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Opportunistic Infections Associated with Immunodeficiency in Patients with Hiv-Aids: A Study of Related Psycho-Socio Factors

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ABSTRACT

The human immunodeficiency virus (HIV) is one of the most important health problems worldwide. At the end of 2020, the World Health Organization estimated that there are 37.7 million people living with HIV infection. Until the middle of this year 2021, 36.3 million deaths related to immunodeficiency have been registered, of which around 680,000 occurred in 2020. The objective of this study is to relate HIV infection with the apparition of opportunistic infections, based on the evolution from the acute phase of infection to a chronic phase. In addition, the deficiency of the host's innate and adaptive immune response is correlated with a decrease in CD4 T lymphocytes and an increase in viral load. For this, a retrospective observational analytical study is carried out where cohort studies and articles published in reliable databases are prioritized. The research describes HIV and its genes, virus replication, cell modulation, detection of infection, the immune response against HIV and colonization of microorganisms in the host. It is concluded that the HIV virus is a predisposing factor for the appearance of opportunistic infections. Also, the etiological agents of the most common opportunistic infections are established, to which infected individuals are exposed based on their immune response. In addition, other factors such as adherence to antiretroviral treatment in the patient and early diagnosis are considered.

Keywords: HIV, opportunistic diseases, immune response.

INTRODUCTION

Human immunodeficiency virus (HIV) belongs to the family *Retroviridae* (Lentivirus) is associated with neurological and immunosuppressive diseases (1). They are considered simple, inside they contain a strand of RNA, of positive polarity, with approximately 9.8 kilo bases (kb). (1,2). This genome encodes polyproteins, among which are: *gag*, *Pol* and *Env*, which will help in the viral life cycle (3,4).

The HIV virus is enveloped by a lipid bilayer, which contains glycoproteins such as gp41 and gp120, which are essential for the progress of the life cycle of the virus Of these, gp41 promotes cell-virion fusion while gp120 varies antigenicity and specificity with receptors since it is highly glycosylated (5).

In humans, the virus can be transmitted even when the patient is asymptomatic, through body fluids (blood, semen, secretions) sexually, perinatally or by blood inoculation (5). People prone to contagion are: addicts to narcotics applied by the parenteral route (6,7), individuals with multiple sex partners, newborns with HIV-reactive mothers,

sex partners of infected individuals, people who have had infected organ transplants (5). In terms of epidemiology, it is a disease that has increased in prevalence (8). However, due to antiretroviral treatment, the mortality rate in infected people has decreased since 2004. (8).

The infection is acute and persistent with chronic stages where there is viral overproduction. The onset of symptoms is related to decreased CD4 T lymphocytes and increased viral load (5,7). It is characterized by a flu-like picture (9). Without antiretroviral therapy, the patient has a prognosis of acquired immunodeficiency syndrome (AIDS) because CD4 T lymphocytes decrease drastically due to the cytolytic action of the virus (10), which increases the predisposition to opportunistic infections.

This literature review will present the evolution from the acute phase of HIV infection to a chronic phase. In turn, deficiency of the host's innate and adaptive immune response will correlate with decreased CD4 T lymphocytes and increased viral load. Finally, the etiological agent of the most common opportunistic infections related to the immune status of the HIV-infected host will be established.

MATERIALS AND METHODS

This bibliographic review is a retrospective observational analytical study where the collection of data from high-impact scientific articles, meta-analyses, cohort studies, among others, is prioritized. The search yielded a total of 785 articles of which 21 were chosen that explained about the immunodeficiency of patients diagnosed with HIV and opportunistic infections. Scientific opinion articles were discarded since they have no scientific evidence.

SOURCES OF INFORMATION AND SEARCH STRATEGY

An exhaustive bibliographic review was carried out in bibliographic search engines such as Scopus, Web de Science, PubMed, Elsevier, ClinicalKey, as well as high impact journals such as The Lancet Infection Diseases, Nature Reserch, Science research Journal, Clinical Trials, looking for keywords such as: HIV, opportunistic infections, immunosuppression, the search began in April 2021.

Articles were selected according to title and abstract, some cohort studies were included. In addition, a qualitative synthesis of the results was performed and HIV infection and opportunistic infections affecting immunocompromised patients were correlated.

