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Helminthiasis: A Systematic Review of the Immune Interactions Present in Individuals Coinfected with HIV and/or Tuberculosis

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Additional information is available at the end of the chapter

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Abstract

Helminth infections are highly endemic in parts of the world where the two killer epidemics caused by *Mycobacterium tuberculosis* (*M.tb*) and the human immunodeficiency virus (HIV) intersect. Sub-Saharan Africa is hardest hit by this epidemiological overlap. Consequently, several studies have investigated the immunological outcomes of helminth coinfection with either HIV or *M.tb*, to elucidate the central hypothesis that chronic infection with helminths exacerbates the course of HIV and tuberculosis disease. However, there is no conclusive evidence to confirm whether helminth-induced immunity modulates HIV- and TB-specific immune responses and their pathogenesis or vice versa. The present chapter summarizes the epidemiology, clinical course, and immune interactions during helminths and HIV/TB coinfections and undertakes a systematic review of the existing literature published from Africa on this subject. The aim was to determine if chronic helminthiasis has a negative impact on HIV and TB infections. A PubMed search was undertaken with no language and time restrictions. Search terms used included a varied combination of “Helminth coinfection and immunity and TB coinfection or TB immunity and HIV coinfection or HIV immunity and Africa.” Names of individual species were also permuted in the search terms. Reviews and bibliographies of selected articles were screened to identify additional relevant articles or studies. Of the total 1021 articles retrieved, 47 were relevant with 31 helminth and HIV coinfection and 16 helminths and TB coinfection articles. While many studies failed to find a negative impact of helminth infection on immune responses to HIV and/or TB, a significant number found evidence of deleterious effects of coinfection with helminths such as immune activation, impaired Th1 responses to TB antigens, higher viral loads, lower CD4+ counts, and increased risks of antiretroviral immunologic failure, mother to child HIV transmission or TB disease. Some of the helminth-induced immune dysregulation was

reversed by deworming, while some studies found no benefit of antihelminthic treatment. More studies particularly in Southern Africa are needed to increase the much sought evidence of the impact of deworming among HIV-infected individuals as this seems the most feasible, cost-effective intervention with little or no serious adverse effects. Lastly, with the expansion of ART and increased access to HIV treatment, the effects of helminths on vaccines, TB, and antiretroviral treatments efficacy also need serious consideration, in light of the suggestive evidence of possible immunologic failure due to helminth coinfection.

Keywords: helminths, *Mycobacterium tuberculosis*, human immunodeficiency virus, coinfection, immune-response, Africa

1. Introduction

1.1. Overview

Helminthiasis is an infection with either flukes (trematodes), tapeworms (cestodes), or roundworms (nematodes) [1]. These worms are highly endemic in parts of the world where the two killer epidemics caused by *Mycobacterium tuberculosis* (*M.tb*) and the human immunodeficiency virus (HIV) intersect [2]. This epidemiological overlap between helminthic infections, TB and HIV, is more common in lower and middle-income countries, particularly sub-Saharan Africa (SSA). This is one of the hardest hit regions with regards to HIV and tuberculosis [2], while helminth infections are also highly endemic in this part of the world [3]. Almost 70% of the population infected with HIV resides in SSA, which also carries two-thirds of the global burden of helminthiasis [2, 3]. Regrettably, helminth infections as part of the neglected tropical diseases (NTDs) are still largely neglected and not a prioritized research domain in most regions where they are highly prevalent and overlap with HIV and *M.tb*. This raises important research questions about the public health implications of helminth coinfection with HIV and/or *M.tb* in terms of pathogenesis and treatment outcomes of all these diseases. Furthermore, although individual helminth-, HIV-, and *M.tb*-specific immune responses have been extensively investigated [2], the precise immune correlates of protection remain mostly unknown.

Several studies have investigated the immunological aspects of helminth coinfection with either HIV or *M.tb*, to elucidate the central hypothesis that chronic infection with helminths exacerbates the course of HIV and tuberculosis disease [2]. Owing to the complexity of the interaction at molecular, cellular, and humoral levels, the differences in study designs resulting from financial and ethical challenges of properly designed randomized control trials for such studies, many of these investigations have reported inconclusive or contradictory results. As a result, to date, there is no conclusive evidence to confirm whether helminth-induced immunity modulates HIV- and TB-specific immune responses and their pathogenesis or vice versa.

There is a need therefore to constantly explore the work on the immunological consequences of dual infections in order to condense and update this knowledge for policy makers in terms

of a holistic management of coinfections in areas where all these infections are coendemic. The present chapter aims to review published research on the immune interactions during coinfection with helminths, HIV, and *M.tb* in the African region, a continent with a very high burden of all three infectious diseases. A brief description of the epidemiology, clinical course, and immune interactions during helminths and HIV/TB coinfections is given and then followed by a systematic review of the existing literature on this subject.

1.2. Epidemiology of helminthiasis

More than 2 billion people worldwide are infected with helminths including geohelminths or soil-transmitted helminths, schistosomes, and filarial worms, the vast majority of whom are in low-/medium-income countries. Individuals who are affected frequently harbor more than one species of worm at a time [4]. The major human helminth species of public health importance include *Ascaris*, *Trichuris*, Hookworms (*Necator americanus*, *Ancylostoma duodenale*), *Trichinella*, *Filaria*, *Onchocercaria*, *Ecchinococcus*, *Enterobius*, *Strongyloides*, *Taenia*, and *Schistosoma* species. It has been estimated that schistosomiasis and soil-transmitted helminths (sTH) together account for 40% of all the tropical disease burden excluding malaria and that infectious and parasitic diseases are the primary causes of death worldwide [5, 6].

Soil-transmitted helminths alone constitute the highest burden. Globally, an estimated 438.9 million people (95% confidence interval (CI), 406.3–480.2 million) were reported to be infected with hookworm in 2010, 819.0 million (95% CI, 771.7–891.6 million) with *A. lumbricoides*, and 464.6 million (95% CI, 429.6–508.0 million) with *T. trichiura* [6]. In underdeveloped regions, geohelminths cycle via pollution of the soil by feces containing worm ova or eggs from infested humans. Individuals get infected through ingesting eggs in undercooked, unwashed, and unpeeled fruits and vegetables, in contaminated water sources, or eggs ingested by children who play in the contaminated soil and then put their hands in their mouths without washing them. In hookworm infections, eggs hatch in the soil, releasing larvae which penetrate the skin of people walking barefoot on the contaminated soil. In the case of schistosomes, water is polluted by urine and/or feces [4]. These epidemiological cycles have been exacerbated because of overcrowding in densely populated informal settlements without adequate sanitation or clean water, owing to rapid urbanization and migration. Transmission is therefore directly linked to availability of clean water supplies, poor hygiene, inadequate sanitation, the presence of infective worm eggs in the environment, and climatic factors. In other developing countries such as Central America and the Caribbean and parts of East and Southeast Asia, socioeconomic and sanitation improvements and rollout of large-scale regular deworming programs have reduced the previously high infection rates. In Central and Southern Asia, large numbers of helminth infections still occur in certain regions owing to variations in environmental and socioeconomic conditions, while in South America helminthiasis is distributed in pockets of poverty-stricken indigenous populations. In the Middle East, transmission is limited by hot and dry weather but high prevalence is still found in areas with suitable climate within informal settlements [3]. In developed countries, the general availability of efficacious deworming drugs, clean water, and effective sanitation has eliminated most of these parasites

such that more serious infections do not occur in these regions and mostly minor or imported cases are reported [7].

In general, helminths develop through three stages: eggs, larva, and adult worms, which determine both their epidemiology and pathogenesis in humans [8]. An example is illustrated in the case of soil-transmitted helminths where the eggs have a 3-week maturation stage in the soil that requires temperate, moist, and humid soil before they become infective [4]. Subsequently, these worms are most prevalent in regions with tropical and subtropical climate. In terms of the pathogenesis, larvae and eventually adult worms may cause direct pathology through migration, metabolic activity, or blockage and damage to the internal organs they finally parasitize.

1.3. Epidemiology of HIV

Globally, 36.7 million [34.0–39.8 million] people were living with HIV at the end of 2015 [9]. During the 35 years of the epidemic, more than 70 million people have been infected with HIV globally and about 35 million people have died [10]. The distribution of the HIV infection varies dramatically from region to region. Globally, sub-Saharan Africa is the most severely affected, with nearly 70% of the people living with HIV worldwide being from the region. At least one in every 25 adults (4.4%) in this region is living with HIV [10]. The data as at the end of 2014 is summarized in **Table 1** and illustrates the skewed distribution of the HIV virus across the globe [11]. The sub-Saharan region has consistently been carrying the heaviest burden of the HIV infection globally.

Region	Number of people living with HIV in 2014
Sub-Saharan Africa	25.8 million
Asia and the Pacific	5 million
Western and Central Europe and North America	2.4 million
Latin America	1.7 million
Eastern Europe and Central Asia	1.5 million
Middle East and North Africa	280,000
The Caribbean	240,000

Adapted from UNAIDS data <http://www.avert.org/global-hiv-and-aids-statistics> [11].

Table 1. Global distribution of HIV infection (2014).

1.4. Epidemiology of *Mycobacterium tuberculosis*

Tuberculosis (TB) remains a major global public health problem and ranks second only to HIV as a cause of death worldwide [12]. TB is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* (*M.tb*). It typically affects the lungs (pulmonary TB) but can disseminate to affect other sites as well (extra pulmonary TB). The disease is spread in the air when people

who have pulmonary TB disease expel bacteria, for example, by coughing. It is estimated that a third of the world's population is infected with *M.tb*. In 2015, the World Health Organization reported 9 million TB cases with 1.5 million deaths annually [13]. Furthermore, according to the WHO, the African region has more than 24% of the world's TB cases and deaths, while approximately 78% of total TB deaths and 73% of TB deaths among HIV-negative people occurred in the African and the Southeast Asian regions combined [13]. On a global scale, the African region alone accounts for at least 80% of TB cases dually infected with HIV worldwide. This is because in many African countries, the tuberculosis and HIV epidemics are fueling each other.

