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MEDICAL ETHICS

Bioethics aspects in the prevention of vertical transmission and management of treatment with antiretrovirals in pennants infected with HIV/AIDS in Brazil

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Abstract

In 2012, the United Nations Organization together with the World Health Organization reported that by the end of 2011 there would be about 34 million infected with the human immunodeficiency virus worldwide. Among other forms, the vertical transmission has been a focus of attention in the sense that there has been an increase in cases of infection in women. In this context, this study aims to present antiretroviral treatment in pregnant women with HIV/AIDS, as well as to discuss the bioethical aspects related to the prevention of vertical transmission. In 1994, protocol 076 showed that the use of zidovudine in pregnant women who had the virus during prenatal and childbirth and in the baby during the first six weeks of life, reduced the transmission of the virus by 2/3 for children. Subsequently, the Ministry of Health adopted measures to reduce the incidence of vertical transmission. Nowadays the doctor can make use of guidelines and must use the treatments available for the good of the patients, according to their capacity and judgment, according to the hippocratic tradition, provided that are adequately measured the risks that such medicines can promote to the pregnant woman and to the baby.

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INTRODUCTION

Sexually Transmitted Diseases (STDs) have worried health managers since the most remote times. Although several efforts and advances have already been made towards the eradication of these diseases, they still remain one of the health problems that most afflict the world population.[1,2] STDs originate from infections that are usually transmitted through intimate contact or sexual intercourse, although they can also be transmitted in other ways, such as from mother to child or through contact with blood or blood products[2].

One of the STDs present today is the Acquired Immunodeficiency Syndrome (AIDS), caused by the Human Immunodeficiency Virus (HIV)[2] Initial reports say that the syndrome arose in Central Africa, probably due to a mutation of the monkey virus. A great scholar in the area, in his article on AIDS and its origin, proposed as correct the hypothesis that the precursor virus had passed from primates to man, however, the mechanism by which this would have occurred is not fully elucidated.[3]

HIV is a retrovirus, classified in the *Lentiviridae subfamily*. These viruses share some common properties: prolonged incubation period before disease symptoms appear, infection of blood cells, the central nervous system, and suppression of the immune system.[4]

The virus has as main targets CD4+ T lymphocytes. It is these leukocytes that organize and command the response to aggressors. Produced in the thymus gland, they learn to memorize, recognize and destroy microorganisms recognized as "foreign" by the organism. HIV binds to a component of that cell's membrane, CD4, penetrating its interior to multiply. As a result, the defense system gradually loses the ability to respond properly, making the body more vulnerable to pathologies. When the body becomes weakened to fight these external agents, the infected person begins to show the symptoms of the syndrome , which is called AIDS[4].

Infection by the HIV virus represents a global, dynamic and unstable phenomenon, whose form of occurrence in different regions of the world depends, among other determinants, on individual and collective human behavior. It stands out among emerging infectious diseases due to the great magnitude and extent of the damage caused.[5]

AIDS, as soon as it was discovered, was strongly associated with risk groups, such as male homosexuals, injecting drug users and sex workers. In recent decades, it has significantly changed its epidemiological profile, since it has increasingly affected the female population, of reproductive age, with low income and schooling and in cities in the interior of the country and, consequently, reaching their children.[6]

Vertical transmission (mother-to-child) of HIV occurs through exposure to the virus during pregnancy, labor, delivery or breastfeeding, and has been the focus of attention as there has been an increase in HIV cases in women. This route of transmission is responsible for 90% of cases of pediatric infection in Brazil.[7]

The rate of mother-to-child transmission of HIV during pregnancy, without any treatment, can be as high as 30%. However, in situations where the pregnant woman or nursing mother follows all the recommendations of the guidelines, the possibility of infection of the baby reduces to levels less than 1%.[8]

In Brazil, the Ministry of Health (MS) adopted prophylactic measures for the prevention of vertical transmission from 1996 onwards. Such measures include: antiretroviral therapy, universal counseling and recommendation of an anti-HIV test for all pregnant women, indication of the mode of delivery - elective cesarean - in specific situations and the suspension of breastfeeding. In recent years, the occurrence of vertical transmission has been decreasing significantly due to the preventive measures adopted in the country.[7,9]

Prior to the prophylactic measures adopted by the MS and the publication of guidelines that help prescribers , there was a great bioethical dilemma related to the choice of treatment capable of preventing vertical transmission to the fetus, without prejudice to the pregnant woman.