RESULTS

HIV and its genes

The genetic material of HIV contains the information for the formation of 3 polyproteins (*GAG, POL and ENV*) and six accessory proteins (Tat, Rev, Nef, Vpr, Vif and Vpu) (2–4). Polyprotein *gag* is synthesized in the cytosol of the host cell, composed of four proteins: capsid (CA), matrix (MA), nucleocapsid (NC), P6 and two short peptides (SP1 and SP2) (3,5). The CA-CA interaction makes possible the formation of the capsid of the new virions (3). MA will form a myristilate protein that lies below the vita envelope, which is called a viral matrix. The NC protein is responsible for wrapping viral RNA and P6 which is important for viral assembly and maturation (4,11). In turn, the polyprotein *Pol* encodes three viral enzymes reverse transcriptase (RT), integrase (IN) and protease (PR) (1–4). Reverse transcriptase will allow the conversion of viral RNA of positive polarity to viral DNA of negative or complementary polarity (1,4). The integrase enzyme allows the coupling of the viral genome to the host genome (3). Protease intervenes in the maturation of new virions by cutting the polyprotein, *gag*, in its smallest and most functional components (3,4). Polyprotein *Env* encodes the glycoproteins gp41 and gp120, which surround the surface of the viral membrane and may interact with the CD4 receptor and the CCR5 or CXCR4 coreceptors (3,5).

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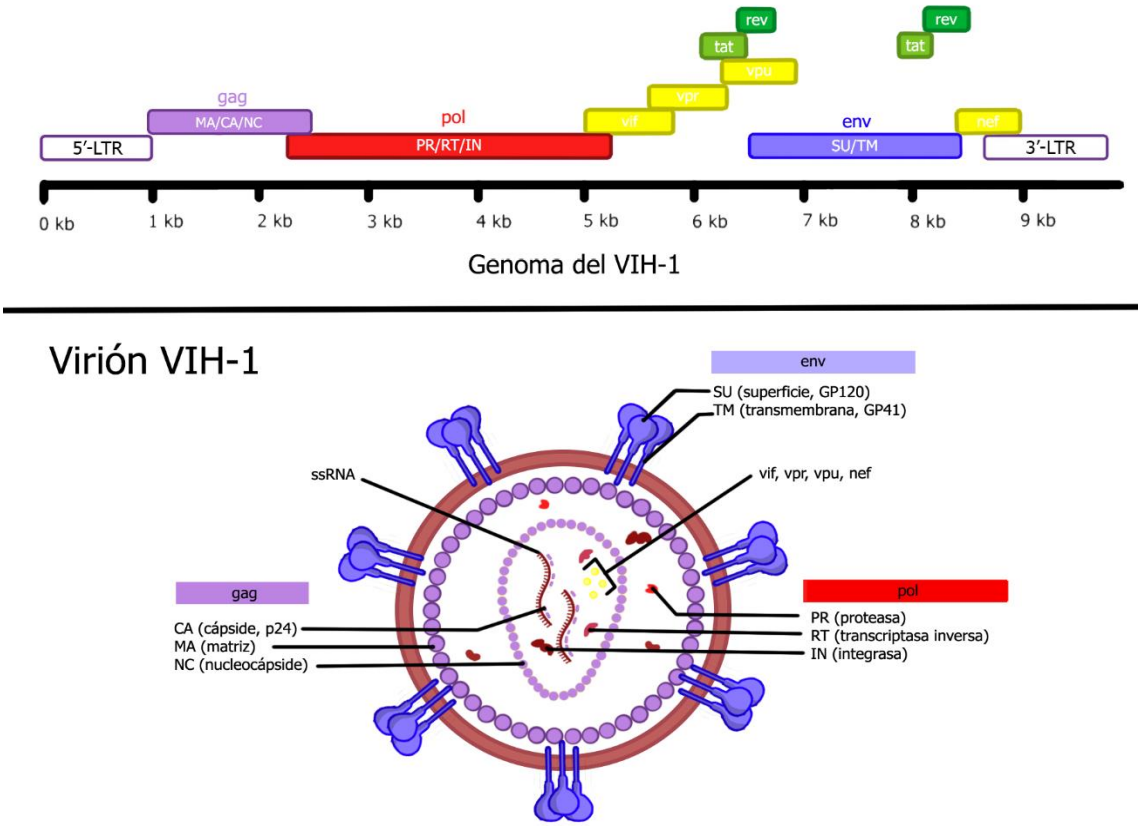

