Universidade de Lisboa

Faculdade de Farmácia

Intestinal helminth infections in HIV-infected individuals: new importance in immunological and clinical evolution

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Mestrado Integrado em Ciências Farmacêuticas

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Monografia de Mestrado Integrado em Ciências Farmacêuticas apresentada à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

A Síndrome da Imunodeficiência Adquirida (SIDA), causada pelo Vírus da Imunodeficiência Humana (HIV) é uma das maiores epidemias em todo o mundo, particularmente, em países menos desenvolvidos, sendo um grande desafio para a Saúde Pública, na tentativa de estabelecer terapêuticas de sucesso e de implementar medidas no estilo de vida, como prevenção e consciencialização das populações. Comummente são associadas infeções oportunistas, como resultado de um sistema imunológico debilitado, decorrente da progressão da infeção por HIV para o seu estadio mais grave - SIDA. Dentro destas, encontram-se as infeções parasitárias por helmintas intestinais, que variam tanto quanto o seu elevado número de espécies. Verifica-se a existência de uma sobreposição entre as regiões geográficas de ambas as infeções, o que é indicativo da frequência com que estas ocorrem em simultâneo, coincidindo com regiões onde as condições sanitárias são muito precárias, nas quais os indivíduos carecem de uma alimentação completa, apresentando défices em micronutrientes significativamente relevantes. Ambas as infeções tornam o hospedeiro imunologicamente debilitado e mais suscetível a novas infeções. Um indivíduo seropositivo para o HIV, que seja, posteriormente, infetado por um helminta intestinal vai ser alvo de uma alteração na polaridade da resposta imunológica, que se altera de uma resposta predominantemente do tipo Th1 para o tipo Th2, o que conduz a uma progressão mais acelerada da doença e um controlo menos eficaz da viremia, pelo que, também afeta a própria transmissão do vírus. Um dos sintomas clínicos mais observados na co-infeção com helmintas intestinais é a diarreia, cujo grau de severidade varia de acordo com a fase da infeção pelo HIV e com a espécie de helminta pela qual o indivíduo está infetado. Outro fator muito importante na suscetibilidade a estas infeções é existência de défices em micronutrientes específicos, que alteram o funcionamento normal dos componentes do sistema imunológico, enfraquecendo os mecanismos de resistência e, consequentemente, expondo os indivíduos com maior vulnerabilidade a diversas doenças infeciosas. Por fim, embora ainda alvo de discussão na comunidade científica, a desparasitação em massa tem impactos positivos e deve ser integrada em programas de terapêutica antirretroviral em regiões endémicas de helmintas onde a co-infeção com HIV é mais frequente.

Palavras-chave: HIV, Co-infeção, Helmintas intestinais, Suscetibilidade, Terapêutica

Abstract

The Acquired Immunodeficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus (HIV) is one of the biggest epidemics worldwide, particularly in less developed countries, being a major challenge for Public Health in an attempt to establish successful therapies and implement lifestyle measures such as prevention and population awareness. Opportunistic infections are commonly associated, as a result of a weakened immune system, resulting from the progression of HIV infection to its most severe stage - AIDS. Within these are parasitic infections by intestinal helminths, which vary as much as their high number of species. There is an overlap between the geographical regions of both infections, which is indicative of the frequency with which they occur simultaneously, coinciding with regions where sanitary conditions are very precarious, in which individuals lack complete nutrition. , presenting deficits in significantly relevant micronutrients. Both infections make the host immunologically weakened and more susceptible to new infections. An HIV-positive individual who is subsequently infected with an intestinal helminth will experience a change in the polarity of the immune response, which changes from a predominantly Th1-type to a Th2-type response, which leads to a progression of the faster disease and less effective control of viremia, so it also affects the transmission of the virus itself. One of the most common clinical symptoms observed in co-infection with intestinal helminths is diarrhoea, whose degree of severity varies according to the stage of HIV infection and the species of helminth by which the individual is infected. Another very important factor in susceptibility to these infections is the existence of deficits in specific micronutrients, which alter the normal functioning of the components of the immune system, weakening the resistance mechanisms and, consequently, exposing individuals with greater vulnerability to various infectious diseases. Finally, although still subject to discussion in the scientific community, mass deworming has positive impacts and should be integrated with antiretroviral therapy programs in helminth endemic regions in tropical countries.

Keywords: HIV, Co-infection, Intestinal Helminth; Susceptibility; Treatment

Acknowledgments

This project marks the end of a 5-year cycle of hard work, resilience, and dedication. In such an atypical year, when we all agree that health is the most important of all, becoming a pharmacist is, for sure, marked forever in my life.

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Thank you all for always supporting my dreams.

Abbreviations

HIV – *Human Immunodeficiency Virus*

AIDS – Acquired Immune Deficiency Syndrome

COVID-19 – Coronavirus Disease 2019

SIV – *Simian Immunodeficiency Virus*

gp160 – Glycoprotein 160

CD4 – Cluster of Differentiation 4

ER – Endoplasmic Reticulum

Gag – Group-specific Antigen

ErManI – Endoplasmic Reticulum Class 1 α

GBP5 – Guanylate-binding Protein 5

90K – Lipoprotein 90K

IFITM2/3 – Family Proteins

MARCH 1/2/8 – Membrane Associated Ring-CH 1, 2 and 8

25-HC – 25-Hydroxycholesterol

IAV – *Influenza A Virus*

MLV – *Murine Leukemia Virus*

EBOV – *Ebola Virus*

WNV – *West Nile Virus*

MPMV – *Mason-Pfizer Monkey Virus*

EBV – *Epstein-Barr Virus*

MeV – *Mink Enteritis Virus*

DENV – *Dengue Virus*

VSV – *Vesicular Stomatitis Virus*

EIAV – *Equine Infectious Anemia Virus*

ZIKV – *Zika Virus*

NiV – *Nipah Virus*

HCV – *Hepatitis C Virus*

RVF – *Respiratory Syncytial Virus*

NTD's – Neglected Tropical Diseases

UNAIDS – Joint United Nations Programme on HIV and AIDS

GALT – Gut-associated Lymphoid Tissue

CCR5 – C-C Chemokine Receptor 5

CXCR4 – C-X-C Chemokine Receptor Type 4

CLR – C-type Lectin Receptor

CD3 – Cluster of Differentiation 3

CD80 – Cluster of Differentiation 80

CD86 – Cluster of Differentiation 86

CD28 - Cluster of Differentiation 28

IgE – Immunoglobulin E

IL - Interleukin

APC – Antigen-presenting Cells

TCR – T Cell Receptor

ILC2 – Innate Type 2 Cells

STAT6 - Transcription Factor Signal Transducer and Transcription Activator 6

TGF – Transforming Growth Factor

ROS – Reactive Oxygen Species

VL – Viral Load

ART – Antiretroviral Therapy

HAART - Highly Active Antiretroviral Therapy

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1. Introduction

The Acquired Immunodeficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus (HIV) continues to be one of the biggest challenges worldwide, particularly in less developed countries, such as Africa, Asia, Central and South America.

Infections are often associated opportunists to HIV-positive individuals since their immune system is weakened as a consequence of the progression of the disease. Thus, co-infection in these individuals, with other pathogens, such as bacteria, fungi, parasites and even other viruses, is one of the most serious complications that can arise due to the impairment of the immune system, characteristic of the progression of an HIV infection.(1) Parasites, in particular, stand out from the others, since they do not belong to a group of pathogenic agents considered to be an etiological factor for opportunistic infections, and according to the UDEH EO et al., parasitic infections in the gastrointestinal tract continue to be an important cause of morbidity and mortality in immunocompromised individuals; therefore, they seem to be a particularly interesting and very relevant topic for research.(2)

In developing countries, particularly in tropical and subtropical regions, the rate of serious co-infections is higher, including co-infections with HIV and helminths. Socioeconomic factors contribute significantly to this. Preventive health measures, from a balanced diet to basic hygiene, through health education and individual awareness, are still very lacking in these regions.(3)

According to PAWELCZYK A et al., on sub-Saharan populations, the proportion of helminth-infected individuals is higher than that of individuals infected by unicellular organisms, with the prevalence of infection by *Ascaris*, *Ancylostoma* and *Trichuris* being 22-25%, 29% and 24% respectively. The same authors also concluded that, of those individuals infected by parasites, it is estimated that around 25% are infected by more than one species of helminths.(4)

As such, the evolution of the HIV-helminth co-infection is very different to the development of an HIV infection in the absence of any other pathogenic agent, for not only does the individual have a weakened ability to fight other infections, but the helminth itself triggers different immune responses as it interacts with HIV.(5)

Thus, it is essential to understand the differences resulting from the activation and modulation of the immune system between an individual who first acquires a helminth infection and, later, HIV, and an HIV-positive individual, who is infected by an intestinal helminth. This leads us to another aspect that is still much debated, which is the influence of a first infection, in increasing the susceptibility to acquiring the second.