OBJECTIVE

In this context, this work aims to present the treatment with antiretroviral drugs in pregnant women with HIV/AIDS, as well as to discuss the bioethical aspects related to the prevention of vertical transmission.

Bioethical aspects of the development of prevention of mother-to-child transmission

The term bioethics was created at the beginning of the 20th century by Fritz Jahr (1895-1953) in the article "Bioethics: a review of the ethical relationship of human beings with animals and plants" (1927)[10], this article summarized bioethics considering life in the first place. In the 1970s, the term was first applied in the United States by Van Rensselaer Potter (1911-2001), who first published the article " *Bioethics: the science of survival* " (1970)[11]; then the book " *A bridge to the Future* " (1971)[12] and created a "Bioethical Creed". The term bioethics is a neologism derived from the Greek words bios (life) and ethiké (ethics). In Europe it began to be used in the 1980s and in developing countries from the 1990s onwards.[13-15]

The emergence of bioethics was a requirement of situations arising, above all, from the scientific and technological revolution. Bioethics is ethics applied to the field of life sciences (philosophy, sociology, biology and medicine). In the health area, it represents the study of human conduct in research, care and treatment in the light of moral values and principles. It covers dilemmas related to the ethics of health professionals, including health care, biomedical investigations in human beings and humanistic and social issues, including the right to health. Bioethics is based on principles, values and virtues such as justice, beneficence, non-maleficence, equity, autonomy, which presupposes responsibility, free will,

conscience, moral decision and respect for human dignity in care, research and social life[14,16].

According to Clotet[17], the principle of beneficence generally requires that the important and legitimate interests of individuals be served and that, as far as possible, harm be avoided. Therefore, this principle is concerned with the search for the well-being and interests of the patient through medical science and its representatives or agents. In this context, the prescriber must use the available treatments for the benefit of the sick, according to their ability and judgment

Regarding the principle of non-maleficence, it is proposed not to cause intentional harm and is in accordance with the well-known Hippocratic aphorism *primum non nocere* (first do not harm), whose purpose is to restrict the adverse or undesirable effects of diagnostic and therapeutic actions[18].

Based on the aforementioned information and considering bioethical aspects related to the prevention of vertical transmission of HIV, beneficence is one of the principles of principlist bioethics that can easily be related to the vertical prevention of the HIV virus to the baby. In order to promote the principle of non-maleficence, therapeutic options capable of promoting few adverse events will be presented, providing safety for both the pregnant woman and the baby.

Treatments available in Brazil

There are several drugs, with different mechanisms of action, approved in Brazil for the treatment of HIV. In 1987, the first drug called zidovudine (AZT) was approved, initially used in monotherapy until the release of didanosine. Then, new antiretroviral drugs (ARVs) emerged, not only nucleoside analogue reverse transcriptase inhibitors (NRTIs), but also non-nucleoside analogue reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PI), fusion inhibitors (IF) and, more recently, inhibitors of integrase (II) and CCR5 receptors[19].

Since 1996 with the decree of Law 9313, in Brazil there is free distribution of drugs that make up the high potency antiretroviral therapy (ART)[20] , according to 2015 data, 455 thousand people were using these drugs. Currently, there are 22 drugs divided into five types: NRTIs that act on the reverse transcriptase enzyme, incorporating themselves into the DNA chain that the virus creates. They make this chain deficient, preventing the virus from reproducing. This class includes abacavir, didanosine, stavudine, lamivudine, tenofovir, zidovudine and the lamivudine/zidovudine combination; NNRTIs that directly block enzyme action and virus multiplication. These being efavirenz, nevirapine and etravirine; PIs that act on the protease enzyme, blocking its action and preventing the production of new replications in HIV-infected cells. This class includes atazanavir, darunavir, fosamprenavir, lopinavir, ritonavir, saquinavir and tipranavir; The IF enfuvirtida that prevents the virus from entering the cell and, therefore, it cannot reproduce; Finally, raltegravir II acts by blocking the activity of the integrase enzyme, responsible for inserting HIV DNA into human DNA. Thus, it inhibits the replication of the virus and its ability to infect new cells.[4]