Figure 1. HIV genome and structure. Formed by a single-stranded RNA chain of 9.8 kb. The polyprotein *gag* that is made up of matrix (MA), capsid (CA), nucleocapsid (NC). The *env* portion will be responsible for the formation of GP 120 and GP 41, surface glycoproteins and transmembrane respectively. The *pol fraction* is responsible for the generation of protease (PR), reverse transcriptase (RT) and integrase (IN) enzymes. In addition, there are accessory proteins vif, vpr, vpu and nef, important in the life cycle of the virion.

Source: Rossi, E., Meuser, M. E., Cunanan, C. J., & Cocklin, S. (2021).

Virus replication

The HIV life cycle can be divided into two phases: early/acute and late/chronic. The early stage begins from the union of the infectious virion with the eukaryotic cell and ends with the integration of the viral genome into the DNA of the host cell. The late stage consists of the period after integration until viral maturation (3).

The early stage begins with the binding of viral glycoproteins (gp120 and gp41) with the primary receptors, the CD4 protein, and with the second receptor, which is a G protein-coupled receptor (CCR5) (3,5). These types of receptors are present on immune system cells, such as macrophages, dendritic cells, and especially CD4 T lymphocytes. (5,9).

These associated coreceptors in the initial HIV infection are also expressed in the central and peripheral nervous system, and in intestinal cells. (3,5). By binding the virus activates the eukaryotic cell, and brings the viral envelope closer to the plasma membrane, allowing gp41 to interact with the CCR5 protein, promoting membrane fusion. (3).

After membrane fusion, the viral genome is released into the cytoplasm of the eukaryotic cell. (3). Inside, the virion capsid binds to MAP1A and MAP1S proteins, which form microtubules in the host cell, to mobilize in the cytoplasm. This binding is stabilized by CLASP2 which is a positive end tracking protein (TIP) that reinforces

the interaction between the N-terminal and C-terminal domains of the capsid with microtubules. In addition to this, there are motor proteins that help the mobilization of the virion, FEZ1 and kinesin-1 (3,4).

Reverse transcriptase (RT), encoded by the gene *Pol*, uses transfer RNA (tRNA) in the virion as the primer and synthesizes negative polarity complementary DNA (cDNA)(3,12). Unlike other retroviruses, the double strand cDNA of HIV and other lentiviruses can enter the nucleus of the host cell through pores in resting T cells. (2). This process of retrotranscription can begin in the cytoplasm and end in the nucleus of the host cell. (3). RT is prone to copying errors, which gives it a high mutagenic capacity (2,12).

Inside the nucleus, the retrotranscription finishes. Viral cDNA is stabilized by cyclophilin A (CylA) and then added to the chromatin of the host cell by the action of the integrase enzyme (1–3,12). Once integrated, the late phase begins. The infected DNA is transcribed as a cellular gene by the RNA polymerase II of the host cell. Genome transcription produces mRNA, which contains the sequences of genes *gag*, *Pol* or *Env*, to synthesize new virions (3,12).

The gene *gag* allows to synthesize glycoproteins, the gene *Pol* enzymes, and the gene *Env* The capsid. Once all the parts of the new virion are formed, inositol hexaphosphate (IP6) coordinates the assembly of the new capsid. (1,4). Once formed, they will approach the membrane of the host cell and then be expelled by budding like an immature viron. (2). As a final step, the interaction of the protease enzyme is needed to cut the polyprotein into segments. *gag*, be able to mature, and thus infect new cells (3). During a person's chronic infection, the *Env* and *gag* can mutate given the error rate during viral genome replication (9).

