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Immunological interaction during helminth and HIV co-infection: Integrative research needs for sub-Saharan Africa

Significance:

Sub-Saharan Africa is heavily burdened with human immunodeficiency virus (HIV) and helminth infections, which are potent activators of pro-inflammatory and anti-inflammatory immune responses, respectively. Considering that helminths (such as *Necator americanus*, *Ancylostoma duodenale*, *Ascaris lumbricoides*, *Trichuris trichiura*, *Schistosoma haematobium*, and *Schistosoma mansoni*) can potentially dampen the production and expression of vital anti-viral pro-inflammatory cytokines, leading to enhanced HIV replication and severity, well-designed intervention studies are needed which will offer conclusive data on the nature of these interactions and the impact of deworming in HIV-infected patients. Such research will impact governmental health policies and deworming programmes, allowing for the implementation of integrated systems that will contribute to the overall improvement of African health systems.

Background

Sub-Saharan Africa has an extensive epidemiological overlap between parasitic helminth infections and human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS).¹ According to the World Health Organization, more than 1.5 billion people worldwide are infected with soil-transmitted helminths, and sub-Saharan Africa has the highest burden.² It is also estimated that 90% of people in need of schistosomiasis treatment live in Africa.³ Approximately 85% of helminth infections in sub-Saharan Africa occur in areas exposed to poverty, overcrowding, inadequate sanitation, poor hygiene practices and unsafe water sources. These living conditions also promote the spread of HIV.¹ The sub-tropical climate in sub-Saharan Africa also contributes to high transmission and infection rates.

During the early stages of helminth infection and pre-adult worm development, epithelial cells secrete thymic stromal lymphopoietin, interleukin (IL)-33 and IL-25, which stimulate the activation and differentiation of type 2 innate lymphoid cells (ILC2) and polyfunctional CD4⁺ T-helper type 2 (Th2) cells, resulting in the secretion of Th2 anti-inflammatory cytokines (IL-4, IL-5, IL-9, IL-10 and IL-13).⁴

CD4⁺ T-cells play an important role in the host defence against HIV.⁵ Unlike the anti-inflammatory Th2 immune response to helminths, HIV is controlled by a pro-inflammatory T-helper type 1 (Th1) immune response.⁶ CD4⁺ T-cell exposure to IL-12 triggers a Th1 response that leads to the secretion of vital anti-viral pro-inflammatory cytokines, including IL-2, tumour necrosis factor (TNF)- α , interferon (INF)- γ , macrophage inflammatory protein (MIP)-1 α /1 β , and regulated on activation, normal T-cell expressed and secreted (RANTES).⁶

The burden, severity and public health implications of helminth and HIV co-infections in South Africa have not been given the attention they warrant. This raises important research questions about the public health implications of helminth co-infection with HIV in terms of pathogenesis and treatment outcomes. Furthermore, although individual helminth and HIV infection-specific immune responses have been the target of extensive investigation, the specific immune mode of protection during co-infection remains unknown. There is no conclusive evidence to confirm whether helminth-induced immunity modulates HIV-specific immune responses or vice versa.^{7,8} By 2017, a number of studies carried out in southern Africa (Mozambique, South Africa, Zambia, Zimbabwe), West Africa (Nigeria) and East Africa (Ethiopia, Kenya, Uganda, Tanzania) reported contrasting findings, with some indicating the detrimental effects of helminthiasis on HIV immune responses, while others reported no evidence of harmful immunological interactions.⁹ Many of these studies were cross-sectional and observational in nature, which may have limited the ability of the results to be conclusive. The West and East African regions have the lowest HIV/AIDS burden when compared to the worst affected southern region, which may explain the lack of studies in the West African region. However, surprisingly, the East African region had the highest number of studies when compared to other African regions.⁹ Epidemiological data support a bidirectional interaction between helminths and HIV; however, it is challenging to distinguish the direction of effects in observational studies, and so in order to reach a definitive conclusion, well-designed, randomised and controlled intervention studies are urgently needed.¹⁰

Treatment of helminthic infections is simple, widely available, relatively inexpensive, and has recently become a priority for public health intervention in Africa.⁶ Albendazole and mebendazole are widely used anti-helminthic drugs.¹¹ Hence, it would be more feasible if more concerted research is done to demonstrate the impact of deworming on HIV/AIDS disease progression. Additionally, a more effective strategy that can be employed to mitigate against the burden of helminth co-infections with HIV is described in the four-pronged approach in Figure 1. The results of such research would point towards identification of correlates of transmission, the immunological responses during co-infection, development of immunotherapeutic interventions, and development of locally relevant vaccines that are geared towards populations that are exposed to helminths.

