sup> The decreases they noted after treatment for helminth co-infection are comparable to decreases in viral load associated with the treatment of malaria and sexually transmitted diseases such as gonorrhea and syphilis.<sup>11</sup>

Although data conflict on the absolute impacts of treatment,<sup>6,15,16</sup> a Cochrane analysis of randomized clinical trials has demonstrated the benefits of deworming on HIV incidence and prevalence.<sup>15</sup> Evidence also suggests that maternal helminth infections increase the likelihood of mother-to-child transmission of HIV, possibly as a result of increased maternal HIV viral load.<sup>6</sup> A plausible mechanism suggests that helminth infections have an immunomodulatory effect, possibly diminishing host innate immunity to HIV, promoting viral replication and T-cell reduction.<sup>11,12</sup> Although the exact immunological mechanisms are yet to be elucidated, it is known that helminths skew the immune response toward Th2 (T helper cell) characterized by cytokines including interleukins IL-4, IL-5, and IL-13.<sup>16</sup>

Growing evidence from two studies in Zimbabwe demonstrates that female genital schistosomiasis occurs in up to 75% of women with *S. haematobium* infection and shows a threefold increase in the risk of women acquiring HIV infection.<sup>17,18</sup> Several reasons have been given to explain this increased correlation. Kjetland et al. suggest increased physical scarring on the vaginal walls of girls with female genital schistosomiasis that may increase transmission of the virus during intercourse.<sup>19</sup> Secor showed that patients with active schistosomiasis exhibit increased expression of the chemokine receptors and major HIV-1 co-receptors (CCR5 and CXCR4) on peripheral CD4 T-cells and monocytes.<sup>20</sup>

These associations are not unprecedented. Years of studies have demonstrated a large amount of evidence in the links between several protozoan diseases and HIV infection. The links between malaria and HIV have been well documented.<sup>5,21,22</sup> Patients with HIV infection frequently have a higher malaria parasite burden, more complications, and higher fatality rates than HIV-negative individuals.<sup>23</sup>

### 4. Evidence on clinical links between NTDs and malaria

Malaria is a leading cause of anemia in pregnant woman and young children. NTD co-infections have been shown to worsen anemia, potentially leading to large numbers of maternal deaths during pregnancy and to premature births.<sup>7,24</sup> Chronic anemia in young children is associated with reductions in physical growth and impaired cognition and school performance,<sup>6,25</sup> and many of the NTDs, but especially hookworm and schistosomiasis, cause anemia in low- and middle-income countries.<sup>7,26</sup> An estimated

7.5 million pregnant women (approximately one-third) living in Sub-Saharan Africa are infected with hookworm.<sup>27</sup> In Kenya, hemoglobin concentrations were found to be 4.2 g/l lower among children harboring hookworm and malaria co-infections than in children with only malaria infection.

Beyond the health improvements that would result from less anemia, some evidence indicates that selected NTDs may immunomodulate their host and promote increased susceptibility to malaria. To date, the data available on the effects of NTDs on malaria have been conflicting, especially in the older age groups. However, a study by Kirwan et al. demonstrated that repeated four-monthly anti-helminthic treatments for 14 months resulted in a significantly lower increase in prevalence of *Plasmodium falciparum* malaria infection in preschool children, coinciding with a reduction in the prevalence and intensity of ascariasis.<sup>28</sup> Research has also demonstrated that the use of an anti-helminthic reduces the clinically observable cases of malaria,<sup>29</sup> and ivermectin mass drug administration for onchocerciasis and lymphatic filariasis in humans has been shown to disrupt malaria parasite transmission in Senegalese villages.<sup>30</sup>

Additionally, research into social aspects of community health has demonstrated co-benefits between malaria and NTD prevention. Community-directed NTD treatments have increased the use of not only antimalarial bed-nets but also micronutrients and childhood immunizations.<sup>31</sup> The control of mosquito-borne diseases such as lymphatic filariasis can work in synergy with bed-net distributions and other disease control measures, such as intermittent preventive treatment and mosquito control, to reduce malaria incidence.<sup>7,25</sup> A study conducted in Nigeria demonstrated a nine-fold increase in households (with children under 5 years old, pregnant woman, or both) with more than one long-lasting insecticide-treated bed-net, when bed-net distribution was coupled with ivermectin and with albendazole treatment for lymphatic filariasis, onchocerciasis, and soil-transmitted helminths.<sup>32</sup> Other opportunities for integration with other diseases are currently being explored, such as combining malaria and trachoma treatments in Ethiopia.<sup>33</sup>

### 5. Evidence on clinical links between NTDs and TB

Soil-transmitted helminth infections have been evaluated as epidemiological risk factors for developing active TB. In one study, among 230 smear-positive TB patients and 510 healthy household contacts, an analysis showed a strong association between TB and intestinal helminth infection (odds ratio 4.2), and the odds of being a TB patient increased with the number of helminth species per person.<sup>34</sup>

TB patients with helminth infections present with more severe pulmonary disease, diminished anti-*Mycobacterium tuberculosis* immunity, and diminished responses to anti-TB chemotherapy.<sup>31</sup> Helminth infections also reduce the immunogenicity of bacille Calmette-Guérin (BCG) vaccine in humans,<sup>35</sup> and have been shown to interfere with diagnostic tests for TB.<sup>36</sup>

### 6. Need for further research

Even as NTD treatment programs scale up and the evidence base of the beneficial health effects of treatment is growing, the scientific knowledge of the health benefits of NTD treatment for HIV, TB, and malaria patients still needs more research. A recent study by Walson et al. noted that there were no significant increases in CD4 cell counts and no reductions in HIV RNA concentrations when people were treated presumptively for helminths.<sup>37</sup> However, they acknowledge that their study may not have been powered to detect the small differences in outcomes in individuals with helminth infection. Earlier work by Walson and

John-Stewart demonstrated that the treatment of known helminth-infected adults produced delayed HIV progression.<sup>38</sup> Such discrepancies between the studies may be explained by differences in the age groups studied, prevalence and intensity of helminth species, type and frequency of medication, and length of time post-treatment before the determination of viral load. Similar issues have been noted in research of NTDs with malaria, and several studies have demonstrated conflicting results. A recent review of these studies demonstrated a trend towards a protective effect of *Ascaris lumbricoides* and *S. haematobium* against severe malaria and a worsening effect of hookworm and *Schistosoma mansoni* on the pathogenesis and incidence of malaria, respectively.<sup>39</sup> The conflicting results listed above demonstrate the need for further studies on how individual NTDs affect the course of HIV and malaria infections and the immunological factors involved. Among the three diseases, scientific knowledge about the links with NTDs and TB remains the weakest.

The World Health Organization recently identified the need for further research into potential pharmacological interactions between antiretroviral and NTD drugs. This could be enhanced by conducting pharmaco-epidemiological studies to evaluate the safety of co-administration of such drugs and their therapeutic efficacy. Last but not least, further research will be required to address the social factors and logistical factors in implementation and operational challenges that arise from linking these programs.

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