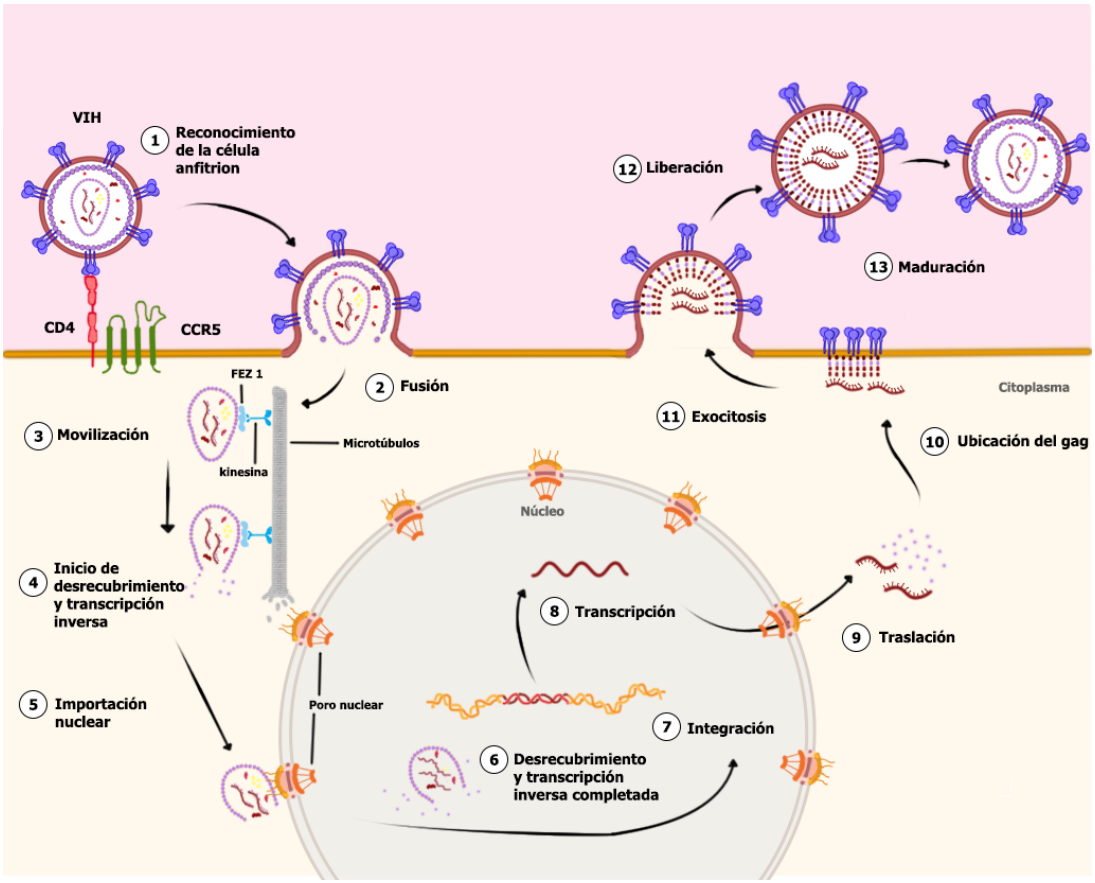

Figure 2. HIV replication and structure.

Source: Rossi, E., Meuser, M. E., Cunanan, C. J., & Cocklin, S. (2021).

Errors during retrotranscription are common, resulting in incomplete sections that will later lead to destruction of the host cell by pyroptysis. (5). Pyroptysis is a type of cell death in response to inflammation. This decreases the number of CD4 lymphocytes in the patient, making them immunosuppressed. (5). In a state of immunosuppression, opportunistic infections appear. The most frequently arising are candidiasis, tuberculosis, diarrhea, Pneumocystis jirovecii, by cytomegalovirus, herpes zoster, and in lesser recurrence, progressive multifocal leukoencephalopathy, cryptococcosis, toxoplasmosis, isosporiasis, Burkitt's lymphoma, Kaposi's sarcoma (9,13–15).

Cell modulation

The human body has an immune system, composed of cells and molecules, capable of responding to stimuli caused by foreign agents. The immune system has two types of responses, the nonspecific immune response, called innate immunity, and the specific immune response, called adaptive immunity. The first is made up of natural barriers, cells and blood proteins (complement system and other inflammatory mediators). The second will develop a response according to the invading agent and consists of B lymphocytes that act in humoral immunity, and T lymphocytes that intervene in cellular immunity. Both systems act in synergy for the protection of the individual. CD4+ T cells consist of populations with different functions that are specified in Table 1(5).