In general, a relatively small proportion of the estimated 2–3 billion people infected with *M.tb* globally will develop TB disease during their lifetime (approximately 10%) [14]. This is because although healthy people often will get infected by the bacilli, they are usually able to fight it off or keep it under control to a large extent. Other people may only succumb to TB disease years later, often when the immune system has been weakened by conditions such as HIV infection, resulting in the reactivation of latent subclinical *M.tb* infection. Thus, it has been established that the two categories of people developing TB disease include (i) those who have been infected with TB bacilli and (ii) persons with compromised immune systems, possibly due to other health conditions. Among the latter, HIV, diabetes, silicosis, low body weight, and certain medical treatments, among others, have been established as known risk factors for the development of TB disease.

Important factors in the management of TB include early detection, treatment, and management of infected individuals in order to curb unabated transmission of this air-borne infection. Detection and treatment relies heavily on the diagnostic capacity and linkage to care. To date, the most widely used method for diagnosing TB worldwide remains sputum smear microscopy, in which bacteria are observed in sputum samples examined under a microscope, a method which was developed over 100 years ago. However, in countries with more developed laboratory capacity, the cases of TB are also diagnosed via the culture method which is currently the gold standard in TB diagnostics. Technological advancements in the last few years have resulted in the use of rapid molecular tests to diagnose TB. Use of these techniques, such as the GeneXpert, is now on the increase, with some countries now gradually phasing out the use of smear microscopy for TB diagnosis [15].

TB is a poverty-related disease. As such, the financial demands of proper diagnosis using laboratory techniques are juxtaposed by the limited resources in poor regions, and the financial deprivation among the poor hinder optimum access to health care facilities. These factors imply that a significant proportion of TB patients remains either unrecognized and untreated or not notified, thus exacerbating transmission. Without treatment, the natural cycle of TB infection is that a person deteriorates progressively, with the term "consumption" having been used in the old days to describe the disease. The death rate in untreated TB cases is very high. Studies from the prechemotherapy era showed that at least 70% of people who had microbiologically confirmed TB died within 10 years of the infection. Currently, the effective chemotherapeutic management of normal drug-sensitive TB lasts for at least 6–9 months. This long treatment duration, coupled with side effects of anti-TB drugs, leads to noncompliance

resulting in the emergence of drug-resistant TB in recent years [15]. The treatment of drug-resistant TB is much more complicated requiring much longer treatment regimens of up to 2 years, an even so, with very poor prognosis and suboptimum treatment outcomes. Treatment outcomes therefore also bear a direct impact on the epidemiology of tuberculosis.

1.5. Clinical course and immune responses during helminthiasis and HIV coinfection

Helminthiasis can be due to infection with a wide range of species which occupy a variety of niches within the human body ranging from intestinal lumen, lymphatics, intravascular, or intracellular compartments [1]. The clinical course will then differ from one species to another depending on the course of infection and maturation cycle in the host and where the adult worms eventually reside. The current work will not attempt to dissect the clinical course of each species. Broadly, the clinical course of helminthiasis is associated with their infection route and the final tissue or organ in which the adult worms reside and multiply.

Helminths have complex life cycles within the human host and undergo a series of developmental stages in different parts of the human body. These different stages result in the host being exposed 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 [1]. 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 [1]. Migrating larvae may also induce immune reactions as they pass through the tissues, such as the cutaneous syndrome as a result of hookworm penetrating the skin. Another is illustrated by the development of *Ascaris lumbricoides* after the ingested eggs have hatched in the human gastrointestinal tract [1, 8]. The larvae migrate through the blood and via the lungs where they cause an eosinophilic pneumonitis syndrome, before being coughed up and reswallowed into the intestinal tract where they establish as adult worms [1]. The worms may cause pathology directly as they migrate through organs causing tissue damage, or indirectly through the immune response they induce. A case in point is the schistosomiasis-induced inflammatory response and the pathological sequelae associated with the eggs lodged in the urogenital mucosa and organs [16].

The parasites have different lifespans, which vary from species to species, for example, adult schistosome worms can live for up to 5 years in the host in the absence of chemotherapy. *Onchoecaria volvulus* has a life expectancy of up to 8–10 years while *Ascaris lumbricoides* is 1 year. Those with a short life cycle have a faster reinfection rate after chemotherapy and are highly fecund, for example, an adult *Ascaris* female can produce 200,000 eggs per day [17].

Helminthiasis 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. 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

[17]. However, owing to the large number of infected individuals globally, this small percentage translates to large numbers of people with such morbidity. Importantly, the full-scale implications of helminthiasis even in the absence of symptoms and overt disease is the result of their subtle but deleterious impact on the other major killer pathogens such as the HIV and *M.tb* as outlined in the following sections.

1.5.1. Immune response to helminths

Although helminths comprise of a spectrum of species, a striking phenomenon found during helminthiasis is an almost universal immune response elicited by these pathogens. The response is characterized by the following archetypical features:

- Consistent induction of a strong T helper 2 (Th2) immune response by CD4⁺ T helper 2 cells with the production of type 2 cytokines: interleukin (IL)-4, IL-5, IL-9, IL-10, and IL-13.
- Increased levels of regulatory cells, molecules, and cytokines.
- Classic eosinophilia, increased numbers of mast cells, and basophils accompanied by very high immunoglobulin E (IgE) levels.
- Existence in the host for protracted periods, sometimes years, in the presence of strong immune responses directed against the parasites.
- The resultant chronic activation of the immune system from the persistent worm and egg or larval antigenic challenge is associated with an increased rate of programmed cell death (apoptosis).
- Induction of specific and generalized immune suppression (anergy) as one of the strategies to survive in the face of strong immune responses [2].

Early in the infection, macrophages and dendritic cells are the first line of defense in the innate immune response. These cells interact with parasite antigens and present them to T cells and also secrete type 1 and inflammatory cytokines such as interleukin (IL)-12, tumor necrosis factor alpha (TNF α), IL-6, and IL-8 [17, 18]. Other cell types such as the NK T cells in the gut mucosa secrete IL-4, promoting the differentiation of the CD4 T cells toward a Th2 phenotype [18]. These Th2 cells will secrete Th2 cytokines and also promote antibody isotype switch to IgE [18]. CD4 T cells therefore play a key role in the development of the strong Th2 adaptive immune response to helminths. Cytokines also recruit and prompt proliferation of other granulocytic cells such as eosinophils, mast cells, and basophils which mediate extracellular killing and expulsion of the worms through increased mucus secretion by goblet cells [18, 19].

A variety of mechanisms through which helminths evade the strong immune responses have been elucidated. Central among these is the increased number of regulatory cells which play a key role in dampening the immune response [2, 19]. These cells secrete the downregulatory cytokines IL-10 and transforming growth factor β (TGF β) which in turn increases cytotoxic T lymphocyte antigen-4 (CTLA-4) expression in T cells. On the other hand, the costimulatory molecule CD28 which facilitates T-cell intracellular signaling and activation in response to antigenic stimulation is decreased during helminth infection [2]. This costimulatory molecule

is essential for completion of T-cell activation after the T-cell receptor binds the antigen presented in association with the major histocompatibility complex (MHC) [18]. CTLA-4 competes with CD28 for binding in T cells, as a regulatory mechanism to prevent uncontrolled immune responses. Cells continually stimulated by parasite antigens in the absence of CD28 fail to mount an effective immune response and remain anergic [2, 18]. Increased CTLA-4 induced by chronic helminthiasis will outcompete the CD28 binding, thereby rendering the T cells partially activated and unresponsive [2].

Other mechanisms of immune diversion by helminths include secretion of decoy molecules and cytokine homologs such as the macrophage-inhibitory factor (MIF) which switches macrophages to differentiate toward a type 2 phenotype that is counter inflammatory. Helminths also secrete protease inhibitors that interfere with antigen presentation and cell proliferation [19]. These pathogens also modulate innate cells such as the dendritic cells and macrophages toward the Th2 phenotype inducing alternatively activated macrophages. The diversion and regulation of the immune response toward a favorable niche such as promoting wound healing; dampening of the inflammatory type 1 toward Th2; induction of alternatively activated macrophages that do not secrete IL-12 (which promotes the differentiation of Th1 cells); and secretion of other molecules that interact with the host tissues are all mechanisms that optimize the existence and survival of the parasites *in vivo* without causing extensive harm and possible death of the host [19, 20].

Other key cellular changes that occur during helminthiasis include decreased numbers of CD4⁺ and increased frequency of CD8⁺ cells [21], increased expression of chemokine receptors CCR5 and CXCR4 in T cells [22], and in vaginal mucosal cells [16]. Another worm-induced immunomodulatory mechanism is the selective upregulation of programmed death 1 ligand, which subsequently binds to program death-1 in T cells, thus rendering them anergic and prone to increased apoptosis [2, 19].