Helminth and HIV/AIDS co-infection immune responses

Helminth-infected individuals have shown increased expression of co-receptors of HIV-1 chemokines on T-lymphocytes and monocytes.^{12,13} This is one of the contributing mechanisms in facilitating easy HIV-1 entry and increasing the pool of cells susceptible to infection. Peripheral blood mononuclear cells (PBMCs) obtained from helminth-infected individuals showed increased susceptibility to HIV-1 infection.^{14,15} Furthermore, a decreased CD8⁺ cytolytic HIV-1-

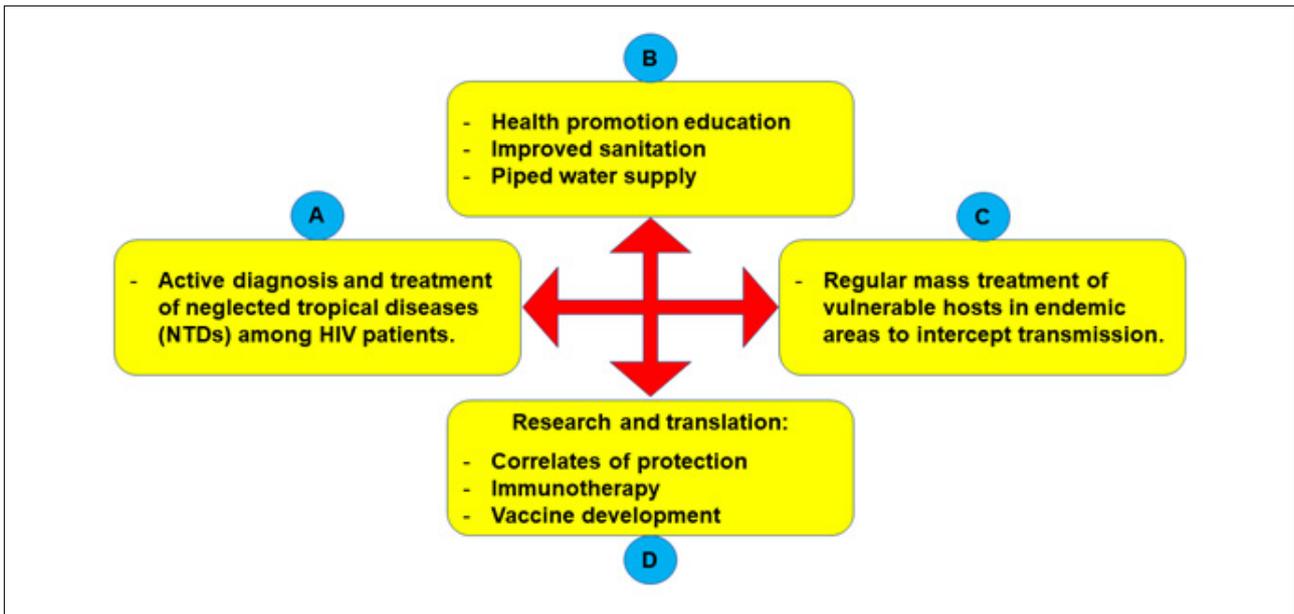


Figure 1: A four-pronged approach for successful mitigation against the burden of helminth co-infections with HIV.

specific T-cell response and increased IL-10 production were observed in HIV patients co-infected with *Schistosoma mansoni* compared to those with HIV-1 infection only.^{16,17} Similarly, reduction of CD4⁺ cells and increased CD8⁺ cells were reported among helminth-infected and HIV-1 uninfected individuals, suggesting that helminths on their own reduce the pool of CD4⁺ cells, which is critical in orchestrating effective immune responses against all pathogens.¹⁸ The predominance of Th2 cellular and molecular components resulting from helminth infections downregulates the dominance of the Th1 component, which is essential for the control of HIV infection.¹⁹

Another classic feature of helminth infection is marked eosinophilia. Eosinophils have been shown to express CD4⁺ molecules upon activation and are easily infectable by HIV.²⁰ The increased number of eosinophils in the mucosa (gut, genital and rectal) may facilitate easy acquisition and cell-cell transmission of HIV in helminth-infected hosts.²⁰ In a placebo-controlled trial, *Ascaris lumbricoides* co-infected HIV-positive patients treated with albendazole showed a significant increase in peripheral CD4⁺ T-cells and a decreasing trend in HIV-1 RNA levels compared to the placebo group.²¹ In summary, the above non-exhaustive account of immune dysregulation, Th2 bias and generalised immunosuppression caused by chronic helminth infections describes a favourable environment where HIV can rapidly replicate and spread in and amongst individuals chronically exposed to helminth infections.²²