The nutritional state is also a factor that has been increasingly studied, as initially it was not given due attention and it has been shown that as a result of an unbalanced diet, nutritional deficits arise that significantly affect the defence mechanisms of the individual and that the leave you more weakened immunologically. However, just as malnutrition leads to increased susceptibility to new infections, so do infections, due to the symptoms presented, have a major impact on the individual's ability to remain nutritionally stable. In other words, it is a difficult cycle to control, especially in less developed countries, due to all the associated factors.

With this, it is natural that many people have already devised strategies to try to combat the emergence of this co-infection. Mass deworming has proved to be a good bet for younger populations, in the most affected regions.

Additionally, if antiretroviral and/or antiparasitic therapy is implemented jointly with the administration, its benefits will be even greater. Even if the occurrence of cases of co-infection between HIV and helminths cannot be stopped, at least it will be possible to slow the progression of associated complications.

Finally, the role of an eventual vaccine in preventing these pathologies will also be discussed.

2. Materials and Methods

The preparation of this monograph was based on the analysis, interpretation, and synthesis of several original and review scientific articles, as well as the consultation of pages on the Internet, published between 1991 and 2020. From all the extensive research, scientific articles, whose results were later proven to be inaccurate or insignificant, as well as the oldest ones, were excluded, to present current data.

For the research act, the following keywords were used: review, helminths, HIV, co-infection, clinic, immunology, deworming, therapeutics.

The sources for obtaining electronic bibliography were the platforms: PubMed (www.ncbi.nlm.nih.gov/pubmed/); the CDC (www.cdc.com); The Joint United Nations Programme on HIV and AIDS – UNAIDS - (www.unaids.org/en) and the World Health Organization (www.who.int/en/). This research was carried out in the period between July 7 of 2019, and day 19 of October 2020.

This monograph follows the provisions of the MICF 2017 internal rules for the preparation and presentation of Monographs - Curricular Internship Regulations for the Integrated Master Course in Pharmaceutical Sciences (Diário da República, 2nd series, of December 18, regulation nr. 856 / 2006, regulated by Directive 2013/55 / EU).”

3. HIV

3.1. Epidemiology

The Acquired Immunodeficiency Syndrome is a chronic epidemic highly challenging the population worldwide, particularly in developing countries.(6) Around 38.0 million people in the world (36.2 million adults and1.8 million children from 0 to 14 years) were living with HIV in 2019.(7)

Nowadays, many analyses are being done to understand the potential impacts that the COVID-19 pandemic could have in low- and middle-income countries around the world on the supply of generic antiretroviral drugs used to treat HIV. The closure of borders to prevent COVID-19 had an impact on both the production of medicines and their distribution, increasing problems and associated costs.(8)

In this context, they are aspects to be considered, taking into consideration the pandemic situation we are going through, as it is known that an interruption of around six-months without treatment for HIV can lead to more than 500,000 additional deaths from AIDS-related illnesses.(7)

3.2. HIV-1 and HIV-2

3.2.1. Evolution

Current evidence indicates that the Human Immunodeficiency Virus (HIV-1 and HIV-2) entered the human population through multiple zoonotic infections from non-human primates infected with simian immunodeficiency virus (SIV).(9)

Scientists compared the nucleotide sequences that code for the gp160 protein, among the various taxa that share a common ancestor with HIV-1. For this, they used the likelihood maximum method that compares the several phylogenetic trees, giving rise to the tree most likely to explain the data under analysis - consensus tree (Figure 1A). These data demonstrate that HIV-1 was initially transmitted around 1920-1930 (Figure 1B).(10)

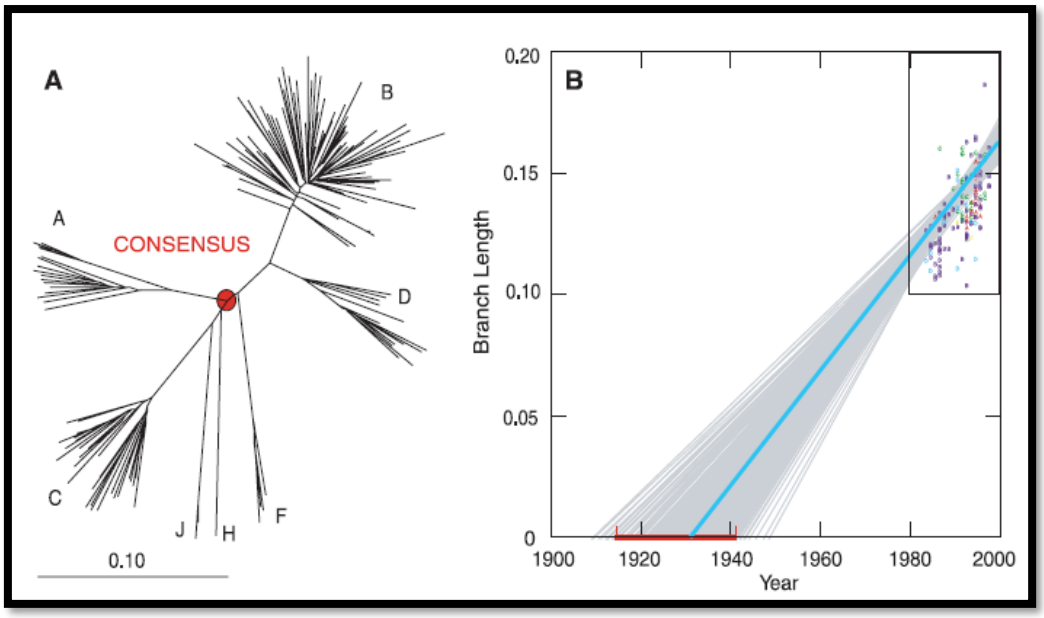

Figure 1 – HIV-1 Phylogeny. Estimating the last common ancestor of the HIV-1 group through a phylogenetic consensus tree calculated using the maximum likelihood method. (A) The gp160 phylogenetic tree used for this calculation. (B) The branch lengths from each leaf to the root of the tree are plotted against time. [Adapted from (10)].

3.2.2. Transmission

The transmission of HIV can occur by permutation of corporal fluids, such as blood, semen, pre-seminal fluid, vaginal fluids, rectal fluids, and breast milk from a HIV-positive individual, only when these fluids are in contact with a mucous membrane or damaged tissue or it can be directly injected from a needle or a syringe into the bloodstream.(9)

3.2.3. Infectious Process

Without a viral protein envelope, viruses fail to start their infectious process by penetrating cells. In this sense, proteins of the viral envelope are a target of extreme importance for the host's immune system, to prevent and, if possible, block an infection. Several mechanisms try to restrict viral entry into cells, as shown in Table 1. However, when these defences fail, the virus penetrates the cell and initiates its replication in the host.(11)

In the case of HIV-1, CD4 helper T cells are infected by the envelope protein (Env) that is synthesized as a gp160 precursor in the endoplasmic reticulum (ER). Subsequently, in the trans-Golgi complex, its glycosylation and cleavage by proteases occurs, giving rise

to a gp120/gp41 trimer, which travels to the plasma membrane, where it joins HIV-1 Gag proteins. When this occurs, infectious viral particles are formed, as shown in Figure 2.(12)