1.5.2. Clinical course and immune response to HIV

The immune response to HIV differs among infected individuals. The course of the infection is determined by several factors such as the viral fitness or virulence, the host genetic factors such as the association of the HLA-B27, HLA-B*5701, HLA-B*5703, HLA-B*5801, and HLA-B57 alleles [23, 24], and CCR-5 mutation [25] with resistance, as well as the immune response particularly the cytokine microenvironment—with the predominance of type-1 cytokines being more favorable. The cells of the innate immune system, the NK cells, are the source of antiviral interferons secreted in the primary phase before induction of the adaptive immune responses [18]. The effective control of HIV is chiefly dependent on the development of potent HIV-specific cytotoxic T lymphocyte response (CTL) mediated by the Th1 CD8⁺ lymphocytes. This was aptly demonstrated in both animal models and human studies early in the advent of HIV [26–28]. The simultaneous appearance of the CTL at the point of peak viremia is followed by the decrease in viral replication and establishment of the viral set point during the early phase of the HIV infection and the association between higher numbers of CTL, viral suppression and slower decline of CD4⁺ cells during all phases of the HIV infection [29].

The development and maintenance of competent CTLs is also dependent on robust HIV-1 specific CD4⁺ responses (particularly HIV-1 gag-specific). Paradoxically, the classic immunological characteristic of HIV disease progression is the extensive attrition of the CD4⁺ lymphocytes, attributed to the fact that during the HIV infection not only HIV-infected cells are affected, but uninfected bystander CD4⁺ cells are also depleted [30]. The overall depletion of the CD4⁺ cells is mediated via several mechanisms, including direct cytopathic effects on infected cells, indirect bystander killing, and increased activation-induced programmed cell death or apoptosis [2].

Other prominent cellular changes during HIV infection include increased numbers of CD8⁺ cells, which remain high throughout the infection phases. The main functions of these cells include the secretion of the antiviral Th1 cytokine, interferon gamma (IFN γ), as well as cytolytic destruction of viral-infected cells through the granzymes and perforin system [18]. The innate cells also secrete TNF α , IL-6, and IL-8. However, it has been shown that the consistently high numbers of CD8⁺ cells are not related to increased antiviral potency [29] and that their function wanes as the infection progresses, although the numbers remain high.

Regulatory cells also increase because of the chronic antigenic challenge and immune activation. These changes are also accompanied by increased expression on T cells, of downregulatory molecules such as the cytotoxic T lymphocyte antigen 4 (CTLA-4), and the negative regulator of T-cell activation molecule, program death 1 (PD-1), as well as decreased costimulatory molecules, particularly CD28, which plays a key role in the induction of T lymphocyte response to antigen [18]. Normally, the CTLA-4 competition with CD28 for binding down modulates the immune stimulation to prevent a pathologic runaway or uncontrolled immune response. During chronic HIV infection, this homeostasis is disturbed by higher-than-normal levels of CTLA-4 secreted by the upregulated regulatory T cells (Tregs) which also secrete high levels of IL-10 and transforming growth factor β (TGF β) [2]. The increased levels of IL-10 and TGF β are responsible for the generalized immune suppression with disease progression. Decrease in type 1 cytokines (IL-2), a lymphoproliferative cytokine and the antiviral interferon gamma (IFN γ) and ascendancy of Th2 cytokines have been associated with HIV disease progression. The total effect is inability of T cells to respond to cognate and unrelated antigens and increased programmed cell death (apoptosis) [2]. The early viremic phase of the HIV infection is also characterized by marked increases of mainly inflammatory cytokines such as IFN γ , IFN α , IL-15, IL-22 TNF α , CXCL10, and regulatory IL-10, known as the cytokine storm. These are secreted by infected CD4⁺CCR5⁺ T cells, activated dendritic cells, monocytes, macrophages, NK cells, NKT cells, and HIV-specific T cells [29].

Owing to the chronic nature of the HIV, chronic immune activation and increased levels of regulatory cells is also another striking feature of the infection. The immune activation correlates with CD4 decline and increased apoptosis [30]. HIV infection is known to stimulate B cell and antibody forming cells. In the past, owing to the rapid mutation of the virus, the protective effects of antibodies remained contentious. However, with the advancement of molecular and computational research tools, there has been recent interest in exploiting the neutralising antibodies for therapeutic vaccine development with promising results [31].

1.5.3. Immune interaction during helminth and HIV coinfection

It is recognized that during coinfection, the effects of immune modulation and regulation is bi-directional, in other words, immune response to HIV can modulate the response to helminths [32] and vice versa. However, the focus of this work is on helminthiasis, and therefore we will examine the influence of helminths on HIV and *M.tb*. Several immune mechanisms suggest that immune responses to helminths are deleterious to immune control of intracellular pathogens such as HIV. The interaction in a dually infected host may either increase susceptibility or enhance cell-cell infection and virus replication thereby indirectly increasing transmission. The key mechanisms that are proposed to drive this interaction are summarized below.

1.5.3.1. Increased viral replication and transmission

The classic induction of a strong Th2 immune response by helminths downregulates the critical Th1 CTL response required for the control of HIV. In addition, HIV has been shown to replicate more readily in Th2 cells [33]. Uncontrolled viral replication increases transmission to other hosts (high viral load) and within the same individual. Helminthiasis and HIV infection are chronic infections, with chronic immune activation being the classic feature in both infections [2]. It is known that the HIV virus hijacks the host's natural transcription process for its own replication. The transcription factor NF- κ B, which is present in all activated cells, binds to both host DNA promoter and viral long terminal repeat sequences (LTR) which then initiates viral transcription [18]. In addition, the nuclear factor of activated T cells (NF-AT) stabilizes the postfusion HIV complex and facilitates reverse transcription of the virus [34]. Proinflammatory cytokine signaling pathways, particularly TNF α , IL-1, and IL-2, induce these transcriptional factors [18]. IL-6 also synergizes with TNF α in monocytes to enhance HIV replication [34]. Increased levels of proinflammatory cytokines such as TNF α and IL-2 are well documented in chronic helminthiasis [2, 35]. In that way, availability of increased numbers infected, activated CD4⁺ T cells enhances viral replication.

One of the classic features of helminthiasis is increased production of immunoglobulin E (IgE). This antibody isotype has been shown to increase viral replication as shown by increased production of the HIV capsid protein 24 (p24) and viral mRNA in a culture system. The crosslinking of the cell surface molecule CD23 by IgE leads to the production of cyclic adenosine monophosphate (cAMP), nitric oxide (NO), and tumor necrosis factor- α (TNF α), which enhance viral replication and thereby accelerate progression to AIDS [36].

1.5.3.2. Increased susceptibility to HIV

Upregulation of chemokine receptor molecules (CCR5 and CXCR4) [16, 22] by helminths increases receptor molecules on CD4-positive cells, thereby increasing the numbers of HIV susceptible cells, enhancing cell-cell infection and replication of the virus. Eosinophils constitute one of the key cellular responses during helminthiasis. Activated eosinophils express CD4 molecules, and have been shown to be infectable with HIV *in vitro* [37, 38]. Their

increased numbers in genital and rectal mucosa may facilitate increased virus transmission during hetero- and homosexual interaction, respectively.

Similar to HIV, helminth infections have been reported to result in the depletion of CD4⁺ cells [21]. This suggests that helminth-infected individuals may be more susceptible to HIV infection as the CD4⁺ cells are critical for both provision of help for CD8⁺ cell (CTL) development, type 1 cytokine secretion as well and mounting an effective immune response to antigenic challenge [18]. In addition, CD4⁺ cell depletion has been directly linked to immune activation [30] which is present in chronic helminthiasis.

Both helminth and HIV infections are accompanied by increased regulatory cell networks. This results in a high degree of reduced capacity to respond to cognate and bystander (unrelated) antigen stimulation. The chronic immune activation is also associated with increased apoptosis and rapid cell turnover which results in clonal exhaustion and diminished numbers of immune cells [2]. Immune activation by both helminths and HIV result in both accelerated CD4⁺ cells depletion and HIV replication. In that way, infected, activated CD4⁺ T cells can therefore be prone to depletion by the viral infection/replication cycle and thus increases susceptibility to HIV and other infections.

1.5.3.3. Uncontrolled HIV infection

The increased regulatory cells dampen immune responses not only to parasite-specific antigens but also to bystander antigens, as well as the ability of helminth infections to diverge immune responses [19] result in a high degree of reduced capacity to respond to antigen and immune stimulation. The chronic immune activation is associated with increased apoptosis and cell turnover results in clonal exhaustion and diminished numbers of immune cells, generally reducing the ability of the immune cells to control infectious pathogens including HIV.

One of the consequences of the induction of alternatively activated macrophages by helminths is the conversion of arginine to ornithine. Arginine is required for the production of nitrogen and oxygen intermediate radicals for intracellular killing [19]. Reduction of the innate intracellular killing capability of the immune system promotes uncontrolled intracellular virus propagation.

1.6. Clinical course of *M.tb* infection during helminthiasis and *Mycobacterium tuberculosis* coinfection

*1.6.1. Clinical course of *M.tb* infection*

While most individuals who acquire TB infection are able to contain the infection as latent TB infection (LTBI), in a small subset of individuals (5–10%), LTBI may progress to active TB disease, a situation that may be prompted by many factors, among them a weakened immune system. LTBI is often detected by the extent of the immune response to *M.tb* antigens such as purified protein derivative (PPD) or tuberculin skin test (TST). This often measures the release of IFN- γ a hallmark cytokine which is central in the TB immune response [39, 40]. Individuals

with LTBI have no clinical or radiological evidence of disease and may live for years without realizing it.

The host mechanisms by which some individuals remain protected while others later develop TB disease remains incompletely understood [41]. However, among the various factors genetic factors of both the host and the pathogen may play an important role in the progression of latent infection to active disease. Other factors such as immune status and the general health condition of the host may also play an important part in this reactivation of latent TB infection. There is now an increasing body of knowledge in the understanding of LTBI being a spectrum of both immunological and microbiological changes rather than binary classification of latent infection and active TB disease [42].

