



## Helminth-HIV co-infection and malnutrition impact on immunity in Africa: dearth of empirical evidence

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### ABSTRACT

Helminthiasis is frequently co-endemic with HIV/AIDS in developing countries and the co-infection induces many consequences of health that can be aggravated by the nutritional status. The relationship between malnutrition and infection is complex, especially in immune deficiency. Given this intricate relationship between malnutrition, HIV epidemic and helminth infection in sub-Saharan Africa, there is a need to understand the dynamics, impact to general health and the burden in the region. This paper provide in a nutshell a systematic review and a quantitative summary of the work focusing on this relationship. A search was conducted to identify studies on malnutrition and HIV-helminth co-infection impact on immunity in Africa, using the search terms “malnutrition” and “HIV” and “HIV-helminth co-infection” and “Africa” or “malnutrition” and “HIV” or “HIV-helminth” limited to Africa. The search was also limited to human studies from the databases available on PubMed, and Google scholar. The database was searched with language, region and year restrictions (only articles in English and French and all publications from 1999 to 2013). The results showed that no study has been conducted on the intersections between malnutrition and HIV/helminth co-infection. So no article met criteria for potential inclusion and these focused on nutrition and HIV-helminth co-infection impact on immunity in Africa. There is no study conducted in Africa that investigated the immune aspect and the relationship between nutrition and HIV-helminth co-infection. The results of this review suggest insufficient data to determine whether malnutrition and HIV-helminth co-infection impact on immunity. There is strong recommendation to conduct such kind of studies in Africa where malnutrition and HIV-helminth co-infection are common.

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**Keywords:** Helminth, HIV, co-infection, malnutrition, Africa.

### INTRODUCTION

Sub-Saharan Africa is endemic to malnutrition, HIV epidemic and helminth

infection (Karp and Auwaerter, 2007; Kalofonos, 2010). The geographic overlap has a significant impact on immune system

competency and helminth-HIV disease progression (Borkow and Bentwich, 2004; Moreau and Chauvin, 2010). Malnutrition may be indicated by deficiency of either of the two nutritional categories, macronutrients (carbohydrates, proteins), or micronutrients (vitamins, minerals and trace elements). In general, a sick person's nutritional status is impacted by malabsorption and loss of appetite resulting in loss of nutrients and further damage to the defense mechanisms or immunodeficiency (Müller et al., 2003). This highlights the pivotal role of nutrition on immune system competency during an infection. Given the intersections between malnutrition, HIV epidemic and helminth infection in sub-Saharan Africa there has been surprisingly limited and inconsistent epidemiological and immunological evidence of important interactive effects (Borkow and Bentwich, 2004).

Intestinal helminth infections result in immune responses that involve cytokines produced by Th2 cells, with IgE production, eosinophilia, and mastocytosis (Kalinkovich et al., 1998). Malnutrition resulting from HIV infection include diminished food intake due to loss of appetite or oral thrush, nutrient malabsorption due to accompanying diarrhea which may result from opportunistic bacterial, viral or parasitic gastrointestinal infections (Katona and Katona-Apte, 2008; Duggal et al., 2012). Reduced appetite, which could be due to difficulty in ingesting food as a result of common opportunistic infections in HIV-infected people, fever or depression, and increased expression of cytokines such as tumor necrosis factor which decreases appetite. Consequently, poor nutritional status may hasten progression to AIDS-related illnesses, undermine adherence and response to antiretroviral therapy and exacerbate socioeconomic impacts of the virus (Raiten, 2011).

## **STUDIES ON IMPACT OF INTESTINAL PARASITIC INFECTION ON IMMUNITY**

Previously studies on impact of intestinal parasitic infections focused on children owing to the well-established impact on cognitive and physical development, their increased exposure, poor hygienic habits and under-developed immune system. However, from the nineties onwards, evidence of the impact of helminthes on TB, HIV/AIDS severity and tuberculosis began to emerge. This necessitated a shift in focus as far as parasitic infections and their impact on these high priority diseases in adults. This has caused a need for assessment of nutritional status in adult. In developing countries helminthiasis is frequently co-endemic with HIV/AIDS (Borkow and Bentwich, 2006; Hotez et al., 2006). Indeed, it is not uncommon for an individual to be co-infected with HIV and one or more parasitic worms (Kjetland et al., 2006). Such co-infections have synergistic effects, such as increased transmission of HIV, and/or may also cause an exacerbated progression of the diseases (Hotez et al., 2006). The relationship of malnutrition, HIV epidemic and helminth infection in sub-Saharan Africa require detailed analysis to understand the epidemiological and immunological implications of the co-infection.

