



HELMINTH-HIV CO-INFECTION

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ABSTRACT

Many people living in areas of the world most affected by the HIV/AIDS pandemics are also exposed to other common infection including those caused by different kinds of endoparasites. Parasitic infections with helminth are common in Africa and affect over half of the population in some areas. Helminth infections may be associated with deleterious effects on the immune responses to HIV in certain groups of susceptible individuals. It has been hypothesized that helminth infections modify HIV susceptibility and disease progression by modifying the human immune system and thus might contribute to the high prevalence of HIV in Africa. HIV in patients with parasite infection alters the natural clinical progression of the parasitic diseases, and reduces the efficacy of parasitic treatment. Many potential helminthic infection are eliminated by host defenses, others become established and may persist for long period of time. Although helminthic infection are often asymptomatic, severe pathology can occur as a result of larval migration, intestinal blockage etc.

INTRODUCTION

The prevalence of helminthic infections in most of the developing countries is overwhelming, and almost a quarter of the world's population is infected by them. Likewise, with the spread of the AIDS epidemic, dual helminthic and HIV-1 coinfections are extremely common, particularly in Africa. Helminth and human immunodeficiency virus (HIV) infection have major effect on the host immune system and co-infection is wide spread. Infection with helminthes are caused by a diverse species of worms and are very common with an estimate of 2 billion people infected worldwide.^[40,34] Most cases occur in resource-limited settings such as Sub-Saharan Africa.^[21,25] Sub-Saharan Africa has also been shown to have the highest regional prevalence (5.0%) of HIV in the world.^[44] It has been assumed that helminthic infection are an important deriver to HIV infection in Africa due to their effect on immune system as demonstrated by the increased susceptibility to HIV infection and clinical progression to AIDS.^[1] In Nigeria, helminthes infections have continued to conquer because of low level of standard of living, poor environmental sanitation and ignorance of simple health promoting procedure.^[45] It is therefore likely that simultaneous infection between one or more helminth and HIV is common in this region.^[46]

Helminth

Helminth (the word is derived from Greek meaning "worms")^[22] have overwhelmed humans since before the era of our earliest recorded history. The eggs of intestinal

helminths can be found in the mummified feces of humans dating back thousands of years,^[8] and we can recognize many of the characteristic clinical features of helminth infections from the ancient writings of Hippocrates, Egyptian medical papyri, and the Bible.^[9]

Helminths are among the most common parasitic infections of the developing world. They require an environment of warmth and moisture, and are thus more commonly found in tropical and sub-tropical climates. In addition, with the exception of *Ascaris* and *Trichuris trichiura*, their life cycle requires direct contact between host feces and host epidermis, favoring communities of lower socioeconomic status with poor access to sanitation and footwear.^[11,24] Soil-transmitted helminths are more commonly found in rural areas than urban areas,^[2,6] although certain slums are ideal for transmission and maintenance of the life cycle. Soil-transmitted helminths, in particular hookworm infection, are more commonly found among farmers and others engaged in agricultural activities. Helminths with a snail intermediate host, such as schistosomes, are commonly found in areas near bodies of fresh water.^[47]

Epidemiology of Helminth

The important aspect of helminth biology establishes a set of transmission dynamics quite different than those for viruses, bacteria, fungi, and protozoa, For example, prevalence, which is the proportion of persons in a defined population at a given time infected with the helminth, is occasionally used as the only measure to

consider the epidemiological situation for helminth infection, because morbidity is associated with the number of worms infecting the host (i.e. the worm burden) rather than the absence or presence of infection.^[35] Prevalence is commonly combined with worm burden (also referred to as the “intensity of infection”) which is commonly measured by the number of eggs per gram (EPGs) of feces for intestinal helminths and schistosomes.^[35] Based on EPGs and their association with morbidity, individuals are classified into categories of light, moderate, and heavy infection by the WHO.^[39]

Furthermore, in the case of soil-transmitted helminths, the WHO recommends use of both prevalence and intensity of infection to classify communities into transmission categories — category I (high), category II (medium), and category III (low).^[23] There are several key determinants underlying the epidemiology of helminth infection.^[39]

Environment: Climate and topography are essential determinants of the distribution of helminth infections.^[23] Helminths transmitted by vectors are limited to backgrounds in which host and vector come together in the same habitat, resulting greatly focal distribution. For example, the distribution of schistosomiasis reflects the biotic and abiotic features (i.e. Climatic, physical, and chemical factors) that affect the survival and development of the snail vector.^[39] In the case of onchocerciasis, the distribution and incidence of the disease are limited by biogeographic variations favorable to exposure to the blackfly vectors.^[14] Soil-transmitted helminths are highly affected by surface temperature,^[23] altitude, soil type, and rainfall.^[33]

