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HUMAN IMMUNODEFICIENCY VIRUS - HIV: A REVIEW

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ABSTRACT

The Human Immunodeficiency Virus - HIV is responsible for causing Acquired Immunodeficiency Syndrome – AIDS. This virus also affects millions of people in the whole world, generating large global impact. It is a member of the lentivirus family of animal retrovirus and has an affinity for defense cells of the body, which the main target is the CD4 + T lymphocytes. Once connected to a component of this cell, the HIV will penetrate it and multiply, destroying them, by weakening the immune system, making it fragile and susceptible to opportunistic diseases. There are two known types of HIV, which are deeply related, named as HIV-1 and HIV-2. HIV-1 is the main cause of AIDS, HIV-2 differs in genomic structure and antigenicity, also causes the disease, but with slower progression. AIDS is the clinical manifestation generated by HIV, once the immune system is compromised. It is estimated that, in Brazil, 718 000 people living with HIV / AIDS. There is, currently, no effective vaccine or cure for AIDS, however effective antiretroviral therapies have been used. Through this literature review the paper aimed to show on the HIV virus, its general features, its immunological changes, the national level of this epidemiology, the diagnosis and treatment, warning about the importance of this infectious agent and its prevention, towards control and reduction to the AIDS epidemic.

KEYWORDS: HIV, immune system, immunodeficiency.

1. INTRODUCTION

Recognition of Acquired Immune Deficiency Syndrome (AIDS) began around 1981 in the United States (US), due to the increased number of patients living in San Francisco or New York, male, gay and adult sex, which presented immune suppression of the immune system, *Pneumocystis carinii* pneumonia and Kaposi's sarcoma[1,2,3].

The Human Immunodeficiency Virus (HIV) causes AIDS. This infection is through the transfer of viral particles present usually in the blood, semen, vaginal fluid of an infected individual to another uninfected, and condom use one of the main prevention means[1,2,5], vertical transmission is also a form of contagion, where there is transfer of the mother's virus to her child during pregnancy, childbirth or breastfeeding[6].

After purchasing the viral envelope glycoproteins virus reach the defense cells, causing immunological changes, the main lymphopenia caused by direct lysis of CD4 + T lymphocytes (CD - Cluster of Differation, specific group number 4), leading to functional defects in immune system. Treatment is by means of antiretroviral drugs (ARVs) which aims to block HIV replication cycle[1,2].

Despite the HIV virus is well known and widespread, the growth in the number of infected individuals is a global concern, as demonstrated by the high mortality rate from the disease progression in humans. Through this literature review sought to show on the HIV virus, their general characteristics, main immunological changes, bring information to forms of prevention, diagnosis, treatment and epidemiology at the national level, contributing to awareness and decrease in the number of cases.

2. MATERIAL AND METHODS

In order to produce the present study, we conducted a research of keywords in the databases: PubMed, Lilacs and SciELO. The Keywords used were HIV, immune system, immunodeficiency. We selected the most relevant studies, which correspond to the period 2000 to 2014.

3. LITERATURE REVIEW

General characteristics of HIV

HIV belongs to the family *Lentiviridae*, animal retroviruses, identified as two strains, HIV-1, which was isolated from patients with AIDS in 1983, known as the most virulent to attain all the world's population; The

second strain, called HIV-2, was discovered in 1986 and is found primarily in West Africa[3,6,7].

HIV-1 is classified according to its nucleotide sequence into three groups: M (main), O (outlier) and N (non-M, non-O), presenting genetic variability, with the M group the main cause of AIDS globally[2].

In its structure, the virus has two identical standing up strands of genomic RNA, measuring 9.2 kilobase[8] of positive polarity, and three enzymes: integrase, protease and reverse transcriptase. These are packaged in a conical core, which is comprised of a p24 capsid protein, surrounded by a circulant matrix with p17 protein, two envelope lined by a phospholipid membrane, originated from the host cell, which presents viral glycoproteins including gp120 and gp41 decisive for infection. Non-covalently bound to transprotein gp41 gp120 has high affinity for CD4 + and expressing all potential targets for the virus cells[6,7]. Following binding of gp120 to CD4 receptor is necessary that conformational changes occur, to facilitate attachment to the correceptor then the entry of the virus into the cell[4].