This paper therefore conducted a systematic literature review of published studies that assessed malnutrition and HIV-helminth co-infection impact on immunity in Africa. Such studies have not yet been overviewed or quantitatively summarized.

## **ANALYSIS OF THE MALNUTRITION AND HIV-HELMINTHS CO-INFECTION STUDIES IN AFRICA**

A search was conducted to identify studies on malnutrition and HIV-helminth co-infection impact on immunity in Africa, using the search terms “malnutrition” and “HIV” and “HIV-helminth co-infection” and

“Africa” or “malnutrition” and “HIV” or “HIV-helminth” limited to Africa. The search was also limited to human studies from the databases available on PubMed, Medline, and Google scholar. The database was searched with language, region and year restrictions (only articles in English and French and all publications from 1999 to 2013). Only studies comparing immunological and nutrition status among HIV-infected individuals with helminthes and HIV-uninfected individuals with helminthes were considered. Eligible study designs were randomized controlled trials (RCTs) or quasi-RCTs, controlled clinical trials, cohort, case-control, or cross-sectional studies. Our primary outcome was immune response either in terms of CD4 counts or percentage, or change in CD4 counts, cytokine profiles, proliferation responses, immune cell counts, lymphocyte phenotypes, cytokine RNA expression, and other immunological parameters.

#### **SPECTRUM OF STUDIES CONDUCTED IN AFRICA ON HELMINTHS-HIV CO-INFECTION AND MALNUTRITION**

Results showed that very few studies have been conducted on the intersections between malnutrition and HIV epidemic or between helminth and HIV or between malnutrition and helminth infection in sub-Saharan Africa. This review, critically analyzed the interaction between “malnutrition and HIV- helminthes co-infections as impacting on immunity in Africa”. Most studies were not conducted along the combined malnutrition, HIV and helminth co-infection cycle, tackling together the impact on immunity in Africa. Indeed, there is no study that focus on the immunity aspect of the three (the intersection between malnutrition, HIV epidemic and helminth co-infection on their impact on the immunity) in Africa. The initial search identified 19 studies and after screening the titles and abstracts only 3 articles remained of which full articles were obtained Out of the selected articles,

these focused on either malnutrition or helminthic or HIV co-infection and immunity as a single entity (Figure 1). There was no article that focused on the impact of nutrition and HIV-helminth co-infection on immunity in Africa.

#### **INFECTION, INFLAMMATION AND ANTI-OXIDANT NUTRIENTS**

Helminths infection (*Schistosoma mansoni*, *Schistosoma haematobium*, *Hookworms*, *Trichuris trichiura*, *Ascaris lumbricoides* etc.), are major cause of human morbidity in tropical countries, and causes liver disease by inducing granulomatous inflammation. Helminthiasis is an important risk factor involved in enhancement of no levels (Hassan, 2002); favouring formation of reactive oxygen species, including superoxide ions, hydrogen peroxide and hydroxyl radicals all of which may induce lipid peroxidation. Patients with helminthiasis have abnormal lipid peroxidation, resulted in attenuated redox capacity of antioxidant agents (Facundo et al., 2004).

The oxidative environment and the antioxidant capacity of the media are critical factors for in vitro propagation of helminths (Bender et al., 2002). Adult worms, in the case of schistosomes, which reside in the hepatic portal system, are exposed to reactive oxygen compounds through respiration and as a result of the host immune response. To minimize oxidative stress schistosomes must possess adequate mechanisms of detoxification. Major detoxification systems rely on reducing equivalents from the disulfide oxidoreductases glutathione and thioredoxin. Maintenance of adequate levels of these thiols in a reduced form is critical. *S. mansoni* possess an unusual thiol redox system centered on thioredoxin glutathione reductase. This enzyme represents an unusual fusion of a pyridine nucleotide disulfide oxidoreductase with a redox active glutaredoxin protein (Alger and Williams, 2002).

The oxidative processes occur at the site of inflammation and are involved in the damaging effects of helminthiasis and indicate that free radicals may be a major component of the disease. Cytokines like IL-4 and IL-10 play a protective role during helminthiasis by controlling the tight regulation of the generation of reactive oxygen and nitrogen intermediates in the liver (La Flamme et al., 2001).