1.6.2. Immune responses to *M.tb* infection

In pulmonary tuberculosis, generally, the immune response is characterized by the involvement of many different cell types with a predominance of CD4⁺ T cells [43]. Once the bacilli reach the lower respiratory tract, alveolar macrophages and lung epithelial cells are the first cells that encounter *M.tb* during primary infection. The defense mechanisms by the macrophages include growth inhibition, innate killing mechanism, phagosome-lysosome fusion, generation of reactive oxygen intermediates, and generation of reactive nitrogen intermediates, particularly nitric oxide as well as participation in the adaptive immune response through antigen presentation to T cells [39]. The macrophages also acquire the ability to stimulate type 1 CD4⁺ Th1 cells or secrete proinflammatory cytokines.

The induction of these inflammatory responses initiates the development of a granuloma [39, 40], where different T-cell populations participate in protective immune responses. Also of note is the effector function of CD4⁺ Th1 cells which is mainly mediated by the production of cytokines, such as IL-12, TNF- α , and IFN- γ [44, 45]. IFN- γ , which is secreted by activated T cells is an important mediator of the immune response to *M.tb*, as it upregulates antimycobacterial processes and antigen presentation by macrophages [39, 43]. The cytokine IFN- γ and natural killer (NK) cells act as the principal activating factors in the control of mycobacterial infection. The induction of IFN- γ is regulated by IL-12. That the Th1 immune response is critical is highlighted by the increased susceptibility to TB disease in patients treated by TNF- α suppressing drugs such as steroids [41]. The induction of significant Th1 (IL-12, IFN- γ , and TNF- α) and Th17 responses (IL-17 and IL-23) is thus central to the control of tuberculosis [46]. In recent years, the realization that Th17 cells also play a critical role in host's control of TB has come under the spotlight. Studies from animal models have shown that the secretion of IL-17 homologs coupled by IL-22 helps to establish an optimal Th1 response [47].

In sub-Saharan Africa, the immunology of TB is further complicated by the widespread association of TB with HIV, the protracted period of chemotherapy which inadvertently may result in poor treatment compliance and, consequently, the emergence of drug-resistant and multidrug-resistant *M.tb* strains [14]. While there is a licensed vaccine against tuberculosis (BCG) [44, 48], the efficacy of protection it offers against pulmonary tuberculosis is variable and has been shown to wane over time, possibly due to immune alteration by prevalent chronic

infections and consequent impairment of immune response to recall antigens [45]. Furthermore, the lack of a point of care diagnostic tool means that TB diagnosis [15] and, consequently, treatment and interruption of transmission does not happen as promptly as required in order to bring the global TB epidemic under control [49].

1.6.3. Mechanisms of interactions between helminths and *M.tb*

The fact that both *M.tb* and helminth infection are widely distributed geographically, on a global scale, allows for considerable overlap of the infections. By nature helminth infections are chronic and their persistent presence can lead to considerable morbidity [46]. The presence of chronic helminth infection has been known to induce a wide range of immunomodulation mechanisms mainly dominated by a Th2 type immune response and the subsequent release of Th2-related cytokines, such as IL-4, IL-5, and IL-13. On the other hand, the immune responses induced by helminth infection tend to be antagonistic to those induced by *M.tb* infection [45, 50]. While helminth and *M.tb* infection mechanisms are vastly different with *M.tb* being a single-celled organism and helminths being multicellular, several authors have demonstrated the negative association between helminth and mycobacterial infections [51]. The predominant Th2 biased response in helminths has been demonstrated to downregulate the Th1 response that is characteristic and constitutes an essential defense for control of *M.tb*. It has been hypothesized that by creating an antiinflammatory environment, helminths exacerbate *M.tb* infection by antagonizing the protective inflammatory responses needed for the tuberculosis infection.

In addition, helminths can modulate the host's adaptive immune responses by inducing T-regulatory (Treg) cells or secreting antiinflammatory and regulatory cytokines [19, 52]. Such effects could induce a significant inhibitory effect on protective *M.tb*-induced immune responses and/or control of mycobacterial infection. Studies examining association between helminth infection immune response indicators and TB infection have illustrated that worms may impair immunity against mycobacterial infections. Other literature also shows that helminth-infected individuals exhibit markedly lower Th1 type responses and IFN- γ production to *M.tb* antigens relative to dewormed controls [53].

Other studies have further dissected the immune mechanisms triggered by each pathogen in isolation and also investigated their interaction. In this regard, it has been demonstrated that coincident infections with helminths can modulate the strong *M.tb*-specific Th1 immune responses by driving Th2 and/or Treg cells [54]. Furthermore, enhanced Treg function associated with helminth infections have been found to potentially suppress Th1 responses [55] suggesting that intestinal helminth coinfection is associated with a reduced Th1 type immune response in active TB cases while both Th1 and Th17 responses have been shown to be diminished in latent tuberculosis [56].

Many soil-transmitted helminths larvae migrate through the lungs where they can potentially cause an eosinophilic pneumonitis [1]. Eosinophils are induced by a Th2 response and may have a deleterious, direct impact on coexisting *M.tb* lung infection which requires a Th1 response. In addition, individuals coinfecting with helminths and *M.tb* were also shown to have more advanced disease shown by the number of diseased zones [56]. It is not known whether

the helminths could have exacerbated the lung pathology directly or indirectly through an inflammatory process.

Another deleterious interaction between helminths and *M.tb* is the induction of alternatively activated macrophages by helminths [19]. The resultant attenuation of nitric oxide production by these cells inhibits one of the key intracellular killing mechanisms against *M.tb* which can exacerbate the intracellular survival and multiplication of the bacilli. IL-4 stimulates the production of IgE antibodies, classically induced by helminths. High IgE levels have been shown to be inversely associated with a positive tuberculin skin test in *Ascaris*-infected individuals [57] suggestive of an impaired *M.tb* response associated with helminthiasis.

While a number of studies point to negative impact of helminth infection to the immune responses to mycobacterial infection, other clinical studies also appear to show that helminth infections have little effect on the pathogenesis or pathology of active TB [50]. However, it is important to note that most of these findings are from observational studies with very few longitudinal studies having been performed to examine these hypotheses. In the absence of such long-term longitudinal studies and clinical trials, it remains important to synthesize the current knowledge and present a summary of the findings to date in order to inform policy and further research efforts.

Table 2 summarizes the main mechanisms through which helminth infections are proposed to modulate the HIV and mycobacterium tuberculosis immune responses and course of the diseases.

Effects of helminth infection	Impact on HIV [1]	Impact on Tuberculosis [1, 13]
Cellular alterations		
<ul style="list-style-type: none"> • Lower CD4 and higher CD8 • Alternatively activated macrophages • Classic Eosinophilia 	<ul style="list-style-type: none"> • CD4 T helper cell critical for HIV control: Uncontrolled HIV replication. • Impaired IL-12 production: impaired NK cell intracellular killing of HIV. • Activated eosinophils express CD4 and are infectable by HIV: Increased HIV replication; promotes hetero- and homo-sexual transmission in genital and rectal mucosa. 	<ul style="list-style-type: none"> • CD4 T-cell help essential for protective interferon gamma production: Enhanced TB infection. • Compromised lung anti-tuberculosis defenses. • Reduced NO and RO intracellular killing • Eosinophilia associated with a Th2 response which dampens Th1 anti-tuberculosis responses
<ul style="list-style-type: none"> • Predominant type 2 response Hyper IgE immunoglobulinaemia 	<ul style="list-style-type: none"> • Decreased type 1 CTL responses essential for HIV control: • Uncontrolled HIV replication • Increased HIV replication and apoptosis 	<ul style="list-style-type: none"> • Reduced Th₁ immunity to mycobacteria. Th1 cytokines (TNFα, IL-6 and IL-8) essential for granuloma formation) • Inhibited TLR-mediated protective immunity to TB • Impaired BCG vaccine efficacy.

Effects of helminth infection	Impact on HIV [1]	Impact on Tuberculosis [1, 13]
Chronic immune activation	<ul style="list-style-type: none"> Increased receptor molecules (CD4, CCR5, CXCR4), enhanced HIV entry to cells, cell-cell transmission; Increased transcription factors and virus replication; increased virus transmission in the population. 	<ul style="list-style-type: none"> High IgE associated with high TB incidence Inability to cope with TB, enhanced active pulmonary TB
Regulatory cytokines; specific and generalized immune suppression	<ul style="list-style-type: none"> Attenuated immunity increases susceptibility to HIV and faster progression to AIDS. 	<ul style="list-style-type: none"> Impaired protective TB immunity, Reactivation of latent TB.
Increased apoptosis	<ul style="list-style-type: none"> Increased CD4 T-cell loss, Uncontrolled virus replication 	<ul style="list-style-type: none"> CD4 T-cell help required for granuloma formation: Inability to contain TB; disseminated infection.

Table 2. Summary key immune interactions between helminthiasis, HIV, and *M.tb* infections.

2. Systematic review of immune interactions during helminth and HIV or *Mycobacterium tuberculosis* coinfection

2.1. Methodology

2.1.1. Search strategy

The electronic database PubMed was searched for relevant articles with no language and time restrictions. Search terms used included a varied combination of “Helminth coinfection and immunity and TB coinfection or TB immunity and HIV coinfection or HIV immunity and Africa.” Names of individual species were also permuted in the search terms. Reviews and bibliographies of selected articles were screened to identify additional relevant articles or studies.

2.1.2. Study selection

All retrieved articles were sequentially searched for relevance by title, abstract, and full text. Two authors independently searched through the titles and abstracts to identify potentially relevant papers for inclusion, and consensus on potential eligibility reached with differences resolved through discussion. Full text articles of potentially relevant articles were screened for relevance (**Figure 1**). Articles were excluded from the review if they were (1) not from Africa, (2) based on experimental animal models, (3) review articles, and (4) epidemiological surveys of coinfections without any immunological outcome assessment being reported. The majority of other potentially relevant articles were from countries from Southeast Asia especially India and were therefore excluded.