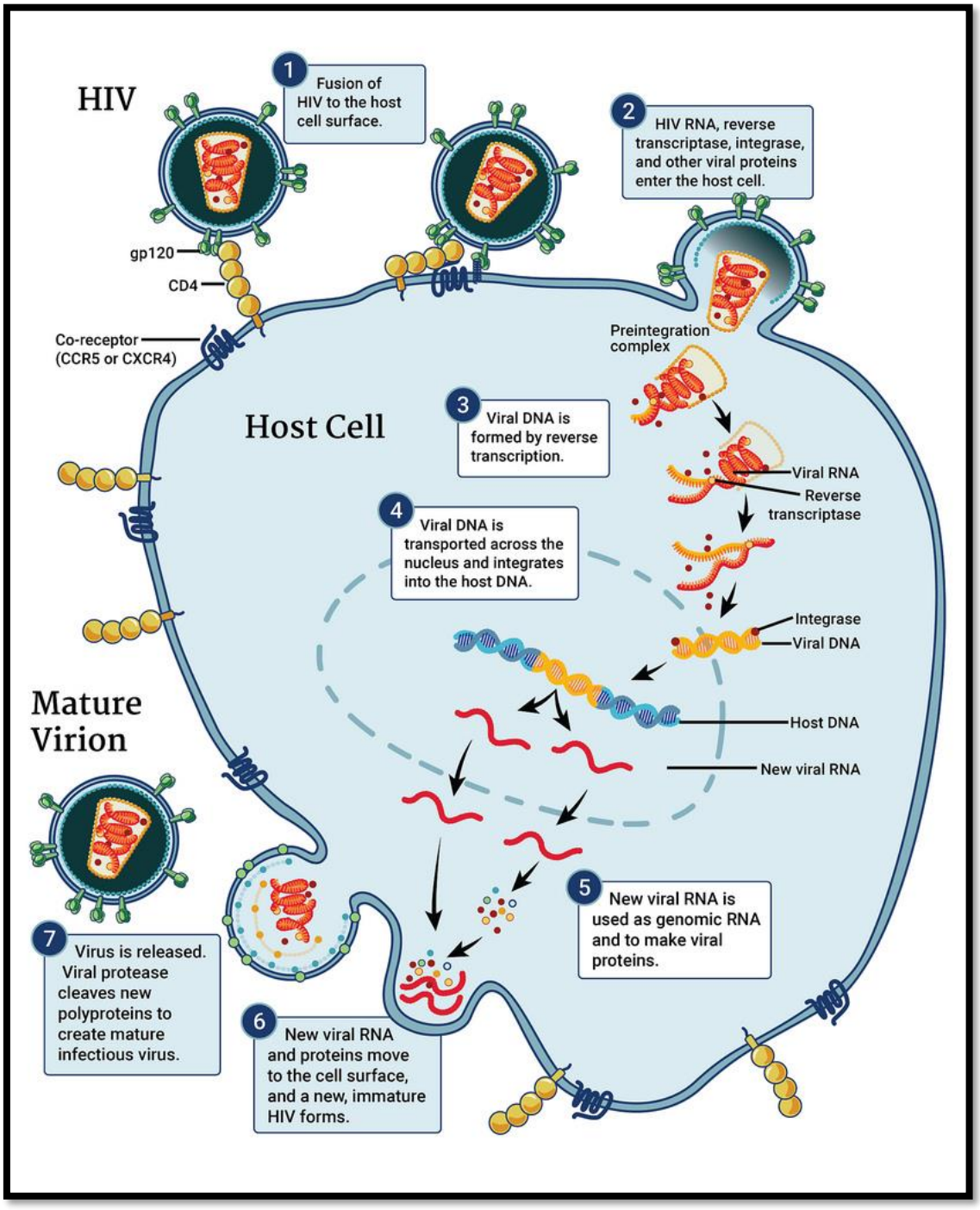

Figure 2 – HIV Replication Cycle. [Adapted from (13)]

Table 1 - Some of the restriction factors that target HIV-1 Env. *To be determined. [Adapted from (11)].

Restriction Factor	Impact on HIV-1 Env	Other Enveloped Viruses Affected	Virus Escape Mechanism
ErManI	Decrease Env expression via ERAD pathway; modulate glycosylation of HIV-1 Env.	IAV	HIV Vpr increases Env expression.
GBP5	Impair cleavage of gp160; alter glycolysation of HIV-1 Env.	MLV	Viral trade-off mechanism to increase Env expression by shutting down Vpu expression.
90K	Prevent gp160 processing; decrease mature gp120/gp41 in virions.	EBOV	TBD*
IFITM2/3	Deter viral entry into virus target cells; impair gp160 processing; promote gp120 shedding decrease mature gp120/gp41 in virions; incorporate into virions and impair viral entry.	MLV, WNV, MPMV, EBOV, EBV, MeV, DENV	Overcome by HIV-1 Env.
MARCH 1/2/8	Downregulate Env from the plasma membrane.	HIV-2, SIV, MLV, VSV	TBD*
SERINC5	Impair virus infectivity; incorporate into virus particles; affect the conformation of the MPER region of Env.	MLV, EIAV, EBOV	Downregulated by Nef from plasma membrane; countered by HIV-1 Env.
25-HC	Modify the secondary structure of the HIV-fusion peptide; prevents membrane fusion.	VSV, ZIKV, EBOV, NiV, HCV, RVF	TBD*

To be able to infect new cells, the gp120 protein binds to the CD4 receptor on the surface of the target cell or triggers conformational changes in the gp120/gp41 trimer, exposing the binding site in gp120 to the CCR5 or CXCR4 co-receptor.(14)

Then, the viral and cell membranes fuse, in which the fusion peptide and gp41 helices are involved. It starts with the junction of the outer lipid leaflets of both membranes in a process called hemifusion. The continuous fusion of the two membranes promotes the

fusion pore formation, which further expands to an adequate size so that the delivery of viral RNA within the central structure of the cytoplasm is carried out successfully.(12) The HIV-1 infectious process and its replication cycle is represented in Attachment A1.

After transmission, the virus replicates within the cells and rapidly spreads to the lymphatic ganglions, particularly GALT.(15) GALT is an important reservoir of CD4+ and CCR5+ T memory cells. Approximately 80% of those cells are lost in the first few weeks following HIV-1 infection.(16)

The direct infection of cells through the CD4 receptor and co-receptors is called cis infection. It has been shown that a group of C type lectins (CLR), expressed in myeloid cell lines, successfully captures HIV-1 and transmits the virus to activated CD4+ T cells. This process is known as trans infection.(17)

A mechanism that affects cellular susceptibility to influence by HIV-1 is a differential expression of chemokine receptors that also serve as co-receptors for the entry of the virus into cells. The greater the cell expression of these receptors, the greater the cells' susceptibility to HIV-1 infection, as shown in Table 2 and Figure 3.(18)

Table 2 - Chemokine receptor expression of patients with cured schistosomiasis patients compared to active schistosomiasis. [Adapted from (18)].

	MCF data for chemokine receptor in:		
Cell and Chemokine Receptor	Patients with schistosome eggs (n=26)	Patients with schistosome eggs (n=16)	P value
CD4+ CD3+ cells	49.3 (24.3; 82.5)	27.2 (2.99; 58.9)	0.068
CCR5	169.1 (147.3; 179.2)	128.4 (87.5; 160.2)	0.033
CXCR4			
CD4+ CD14+ cells	2.5 (0.0; 13.1)	0.0 (0.0; 7.1)	0.423
CCR5	89.1 (64.6; 121.5)	57.3 (41.3; 74.1)	0.013
CXCR4			

The post-treatment levels of CCR5 and CXCR4 on the surfaces of the CD4 and CD3 cells revealed to be lower than the pre-treatment levels, as shown in Figure 3.

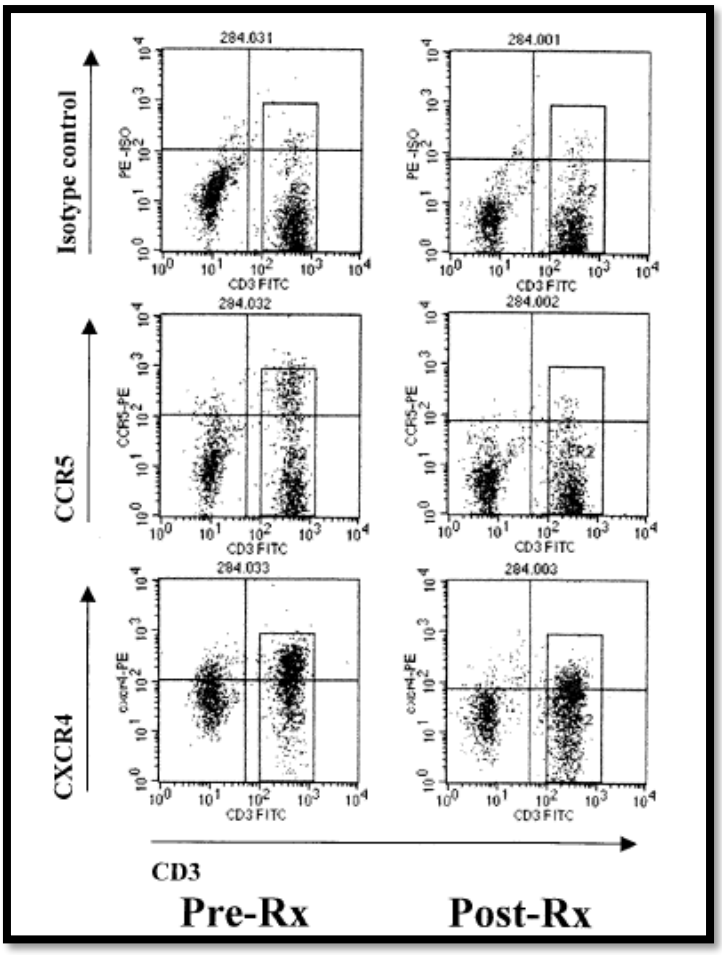

Figure 3 - Comparison of staining profiles of the chemokine receptor in a patient with active schistosomiasis and after healing. Pre-Rx and Post-Rx: before and after treatment for schistosomiasis, respectively. [Adapted from (18)].

3.2.4. HIV/AIDS

The stage 1 or acute HIV infection phase is characterized by a higher amount of viral load. HIV-positive individuals are very contagious on this phase. It is common to have flu-like symptoms, but some people don't feel sick at all.(19)

As shown in Figure 4 the stage 2 or chronic HIV infection is named as asymptotic phase and at this point HIV is continuing to replicate but at very low levels.