Oxidative stress might contribute to helminthes-associated pathology in man (Pascal et al., 2000), and in mice, the livers had a marked increase in lipid peroxidation (Fallon et al., 2000). Eosinophil peroxidase and its substrate  $H_2O_2$  are released by inflammatory cells in the immediate vicinity of the parasite ova. *Schistosoma mansoni*, an intravascular parasite, lives in a hostile environment in close contact with host humoral and cellular cytotoxic factors. The parasite has evolved a number of immune evasion mechanisms, such as antioxidant enzymes. The expression of antioxidant enzymes is developmentally regulated, with the highest levels present in the adult worm, the stage least susceptible to immune elimination, and the lowest levels in the larval stages, the most susceptible to immune elimination (Lo-Verde et al., 2004). One mechanism that seems to aid the adult worm in evading immune killing is the expression of antioxidant enzymes to neutralize the effects of reactive oxygen and nitrogen species (Cook et al., 2004). Helminthes infection may modify the inflammatory response to gastric *H. pylori* infection manifested by the reduction of oxyradical-induced DNA-damage, apoptosis and cellular proliferation activity, and the increase in antioxidant production (Elshal et al., 2004). The inhibition of GST and, to a lesser extent also SOD enzymes, could lead to increased schistosome susceptibility to oxidant attacks and might be linked with the antischistosomal action of artemether (Xiao et al., 2002).

Defense against oxidative damage can be mediated through glutathione and/or thioredoxin utilising systems. Thioredoxin participates in processes vital to the parasite and may facilitate the passage and survival of eggs across inflamed host tissues (Alger et al., 2002). The limiting step in the parasite's detoxification process appears to be at the level of hydrogen peroxide neutralization. Oxidative processes occur at the site of granulomatous inflammation and on the other hand the antioxidant capacity of the liver decreased, leading to the generation of lipid peroxides. The resulting imbalance between pro- and anti-oxidant processes may play a central role in the pathology associated with schistosomiasis (Gharib et al., 1999). Better understanding of antioxidant status as well as biomarkers of oxidative stress, will highlights how the parasite invasion is manifested, and consequently an appropriate mechanism for treatment can be identified.

Helminths and HIV co-infection provide a complex oxidative and inflammatory condition in which helminths are provided with a conducive environment to proliferate while the infected cells undergo proliferation thereby provide an opportunity for viral increase. Anti-oxidative nutritional supplements may be vital to withhold otherwise a very explosive and inflammatory condition. There is a dearth of studies in this co-infection status and more insights are required to understand the contribution of nutritional intervention in reducing immune evocation during helminths – HIV co-infection likely to reduce HIV transmissibility that depends on inflammatory condition and HIV viral load.

## **OXIDATIVE STRESS, IMMUNITY AND HIV REPLICATION**

Patients infected with the human immunodeficiency virus (HIV) are under chronic oxidative stress. So oxidative stress may contribute to several aspects of HIV disease pathogenesis, including viral

replication, inflammatory response, and decreased immune cell proliferation, loss of immune function, apoptosis, chronic weight loss, and increased sensitivity to drug toxicities. Glutathione may play a role in these processes, and thus, agents that replete glutathione may offer a promising treatment for HIV-infected patients (Pace and Leaf, 1995).

Highly active antiretroviral therapy (HAART) oxidative stress increases in endothelial cells and induces mononuclear cell recruitment, which may eventually precipitate the cardiovascular diseases on HIV-1+ individuals on antiretroviral therapy (Debasis et al., 2004).

Micronutrient deficiencies affect the progression to acquired immunodeficiency syndrome (AIDS) and death. So, micronutrient deficiencies may exacerbate the oxidative stress induced by HIV. In addition, infection and its evolution likely lead to an increased requirement for nutritional micronutrients, especially antioxidants.

There is no differences between the calorie or protein intake across Oxidative stress indices and CD4+, CD38+/CD8+, and CD95+ T-lymphocyte, but vitamin A, C, and E intakes all increased. (Lizette et al., 2005). However related to other metabolic events not directly to oxidant overproduction.

Immune functions strongly influenced by redox potential and the constitutive difference in Glutathione (GSH) plays an important role in the regulation of human immunodeficiency virus (HIV) transcription and replication *in vitro*, through modulation of signal transduction by inflammatory cytokines. Moreover, intracellular GSH levels are known to regulate T-lymphocyte function.