In South Africa, there is a striking paucity of data on the immunological consequences and therapeutic outcome of infection with helminths among HIV/AIDS infected individuals. For example, a South African study reported that dual HIV and helminth infection, together with helminth egg excretion and/or high levels of *Ascaris*-specific IgE, may be linked to a poor proliferative capacity and deleterious cytokine profile with regard to HIV control.²³ In addition, results from the same study population concluded that people with both helminth egg excretion and high anti-*Ascaris* IgE levels had dysregulated immune cells and high viral loads.²³ A modified Th2 helminth response in individuals with egg-positive stools and low levels of anti-*Ascaris* IgE showed an improved HIV-related immune profile.²³ The association between HIV and helminth co-infections and lower biochemical micronutrients, protein and carbohydrate levels in humans has also been shown.²⁴ Additionally, several nutrient deficiencies have been found to increase the likelihood of HIV and helminth co-infection.²⁴ It is understood that various nutrient deficiencies cause impaired immunity.²³ These findings illustrate the need for further research that may better describe and explain the effects of helminth immune modulation in individuals co-infected with HIV,

leading to successful development of helminth and HIV-related vaccines which will be effective and timely accessible to save lives and improve the general health of those co-infected.

Helminth treatment effect on HIV/AIDS co-infected patients

Treatment recommendations in regions where soil-transmitted helminths and schistosomiasis are co-prevalent include albendazole and praziquantel, respectively.²⁵ Helminths are known to reduce the efficacy of the tuberculosis vaccine, Bacillus Calmette-Guérin, and reduce tumour immunosurveillance activities.¹⁴ Effective deworming has been associated with a reduction in HIV viraemia, leading to the slower progression to AIDS, and has been shown to normalise immunological parameters related to immune activation, Th2 immune response, and Treg-induced T-cell hypo-responsiveness.²⁶ The synergy between antiretroviral therapy and albendazole in down-regulating the Th2-biased immune response strongly suggests that deworming can be a safe and effective strategy for improving the health and quality of life of co-infected individuals.²⁶ More interventional research to demonstrate the impact of deworming on HIV/AIDS disease progression is thus required to improve our understanding of the detrimental and beneficial effects of helminth co-infection with HIV.

Knowledge gaps and way forward

The burden and severity of helminth and HIV co-infections have not been given the attention they warrant. Many questions remain unanswered regarding the immunological and pathological consequences of helminth and HIV co-infections. Several human studies investigated the immunological interactions between these infections but results thus far remain inconclusive. This raises important research questions about the public health implications of helminth co-infection with HIV in terms of pathogenesis and treatment outcomes. Furthermore, despite extensive research into individual helminth and HIV infection-specific immune response, the specific immune mode of protection by helminths remains unknown. It is, however, conceivable that the mechanisms involved in both pro-inflammatory and regulatory responses may impact the outcome of HIV/helminth exposure and infection.

There is a real need for interventions that can address the burden of helminth and HIV co-infections. The 95-95-95 targets set by UNAIDS were designed to end the AIDS epidemic by 2030. The three focal targets are that: (1) 95% of those living with HIV must be aware of



their status, (2) 95% of those who are aware of their status must be receiving treatment, and (3) 95% of those receiving treatment must have suppressed viral loads. In addition, other targets include achieving zero discrimination and reducing the annual number of new HIV infections among adults to under 200 000 per year. In addition to our proposed four-pronged approach to helminth elimination, similar to the UNAIDS 2030 target goals, the United Nations should also consider having a 95-95-95 target approach to eliminate helminthiasis by 2030. The three proposed focal targets to eliminate helminthiasis should include (1) having 95% of those living with helminth infections be aware of their status, (2) having 95% of those who are aware of their helminth infection status be on anti-helminthic treatment (albendazole, mebendazole and praziquantel) and (3) 95% of those receiving anti-helminthic treatment be educated on good hygiene practices to reduce the cycle of re-infection.

In addition, more transdisciplinary studies are needed to investigate the (1) immunomodulating effects of chronic helminth infection and the impact of such effects on HIV infection, with a focus on the functional and molecular profile of HIV-specific immune responses, (2) association of immunologic markers of helminths and HIV, with control of pathogen replication and disease, (3) impact of helminth co-infections on measures of disease activity for HIV, to promote the understanding of interactions between helminths and HIV, their influence on disease activity, and (4) impact of co-infection on treatment outcomes for HIV.

In conclusion, medical and technological advancements, as well as strengthened multi-pronged interventions, such as (1) early infection detection, (2) mass deworming programmes, (3) continuous surveillance, (4) proper sanitation and clean water provision, (5) development of sensitive diagnostic tools, (6) allocation of more research funds, (7) new therapeutic agents, and (8) prophylactic vaccines, are required for successful helminthiasis elimination.²⁷

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated institutions of the authors.

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Competing interests

We have no competing interests to declare.

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