Finally, the last stage of HIV infection is known as Acquired Immune Deficiency Syndrome and it is the most severe phase as the immune system is so fragile that many infections occur – opportunistic infections.(9) According to UNAIDS, around 32.7 million people have died of AIDS-related illnesses since the epidemic began and in 2019, 690,000 people died of it.(7)

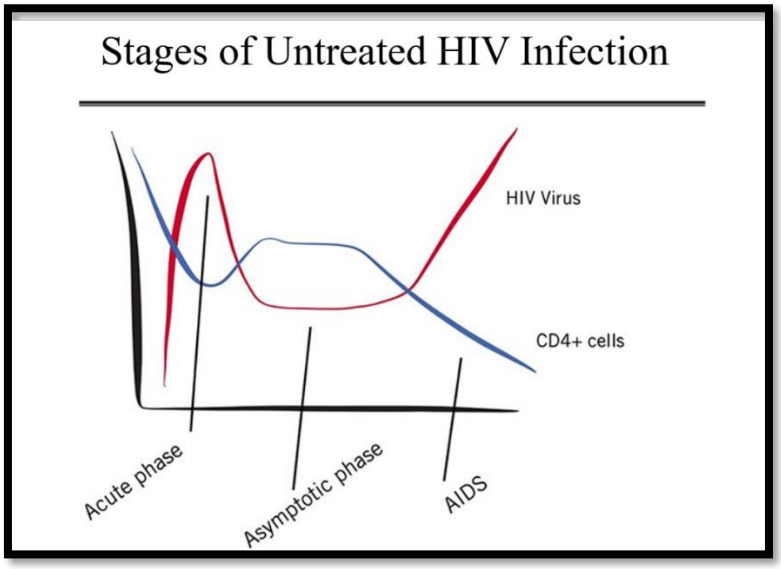

Figure 4 - Different stages of HIV infection progression. [Adapted from (19)].

4. Neglected Tropical Diseases (NTD's)

In recent decades, several studies have been conducted to try to prove that helminth infections increase susceptibility to HIV infection and that in developing countries, they contribute significantly to the spread of this virus.(20) However, almost all helminthic infections belong to the group of "Neglected Tropical Diseases", as defined by the World Health Organization. Therefore, there is still a long way to go before this relationship is well established, to prevent and treat effectively.(21)

4.1. Epidemiology

The large group of Neglected Tropical Diseases (NTDs) comprises parasitic and bacterial pathologies that have a mitigating impact on more than a billion people worldwide, low and middle income countries in Africa, Asia and Latin America.(22) By the geographical distribution of these diseases, we can infer that these are the most common in poorest regions and, therefore, the majority of patients live in poor conditions, with lack of sanitation and with increased contact with infectious vectors.(23) The distribution of some NTD's are represented below, (Figure 5, 6 and 7).

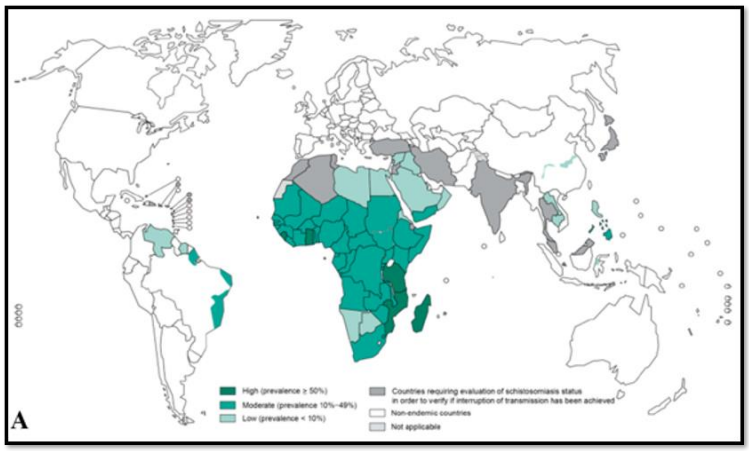

Figure 5 – Worldwide distribution of Schistosomiasis.[Adapted from (24)].

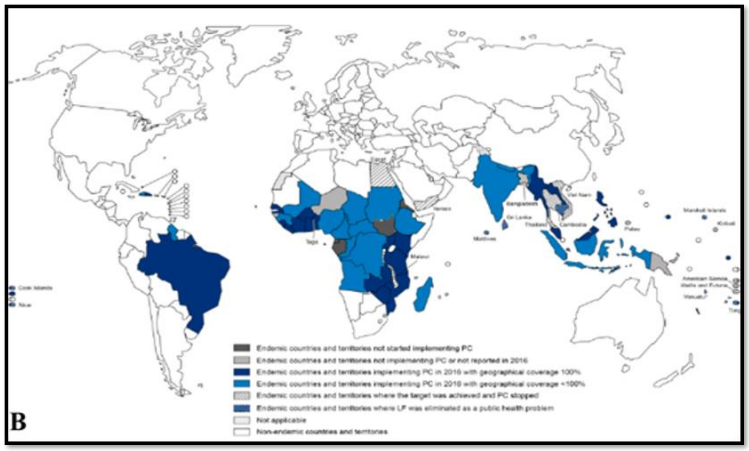

Figure 6 - Worldwide distribution of Filariasis. [Adapted from (25)]

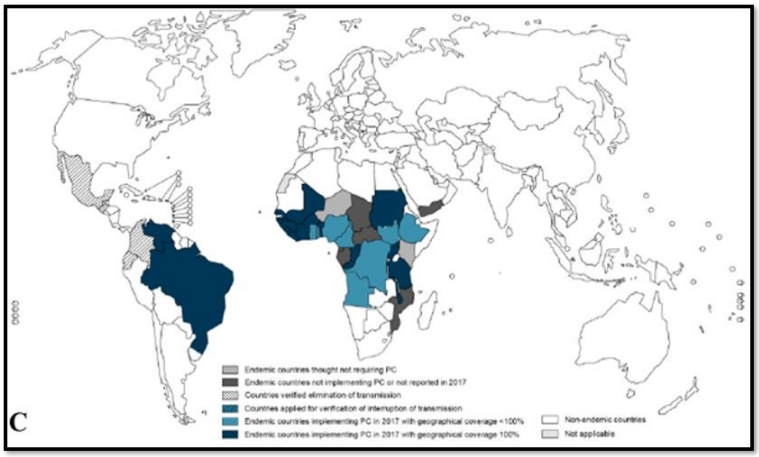

Figure 7 - Worldwide distribution of Cysticercosis. [Adapted from (26)]

4.2. Parasites

A parasite is a living organism that can live on or in another organism – host organism - and gets its food from it. There are three main classes of parasites that can cause disease in humans: protozoa, helminths and ectoparasites.(27)

4.3. Helminths

Helminths are large, multicellular parasitic microorganisms. Estimates suggest that approximately a third of the global human population may be infected with helminth parasites, causing important public health concerns, especially in regions with poor sanitation or limited access to clean drinking water. Like protozoa, helminths can be either free-living or parasitic in nature.(28)

4.3.1. Classification

Helminths are commonly referred to as parasitic worms and can include the following groupings: roundworms (nematodes), hookworms, flukes (trematodes) and tapeworms (cestodes), as shown in Table 1.(27)

Table 3 - Helminths classification. [Adapted from (27)].

Platyhelminths (Flatworms)	**Acanthocephalins (Thorny-headed worms)**	**Nematodes (Roundworms)**
Trematodes (flakes) and Cestodes (tapeworms).	The acanthocephala are thought to be intermediate between the cestodes and nematodes. The adult forms reside only in the gastrointestinal tract.	The adult forms can reside, not only in the gastrointestinal tract, but also, in blood, lymphatic system and subcutaneous tissues.

Table 4 - Classes and phyla of intestinal helminth species. *** Helminth species most often found in HIV co-infection.** [Adapted from (29)].