Glutathione (GSH) levels decrease in CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, B cells, and monocytes in intracellular GSH occur in subsets of T cells in individuals in the later stages of the HIV infection. The low intracellular GSH levels may be an important

factor in HIV infection and in the resulting immunodeficiency.

Vitamin E ( $\alpha$ -tocopherol) and vitamin C (ascorbic acid) react rapidly with organic free radicals, and it is widely accepted that the antioxidant properties of these compounds are responsible in part for their biological activity. Tissue vitamin C levels are often considerably greater than those of vitamin E, for example in liver the values are approximately 2 mM and 0.02 mM, respectively. Nevertheless, vitamin E is considerably more lipophilic than vitamin C, and in bio-membranes has been found to be the more potent antioxidant, particularly with respect to lipid peroxidation; penetration to a precise site in the membrane may be an important feature of the protection against highly reactive radicals. Tappel has suggested that the two vitamins act synergistically, vitamin E acting as the primary antioxidant and the resulting vitamin E radical then reacting with vitamin C to regenerate vitamin E. This review paper now report direct observation of this interaction, which it feel may be an important feature in the maintenance of vitamin E levels in tissues (Packer et al., 1979)

Vitamins A, C, and E are the most important antioxidants concerned with cell-mediated immunity and toxic hepatitis (Stehbens, 2003). Vitamins C and E are major antioxidants in plasma (Stehben, 2004).

#### **HELMINTHS-HIV CO-INFECTION AND MALNUTRITION IN AFRICA**

Nutritional deficits induce immunosuppressive responses that make the host vulnerable to chronic helminth infection and HIV infection (Moreau and Chauvin, 2010). The susceptibility to infections results from both protein and energy malnutrition (macro-nutrition) and deficiencies of specific micronutrients, such as iron, zinc, and vitamins. Infection and malnutrition are synergistic; minor illnesses can cause lack of appetite, which is very dangerous in a person

who is already nutritionally deficient, and parasite-laden (Scrimshaw and San-Giovanni, 1997). Parasitic intestinal infections are thought to contribute to under nutrition through various mechanisms such as subtle reduction in digestion and absorption, as well as chronic inflammation and loss of nutrients, anemia and the change of plasma proteins and production of gastrointestinal hormones causing reduction in voluntary feed intake (Raiten, 2011). Intestinal helminth infections result in immune responses that involve cytokines produced by Th2 cells, with IgE production, eosinophilia and mastocytosis (Kalinkovich et al., 1998) Malnutrition resulting from HIV infection include diminished food intake due to loss of appetite or oral thrush, nutrient mal-absorption due to accompanying diarrhea which may result from opportunistic bacterial, viral or parasitic gastrointestinal infections (Duggal et al., 2012; Katona and Katona-Apte, 2008). Given the intersections between malnutrition, HIV epidemic and helminth infection in sub-Saharan Africa there has been surprisingly limited and inconsistent epidemiological and immunological evidence of important interactive effects (Borkow and Bentwich, 2004):

- Children - malnutrition and infection cycles (Figure 2).
- Adults' malnutrition, infections and treatment.

Malnutrition may be indicated by deficiency of either of the two nutritional categories: macronutrients (carbohydrates, proteins) or micronutrients (vitamins, minerals and trace elements). In general, a sick person's nutritional status is impacted by malabsorption, loss of appetite, diversion of nutrients for the immune response development, all of which result in loss of nutrients and further damage to the defense mechanisms or immunodeficiency (Müller et al., 2000). This highlights the pivotal role of

nutrition on immune system competency during an infection.

Previously studies on impact of intestinal parasitic infections focused on children owing to the well-established impact on cognitive and physical development, their increased exposure, poor hygienic habits and under-developed immune system. However from the nineties onwards, evidence of the impact of helminthes on TB, HIV/AIDS severity and tuberculosis began to emerge. This necessitated a shift in focus as far as parasitic infections and their impact on these high priority diseases in adults. This has caused a need for assessment of nutritional status in adult. In developing countries helminthiasis is frequently co-endemic with HIV/AIDS (Borkow et al., 2006, Hotez et al., 2006). Indeed, it is not uncommon for an individual to be co-infected with HIV and one or more parasitic worms (Kjetland et al., 2006). Such co-infections have synergistic effects, such as increased transmission of HIV, and/or may also an exacerbated progression of the diseases (Hotez et al., 2006).