Heterogeneity: Heterogeneity in the worm burden among different individuals infected with the same helminth is a hallmark feature of helminth epidemiology.^[48] A significance of such heterogeneity is the aggregated distribution of helminth infection in endemic communities, such that a small proportion of hosts are rapidly, frequently, and/or heavily infected.^[36] The combined distribution of helminth infection has led some to hypothesis that certain “wormy” people are “predisposed” to heavy infection from as yet undefined genetic, immunogenetic, ecological, behavioral, and social factors.^[41] Predisposition refers to studies in which intensity of infection prior to anthelmintic treatment positively correlates with intensity of reinfection 12–24 months after treatment.^[41] The bases of both heterogeneity and predisposition to helminth infection have yet to be fully elucidated. However, among the major factors under consideration are age, household clustering, and genetics.^[39]

Age dependency: Much epidemiologic research has focused on heterogeneity in the intensity of helminth infection by age.^[39] Changes with age in the average intensity of infection tend to be curving, rising in

childhood and declining in adulthood. For *Ascaris lumbricoides* and *Trichuris trichiura*, the heaviest and most frequent infections are in children aged 5–15 years, with a decline in intensity and frequency in adulthood.^[39] Similarly, for all the major schistosomes, the heaviest and most frequent infections are in older children aged 10–15 years^[39] in contrast, hookworm frequently exhibits a steady rise in intensity of infection with age, peaking in adulthood.^[24] Similarly, the pathologic events that occur with filarial infections also predominate in adulthood. Briefly, if age-infection data are compared across host populations, the peak level of infection intensity (e.g. EPGs for intestinal helminths) is higher and occurs in younger individuals while transmission is also higher, but the peak intensity of infection is lower and occurs in older individuals when transmission is lower.^[29] This shift in the peak level of infection intensity and the age at which this peak occurs is consistent with mathematical models that assume a gradually acquired protective immunity, an interpretation supported by experimental studies in animals.^[39]

Life Cycle of Helminth

In general, helminths develop through three stages: eggs, larva, and adult worms, which determine both their epidemiology and pathogenesis in humans.^[30] An example is illustrated in the case of soil-transmitted helminths where the life cycle begins with transmission through the skin into the microcirculation. Larval helminths, with the exception of *Trichuris trichiura*, travel to the alveolar spaces, where the eggs are expectorated into the trachea and swallowed. Mature worms develop upon reaching the small intestine, where mating between male and female worms occurs. Female worms then release eggs; detection of the eggs in stool serves as the primary method of diagnosing helminth infection. The eggs excreted in human feces develop into the larvae in the soil, where they continue the life cycle by making contact with the feet of another human host.^[30] Helminth infection causes persistent host immune stimulation as a result of the hundreds of thousands of eggs and secretory products excreted by the intestinal parasites.^[47]

Laboratory Diagnosis of Helminth

The detection and diagnosis of this parasitic helminth depend solely on clinical history, travel history, sign and symptoms and geographical location.^[5] Unfortunately, there have been few major advances in diagnostic methods for parasitic infections, to have the most significant diagnostic impact, new techniques and assays should be simple and yield rapid results.^[10] Currently, diagnostic and reference laboratories use several techniques, including microscopy, molecular assays, and serological assays.^[10]

Microscopy: For many years, microscopy has been the only tool available for the detection of parasites through inspection of blood smears^[19] tissue specimens, feces, lymph node aspirates, bone marrow, and even

cerebrospinal fluid.^[17] The standard methods involved in diagnosing helminth infections rely on direct examinations of a parasite structure either by microscopy or other imaging techniques. In reality, all major intestinal helminth infections are still solely dependent on microscopy for diagnosis.^[5]

Serology-Based Assays: Serology-based diagnostic tools would allow for faster diagnosis of helminth infections, and in situations where microscopic results are confounding, serological examinations could provide additional insight with higher sensitivity and specificity. They are classified into two categories antigen and antibody based assay which include Enzyme-linked immunosorbent assay (ELISA) and also called enzyme immunoassay (EIA), and its derived tests such as the Falcon assay screening test ELISA (FAST-ELISA) and the dot-ELISA. Other assays include the hemagglutination (HA) test, indirect or direct immunofluorescent antibody (IFA or DFA) tests, complement fixation (CF) test, and immunoblotting and rapid diagnostic tests (RDTs).^[5]

Molecular: Molecular techniques could render the diagnosis of helminth infections more sensitive and specific. The nucleic based approach permit the detection of infections from very low parasitized samples including those from asymptomatic patient's samples.^[38] Moreover, multiplexed PCR allows for the detection of multiple sequences in the same reaction tube proving useful in the diagnosis of several parasitic infections simultaneously.^[32]

Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus (HIV) is a retrovirus which causes Acquired Immunodeficiency Syndrome (AIDS). AIDS is a clinical syndrome characterized by the progressive depletion of CD4+ T-lymphocyte population of the blood, leading to a progressive deterioration of the immune system and leaving the infected person vulnerable to a variety of infections. The clinical syndrome of AIDS was first recognized over 30 years ago and the discovery of HIV-1, the causative virus, followed soon after. Two types of HIV that are recognized as causative agents of AIDS in humans are HIV-1 and HIV-2. HIV-1 is diverse, virulent and has a wider distribution accounting for the Global AIDS pandemic while HIV-2 is concentrated and has remained isolated in West Africa and countries with strong ties to such regions.^[4] Since the beginning of the epidemic, about 75 million people have become infected with HIV and an estimated 36 million people have died of AIDS-related illnesses.^[4]

Nigeria has the second largest HIV burden in the world, with approximately 3.5 million people living with HIV. Six states account for 41% of people living with HIV, including Akwa Ibom, Benue, Lagos, Oyo and Kaduna.^[4] It is estimated that almost two third of HIV infection in west and central Africa in 2016 occurred in

Nigeria, despite achieving 15% reduction in new infection between 2005 -2016.^[4]

HIV -Helminth Coinfection

Of the 738 million people living in Africa, approximately 26 million (3.5%) are infected with HIV. As many as 50-90% of this population may be co-infected with soil-transmitted helminths such as *Enterobius vermicularis*, *Ascaris lumbricoides*, Necator, ancylostoma, *Trichuris trichiura*, *Hymenolepsis nana*, and *Strongyloides stercoralis*.^[18,31]

Helminth and HIV are, however, quite different in respects that are important to their interactions. First, helminth infections are caused by diverse species from three phyla: generalizations regarding the mechanism and nature of their effects may not be appropriate. HIV is essentially a single entity. Secondly, helminth infection may be, in a sense, normal to the mammalian immune system. The association between mammals and helminths is ancient: some species probably co-evolved with primates and humans; others, co-evolved with other mammals, may have crossed and adapted to humans following exposure through domestication of animals. In some host-helminth relationships adaptation appears almost perfect. Most people with helminths are unaware of their infection: the persistence of widespread infection, despite disease caused by some high intensity infections, is compatible even with a selective advantage of low intensity infection to the host. By contrast, HIV infection is not normal; it has attained a significant prevalence in humans only in the last 25 years and is universally fatal. Third, helminths modulate the immune system, but HIV destroys it. Immune modulation by helminths may have both beneficial and detrimental effects in relation to human disease.^[20] There is evidence for benefit of helminth infection in relation to atopic disease.^[3,20]

Clinical Development and Immune Responses During Helminth and HIV Co-infection

Helminth infection involves a wide range of species which occupy a variety of places within the human body ranging from intestinal lumen, lymphatics, intravascular, or intracellular compartments.^[16] The clinical development vary from one species to another depending on the progress of infection, series of development and maturation cycle in the host and where the adult worms may be present in.^[27] These different phases result in the host being open to various stage-specific antigens in a range of host tissues and organs such as the skin, lungs, gut, heart, liver, bladder, and brain and pass through the circulatory and lymphatic systems. Subsequently, the clinical manifestations can be associated with the early infection phases such as during the larval entry and migration such as the hookworm's ground itch skin, the perianal itch, and pruritis vulvae in enterobiasis.^[16] Migrating larvae may also induce immune reactions as they pass through the tissue, organs causing damage, or indirectly through the immune response they induce. A

case in point is the schistosomiasis-induced inflammatory response and the pathological outcome associated with the eggs lodged in the urogenital mucosa and organs.^[27]

Helminth infection is also associated with a wide variety of clinical symptoms ranging from gastrointestinal (diarrhoea, vomiting, pharyngeal irritation, cough, dyspnea, hoarseness, nausea, bloating, malabsorption), systemic (anemia, lymphedema, cystercercosis, epileptic fits) to organ occlusion.^[30] Some infections are cleared by the host's immune response while most establish and become chronic. It is noted that clinically, many infected individuals experience minor symptoms or remain asymptomatic. Eighty percent of the heavy infections are carried by 20% of the infected population and these individuals suffer serious life-threatening disease.^[3]