Helminths		**Species**
Nematodes		*Enterobius vermicularis*
		Ascaris lumbricoides*
		Trichuris trichiura*
		Ancylostoma duodenale e ***Necator americanus****
		Strongyloides stercoralis*
		Anisakis simplex
Platyhelminths	**Cestodes**	*T.saginata, T.solium, Diphyllobotrium latum, Hymenolepsis nana*
	Trematodes	*S.intercalatum,* ***S. mansoni****, S.japonicum;*
		Fasciolopsis buski, Heterophyes heterophyes, Euparyphium ilocanum

4.3.2 Transmission

Helminths are transmitted in several different ways. The most common is through contaminated animals. They can pass them on to people, through blood or undercooked food, or even through direct contact, for example, between children and pets.(30) Insects may serve as mandatory hosts, acting as a parasite vector.(27) However, many of these helminth parasites are soil-transmitted and cause gastrointestinal infections following ingestion of pasture or water contaminated with their eggs.(31) Furthermore, parasites can also be transmitted through risky sexual behaviours. (27)

4.3.3 Pathogenes

The parasites have very different life cycles and, some of them, covering different stages that involve several hosts. In hosts, helminths undergo a process of growth and differentiation whose ultimate goal is to reach the stage that allows them to be transmitted to the next intermediate host, usually the larva, which migrates, in the host, to the appropriate niche, to grow and reproduce.(32) All this indeed depends on the species of helminth in question, however, despite the extreme variability and complexity, in most cases, the immune responses of the hosts to helminth infection translate into a predominant activation of the Th2 cellular response with a production of significant amounts of interleukin-4 (IL-4), IL-5, IL-9, IL-10 and IL-13 and, consequently, the development of strong responses of immunoglobulin E (IgE), eosinophils and mast cells.(33)

Helminth infections trigger the disease as they migrate through the host's tissues after transmission. These chronic infections are associated with the development of immune responses mediated by type 2 T cells (Th2).(34) There is an increased expression of cytokines, such as IL-4, IL-13, eosinophilia, IgE production and stimulation of alternatively activated M2 macrophages and type 2 innate lymphoid cells (ILC2). Alternatively, activated macrophages play an important role in correcting tissue damage induced by helminth infection.(35)

5. Susceptibility to Co-Infection

The effect of HIV on T helper lymphocytes, macrophages and neutrophils result in increased susceptibility in individuals to contracting multiple gastrointestinal parasitic infections.(36) The intestine of HIV-positive individuals is not a very favourable environment for the colonization and survival of extracellular parasites, however, it doesn't seem to be detrimental enough to the survival of intracellular parasites and those who inhabit the mucous membranes.(37) In fact, HIV infection leads to an enteropathy that promotes the colonization of the gastrointestinal tract by parasites.(2)

The susceptibility to co-infections may depend on other factors like particular locations where each pathogenic agent lives in the host, for example, gastrointestinal mucous membranes vs. systemic.(38) In other cases, the induction of a strong pro-inflammatory response to a parasitic infection can exacerbate the susceptibility and/or disease after co-infection with another pathogenic agent that induces a similar pro-inflammatory response.(6)

Parasitic infections contribute significantly to the increase in the risk of vertical HIV transmission and to the progress of this infection. Furthermore, the development of the disease to its worst stage, acquired immunodeficiency syndrome, is twice as common when part of a co-infection.(4) Therefore in children, it is most common for HIV to be the first to occur, through vertical transmission during labour, followed by the helminth infection.

5.1. Co-Infection

The immune responses to infectious agents involve type 1 and 2 helper T cells (Th1 and Th2, respectively). Th1 cells are responsible for cell-mediated immunity against parasitic, bacterial, protozoal, viral and intracellular infections, whilst Th2 cells mediate antibody-dependent immunity against extracellular parasites, including intestinal helminths.(39)

The role of Th1 and Th2 cells in controlling the immune response and overcoming infections is already known. While cytokines produced by Th1 cells induce a cellular immune response, the cytokines produced by Th2 cells induce a humoral immune response.(37) These two types of cells are mutually regulated, therefore the cytokines

produced by one subgroup can suppress the production or activation of cytokines from another subgroup.(40)

Because T CD4 lymphocytes are the main cell type infected by type 1 human immunodeficiency virus (HIV-1), the immune responses generated due to the matrix of co-infecting pathogenic agents probably influence the transmission of the virus, as well as the progression of the disease.(41) Elevated levels of IgE have also been associated with the progression of the disease and are reported as an initial sign of opportunistic infections in patients with advanced HIV infections and reduced levels of CD4+ T cells. The host's immune response to helminth infections correlates with the production of interleukins 4, 5, 9, 10 and 13, and therefore with the increased production of IgE.(42)

HIV co-infection with parasites correlated with significantly lower levels of CD4 T cells in peripheral blood than in HIV-positive individuals without co-infection. This suggests that HIV seropositive individuals with parasitic infections are immunologically disadvantaged compared to individuals infected with only one of these pathogenic agents.(43)

During the development of the helminth infection, as the immune system is chronically activated, its modulation may contribute to the activation of the HIV life cycle, including its replication.(43) Through *Trichuris trichiura* infection there is an increase in the expression of CCR5 (cysteine-cysteine chemokine receptor 5) on the surface of T CD4 lymphocytes. This facilitates the binding of HIV to the cell surface, thereby promoting its penetration into the cells.(4)

The consequences of the parasitic infection depend largely on very specific aspects of the parasite's life cycle, such as the time and place of transitions between particular stages of development.(29) Helminths such as *Schistosoma mansoni* are relevant in this context as they have the capability to mitigate and wrest the immune system, including the modulation of CD4 T cells. In addition, the association of high rates of HIV-1 prevalence with endemic regions of *Schistosoma mansoni* is frequent, which indicates that co-infection between these two microorganisms is very common.(16)

5.2. Immunological Mechanisms

According to the previously mentioned, individuals infected with helminths will be immunologically activated and, consequently, more likely to be infected with HIV. Some

of the immunological mechanisms resulting from recurrent or chronic infections are the activation of pro-inflammatory cytokines, disturbances in the proliferation and distribution of the immune response of type 1 and 2 T helper lymphocytes (40). Thus, there are immunological differences between a HIV-positive individual who gets a helminthic infection and an individual infected by a parasite who is lately infected by HIV. This changes in the immunological system will be discussed below in this chapter.

5.2.1. HIV-positive individual infected with intestinal helminth

Once infected with the virus, an infection will progress more rapidly as a consequence of a weakened immune system and thus the eradication of the parasites in co-infected individuals will slow the progression of the HIV disease.(29) As a standardized immune response predominantly of the Th1 type is, to a certain extent, that seen in viral infections, in the case of HIV, its maintenance has a beneficial and protective performance in the individual, including in the control of viremia, in the sense that disease progression will not occur as quickly.(44) If co-infection occurs and the pattern of the immune response changes to a predominantly Th2 type, the development will be higher, so the individual will be left unprotected.(45) Activation of the immune system, a recurrent parasitic infection, leads to an increase in the viral load (VL) of HIV in the plasma and therefore will also have a significant impact on HIV transmission.(46)

These characteristic of helminth infection - the ability to distort the immune response profile, from a predominantly Th1 profile to a profile of mostly Th2 - leads to a state of hyporesponsiveness and anergy, concepts that will later be discussed, and that will affect the host's ability to generate strong and protective immune responses.(29) Both immune activation and dysregulation are characterized by a specific pattern of cytokine production, expression of plasma membrane activation molecules in cells of the immune system as well as changes in the level of various immunological parameters in the blood.(44) Th2 response are typically known by increased expression of cytokines such as (IL-4), IL-13, eosinophilia, production of immunoglobulin E (IgE) and stimulation of alternatively activated macrophages (M2) and innate type 2 cells (ILC2).(5) The production of Th2 cytokines during helminth infections is associated with the expression of the transcription factor signal transducer and transcription activator 6 (STAT6) by activated macrophages.(47)

Changes in the cellular mechanisms during chronic immune activation are represented in the Figure 8. Increased levels of CTLA-4 disrupt the cellular response and promote expression of the negative TGF-regulatory cytokine. T cells stimulation through the T cell receptor (TCR) requires co-stimulatory signalling through the binding of the CD28 receptor to the CD80 or CD86 ligands of antigen-presenting cells (APC), therefore, with the downregulation of CD28, the stimulation of TCR in the absence of CD28-mediated co-stimulation induces a hyporesponsive state of the long term. The reduction in CD80 in APC decreases the effective stimulation of T cells and an increase in the constitutive levels of negative intracellular regulators, such as Cbl-b. Decreased phosphorylation of ERK 1/2 impairs cytoplasmic signal transduction. Increase in the number of Treg cells, which induce T cell hyporesponsiveness directly through cell contact and negative regulatory cytokines, such as IL-10 and TGF-β. The distorted immune profile TH2 associated with HIV-1 and helminth infections results in the positive regulation of negative regulatory cytokines and, probably, Treg cells. Also, soluble factors originating from HIV or helminthic parasites, such as gp120 and ES-62, interact with T cells, increasing cellular deficiencies and hyporesponsiveness.(37)(43)(44)