#### **ROLE OF IMMUNITY ON MALNUTRITION AND HIV-HELMINTHS CO-INFECTION**

Nutritional deficiencies interact with parasite infection to make a combined assault on nutrition and immune support (Kurtis Friedman et al., 2003). Through their effect on nutrition and specific synergies with HIV transmission, elaborate on the parasitic infection and increased spread of HIV. Malnutrition and micronutrient deficiencies weaken the immune system and make individuals more weak so vulnerable to more infections including HIV and parasitic diseases, regardless of whether they are transmitted by water, food, air, soil, or sex. The susceptibility to infections results from both protein and energy malnutrition (macro

nutrition) and deficiencies of specific micronutrients, such as iron, zinc, and vitamins. Infection and malnutrition are synergistic; minor illnesses can cause lack of appetite, which can exacerbate nutritional deficiencies in an individual who is already nutritionally deficient, and parasite-laden (Scrimshaw and San-Giovanni, 1997).

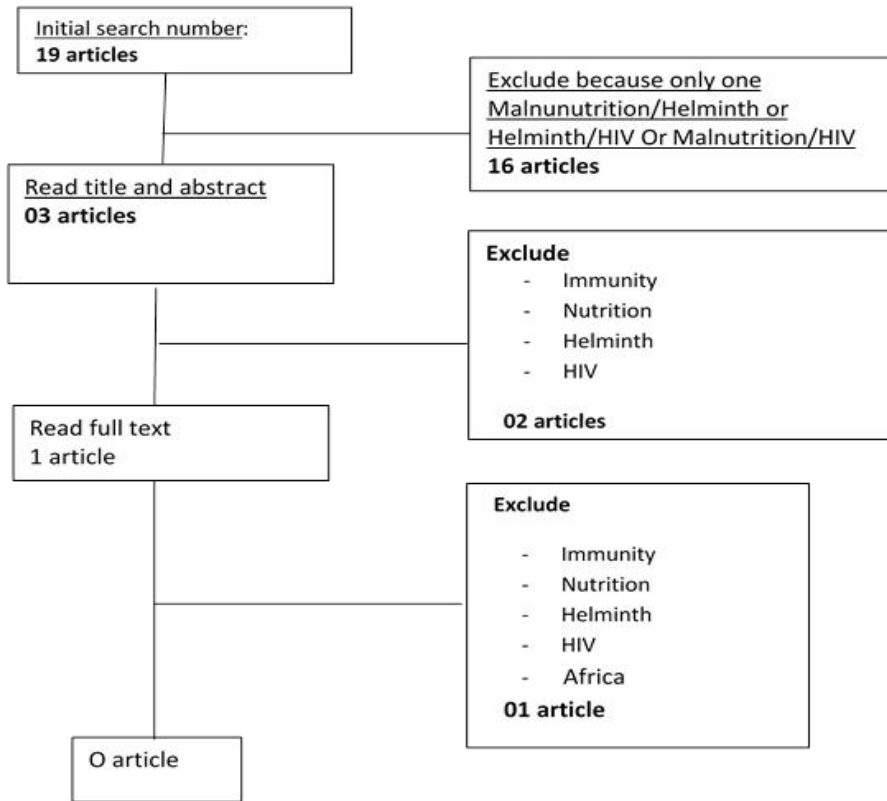
When helminthic infections cause mucosal damage in a person, and immunological system change; the person becomes vulnerable and susceptible to HIV infections and may facilitate HIV replication and accelerate disease progression. Such situations are common in developing countries, where food intake alone plays a significant part in poor health. Sub-Saharan Africa is the part of the world where there is large number of the developing countries and the region has the highest prevalence of malnutrition. So the concurrent distribution of HIV and helminths has been shown to occur in large in this part of the world (Borkow and Bentwich, 2004). In developing countries, helminthiasis are frequently co-endemic with HIV/AIDS (Borkow et al., 2006, Hotez et al., 2006). Indeed, it is not uncommon for an individual to be co-infected with HIV and one or more parasitic worm (Kjetland et al., 2006). Such coinfections have synergistic effects, such as increased transmission of HIV, may cause an exacerbated progression of the diseases (Hotez et al., 2006). A balanced nutrition can contribute to the wellness of an HIV infected person at all stages of the disease and can maybe prolong life. Nutrition is the key element for the health of sick person. Poor nutrition due to malnutrition or food intake, increase loss of nutrients from the body and decrease immune system, so the body cannot fight against other infections, as nutrition help in reinforcing the immune system and reduce vulnerability to pathogenic agents.