Immune Response to Helminths and HIV Coinfection

Immune hyperactivation, which is characteristic of helminth infection, may play a crucial role in HIV disease progression. Several studies have found an association between helminth co-infection and more rapid progression of HIV disease. Helminth infection in the developing world is common in children, many of whom live with the parasite into adulthood.^[52] As such, there may be a large number of individuals who have chronic helminth infection at the time they are infected with HIV. There is evidence that extant helminth infection increases susceptibility to progression of HIV. First, helminth infection causes a significant increase in CD4+ memory cells and a decrease in naive CD4+ cells, suggesting that helminth-infected individuals might be less able to respond effectively to HIV-1 infection.^[49] Second, helminth infection shifts the immune system toward a Th2 response, characterized by eosinophilia and increased serum IgE. Although not conclusive, data suggest that activation of the Th2 immune subset facilitates more rapid HIV replication and progression. Some studies have also failed to find a correlation between helminth infection and HIV-1 viral load.^[53]

Among immunocompetent patients, chronic helminth infection induces several alterations similar to the changes seen in HIV. First, chronic helminth infection has been shown to cause a decrease in peripheral CD4+ lymphocytes.^[49] Second, helminth infection has been found to lower the CD4/CDS ratio in HIV-negative patients.^[49] Third, helminth infection causes a significant decrease in the number of CD2S+ CDS+ T cells, similar to the decreased expression of CD2S seen in HIV-1 infection.^[50,51] Taken together, the data suggests that chronic helminth infection and HIV-1 may have a synergistic effect in altering host immune response.

Several studies have since lent further support to this association: (i) T cells and monocytes obtained from helminth infected individuals have increased expression of HIV-1 chemokine coreceptors^[54-55]; (ii) peripheral blood mononuclear cells obtained from helminth-

infected individuals are more susceptible to HIV infection, and the increased susceptibility is correlated to the chronic immune activation of the cells^[56,57]; (iii) the risk of mother-to-child HIV-1 transmission in pregnant women coinfecting with one or more helminths was found to be significantly higher than in women without helminth infections^[58]; (iv) an association was found between genital lesions caused by *Schistosoma haematobium* infection in women and susceptibility to HIV infection^[59]; and (v) people coinfecting with HIV and *S. mansoni* have decreased CD8+ cytolytic HIV-1-specific T cell responses and increased interleukin-10 production compared to individuals infected with HIV-1 only.^[60]

Perhaps more compelling with regard to the effect helminth infection may have on HIV infection are the results of recent studies in primates dually infected with *Schistosoma* and simian human immunodeficiency virus (SHIV), which show that: (i) *Schistosoma*-infected monkeys required significantly less SHIV to become infected with the virus in comparison to *Schistosoma* non infected animals;^[61] (ii) primates infected with *S. mansoni*, when acutely infected with SHIV, developed higher levels of plasma SHIV in comparison with *Schistosoma*-non infected animals, and regardless of the intensity of the parasite infection; (iii) re-exposure to *Schistosoma* of monkeys infected with SHIV resulted in additional significant increase of the SHIV viral load;^[61,62] and (iv) primates chronically infected with SHIV, when also infected with *Schistosoma*, showed a significant increase of SHIV plasma viral load together with a decrease in the percentage of their CD4(+) CD29(+) memory cells.^[63]

CONCLUSION

Helminth infections have an ongoing prolonged and wide negative effect on the health of the population, irrespective of their effects on HIV and possibly other infections as well. Thus, control of helminths should be pursued in large parts of the developing world without delay and should not await the results of studies on the impact of helminths on HIV or other infections. If the eradication of helminth infection in HIV infected individuals can lead to significant slowing of disease progression, the public health benefits would be enormous. A reduction in the rate of disease progression of even a very modest amount would lead to significant public health benefits by delaying the need for antiretroviral therapy for many individuals and improving the functional status of the group as a whole. Despite the large amount of immunological evidence, there is a dearth of epidemiological data for helminth infection in the HIV infected population. To guide policymakers and clinicians in deciding when and whether to empirically treat helminth infection in HIV infected patients, more epidemiological data specific to this population is needed.

RECOMMENDATIONS

1. All diagnostic techniques for parasite detection should be made widely available at HIV clinics. It is recommended that clinicians caring for HIV/AIDS patients request routine stool examination for the specific diagnosis of opportunistic helminth parasites, especially in patients at the symptomatic stage.
2. Since HIV/AIDS disease coexist with helminth infections as indicated in this review, it is vital that the National AIDS control Programme provides the necessary logistics required to diagnose specific helminth parasites. This should include; PCR, Isoenzyme Analysis and Antigen detection which has proven to be a very effective means of diagnosing these parasite. Training programs should be held for laboratory professionals to improve their knowledge on these special diagnostic procedures aimed at diagnosis.
3. There is the need for ART service providers to consider adding anthelmintic drugs as part of the drug regimen to treat specific helminth parasites which are known to coexist in HIV/AIDS condition. Proper sanitation and improvement of personal hygiene should also be encouraged in the society indiscriminate defecation and urination close to water bodies should be discouraged.

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