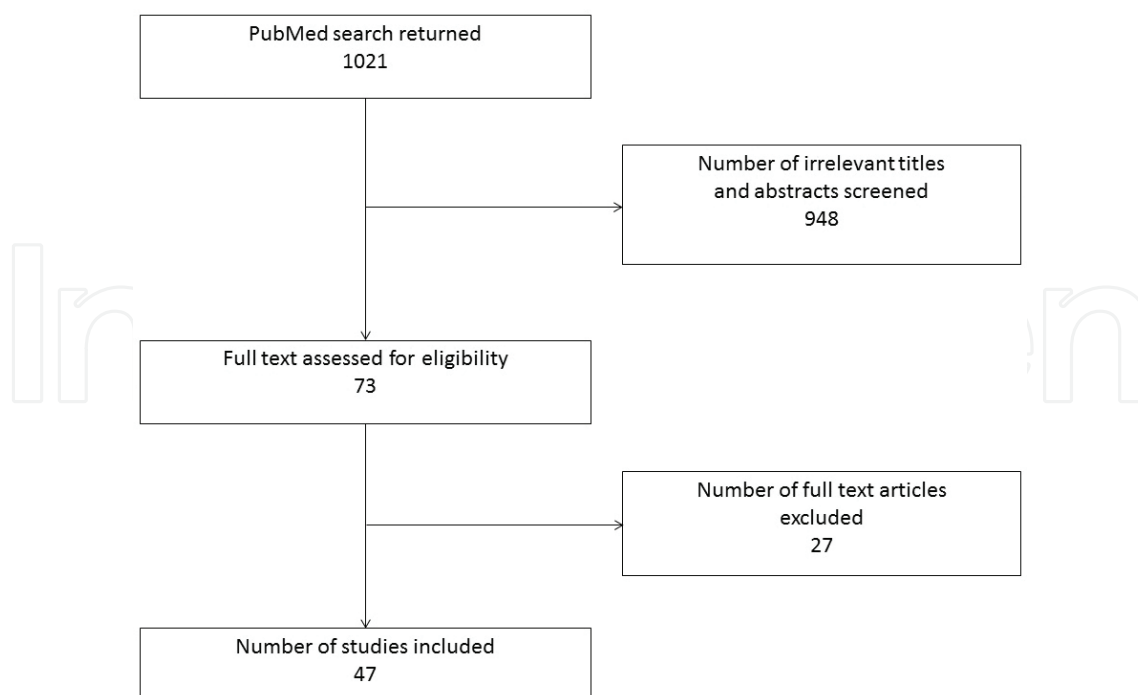


Figure 1. Flow chart showing study selection.

2.1.3. Inclusion criteria for immune interaction

Included were those studies that investigated immune interactions that will worsen HIV disease progression defined by lowered CD4 counts, immunologic failure, increased viral load, impaired immune response, altered immune response-impaired Th1 responses (low IFN γ , IL-12); alternatively activated M ϕ ; highly activated immune system; altered distribution of immune cells; altered cytokine profile (Th2 biased; increased Tregs); and anergy (decreased capacity to respond to antigens). For TB, immune interactions were defined by outcomes that result in impaired granuloma formation; impaired Th1 responses (low IFN γ , TNF α , IL-12); alternatively activated M ϕ ; altered cytokine profile (Th2 biased; increased Tregs); and anergy (decreased capacity to respond to antigens).

2.1.4. Data extraction

A structured data extraction form was used with the following information being extracted: author(s), year of publication, country, subregion, study design, type of coinfection, study population, and main immunological outcome. Diagnosed and/or reported helminth species were also recorded where available.

3. Results

Literature search in the electronic bibliographic database resulted in 953 unique references and 68 more were extracted from the additional manual searches (**Figure 1**). Of these, 73 articles

were considered relevant and assessed for eligibility. A total of 47 relevant articles were identified through PubMed search and cross-referencing of selected articles. Of these 12 were from Southern Africa, 32 from East Africa, and three from West Africa.

A total of 31 relevant studies were on helminth coinfection with HIV, and 18 were from East Africa (seven Ethiopian, five Kenyan, three Ugandan, and four Tanzanian), 10 from Southern Africa (four South African, two Zimbabwean, two Malawian, and one Zambian), and two from West Africa (both from Uganda). In addition, 16 relevant studies were on helminth coinfection with TB, and 13 were from East Africa (nine Ethiopian, three Ugandan, and one Kenyan), two from Southern Africa (all South African), and one from West Africa (Cameroon).

3.1. Helminth and HIV coinfection immunological outcomes

Of the 31 helminth and HIV coinfection studies, 22 (71%) reported some negative effect of helminthiasis on HIV parameters (**Table 3**). Fifteen studies investigated the effects of treating helminth infection on HIV viral load, CD4 count, immune activation, or disease progression. Eight of the 15 (53%) reported a positive impact of treating worm infection by either stabilizing or decreasing viral load [59, 62, 65, 73] or increasing or stabilizing CD4+ counts [16, 62, 65, 68, 82] or decreasing IgE levels [85] and seven reported no impact of deworming [16, 34, 63, 64, 72, 77, 80], two of which reported no benefit of empiric deworming of HIV- and helminth-coinfected individuals [73, 79]. Two studies reported high immune activation associated with coinfection [71, 80] which was not affected by anthelmintic treatment [80]. Five studies reported increased HIV coreceptor molecules CCR5, CXCR4 [16, 22, 60, 71, 81], or CD4 molecules [70], among helminth-infected individuals. One study reported increased odds of antiretroviral treatment immunological failure induced by helminthiasis [74], while another reported increased expression of inflammatory markers [66] and another showed increased HIV susceptibility of peripheral blood monocytes obtained from helminth-infected individuals [58]. An increased risk of mother-to-child transmission by helminth-infected mothers was reported in one study [61]. One study reported decreased capacity to proliferate in response to antigen stimulation and reduced type I cytokines among HIV-/helminth-infected individuals [78].

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
Shapira-Nahor et al. [58]	1998	Ethiopia	East Africa			PBMCs of helminth-infected, immune-activated individuals	Increased HIV susceptibility of PBMCs from helminth-infected individuals.
Lawn et al. [34]	2000	Kenya	East Africa	Prospective cohort	30	Schistosomiasis HIV-infected persons	No correlation between eradication of Schistosoma infection and reduction in HIV load. Instead, a

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
Wolday et al. [59]	2002	Ethiopia	East Africa	Prospective cohort	56	Helminth-infected and noninfected in asymptomatic HIV-1-infected individuals	transient posttreatment interval-dependent increase in viral load was found. At baseline heavier egg load was associated with higher virus load. At 6 months' follow-up, there was a mean decrease of -0.36 log ₁₀ in HIV load among 13 successfully treated participants.
Elliot et al. [60]	2003	Uganda	East Africa	Prospective	68	Helminth-infected and uninfected HIV-1 positive, ART-naive individuals	There was increased expression of HIV coreceptor molecules CCR5 and CXCR4 on cells of <i>Schistosoma</i> -infected adults.
Secor et al. [22]	2003	Kenya	East Africa	Prospective		<i>Schistosoma</i> -infected HIV-1-positive and negative individuals	Increased expression of HIV coreceptor molecules CCR5 and CXCR4 on cells of <i>Schistosoma</i> -infected adults.
Gallagher et al. [61]	2005	Kenya	East Africa	Retrospective cohort	936	Helminth and/or malaria-infected HIV-positive and HIV-negative pregnant women	Helminth-infected mothers had in increased risk for MTCT of HIV compared to uninfected mothers, which correlated with cord blood lymphocytes production of interleukin-5/interleukin-13 in response to helminth antigens.
Kallestrup et al. [62]	2005	Zimbabwe	Southern Africa	Prospective cohort	287	Schistosomiasis in individuals with or without HIV-1 infection	Early treatment of schistosomiasis was associated with a significant increase in CD4 counts, and

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
Modjarrad et al. [63]	2005	Zambia	Southern Africa	Prospective	428	Helminth-infected and uninfected HIV-1 asymptomatic individuals	arrested increase in viral load, while there was an increase in HIV RNA load in the delayed-treatment group. No significant association between treatment of helminths and reduction of viral load was found
Hosseini-pour et al. [64]	2007	Malawi	Southern Africa	Prospective	389	Helminths in HIV-uninfected and HIV-infected individuals	Neither helminth parasitic infection nor treatment thereof had an impact on HIV viral load.
Nielsen et al. [65]	2007	Tanzania	East Africa	RCT	27	Filarial parasite-infected and uninfected HIV-infected individuals	A significant decrease in HIV load (54%) and an insignificant increase in CD4% were observed in the HIV-positive individuals with filarial co-infection at 12 weeks after treatment.
Zinyama-Gutsire et al. [66]	2009	Zimbabwe	Southern Africa	Prospective cohort	379	Schistosomiasis infection and HIV-1 co-infection	<i>S. haematobium</i> - and <i>S. mansoni</i> -infected participants had significantly higher MBL levels than uninfected participants. All MBL2 variants were not associated with HIV-1 infection but promoter variants LY and LL were significantly associated with <i>S. haematobium</i> infection.
Babatunde et al. [67]	2010	Nigeria	Western Africa	Cross-sectional	135	Intestinal parasites in HIV patients	Patients with CD4+ count <200/ μ l had more coccidian parasites in their