Characteristics of the immune system

The immune system has the function of protecting the body against infectious agents, consisting of cells, tissues and molecules[9], is divided into primary and secondary lymphoid organs. Leukocytes known as white blood cells are the immune cells of the body, among these are the CD4 + T lymphocytes that are produced in the thymus and are responsible for organizing and command responses by the actions of aggressors[10,11].

Immunity can be natural or acquired, natural, presents defense against microorganism, with an initial line of defense, having biochemical and cellular defense mechanisms and is programmed to act quickly to infections. The adaptive immune response or have acquired the ability to remember, responding in cases of repeated exposure to more aggressively when a microorganism is known, and have specificity for different molecules, having as main components lymphocytes[1].

The acquired immune response has two types, humoral immunity and cellular immunity. Known as humoral, that is mediated by molecules present in the blood and mucosal secretions, called antibodies, which are produced by B lymphocytes by T-lymphocyte mediated cellular immunity acts on intracellular microorganisms such as some bacteria and viruses causing the destruction of these or of infected cells, promoting the removal of reservoirs of infection[1].

In acquired immunity there are three main cellular types involved in this process: T cell that matures in the thymus, cell B is mature in the bone marrow and a third type known as antigen-presenting cell (APC) such as macrophages and dendritic cells the these interact in a complex manner to the immune response that occurs as a whole[6,7].

Immunological characteristics of the HIV

In addition, to the high affinity of the viral glycoprotein gp120 to cellular receptors, especially CD4, it is necessary a group of chemokine receptors, which act as a coreceptor for HIV, are known as the principal chemokine receptor type 5 (CCR5) and receiver chemokine type 4 (CXCR4), they facilitate viral entry into the cell[4,9].

The CD4 + T lymphocytes are considered target cells from infection by HIV, they have high levels of CD4 and expressing co receptor. There are also other types of cells that can be infected by HIV, they express low levels of CD4 and co receptor are known as macrophages, dendritic cells and microglia cells[1,4,9]. This binding of gp120 to the receptor and co receptor allows a domain of viral glycoprotein gp41 inducing fusion of the virion to the target cell cytoplasm, leading to release of the core of HIV to the cytoplasm of the host cell, initiating the viral reproductive cycle[12].

In the cytoplasm of the cell, the viral RNA is retrotranscribed into a double-encoded DNA strand (cDNA), i.e. by the enzyme reverse transcriptase. Subsequently the cDNA binds to viral and cellular proteins to form a nucleoprotein pre-integration complex, which goes into the cell nucleus. The viral integrase enzyme also adheres to the core catalyzing the coupling of the viral cDNA into the genome of the host cell. Thus the integrated cDNA is now called provirus, may remain idle for a specified time, with little or no production of viral protein. This process occurs in individual cells seemed to be CD4 + memory T cells and macrophages sleepers, yielding the latent form of the virus[1,2,4,12].

To place the transcription of HIV provirus the presence of its long terminal repeats necessary, known as long-terminal repeats (5'LTR) where a gene promoter and enhancer sequences; also necessary to make the sequences that collaborate in polyadenylation, located in 3'LTR. In the promoter are ligated cellular transcription factors NF-kB (nuclear factor kappa B) and (SP1 selective promoter factor 1) to be transcriptional activation. However, this transcript only becomes present when there is activation of T cells and macrophages. After activation few full-length transcripts are formed in the core, they produce messenger ribonucleic acid (mRNA) encoding regulatory proteins, and even transported from the nucleus to the cytoplasm of the cell, where they are translated. As for the structural proteins are produced from the accumulation of regulatory proteins in the nucleus[1,2,4,12].

Like other retroviruses, HIV has three structural proteins. Its proteins as described above, are responsible for most of their origin, are known as gag (group-specific antigen), pol (polymerase) and env (envelope), such

proteins has the function, respectively, encoding the viral proteins of the viral core, production of enzymes that assist in replication and integration of the virus and finally the envelope glycoprotein production. There are also six other genes encoding proteins and contribute to the regulation of viral replication and infectivity are classified as regulatory genes Tat (transactivator) and Rev (regulator of viral expression) essential for viral replication and transported to the nucleus by binding to HIV RNA. The Tat protein will join the 5 'end of the transcript of HIV, and cellular factors, accelerating to 1000 times the full production of transcripts. Have the Rev protein binds to the isolated transcripts or unprocessed allowing your core output[1,2,4,12].