The initial HIV infection begins when it passes through the mucosa, then goes to lymph nodes where the virus will increase its viral load. In the first 10 days that the individual is infected, the eclipse phase occurs, which refers to the period between exposure to the infection and its spread in the body. At this stage the viral RNA is still undetectable in the plasma. The entry of a primary virus preferentially infects CD4+ T lymphocytes which, with virus-induced apoptosis into the cell, contributes to disease progression with deterioration of cellular machinery, decrease in lymphocytes and subsequent loss of immune functions (2,5,7).

The capacity of the innate immune system will also be affected by the progression of infection, if it is not controlled in the early stages by neutralizing antibodies or cytotoxic T lymphocytes. A compromised immune system and viral mutagenic capacity are counterproductive to the control of its replication. This will allow acute-persistent infection and an overproduction of the virus that will cause quantitative depletion of white blood cells accompanied by functional alterations and deterioration of lymphoid organs triggering immunodeficiency (5).

HIV Screening

When the presence of the virus is detectable in blood it is called moment zero, T0, (10 days from infection). There is an increase in the number of virions in the plasma that occurs on days 21-28 in which the patient may present symptoms due to the decrease in CD4+ T lymphocytes. The time between infection and the peak of viremia includes the first 25 days, which is the period in which a treatment would be effective in stopping the advance of viral replication, preventing the reduction of CD4 + T lymphocytes and normalizing the generalized immune response (5).

Early immune response to HIV and colonization of microorganisms towards the host

HIV infection is usually detected many years later due to its nonspecific prodromal picture. Prior to the acute phase, it produces flu-like symptoms: headache, nausea, lymphadenopathy, pharyngitis, which resembles infectious mononucleosis (9). The next few weeks will develop the acute phase. The virus will find cell reservoirs, even in cells that do not divide, that will continue to allow its replication, both in the immune system and in the central nervous, genitourinary and intestinal systems.

The chronic phase has no symptoms, but the decrease in white blood cells continues and allows the appearance of infections. Finally, with a number of CD4+ T lymphocytes less than 200 cells/L of blood, the patient has AIDS, which favors the development of opportunistic infections. (4,9,10). It should be borne in mind that the prevalence of these opportunistic diseases is related to risk factors such as: low CD4+ lymphocyte count, smoking, alcohol and history of tuberculosis. The introduction of combination antiretroviral therapy and the use of prophylactic antimicrobials for diseases have changed disease prevalence over time.

	To	B	C
CD4+ Lymphocyte Categories	Acute infection Asymptomatic infection	Infection Symptomatic not A or C	Conditions AIDS Indicators
(1) ³ 500 cell/mm^3	A1	B1	C1
(2) 200-499/mm3	A2	B2	C2
(3) < 200/m L	A3	B3	C3

Table 1. Classification of HIV infection according to the CDC (Control Diseases Center).