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
Walson et al. [68]	2010	Kenya	East Africa	RTC	1551	Helminth co-infection in HIV-1-infected adults	stool and also had higher prevalence of intestinal polyparasitism ranging from 2 to 4 different species per stool sample. Treatment of <i>A. lumbricoides</i> with albendazole in HIV-1coinfected adults resulted in significantly increased CD4 cell counts during 3-month follow-up.
Akinbo et al. [69]	2011	Nigeria	West Africa	Serial sampling method	2000	Intestinal parasites in HIV-infected patients	Anaemia was associated with CD4 count while <i>Cryptosporidium</i> species, <i>Ascaris lumbricoides</i> , hookworm, and <i>Taenia</i> species were the intestinal parasitic agents associated with anemia.
Jourdan et al. [70]	2011	Malawi	Southern Africa		89	Women with <i>S. haematobium</i>	<i>S. haematobium</i> may significantly increase the density of HIV target cells (CD4+ T lymphocytes and macrophages) in the female genitals, creating a beneficial setting for HIV transmission
Mkhize-Kwitshana et al. [71]	2011	South Africa	Southern Africa	Cross-sectional	62	Helminth and HIV singly infected, dual-infected and uninfected individuals	People with both helminth egg excretion and high <i>Ascaris</i> -IgE levels had dysregulated immune cells, eosinophilia, higher viral loads with more immune activation (HLADR, CCR-5 and

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
							CD38 upregulated). A modified Th2 helminth response in individuals with egg positive stools and low Ascaris IgE showed a better HIV related immune profile.
Idindili [72]	2012	Tanzania	Eastern Africa	Longitudinal descriptive	421	Parasitic infections in HIV-infected patients	Patients coinfecting with helminths and HIV had higher HIV p24, and parasite-infected patients had lower CD4 cell counts than parasite free patients, but this was not statistically significant. Multiple infection was associated with CD4+ T cells <200/μl compared to one parasite coinfection.
Walson et al. [73]	2012	Kenya	East Africa	RCT	948	Helminth and helminth-coinfecting adults	There was no evidence of the effect of empiric deworming in the delaying of HIV disease progression in adults with HIV
Webb et al. [74]	2012	Uganda	East Africa	RCT	264	Helminths in HIV-infected pregnant women	Hookworm and Trichuris infections were associated with higher mean viral load at enrolment, and there $p = 0.05$ was some evidence that albendazole reduced viral load at 6 weeks posttreatment ($p = 0.05$).
Efraim et al. [75]	2013	Tanzania	East Africa	Retrospective cohort study	351	Schistosome infection in HIV-infected patients' responses on ART	Odds of developing immunological failure were four times greater in patients with

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
							schistosome coinfection. Schistosome-infected patients also had significantly lower CD4 count increases on ART than schistosome-uninfected patients.
Mulu et al. [76]	2013	Ethiopia	Eastern Africa		220	Helminthic-infected and uninfected HIV-1 patients	Twelve weeks after antihelminthic treatment, helminth infestations and their treatment had no significant effect on CD4+ T-cell counts. However, helminth-infested individuals had a higher level of CD8 (+) T cells at baseline, which was significantly reduced at 12 weeks after antihelminthic treatment.
Gebreegiabiher et al. [77]	2014	Ethiopia	East Africa	Cross-sectional	85	Helminth-HIV-co-infected pregnant women	There was no significant difference in IL-4 response of CBMCs between helminth negative and positive participants. Maternal helminth infection had a significant association with the IFN- γ response of CBMCs, total IgE, and cross-placental transfer of TB-specific IgG.
Mkhize-Kwitshana et al. [78]	2014	South Africa	Southern Africa	Cross-sectional	62	Helminth and HIV singly infected, dually infected and uninfected individuals	Dual HIV/helminth infection with egg excretion and/or high Ascaris IgE phenotype may be linked with poor proliferative capacity

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
Lankowski et al. [79]	2014	Uganda	East Africa	Retrospective observational	5379	Helminth in HIV-infected adults on ART	and deleterious cytokine profile with regards to HIV control. Empiric deworming of HIV-infected individuals on ART conferred no significant generalized benefit on subsequent CD4 count recovery. A significant association was observed exclusively in females and during the initial year on ART
Chachage et al. [80]	2014	Tanzania	Eastern Africa	Prospective cohort	386	Helminth coinfection with HIV in adults	Trichuris, Ascaris, and <i>S. mansoni</i> infections correlate with increased expression of T-cell activation markers with relatively little effect of helminth treatment compared to helminth-negative controls. Contrary, hookworm infection was associated with slightly decreased frequency of HLA-DR expressing.
Kleppa et al. [16]	2014	South Africa	Southern Africa	Prospective cohort	853	Female genital schistosomiasis and HIV target cell density and expression of the HIV co-receptor CCR5 in blood and cervical cytobrush samples	Increased expression of CD14+ monocytes and CCR4+ CD4 cells among schistosomiasis-infected (FGS+) individuals (FGS+) than from FGS-women (4.7% vs. 1.5%, $p=0.018$) in blood and genital samples which decreased significantly in both

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
Noormahomed et al. [81]	2014	Mozambique	Southern Africa	Cross-sectional	601	Cysticercosis, Schistosomiasis, Toxocariasis, and Echinococcosis in HIV patients	compartments after anti-schistosomal treatment ($p=0.043$). Patients with CD4+ count between 200 and 500/ μl had a higher seroprevalence to all helminths than those with less than 200/ μl cells and those with more than 500 cells/ μl .
Abossie and Petros [82]	2015	Ethiopia	East Africa		97	Helminth/HIV coinfection	CD4+ T-cell count in the <i>Ascaris lumbricoides</i> /HIV-coinfected was significantly higher and after 15 weeks and 6 months postantihelminthics treatment, respectively. Also, after antihelminthic therapy, the CD4+ T-cell count significantly increased in all treated helminth infections.
Kleppa et al. [83]	2015	South Africa	Southern Africa	Cross-sectional	792	<i>S. haematobium</i> infection and in HIV infected	Urogenital schistosomiasis does not influence the number of circulating CD4 cells.
Mengist et al. [84]	2015	Ethiopia	East Africa	Cross-sectional	550	Intestinal parasitosis in HAART initiated and HAART naive pediatric HIV patients	Hook worm and Taenia species were IPs associated with CD4+ T-cell counts <350 cells/ μl in HAART naive patients
Mulu et al. [85]	2015	Ethiopia	East Africa	Prospective cohort	130	Helminth-infected and uninfected HIV-infected individuals	Helminths showed a high level of serum IgE compared to HIV patients without helminths

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcomes
							coinfection. A significant decline in serum IgE level was observed 12 weeks after deworming and ART of symptomatic HIV-infected patients with and helminths coinfection. There was no significant decrease in serum IgE level among asymptomatic HIV-infected individuals.

Table 3. Helminth HIV coinfection studies included in the systematic literature review.

As indicated in the summary results, the overall picture indicates that while some studies reported no impact (on HIV infection) of deworming on helminth-infected individuals, the majority actually showed a beneficial effect. Other studies that analyzed different aspects such as immune activation, proliferative capacity, inflammatory markers, and expression of coreceptor molecules indicated a negative impact of helminth infection on HIV disease markers. Indeed a sizeable proportion of these also failed to show any negative interaction between helminths and HIV.

3.2. Helminth TB coinfection immunological outcome

The 16 helminth and TB coinfection studies investigated (1) the general immune responses of helminthiasis with mycobacterial coinfections and (2) effect of intestinal helminths on the immune response to naturally immunized or BCG-vaccinated humans, and (3) effect of antituberculosis chemotherapy on helminth-infected TB patients with and without HIV (Table 4). Generally, immune response studies of helminth- and mycobacterial-coinfected individuals revealed that co-infection with helminths appear to dampen the proinflammatory cytokine response while promoting a regulatory/Th2-mediated immune response [90]. Studies that analyzed the interaction of helminth infection and response to *M.tb* antigen, purified protein derivative (PPD), also showed a T-cell-mediated immune response skewed toward a Th2 type response against helminth and PPD antigens. Similarly, BCG-vaccinated individuals infected with various helminths species also exhibited attenuated T-cell and skin responses with Malhotra et al. reporting a 26-fold magnitude difference in IFN-gamma production in BCG-vaccinated infants who were not exposed versus those who were prenatally exposed to filariae and schistosomes [96, 93]. Thus, chronic worm infection was noted to reduce the immunogenicity of BCG in humans [86]. In their study, Adams et al. reported that TB patients were observed to have a higher total IgE and *Ascaris*-specific IgE (in comparison to controls), which declined significantly after treatment [87]. IgE levels were

reported to be significantly higher in TB patients coinfecting with HIV and helminths compared to those without helminth coinfection with anti-TB chemotherapy significantly reducing the serum IgE levels in HIV seronegative TB patients. Several other studies also showed that the immune response in helminth-TB-coinfecting individuals was characterized by elevated IgE levels [87, 91]. Elliott et al. also reported a significant association between eosinophilia, elevated IgE levels, and asymptomatic infection which improved with anti-TB treatment [89]. Asymptomatic helminth infection was also observed to be associated with increased regulatory T-cell and Th2 type immune responses by the same authors [92].