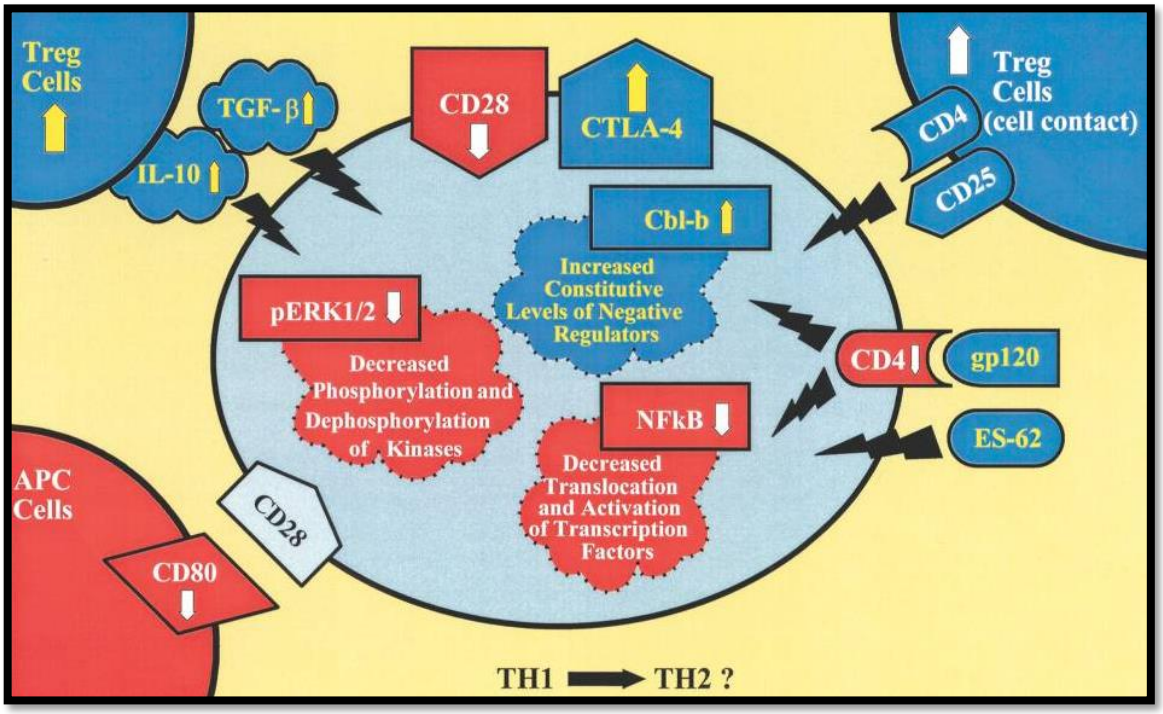

Figure 8 - Cellular aspects related to hyporesponsiveness and anergy. [Adapted from (37)].

5.2.2. Individuals with parasites infected with HIV

First, if the individual is infected with intestinal helminths, his immune response will be predominantly Th2, so the individual will be more weakened and may be more susceptible to being infected with HIV.(38)

The reversal of the response by the immune system - the ability to change a Th2-like immune response to Th1 - would be beneficial for a new HIV infected individual, because, although weakened by parasitic infection, viremia would be more controlled, and the progression of the disease would be slowed. Although, it is not proven that the immune system of individuals has this ability. Despite being a very important topic, it is still a target of study by the scientific community, so there are not enough data to show that Th2 type responses become Th1.

5.3. Clinical Manifestations

One of the most commonly observed clinical symptoms in the co-infection with intestinal helminths is diarrhoea, whose degree of severity varies depending on the stage of HIV infection, which determines a greater or lesser vulnerability on the immunological level.(48) Furthermore, it greatly depends on the species of helminth by which the individual is infected.

However, it should be noted that, despite being a very characteristic symptom of HIV-positive and helminth-infected individuals, it is still possible to suspect HIV and helminth co-infection in the absence of diarrhoea. Abdominal pain and nausea are also frequently observed symptoms, as is remaining in a sub-febrile state.(2)

It is also common to have anaemia, which is observed in both children and adults, vomiting, hematemesis, bacteraemia, sepsis, cough, respiratory distress, chronic obstructive pulmonary disease, hypoxemia, diffuse alveolar haemorrhage and meningitis.(49)

5.3.1. Eosinophilia

Eosinophils stand out concerning other types of cells, about the defence of the host not only against parasitic infections, mainly caused by helminths but also in their role in the immunopathogenesis of viral infections.(45) In the bone marrow, about 6% of the nucleated

cells are eosinophils. When the absolute count of these cells exceeds 450–500 cells / μL, we consider that individuals have eosinophilia.(50)

Its development and maturation occur in the bone marrow over approximately one week under exposure to myeloid precursors such as IL3, GM-CSF and IL5. IL-5 is a key cytokine in the survival and persistence of circulating and tissue eosinophils, preventing apoptosis and promoting cell activation.(51) These cells infiltrate the primary and secondary lymphoid organs, such as the thymus, lymph nodes and spleen, as well as Peyer's patches in the intestine. Besides, ILC-2, which plays an important role in the physiological traffic of eosinophils, is also likely to be co-opted to divert eosinophils at inflammation sites under pathological conditions.(52)

Eosinophils are part of a complex network of interactions that involve a large number of immunocompetent and non-immunocompetent cells and tissues (Figure 9). The most relevant in this context is probably the axis between eosinophils and Th2 cells, which constitutes the nucleus of the so-called delayed hypersensitivity reaction of type IVb.(51) Th2 cells can stimulate eosinophils directly, through the release of IL5 or indirectly, promoting an adaptive humoral response and, in particular, the production of IgE.(53) Class E immunoglobulins can be recognized by eosinophils or activate mast cells during type I (immediate) hypersensitivity reactions.(50) Compounds derived from mast cells (such as prostaglandin D2, leukotrienes, CCL5 and IL5), in turn, stimulate eosinophils, which eventually cause tissue damage and are affected by the persistent immune response after acute mast cell activation. Also, they provide a crucial link between the eosinophil / Th2 axis and inflamed tissues, since they motivate the release of inflammatory stimuli, such as IL25, IL33 or TSLP from epithelial cells and stimulate Th2 through the release of IL4.(51)

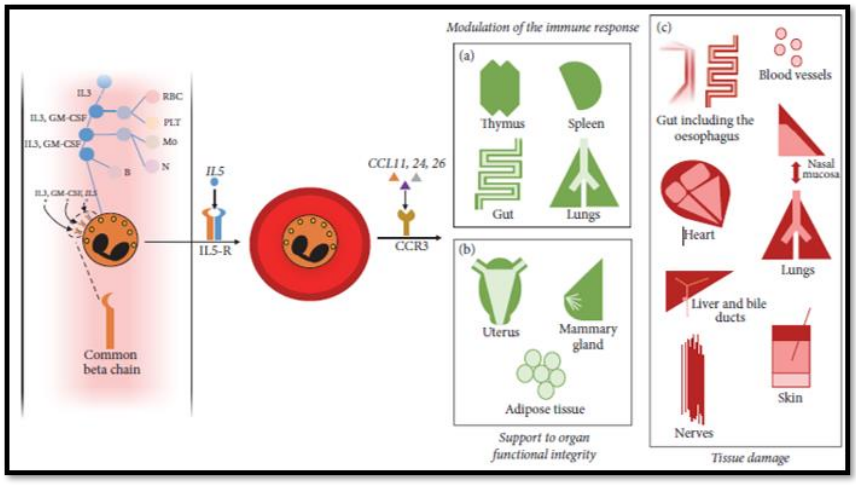

Figure 9 - Eosinophils - Development and maturation. [Adapted from (50)].

6. Undernutrition

Malnutrition and the risk of multiple micronutrient deficiencies is high in developing countries, due to plain diets based on basic, non-nutritious foods, as well as intestinal parasitic infections.(3) As expected, the overlap of their geographic distributions is similar.

Although the importance of nutrients is sometimes underestimated, there is a correlation between a person's nutritional state and their susceptibility to acquiring new infections.(54) Deficits in specific micronutrients disturb the normal function of components of the immune system, weakening its resistance mechanisms and, consequently, exposing them with more vulnerability to several infectious diseases.(39)

Nutritional status plays a fundamental role in maintaining the disease caused by HIV, namely concerning symptoms such as diarrhoea, anorexia, mouth sores, fever and loss of muscle mass. Food intake increases the therapeutic effect of drugs, stimulates the immune system, helps to defend against opportunistic infections and prolongs the progress of the disease, increasing the longevity and quality of life of patients.(55) Therefore, it is of great importance to know the immunomodulating effects of micronutrients and their interactions with HIV and the chronic parasitic intestinal infection in the planning of inclusive strategies, to promote nutritional health and increase specific therapeutics.(56)

However, it is not only malnutrition that favours the appearance of new infections. The infection itself is associated with the appearance of negative effects on the host's nutritional state, resulting from the decreased ingestion of nutrients due to the loss of appetite, decreased absorption of nutrients as a result of damage to certain organs, poor intestinal absorption of nutrients and loss of nutrients because of diarrhoea and the increase in urinary excretion.(57)

Thus, multivitamin supplementation in HIV-positive individuals can result in a lower viral load and, consequently, a higher CD4 + and CD8 + cell count, delaying the progression of HIV or its final stage - AIDS, also the risk of death.(58)

Malnutrition is a threat to the successful implementation of antiretroviral therapy regimens. For example, we may be facing a very effective ART therapy, but a population that is becoming so malnourished that they end up not resisting and dying for lack of nutritional deficits and not of HIV itself.(59) As such, the scientific community has, in

recent decades, tried to understand the relationship between nutritional deficits in HIV-positive individuals and an ART therapy instituted in them.