The HIV genome also encodes the accessory proteins, Nef (negative regulatory factor), vif (viral infectivity), Vpr (Viral protein R) and Vpu (U viral protein) responsible for efficient virus production[1,2,4,12].

The structural genes have long polypeptide chains produced by mRNA, which is subsequently cleaved by viral protease into mature proteins in the cytoplasm. The result of the cleavage of Gag gene are four proteins: CA (capsid, p24), MA (matrix, p17), NC (nucleocapsid p7) and p6; have the env gene produces glycoproteins, gp120 and gp41, these are structured as trimers in the viral envelope. Finally, the cleavage of the pol gene, which will result in the formation of three proteins essential for virus multiplication, are also known as p11, p66/ p51 and p32, are found in the same protease enzymes, reverse transcriptase and integrase respectively . The proteins mentioned organize and form the cores of HIV which undergo sprouting containing the glycoproteins gp41 and gp120 in the plasma membrane resulting in the HIV virion, is released from the host cell into the surrounding medium, which may or may not infect new cells[2,4,9].

Disease Stages

The natural history of HIV disease, has beginning in the transmission of the virus to the individual death is defined as a natural progression of the infection without antiretroviral therapy[13]. The HIV infection is characterized by four phases: acute or primary infection, asymptomatic phase or clinical latency, initial or early symptomatic phase and AIDS [3].

The acute phase is the period which corresponds from the transmission of disease to the formation of anti HIV antibodies, are observed with high levels viraemia marked decline in CD4 + T cells and an increase in CD8 + circulating lymphocytes[13]. The most common symptoms are fever, sweating, malaise, myalgia, anorexia, nausea, diarrhea and pharyngitis non-exudative, and headache, photophobia, meningism and maculopapular rash may occur neurological symptoms in a minority and aseptic meningitis, encephalitis, peripheral neuropathy is a polyneuropathy acute ascending known as Guillain-Barré syndrome. In some cases may occur aphthous ulcers or esophageal[14]. The symptoms are self-limiting, and last an average of 14 days, their persistence may be associated with more rapid progression to AIDS[3]. Acute infection is controlled only partially by the adaptive immune response and advances to the progressive infection of peripheral lymphoid tissues. At this stage, HIV virions penetrates the individual cells by fusion events, mediated by cellular receptor gp120/ gp41[1].

After primary infection there is a second phase of the disease, where the infected patient may remain asymptomatic for several years, may also have some very specific symptoms such as persistent generalized lymphadenopathy, fatigue, low-grade fever, night sweats, intermittent diarrhea and weight loss[14]. This phase of the disease is called the HIV latency period where new viruses are produced in low levels, only a few T cell harboring the virus, but the destruction of CD4 + T cell progresses slowly in lymphoid tissues and the number of such cells decreased progressively in blood. The body continues to produce, however are destroyed with the same speed with which they are produced. Over a period of years, this continuous cycle of infection and death of T cells and new infections lead to a steady decline in the number of CD4 + T cells in lymphoid tissues and circulating[1].

In early symptomatic phase, some symptoms present nonspecific and variable intensity, the changes are night sweats, weight loss and thrombocytopenia. The most common opportunistic processes found in this phase are known as oral and vaginal candidiasis, oral hairy leukoplakia, gingivitis, aphthous ulcers, diarrhea, sinusitis, recurrent herpes simplex and herpes zoster[3].

The last stage of the HIV infection, AIDS, is characterized by drastic increase viraemia, increasing the replication of the virus rapidly and without control. Presents combinations of opportunistic infections, cancer, cachexia, renal failure and degeneration of the central nervous system. The patient becomes susceptible to various diseases due to marked decrease in CD4 + T cells, reaching very low levels. Many tumors that appear in individuals with AIDS are due to viral and incapacity of the patient infected by HIV mount an immune response against oncogenic viruses[1,14].

Epidemiology

According to the Department of STD, AIDS and Viral Hepatitis, since when did the epidemic in 1980 until June 2012, Brazil has 656,701 registered cases of AIDS. It is currently estimated that the country about 718 000 people living with HIV/AIDS. In 2012 were reported 39,185 cases of the disease in the country, remaining stable this value in the last five years, leaving the national detection rate of 20.2 cases per 100,000 inhabit-

ants (Figure 1).