## **THE FUTURE OF NUTRITIONAL IMMUNOLOGY**

The immune system is crucial to human health, and nutrition is one of the major exogenous factors modulating different aspects of immune function. The different domains of immune function: defense against pathogens; avoidance or mitigation of allergy; control of low-grade inflammation mainly focusing on metabolic inflammation. Other aspects of immune function such as autoimmunity and surveillance against tumors were not included at this stage (Albers et al., 2013).

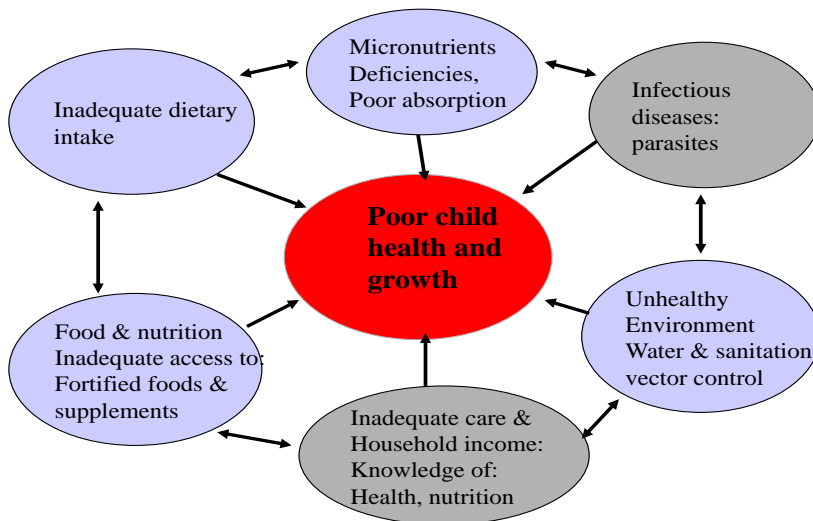
The probiotics are used in the prevention and treatment of a dramatic list of acute and chronic diseases, immune deficiencies, as well as infectious lesions of bacterial, viral and fungal etiology. So the mechanisms of probiotic activity are based not only on their metabolites, but also include the immune modulating activity of the structural components of the cells themselves, motifs of cell wall peptidoglycans (PGs), muramyl peptides (MPs), lipoteichoic acids (LPA) and nucleotide containing components or DNA motifs, act as Microbial Associated Molecular Patterns (MAMPs) and activate the corresponding receptors of innate immunity (PRRs), including TLRs and NLRs.

It has been shown potent ability to stimulate the macrophages when there is production of various kinds of cytokines, IFNs, TNF, NK cells. The major modifiable factors affecting immune function is nutrition (the primary factor being vaccination); under nutrition is often related to decreased immune function, whereas over nutrition and obesity can contribute to chronic low-grade inflammatory changes. Whole diets, individual nutrients and food components such as phytochemicals, prebiotics and probiotics influence distinct aspects of the immune system (Calder et al., 2009; Yan and Polk, 2011).



**Figure 1:** Search scheme showing the number of articles identified and selected for consideration.

Nutrition and infection determinants of poor child health and growth



**Figure 2:** Conceptual framework: how nutrition and infection determinants of poor child health and growth.



## Conclusion

Even though not much research on the topic, there has been much progress in for of attempt to holistically address the impact of infection on immunity for many governments instance are all nutritional supplement and fats on HIV and TB treatment receive nutritional supplement. However, the less attention is given to the co-infection with the Neglected Tropical Disease on immunity and general outcomes of these infection and malnutrition. More attention need to be done in:

- The well-designed controlled trials to the impact of malnutrition and Helminth/HIV co-infection on immunity
- To increase awareness on the subtle but deleterious effects of NTD's on the pathogenesis and outcomes of three priority diseases (HIV, TB, Malnutrition)
- To sociological aspect include in this review.

More investigations to look at nutritional aspects in adults especially during infectious diseases co-infections. Further some chemotherapeutics require improved nutritional intake.

## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal ; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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