6.1. Metabolic Dysfunctions

HIV infection is also accompanied by severe metabolic dysfunctions. Oxidative stress is one of these dysfunctions resulting from the imbalance between the production of reactive oxygen species (ROS) and the concentration of antioxidants.(58) The exposure to oxidising agents challenges cellular mechanisms, and therefore their responses may create favourable conditions for the replication of HIV, becoming a cause of the increase in morbidity and mortality amongst patients with HIV/AIDS.(39)

7. Deworming and Therapeutics

7.1. Importance of Deworming

As already mentioned, although AIDS is present in tuberculosis and is one of the main causes of death of people infected with HIV worldwide, helminth infections, many of them serious, are widely spread around the world and to a large extent associated with HIV.(26) All parasites can elicit strong immune responses by releasing large amounts of antigens that have altered the immune system. Immunological activation of the host is the most critical determinant in the pathogenesis of HIV infection, with chronic immunological activation of the host due to helminth infections, often responsible for the progression of HIV, as previously reported.

Since helminth infections are widespread in most developing countries and are present in populations where HIV-1 is highly endemic (Figure 10), the interaction between these infections, both on the same host and at the population level, is of excellent importance and has potential practical implications.

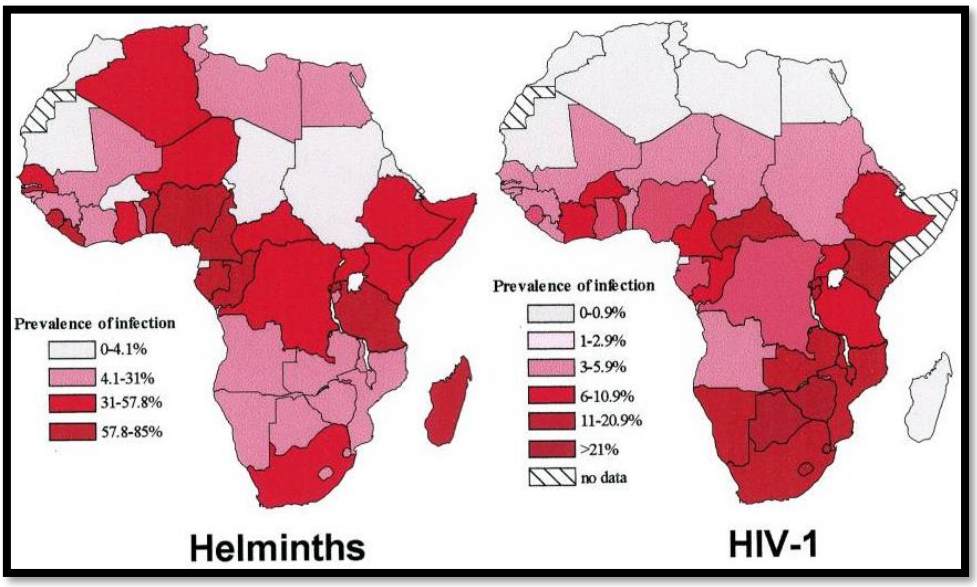

Figure 10 - Distribution of helminths and HIV-1 in Africa. [Adapted from(37)].

The immunological activation caused by the parasitic infection makes the individual more susceptible to HIV infection and, once acquired, the infection progresses much more

quickly.(29) The concept of deworming large populations has been the subject of growing awareness of its health benefits, particularly concerning general morbidity, anaemia and growth. The purpose of this practice is to deworming entire populations around the world, especially targeting younger generations.(32) Following this logic, the eradication of parasites in co-infected individuals should slow the progression of HIV.(34)

With the activation of the immune system by parasitic infection, an increase in the viral load (VL) of HIV occurs in the blood plasma, which means that HIV transmission is also favoured in co-infections.(60) The effect of deworming on the immune system was analysed by some scientists and the results, shown in Figure 11, exposed that 6 to 12 months after deworming there is a significant reduction in eosinophilia, blood IgE levels and immune activation (HLA-DR in CD3 cells). This suggests that the deworming itself caused normalization of the immunological profile of the individuals in which it was performed, which was not found in those with persistent parasitic infection. (34)

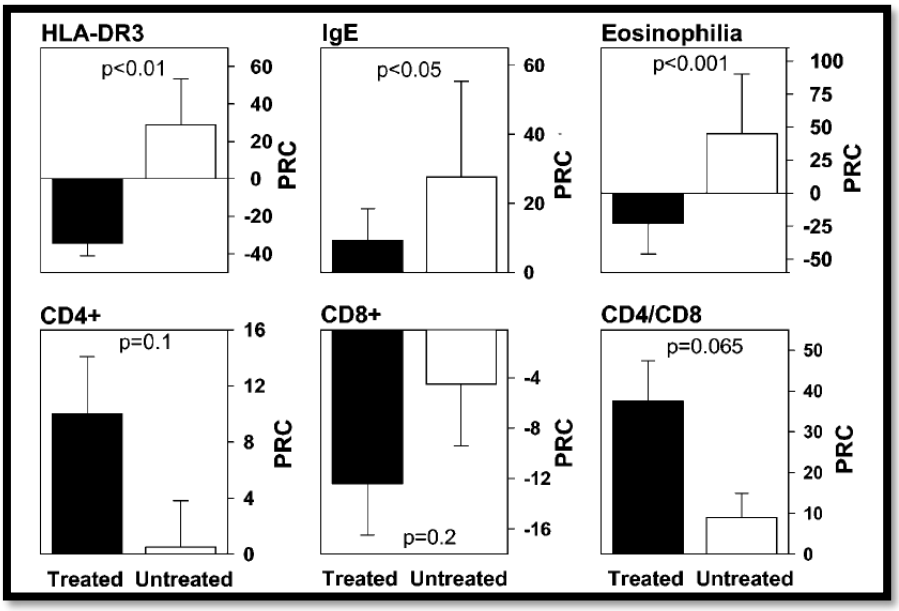

Figure 11 - Decreased immune activation following deworming. Effect of helminth eradication on the immune system. The graphs show the percentage relative changes (PRC) of immunological parameters between two consecutive blood tests taken 6 to 12 months apart. [Adapted from (37)].

In helminth infections a discrepancy can be observed between the peripheral CD4 and CD8 lymphocytes. There is a decrease in the number of CD8 T lymphocytes and an increase in the number of CD4 T lymphocytes, which results in a reduction of the CD4/CD8 ratio. A sharp increase in the proportion of activated T cells (HLA-DR) and CD8 and a significant increase in the number of CD4 and CD8 memory T cells (CD45RO), with

a concomitant significant decrease in the proportion of CD4 cells (CD45RA) and an important decrease in the number of CD8 and CD28 T cells. All these changes in the lymphocyte subgroups of peripheral blood mean that the capacity to develop immune responses against pathogenic agents is reduced. To confirm the importance of deworming, it is important to remember that most of these changes return to normal levels after the helminth infections are eradicated. In a study by ANDARGACHEW M. et al., Several groups of individuals were tested to try to understand whether the effect of deworming with and without antiretroviral therapy would have any effect on the control of co-infection. The groups used were divided into symptomatic and asymptomatic HIV seropositive individuals and healthy individuals, with and without helminth co-infection, from a population in Ethiopia. The total serum IgE levels served as a factor for the interpretation of immunological changes.(42)

As expected, both groups demonstrated high amounts of IgE, because the African population alone has higher IgE values, compared to individuals on the rest of the continents. However, the increase in the levels of total serum IgE in patients with HIV and infection by helminths may also be due to the immunological modulation caused by a parasitic infection that leads to a change in the polarity of the immune response, changing the production of Th1 cytokines to Th2 and polyclonal activation of B lymphocytes, which increase IgE secretion. These authors concluded that the decrease in IgE levels in HIV-infected and symptomatic individuals, after 12 weeks, regardless of whether or not they had co-infection with intestinal helminths, compared to asymptomatic individuals, the production of Th2 type cytokines (critical change in the cytokine balance) evolved to the stage of AIDS. Also, the increase in IgE levels in HIV-positive and asymptomatic individuals, in 12 weeks, in the absence of antiretroviral and albendazole therapy occurs simultaneously with the decrease in CD4 T cell levels, which allows us to associate it with a faster disease progression. Finally, in the same 12 weeks, the fact that there was a decrease in the total serum IgE levels with deworming, indicates that the eradication or decrease of helminths in individuals infected concomitantly with HIV will slow the progression of the HIV/AIDS disease.(42)