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcome
Malhotra et al. [86]	1999	Kenya	East Africa	Cross-sectional	33	Schistosoma filariasis-infected mothers and BCG-vaccinated infants and 2–10 year-olds	T-cell IFN- γ production evaluated 10–14 months after BCG vaccination was 26-fold higher for infants who were not sensitized to filariae or schistosomes <i>in utero</i> relative to subjects who experienced prenatal sensitization.
Adams et al. [87]	1999	South Africa	Southern Africa		740		TB patients had higher total IgE and Ascaris-specific IgE than controls before TB treatment and declined after treatment. Tuberculin induration correlated inversely with IgE in patients but not in controls.
Stewart et al. [88]	1999	Cameroon	West Africa		50	Helminth and mycobacterial infections in 5–16 year olds	There was a MF density-related downregulation of cellular responsiveness and age-related skewing toward type 2 which was paralleled in response to both the helminth antigen and PPD.
Elias et al. [53]	2001	Ethiopia	East Africa	Prospective cohort	240	Intestinal helminths in naturally immunized or BCG-vaccinated College students	BCG-vaccinated individuals infected with various helminths had attenuated T-cell and skin test responses.
Eliot et al. [89]	2003	Uganda	East Africa	Prospective follow-up	625	Helminth and TB in adult	High rates of subsequent progression to active TB were associated with eosinophil counts $\geq 0.4 \times 10^9/L$ at enrolment. (Eosinophilia associated

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcome
							with schistosomiasis in this study).
Kassu et al. [90]	2003	Ethiopia	East Africa	Long-term cohort	64	Parasitic infection in HIV-1-infected and uninfected adult	Incidental intestinal parasitic infections resulted in a significant increase in memory CD4+ T-cell numbers both in HIV-negative and HIV-positive subjects. There was also a significant increase in the percentage of CD8+ HLA-DR+ T cells ($p < 0.05$) in HIV-positive subjects coinfecting with parasites.
Kassu et al. [91]	2004	Ethiopia	East Africa	Consecutive sampling	241	Tuberculosis patients with or without intestinal helminthic infection and/or HIV infection	IgE level was significantly higher in patients coinfecting with intestinal helminthes and HIV compared to those infected with helminthes or without coinfection. Antituberculosis chemotherapy significantly reduced serum IgE levels in HIV seronegative tuberculosis patients.
Elias et al. [92]	2006	Ethiopia	East Africa	Case control	Cases ($n = 230$) Control patients ($n = 510$)	Helminth infections in active tuberculosis patients	The odds of being a TB patient increased with the number of helminth species per person: in individuals with monoinfection it was 4.3 (95% CI 2.8–6.8); in people infected with two species was 4.7 (95% CI 2.5–8.7), and in patients infected with three or more helminths was 12.2 (3.9–52.6).
Elias et al. [93]	2008	Ethiopia	East Africa		280	Volunteers with prior mycobacterial infection and asymptomatic helminths infection	Chronic worm infection reduces the immunogenicity of BCG in humans and this was associated with increased TGF-beta production but not with enhanced Th2 immune response.
Webb et al. [94]	2011	Uganda	East Africa	RCT	Women ($n =$	Helminth- and HIV-infected women and	Neither albendazole nor praziquantel treatments

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcome
					2356) Infants (<i>n</i> = 1115)	BCG-vaccinated infants	affected infant response to BCG, tetanus, or measles immunization.
Abate et al. [94]	2012	Ethiopia	East Africa	Consecutive sampling	295	Helminth-infected TB patients with and without HIV	Eosinophilia and elevated IgE levels were significantly associated with asymptomatic helminth infection. During TB treatment, the worm infection rate of HIV+/TB patients declined from 31% (10/32) at week 0 to 9% (3/32) at week 2 of TB treatment, whereas HIV -/TB patients showed no change from baseline to week 2, 29% (13/45) vs. 22.2% (10/45).
van Soelen et al. [57]	2012	South Africa	Southern Africa	Cross-sectional	271	<i>A. lumbricoides</i> and <i>M.tb</i> in children	There was an inverse association between <i>Ascaris</i> IgE status and a positive TST (OR = 0.6, <i>p</i> = 0.08), when adjusted for age, and <i>M.tb</i> contact score. The effect of being <i>Ascaris</i> IgE positive significantly reduced the odds of being TST positive amongst younger children while this effect weakened with increasing age.
Wassie et al. [95]	2013	Ethiopia	East Africa	Cross-sectional	245	Healthy school children aged from 12 to 20 years	A subset of children who had a positive QuantiFERON™ result but a negative tuberculin skin test.
Biraro et al. [96]	2014	Uganda	East Africa	Prospective cohort	291?	Helminth-coinfected and newly infected TB patients	Household contacts with LTBI had elevated cytokine responses to tuberculosis antigens but coinfections had little effect on cytokine responses.
Gebregeziabihe et al. [77]	2014	Ethiopia	East Africa	Cross-sectional	85	Helminth infections in pregnant women and immunity after infection with TB and neonatal	The IFN- γ response of CBMCs to ESAT-6/CFP-10 cocktail was significantly lower in helminth-positive than helminth-negative

Authors	Year	Country	Subregion	Study design	Sample size	Coinfections and study population	Immunological outcome
Abate et al. [97]	2015	Ethiopia	East Africa	Consecutive sampling	121	Helminth-infected TB patients	immune function and immunity to TB participants. Maternal helminth infection had a significant negative association with the IFN- γ response of CBMCs, total IgE, and cross placental transfer of TB specific IgG. Asymptomatic helminth infection is associated with increased regulatory T-cell and Th2- type responses and a lower rate of sputum smear positivity

Table 4. Helminth TB coinfection studies included in the systematic literature review.

A clinical trial by Webb et al. reported that neither treatment with albendazole nor praziquatel affected infant BCG immune responses [94]. Another interesting finding was the increased odds of being a TB patient for individuals who had more than one species of helminths reported by Elias et al. [92]. In newly infected/latently infected TB household contacts, cytokine responses to TB antigens were higher compared to coinfecting individuals [96]. Furthermore, several studies showed that chronic worm infection reduces the immunogenicity of BCG in humans [96, 98]. Improved mycobacterial antigen-specific cellular responses in BCG-vaccinated persons were observed after treatment of helminthes.

4. Discussion

The extent of convergent distribution of tuberculosis, HIV, and helminth infection in sub-Saharan Africa is evident in the selected literature in this review. Likewise, the contrasting immune responses elicited by the extracellular helminthic parasites and intracellular HIV and *M.tb* infections provide an immunobiologically plausible support for the antagonistic interaction in coinfecting hosts. The review extracted 47 studies that investigated the immunological interactions between helminthiasis and HIV and/or mycobacterium tuberculosis. The studies were spread across the Western, Southern, and East Africa, the latter having the most relevant articles (31 of 46) and the Western Africa the least (three articles). The scarcity of such studies in West Africa may be due to that fact that this region, together with East Africa, has the lowest HIV/AIDS burden compared to the worst affected Southern region. Interestingly though, the East African region has a leading number of such investigations.

4.1. Immune response to helminths and HIV coinfection

Immunological consequences of coinfection with HIV and helminth infections were also investigated. Different aspects of immunological outcomes were measured, and some studies

did not find evidence of a negative interaction, others indicated a deleterious effect of helminthiasis. The hallmark of helminth infections—(i) cellular changes, (ii) immune activation, (iii) a Th2 biased immune profile, and (iv) increased regulatory cells associated with anergy were addressed by the studies reviewed as well as other immune-related aspects of HIV such as viral replication, increased susceptibility to HIV, and increased risk of transmission. Cellular changes induced by helminthiasis include reduction of the central adaptive immune response subset—the CD4⁺ cells. Helminth infections have been shown to be associated with decreased frequencies of these cells [21].

It is generally accepted that a CD4 count less than 200 cells/ μ l predisposes HIV-infected persons to opportunistic infections. Several investigations in this review demonstrated an association between reduction of these cells and helminthiasis [67, 81, 84]. In their study, Akinbo et al. [69] showed that a CD4 count of less than 200 cells/ μ l resulted in a significantly higher prevalence of intestinal parasitic infections and Idindili et al. [72] reported that multiple infection was associated with CD4⁺ T cells <200/ μ l compared to one parasite coinfection. In addition, the prevalence of anemia in HIV-infected patients is high, while low CD4 count is a significant risk factor of acquiring anemia. Some parasite species also induce anemia, such as the *Trichuris* which burrow and suck blood from the small intestine of infected individuals. Akinbo et al. [69] further demonstrated that *A. lumbricoides*, hookworm, and *Taenia* species in HIV-infected individuals are parasitic agents associated with anemia. These human studies lend support to the negative association between immune modulation by helminthiasis and HIV infection. However, one study in this review failed to show this association, where urogenital schistosomiasis was not found to influence the number of circulating CD4⁺ cells [83].

Another change in the distribution of peripheral blood cells during helminthiasis is marked increase in eosinophils, the key effector cells which play a specialized role in immunity to helminths. These cells together with IgE are produced by CD4⁺ Th2 cells, indicating a predominance of these cells during helminthiasis. In the current review, the significant decline of serum IgE level 12 weeks after deworming of both symptomatic and asymptomatic patients [85] confirms the Th2 immune response induced by helminths [66]. As indicated earlier, increased numbers of activated eosinophils that express CD4 molecules provide an extra supply of HIV target cells at convenient sites for HIV infection during sexual encounter in homosexual (rectal) or heterosexual (genital) mucosa of helminth-infected sexual partners. Furthermore, the helminth-induced Th2 polarized immune response spills over to bystander cells, influences the response to other nonparasite antigens, and skews them toward a Th2 phenotype [19]. In humans, ascariasis was associated with impaired Th1 responses to vibrio cholera [99], which was later improved by deworming—treatment of *Ascaris lumbricoides* resulted in enhanced antivibrio antibody production [100]. Likewise, significantly impaired proliferative, T helper 1 (IL-2 and interferon γ) tetanus responses have been documented in tetanus toxoid-vaccinated, onchocerciasis-infected children [101]. Gopinath et al. attributed all these phenomena to a Th2-biased immune profile induced by helminths.