Candidiasis (Candida albicans)	It is considered an opportunistic infection when it causes severe or persistent infections in the mouth or vagina, or when it occurs in the esophagus and lower respiratory tract.
Candidiasis *(Candida albicans)*	It is considered an opportunistic infection when it causes severe or persistent infections in the mouth or vagina, or when it occurs in the esophagus and lower respiratory tract.
Coccidioidomycosis *(Coccidioides)*	Lung infections
Cryptococcosis *(Cryptococcus neoformans)*	Usually affects the lungs or central nervous system (brain and spinal cord)
Cryptosporidiosis *(Cryptosporidium)*	Digestive tract infections
Kystoisosporiasis *(Cystoisospora belli)*	Generalized malaise manifesting with diarrhea, fever, headache, abdominal pain, vomiting, and weight loss
Cytomegalovirus *(CMV)*	It can infect multiple parts of the body and cause pneumonia, gastroenteritis, encephalitis, and retinitis
Herpes simplex virus	It can cause bronchial infections, pneumonia, and esophagitis.
Histoplasmosis *(Histoplasma ssp)*	It usually starts in the lungs and produces symptoms similar to those of influenza or pneumonia.
Kaposi's sarcoma *(Herpes virus VIII)*	They can be life-threatening when they affect organs within the body, such as the lungs, lymph nodes, or intestines.
Lymphoma	Some, such as non-Hodgkin's lymphoma and Hodgkin's lymphoma, are associated with HIV.
Tuberculosis (Mycobacterium tuberculosis)	It can cause infection in the lungs.
Mycobacterium avium *complex*	Infections with these bacteria spread throughout the body
Pneumocystis *pneumonia*	The first signs of infection are shortness of breath, high fever and dry cough.
Pneumonia	Infections with the bacterium *Streptococcus pneumoniae*, also called *Pneumococcus.* People with HIV should be vaccinated to prevent *Streptococcus pneumoniae infections.*
Progressive multifocal leukoencephalopathy	Symptoms may include loss of muscle control, paralysis, blindness, problems with speech, and altered mental status.
Salmonella septicemia	It can affect anyone and usually causes nausea, vomiting and diarrhea.
Toxoplasmosis *(Toxoplasma gondii)*	Infection can occur in the lungs, retina of the eye, heart, pancreas, liver, colon, testicles, and brain.
Consumptive HIV syndrome	Wasting refers to the loss of muscle mass, although some of that loss may also be due to fat loss.

Table 2. Common opportunistic infections. Source Center for Disease Control and Prevention.

DISCUSSION

In this study it is possible to determine the relationship between HIV infection and its progression towards opportunistic infections. The appearance of the latter is favored by ignorance of the presence of viral infection in the individual, by not having antiretroviral treatment (ART) or because such treatment is deficient (20). The risk of these infections is because the virus causes a depression of the immune system in individuals.

The classification of the stage of the disease is considered based on a relationship between the symptoms that occur in the acute phase, chronic phase and conditions indicative of AIDS, and the number of CD4 lymphocytes in the blood, based on the categorization made by the Center for Disease Control and Prevention (CDC) (20).

A considerable decrease in these lymphocytes can lead to immune system deficiency with a number of CD4 cells less than 200 cells per milliliter in blood. It is proposed that the depletion of CD4 lymphocytes continues during the chronic phase, which leads the patient to be an imminent candidate of suffering infections despite continuing to receive an ART. (9, 16).

The CDC and the World Health Organization (WHO) agree that most opportunistic infections are caused by fungi that affect a high percentage of the respiratory system, followed by complications at the nervous level. Above all, in a chronic phase of the disease infections can also be bacterial or viral.

Candida spp *infection*;It is the most common, considered opportunistic when it causes severe or persistent infections that affect the respiratory and digestive system (20). Other microorganisms responsible for infections directed to the respiratory system are *coccidioides, cryptococcus neoformans, CMV, histoplasma, pneumocystis jirovecii and mycobacterium tuberculosis.* On the other hand, complications in the nervous system are associated with *cryptococcus neoformans, CMV, JC polyomavirus and toxoplasma gondii,* to mention the most relevant (20).

These data are corroborated by reviewing a cohort study conducted in Korea between 2006-2013, which establishes that the most frequent opportunistic infection was Candidiasis, followed by tuberculosis, pneumocystis jirovecii, *cytomegalovirus* CMV and herpes zoster, less frequently Kaposi's sarcoma and toxoplasmosis(13). However, it contrasts with a cross-sectional study conducted in Taiwan in 2018, which establishes *Pneumocystis jirovecii* as the most frequent, followed by *Cytomegalovirus*, tuberculosis, and finally candidiasis (14).

Also, a cross-sectional study, using a random sampling method conducted in Ethiopia in 2018, established that the diseases with the highest prevalence in immunocompromised patients were skin diseases, diarrhea, bacterial pneumonia, recurrent upper respiratory tract infections, and to a lesser extent, tuberculosis. (15)

HIV infection is a risk factor, patients are exposed to other infections responsible for the development of subsequent morbidities or responsible for increasing the mortality rate (14, 15). The evolution of the disease also depends on the sociodemographic and clinical situation, that is, the patient's environment, access to adequate ART, the risk of contracting other infections and the management of patients with HIV (14, 15).