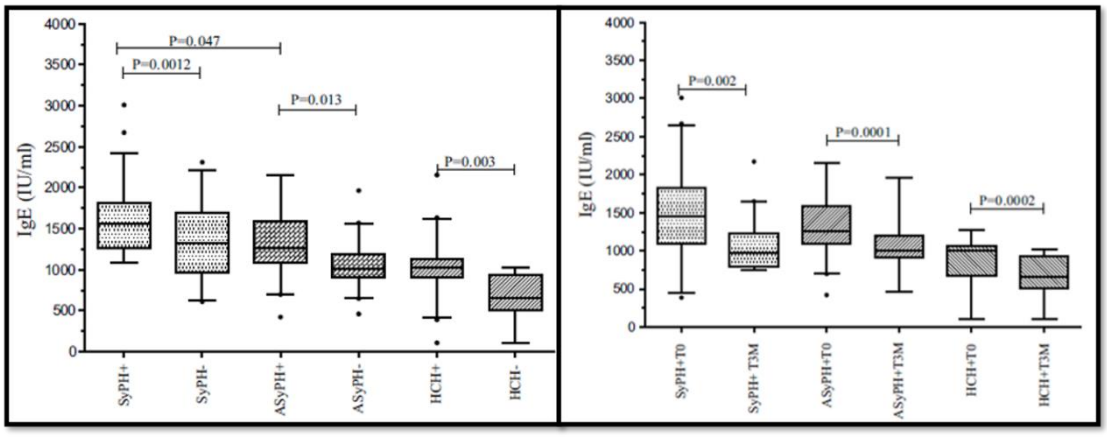

Figure 12 - Effect of deworming populations with HIV-positive individuals symptomatic and asymptomatic and healthy controls with and without co-infection with helminths. [Adapted from(42)].

7.2. Antiparasitic Therapeutic

Following the previous study done by ANDARGACHEW M. et al., we can conclude that the decrease in total serum IgE levels after antiparasitic therapy, in this case, with Albendazole, will contribute to a change in the immune response towards Th1, which is a very favourable prognosis for HIV-positive patients. HIV, as it delays the progression of the disease and does not leave them so fragile. Therefore, both deworming and albendazole play a very important role in delaying complications and controlling the disease.(42)

7.3. Antiretroviral Therapeutic

Despite the high rate of co-infection with helminths and the benefits of deworming, there is no routine triage for helminth infections and/or regular mass deworming in most tropical countries, including Ethiopia, even for patients with HIV/AIDS.(42) There is little evidence regarding the benefits of deworming in HIV-infected individuals who have ART. Consequently, it has been suggested that deworming during the beginning of ART will significantly reverse the elevated Th2 immune response.(5) The impact of deworming was evaluated jointly with TARV on immunological activations in HIV-infected patients, asymptomatic HIV-positive individuals, and healthy controls. According to previous suggestions that Africans generally have elevated total serous levels of IgE, patients in this study also showed a high total serous level of IgE, as shown by the total levels of IgE three times higher than the reference intervals, independently of HIV and helminth co-infections.

Also, the very elevated serous level of IgE in HIV patients and in those co-infected with helminths may be a result of the immunological regulation induced by these, which provokes a change in the production of Th1 and Th2 cytokines and the resulting polyclonal activation of B cells which increase the secretion of IgE.(42)

However, the change of the immune response during helminth co-infection reverted back to normal after deworming amongst the Ethiopians, which suggests that decrease was in fact the result of an isolated helminth infection, without the influence of other environmental factors.(42)

This is due to the fact that helminth infections are powerful stimulators of the IL-4 dependent helminth-specific IgE synthesis. The increase of serous IgE levels amongst symptomatic patients, independently of helminth co-infection and the high level of IgE reduction 12 weeks after TARV and deworming when compared to asymptomatic HIV-infected individuals, suggesting that a Th2 response occurred in advanced conditions of the HIV / AIDS disease.(5)

Furthermore, the increase in serous levels of IgE in asymptomatic HIV-positive individuals within 12 weeks in the absence of TARV and albendazol is similar to the decrease in CD4+ T cell count and may be associated with the rapid progression of the diseases after following its natural course. A significant decline in the serous IgE level 12 weeks after deworming in this study agrees with the finding that the reduction or elimination of helminths resulted in a significant improvement in the proliferation of T cells and supports the notion that deworming of individuals co-infected with helminths may delay the progression of HIV disease.(42)

Surprisingly, a significant decline was observed in the serous level of IgE 12 weeks after the simultaneous administration of ART and albendazol. This supports the fact that the administration of TARV reduces the indices of immune activation and shows the presence of synergism between the two drug classes.(42)

However, it is difficult to attribute the reduced IgE solely to TARV and albendazol, seeing as symptomatic HIV-infected patients were also on prophylaxis with cotrimoxazole and the anti-helminthic effect of cotrimoxazole cannot be discounted, acting like a confounding effector.(42) Therefore, mass deworming should be integrated in the ART programme in helminth endemic areas of tropical countries.(5) Although the treatment of

helminth and schistosomiasis intestinal infections is relatively simple and inexpensive, current options are limited to certain drugs and resurgence is expected.

The influence of antiretroviral therapy is studied by other authors, showing that a significant decrease in the prevalence of certain parasitic infections has been found in patients with antiretroviral therapeutics, which suggests that improving the functions of the immune system contributes to the elimination of intestinal parasitic infections.(51) At the end of 2019, 25.4 million people were accessing antiretroviral therapy, compared to 6.4 million in 2009.(7)

Besides a decrease in the levels of HIV viremia, HAART (highly active antiretroviral therapy) causes a decrease in the levels of IgE antibodies.(2) It is hoped that patients who have undergone HAART will increase their values of CD4+ T lymphocytes and recover their immune functions. Finally, the treatment is considered successful as long as there is no decrease of 30% or above in the number of CD4+ T lymphocytes.(1)

8. Vaccines and Future Perspective

As we have seen before, most people living in endemic regions are infected with at least one species of helminths and about 50% of these people are co-infected with HIV.(43) Also, in these regions, reinfection with helminths is very common after successful treatment has been administered.(42)

Anthelmintic therapies or helminth-specific vaccines are unlikely to have beneficial effects in regions with a high incidence of helminth infections and HIV. However, studies are still being done and it is necessary to take into account aspects that have not yet been considered, such as the age of the host, the intensity of helminth infection or the magnitude of the viral load affect the effectiveness of the therapy.(2)

Currently, it is estimated that an HIV vaccine to be effective must induce a Th1-type cellular response. It should induce specific cellular responses to destroy cells infected with the virus and neutralize it, to eliminate the virus before it spreads to tissues or to block the virus from entering mucous membranes. In this sense, it is expected that future HIV vaccines will be administered to co-infected people.(47)

9. Conclusion

As discussed previously, there are several types of co-infection with HIV, with helminth co-infection being less valued, as they belong to NTD's. The precarious conditions, malnutrition, and susceptibility to new infections, namely by HIV and parasites, are a cycle that is still far from being fought in regions where its incidence is higher, especially in African countries.

The antiretroviral therapeutic itself can be a cause of diarrhoea, so there are many aspects to consider in future studies because it is necessary more research in the different classes of antiretroviral drugs, such as protease inhibitors, namely, in pharmacokinetic parameters like the dosage.(61)

The burden of HIV infections occurs in Sub-Saharan Africa, and so, the helminths incidence does. Parasitic infections caused by helminths are not the target of attention by the scientific community; these pathologies are dissembled since these regions are less developed and there is no much interest init. Prevalence studies of enteropathogens are needed, both to inform regional and national treatment strategies and to highlight the burden of disease attributable to neglected or newly discovered pathogens. Finally, new therapies for these pathogens are urgently needed for both HIV infected and uninfected patients.(61)

Co-infection between HIV and intestinal helminths leaves the individual more weakened, as it changes the polarity of the immune response towards a predominantly Th2 cell response. Helminths are known to distort immune responses in relation to the Th2 phenotype, which according to the possibility above would be harmful to individuals co-infected with HIV-1. This led to the supposition that the treatment of helminth infections in co-infected individuals would be beneficial to their HIV-1 disease.(7)

Several authors report correlations between changes in specific immunological parameters, such as T cell polarity and susceptibility to pathogenic agents, raising the possibility that many of the effects of the co-infection are mediated by the immune system itself.(6)

Nevertheless, the administration of antiretroviral therapy and the treatment of helminthic infections showed a tendency to negatively regulate the observed

immunological activation. Besides, the role of helminths in the host and in other infections cannot be overestimated, and so should be adequately considered in the treatment of HIV during helminth co-infection.(5)

If we combine antiparasitic therapeutics with ART, then better results will be observed regarding antiretroviral therapeutics. This allows us to conclude that the solid deworming of HIV-positive individuals should be accompanied by ART.(2)

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