Were declared in 2012, 11,896 deaths from AIDS in the country, accounting for one by AIDS mortality rate of 5.5 per 100,000 inhabitants. Taking into account the accumulated data from 1980 to 2013 were notified, declared and registered a total of 686,478 AIDS cases. These cases where 445,197 - 64% correspond to the male and 241,223 sex - 35.1% female, this total cases registered between 1980 and June 2013, 379,045 (55.2%) are the Southeast, 137,126 (20.0%) of the South, 95,516 (13.9%) in the Northeast region, 39,691 (5.8%) in the Midwest and 35,100 (5.1%) in the North region[15].

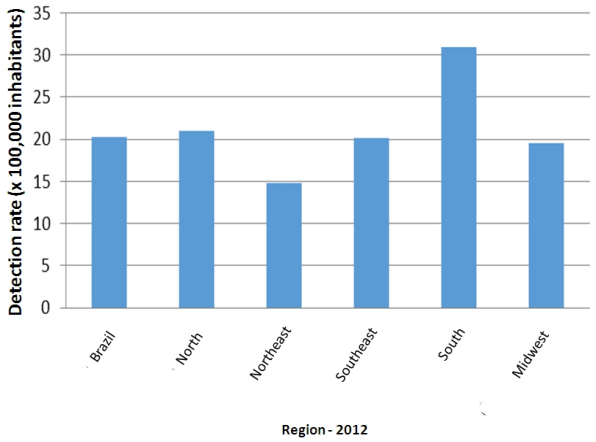

Figure 1. AIDS detection rate for Brazilian regions in 2012. In 2012 the detection rate of people living with HIV/ AIDS in Brazil was 20.2 / 100,000 inhabitants. In the Brazilian regions, we could observe the highest detection rate in the South, 30.9 / 100,000 inhabitants, followed by the Northern region 21.0, Southeast region 20.1, Midwest 19.5 and Northeast region 14,8[15].

In 2012 the men the AIDS case detection rate was 26.1 per 100,000 population, while for women it was 14.5. In both sexes, the age group in which AIDS is more prevalent is the 25-49 years old. Regarding the mode of transmission, the prevailing sexual among over 13 years old. Even in higher concentration the number of AIDS cases in males among heterosexuals, there is a large concentration of the epidemic in the country in groups with behaviors in which they are vulnerable to an increased risk of HIV infection, such as homosexuals, sex workers and drug users[15].

Laboratory diagnosis

Following infection, antibodies to HIV are, on average, 3 to 12 weeks in serum or plasma[3]. Essentially are divided into four groups of tests for detection of HIV, known as antibody detection tests, antigen detection tests, culture technique, and the virus genome amplification assays. Routinely used in the initial screening antibody detection tests against the virus, known as Enzyme Linked Immuno Sorbent Assay (ELISA) is intended for the detection of antibodies, anti-p24, gp41 and gp120, and is considered a highly sensitive and specific test. For confirmation of positive ELISA test, it is necessary to conduct the Western blot test (WB), which are detected viral proteins[3,16].

In its second edition the technical manual for the diagnosis of HIV infection currently is approved by Ordinance No. 29 of 17 December 2013. The manual provides STD and AIDS Department's policies for the diagnosis to be amplified and are including people who are diagnosed and can start treatment soon after confirmation of diagnosis, contributing to quality of life of and reducing the likelihood of HIV transmission. The main purpose of this manual is to expand the possibilities for diagnosis and also mainly instruct healthcare professionals to secure completion of the diagnosis of infection, comprising in its six flowcharts infrastructure that allow the diagnosis, enabling this in different locations and situations with laboratory infrastructure or not taking active responsibility to meet all looking for this diagnosis[17].

Treatments

In November 1996, Brazil became the first country to make available free of charge through the Unified Health System (SUS), all drugs necessary for the treatment of patients living with HIV / AIDS[18].

Are currently used in Brazil, four classes of antiretrovirals, which are considered more potent and less toxic, divided as Nucleoside Reverse Transcriptase Inhibitors (NRTIs) Nucleoside Inhibitors No Reverse Transcriptase (INN-TR), inhibitors protease (IP), and Integrase Inhibitors[19].