It should be noted that the prevalence of these opportunistic diseases is related to factors such as: low CD4+ lymphocyte count, smoking, alcohol and history of tuberculosis, as established in the Korean Journal cohort study. In addition, this study clarifies that the introduction of combination antiretroviral therapy and the use of prophylactic antimicrobials for diseases have changed the prevalence of these over time. This last fact is reiterated in the BMC Infectious Diseases study, as well as in the information given by the CDC. (14, 15, 20)

The disease is not the same in all patients, the infection can be controlled by so-called elite controllers. In whom the components impede the normal course of the viral life cycle referring to the effectiveness of TCD8 + cell response. However, these make up a small group that are of interest to establish an effective therapy (9,16).

CONCLUSION

Based on the information, the HIV virus is presented as a predisposing factor for the appearance of opportunistic infections, and the classification of the stages of infection is established. At the same time, the etiological agents to which infected individuals are exposed are exposed based on their immune response and the phase of infection

through which they occur, taking into account other factors such as adherence to antiretroviral treatment in the patient and early diagnosis.

In the acute phase, flu-like symptoms appear that usually go unnoticed, HIV has an affinity for cells that have CD4 and CCR5 receptors, such as macrophages, dendritic cells and, especially, CD4 T lymphocytes. In this first stage, infection by microorganisms that cause opportunistic infections is less likely. These appear in the chronic phase in which the already described host cells begin to decrease, especially CD4 lymphocytes, responsible for acting in infectious processes and fundamental for the performance of the immune system. In people with AIDS, the CD4 lymphocyte count is less than 200 cells/ml in the blood, so the immune system is highly compromised and more likely to infection.

The most common infections are caused by fungi such as candidiasis that affects the skin, mucous membranes and membranes throughout the body, followed by *coccidioides, cryptococcus neoformans, CMV, histoplasma, pneumocystis jirovecii, mycobacterium tuberculosis, polyomavirus JC and toxoplasma gondii,* which are related to affections to the respiratory tract and nervous system correspondingly.

The importance of timely diagnosis and indication of ART to achieve infection control needs to be raised. According to the research, there is information that allows the establishment of ideas for future research to be carried out, with a focus on the small but important group called elite controllers, who may be the key to the development of new therapies with greater effectiveness than the current ones.

Cells	They are formed in the presence of cytokines	Produce	Function	Action	Examples of microorganisms	Diseases
Th1	IL-12	IL2 and IFN-γ	Activate macrophages and promote B lymphocytes to produce IgG	Control infections by viruses and intracellular organisms IFN-γ activates CD8+ macrophages and T lymphocytes	Mycobacteria, *Toxoplasma gondii, Aspergilus spp.*,	Tuberculosis Leprosy Toxoplasmosis Aspergillosis

Th2	IL-4	IL-4, 5, 6, 10 and 13	Activates mast cells and eosinophils, and promotes IgE production	Direct IgE-mediated responses and parasitic infections		Common allergic reactions
Th17	TGF-β, IL-6 and IL23	IL-17, IL-21 and IL-22	It induces the formation of IL-8 and recruitment of neutrophils and macrophages.	It attracts neutrophils, protects in epithelial and mucous barriers. Inhibits fungal infections	In skin *S. aureus*; in colon *Citrobacter rodentium*; in lungs *Klebsiella pneumoniae, Pneumocystis carinii*; in the mouth *Candida albicans* and in the vagina *Chlamydia*.	Epidermitis Colitis (infectious diarrhea) Pneumonia Muthrush Chlamydia
T reg	TGF-β only	TGF-β and IL-10	Suppress immune response	They regulate the proliferation of T lymphocytes and maintain tolerance to self antigens.		Autoimmune diseases
Macrophages	CD23s, ICAMs, CD14s, CD163s	Pro-inflammatory cytokines	Initiation of the inflammatory process by releasing cytokines	Activation of other cells in response to inflammation	*M. tuberculosis*	Tuberculosis

Table 3: Cellular and molecular immunology 8th edition; Colombian Journal of Endocrinology, Diabetes and Metabolism.

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