Thirty-two cases of new HIV cases were recorded in a 5-year cohort study involving 1055 individuals who were initially HIV negative, with a confirmed prior filarial infection [102]. This study demonstrated for the first time in humans, a significantly increased risk of HIV

acquisition among lymphatic filariasis-infected individuals, lending strong support to the *in vitro* study in this review that showed increased HIV susceptibility of PBMCs obtained from filarial-infected individuals [58]. In another study, PBMCs from filarial-infected individuals were also shown to be more susceptible to HIV infection [103]. In this study, viral replication as measured by reverse transcriptase (RT) values were higher but not statistically significant among the infected compared to the uninfected group and viral replication was significantly reduced 1–2 years after treatment of filariasis. These *in vitro* findings, together with the four studies extracted in the current review that reported increased expression of HIV coreceptors among filarial- or schistosoma-infected individuals [16, 22, 60, 71], provide strong suggestive evidence of increasing susceptibility to HIV by helminthiasis. These exemplify suggestive evidence of a negative immune regulation consequence of helminthiasis on HIV control.

Chronic immune activation resulting from prolonged exposure to helminths is widely described during helminthiasis [2, 19]. In this review two studies reported highly activated immune profiles among HIV- and helminth-coinfected adults [71, 80]. Immune activation was shown to correlate better with HIV disease progression and CD4+ cell decline [30]. Indeed, treatment of parasitic infections showed a tendency to reduce the activation suggesting that, together with other community-based intervention strategies, such treatment could be used to downregulate immune activation and hence protect the host from being easily infected by HIV. In a practical illustration of the deleterious effects of immune activation was the study by Rizardi et al. [104] where simultaneous initiation of antiretroviral therapy (ART) and administration of cyclosporin-A (immunosuppressant) improved CD4 counts restitution in HIV-infected individuals compared to their ART-only counterparts [105]. This finding strongly demonstrated the negative relationship between immune activation and HIV pathogenesis, and implications thereof for helminthiasis-induced chronic immune activation on HIV aggravation.

In this review, helminths have been shown to modulate other aspects of the immune system with potential negative consequences to other microbes. Mannose-binding lectin, part of the innate mechanism required for nonspecific pathogen binding of foreign antigens, was increased among schistosoma-infected individuals [66], which could impair this pathway of immune response for other pathogens. In addition, other deleterious effects of helminthiasis, such as increased risks of mother-to-child transmission of HIV [61] and immunological failure on ART [75], as well as increased levels of HIV p24 (indicative of high virus load) [73], were reported in studies extracted in the review. Decreased proliferative capacity of lymphocytes and reduced type 1 cytokines among HIV-helminth coinfecting individuals [78] were also reported.

One of the major attempts at addressing the possible deleterious effect of helminthiasis on HIV infection is to determine whether deworming would reverse the immune dysregulation induced by helminths among HIV-infected individuals. Like in many reported studies, the results remain controversial. Of the 15 such studies, seven reported no impact of deworming coinfecting individuals, one even reported a transient increase in viral load after anthelmintic treatment [34]. On the other hand, eight of the 15 studies reported a positive effect of deworming coinfecting individuals, some reported an arrest or reduction of viral load after antihel-

minthic treatment or an increase in CD4+ counts. Kleppa et al. [16] reported a significant reduction of CD4+ CCR5 expressing T cells and monocytes in blood and vaginal samples after antischistosomal treatment among young women. Mulu et al. [85], on the other hand, reported a reduction of IgE levels among helminth-infected individuals after deworming, supporting the concept that deworming positively impacts HIV/AIDS diseases progression.

In one study in Kenya, Walson et al. reported that albendazole-treatment of *Ascaris lumbricoides* resulted in a significant increase in CD4+ counts in HIV-helminth-coinfected adults [68]. Two years later the authors reported no benefit of empiric deworming of HIV coinfecting individuals in the same country [73]. Lawonski et al. [79] also reported no general benefit of deworming helminth-HIV-coinfected individuals. Nonetheless, the latest Cochrane review (last updated on the 29 September 2015) which included eight trials that enrolled 1612 participants concluded that there is low quality evidence that treating helminth infections in HIV-infected adults may have small short-term benefits on HIV disease progression and that deworming does not have serious adverse effects [105]. It is important to note that conclusive results of empiric deworming of helminth- and HIV/*M.tb*-coinfecting individuals are required. This approach would be more cost-effective compared to targeted deworming of confirmed helminth-infected individuals. The diagnosis and confirmation of helminthiasis is expensive as it requires laboratory equipment such as microscopes, culture systems for some species such as for the strongyloides larva, ELISA readers and washers for serological confirmation in order to increase the low sensitivity of microscopy, as well as a well-trained microscopist. Empiric deworming will obviate the need for such expensive resources, particularly in poorly resourced settings where these three infections frequently coexist.

4.2. Immune response to helminth and TB coinfection

Among 16 studies that analyzed immunological interactions between helminths and *M.tb* coinfection there was evidence for a reduction in type 1 dependent cellular responses as shown by decreased IFN γ production by T cells [77, 86] or low tuberculin skin test responses [57]. A study by Guadalupe et al. [106] showed evidence of increased frequencies of IL-4 and IFN γ CD4+ responses to *Ascaris lumbricoides* antigen stimulation in the cord blood of neonates born of infected mothers. Frequencies of IFN- γ and IL-4 expressing CD4+ T cells in newborns born of infected mothers were attenuated compared to those of noninfected mothers [106]. The authors assert that the data provide evidence of *in utero* sensitization to *Ascaris lumbricoides*, and raise the possibility that the immunological effects of infection start in the fetus. In an earlier study, Malhotra et al. also reported related findings where they observed infants who had experienced prenatal sensitization [86]. In such infants, the immune response to BCG vaccination was shown to be biased against the Th1 response in those infants who were exposed to filariae or schistosomes compared to those who were not exposed and that this immune status persists beyond infancy. These findings indicate a reduction of BCG immunogenicity or impaired TST responses by chronic helminth infection, which were further corroborated by Gebreegziabiher et al. [77]. Thus, helminth infections have significant practical implications and pose a significant threat to the effectiveness of the BCG vaccine, particularly in areas with a high burden of helminth and TB infections.

In another study, evidence of elevated Th2 responses, a classic feature of helminthiasis was reported either through high total and *Ascaris*-specific IgE which declined after TB treatment [87, 97] or IgE and eosinophilia, the latter associated with high rates of progression to active TB disease [89]. In addition, helminth-induced upregulation of regulatory cells and Th2 responses were also associated with lower rate of sputum positivity [97]. These findings indicate that helminths may have adverse consequences for TB disease and diagnostic efforts, directly impacting on transmission control of TB disease. Yet another study reported increased odds of having TB disease among helminth-infected individuals [92]. However, few studies did not find such an interaction, for example, albendazole treatment did not have any effect on BCG immune response in infants while Biraro and coworkers reported that helminth-latent TB coinfection had no effect on cytokine responses to TB antigens [94, 96]. In one Ethiopian study the immune responses to quantiferon and TST antigens in healthy children from an endemic setting were found to be discordant [95].

In the main, these studies suggest a negative relationship between helminth infection and TB. By and large, most of the studies showed that coinfection with helminth infection dampens the immune response to both latent and active disease. This effect of a suppressed characteristic antitubercular Th 1 immune response was observed regardless of age as the studies reported corroborative findings for prenatally/*in utero* sensitized infants, young children, adolescents, and adults alike. These findings have important implications in the prevention (vaccination) and control of TB in helminth-TB endemic regions such as much of the developing world. With helminthiasis being a silent disease and so very often asymptomatic, the results we present in this study suggest that important policy and public health measures must be adopted in order to bring under control or eliminate the two infections. An important intervention would be comprehensive medical packages for suspected TB-helminth infections particularly in endemic areas. In areas of the world with a high burden of HIV and TB, the WHO policy now recommends screening for HIV for all TB patients and vice versa. In this same way our results suggests that investigating for asymptomatic helminth infections in any suspected TB cases may have important implications for the control of TB in coinfecting individuals.

We however note that the results presented here were mainly derived from observational and cross-sectional studies with very few clinical studies. Although a randomized clinical trial could potentially be useful in providing more definitive evidence the ethical and cost implications of conducting such a study are difficult to justify. Prospective studies could also be useful to determine whether the immune system rebounds after the treatment of both TB and helminth infections. Although a few such studies were reported in the studies we examined, the study design and research questions did not clearly address this question, hence the findings were not very definitive.

5. Conclusion

The reviewed studies, like all others in this field have provided results in support and against the hypothesis that chronic infection with helminths result in poor immunological and disease

outcomes in coinfecting hosts. However, there is evidence of immune alteration such as reduced type 1 responses and increased Th2 and regulatory responses induced by helminth infection in humans. Evidence for possible vaccine inefficiency, increased risks of mother-to-child transmission, and unfavorable treatment outcomes shown in some of these studies confirm the likelihood of a serious public health implication for both major infectious organisms, HIV, and *M.tb*. In the face of the huge financial investments needed for vaccine development, these efforts must be accompanied by insightful consideration of the fact that those vaccines which ultimately reach the market will be rolled out in areas where there is a high likelihood of widespread immune regulation. The fact that TB and helminths are diseases of poverty, contrasts the large financial investment demand for vaccine and drug development with a discouraging likelihood of a low return. Other mechanisms are therefore required to counter widespread immune activation and regulation among the poor individuals exposed to coinfections, as shown in this review. More studies particularly in Southern Africa are needed to increase the much sought evidence of the impact of deworming among HIV-infected individuals as this seems the most feasible, cost-effective intervention with little or no serious adverse effects. Lastly, with expansion of ART and increased access to HIV treatment, the effects of helminths on antiretroviral treatment efficacy also need serious consideration, in light of the suggestive evidence of possible immunologic failure due to helminth coinfection.

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