Antiretrovirals NRTIs are drugs that block the action of the enzyme reverse transcriptase. Activation of nucleoside inhibitors of metabolites occurs in the first phosphorylation. Due to difficulties in many molecules monophosphorylated be created is analogous drugs possessing a nucleotide phosphate group in its structure, requiring only two phosphorylations to prevent transcription of RNA into DNA, and thus preventing viral replication. Hoewver, the antiretroviral group NNRTI are considered as non-competitive binding to an allosteric site of the enzyme. This interaction causes the active site responsible for the formation of the double helix of DNA, has restricted their mobility and flexibility, which results in a drastic reduction in enzyme efficiency[20].

Protease inhibitors (PIs) interfere in the last stage of viral replication, preventing the formation of new viruses. Protease is the enzyme responsible for processing the gag and gag-pol polyproteins, these are responsible for the formation of structural and functional proteins formed virus particles[20].

Finally, are known drugs that inhibit integrase, which are considered one of the new classes of anti-HIV drugs,

with low toxicity compared to other drugs[12]. The integrase enzyme is responsible for inserting the proviral DNA into the host chromosome and catalyze the incorporation of this proviral DNA into the genome of the infected cell, which is essential for viral replication[20].

Prevention

According to the Department of STD, AIDS and Viral Hepatitis the most efficient way of AIDS prevention is the use of condoms in all sexual relations, decreasing the risk of transmission to 5%[17], *blood or blood products, semen, body fluids and breast milk of infected person should be avoided for contacts unprotected*[2].

In pregnant women, for prenatal tests should be performed to detect viruses and if positive for HIV treatment must be performed in order to prevent contamination of the embryo in order that vertical transmission, ie from mother to child can occur often in utero or during birth, there is also the possibility of transmission through breast milk[1].

Health professionals can be contaminated through occupational transmission, generated by the accident at work, where they can be injured with cutting and sharp instruments contaminated with blood of patients with positive serology for HIV. Some factors that may contribute occur occupational contamination, such as the extension and the depth of the wound, the presence of blood in the instrument causing the accident and the patient is a source with a high viral load with advanced immunodeficiency signals. Control measures should be adopted in order to minimize the risk of transmission by this type of contamination among which we highlight: the effective practice of biosecurity standards in invasive procedures to implement new technologies and the study to determine the risk factors associated seeking their elimination[3].

Routine screening for HIV in blood donors have significantly reduced the rich transmission this way. To control the epidemic by HIV effective prevention is extremely important, adopting public health measures to decrease the use of contaminated needles used by intravenous drug user and the use of condoms, even among HIV-positive partners, avoiding reinfection of viral strains resistant to drugs which can have serious complications health, and campaigns on HIV/ AIDS for public awareness[1,17].

4. DISCUSSION

The human immunodeficiency syndrome yet acquired is a challenge for medicine, however, major advances in research has enabled accurate diagnoses and effective treatments, promoting the survival of HIV/ AIDS. Via the public health policy allowed to join the diagnosis, treatment and follow-up, which brought improved quality of life and new perspectives. Overall Brazil has advanced as to the means of dissemination through campaigns on prevention and encouragement in testing. Government actions mediated programs a strategy of reduction and elimination of new cases, keeping track of the epidemic, however the involvement of all this preventive current is necessary to achieve this goal.

Despite the government action the effects are devastating in society as a whole, AIDS has no cure established, despite scientific and therapeutic advances the clinical picture of the disease has cost many lives. Many allies of AIDS, such as discrimination, prejudice and lack of knowledge, should be considered for a confrontation set of combating the epidemic. Strategies for prevention, early diagnosis combined with promotion of treatment are established actions that should be considered as an effective way to combat new HIV infections, intolerance and reduced AIDS deaths.

5. CONCLUSION

Despite constant efforts of science in search of permanent cure for HIV, yet we know that this outcome was not completed, totaling a high morbidity and mortality national and world, becoming, since its discovery, a major epidemic, can be considered a pandemic. The weakening and the weakness of the immune system occur by lysis or decrease in lymphocytes of type CD4 +, a cell that is part of the defense system, making the white blood cells, it causes the body becomes susceptible to opportunistic infections and/ or tumors, since these are responsible for organizing and directing the response by the aggressors attack. The adherence to antiretroviral therapy has provided better quality of life and has contributed to decrease the spread of HIV. However, prevention is still the best way to control the disease, since its spread is mainly through sexual contact, leading to many individuals to become vulnerable. The changes caused by the fact that HIV compromises the immune system, hence the importance of investments in research, awareness, government and popular actions, so there in the near future to reduce the epidemic and the much desired cure this disease.

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