Protocols and treatment guides for pregnant women

The MoH gathered the Advisory Committee for Recommendations for Prophylaxis of Mother-to-Child Transmission of HIV and Antiretroviral Therapy in Pregnant Women, which reviewed the Recommendations for Antiretroviral Therapy and other procedures related to the prophylaxis of mother-to-child transmission of HIV and published the Treatment Guide of Recommendations for Prophylaxis of HIV Vertical Transmission and Antiretroviral Therapy in Pregnant Women in 2010[21].

The guide points out that treatment is indicated for women with severe clinical and/or immunological repercussions of HIV infection, regardless of pregnancy and at any gestational age. Therefore, symptomatic or asymptomatic pregnant women with an LT-CD4+ count ≤ 350 cells/mm3 have criteria for starting treatment, as recommended for adults living with HIV, and should start it with the aim of treating the disease or reducing the risk of infection. progression[21].

According to the guide, the incidence of adverse reactions in pregnant women and children exposed to ARVs for prophylaxis of mother-to-child HIV transmission is low. In addition to being infrequent, adverse effects are usually transient and of mild to moderate intensity, both in pregnant women and children. Such effects rarely determine the suspension of the use of ARVs, since the effectiveness of these drugs in preventing mother-to-child transmission of HIV clearly outweighs the risks of adverse reactions to them[21].

The guide cites that among the available antiretrovirals, AZT is the one with the most data regarding safety during pregnancy, and information on other antiretrovirals is limited. AZT therapy caused anemia in 2 to 40% of pregnant women using the drug for prophylaxis of mother-to-child transmission of HIV, including prophylactic regimens used for very variable periods[21].

With regard to other treatments, pancreatitis, hepatic steatosis and lactic acidosis have been reported, with maternal death occurring in women who were using the combination of didanosine and stavudine as part of their ARV regimen. Such changes may be associated with prolonged use of NRTIs (over six months of use), which are possibly related to mitochondrial toxicity[21].

In 2015, the Clinical Protocol and Therapeutic Guidelines for the Prevention of Vertical Transmission of HIV, Syphilis and Viral Hepatitis was published, this document was published by the MS and was prepared by the Health Surveillance Department - STD Department[22]. According to the protocol, ARV is indicated for all HIV-infected pregnant women, regardless of clinical and immunological criteria, and should not be discontinued after delivery, regardless of the LT-CD4+ level at the time of treatment initiation. This indication has level of evidence 1A and degree of recommendation A[22].

Also according to the aforementioned protocol, this guideline, internationally known as Option B+, aims to suppress viral replication in a sustained manner, preventing

vertical and sexual transmission of HIV; reduce the risk of disease progression, decreasing morbidity and mortality associated with HIV; improve the life quality; preserve and, when possible, restore the immune system; avoid intermittent use of antiretroviral therapy in different pregnancies; promote early protection, in relation to vertical transmission, in future pregnancies[22].

This protocol published by the MS points out that treatment for pregnant women should consist of - ARV regimen with NNRTI. Initial therapy should always include combinations of three antiretrovirals, two of which are nucleoside and nucleotide analogue reverse transcriptase inhibitors associated with an NNRTI. The preferred first-line regimen should be: tenofovir + lamivudine + efavirenz in the fixed-dose combination presentation, whenever available[22].

DISCUSSION

HIV infection is a serious public health problem. In 2012, the United Nations together with the World Health Organization reported that, by the end of 2011, there would be about 34 million people living with HIV in the world, thus being considered a pandemic[23].

Since the 1980s, vertical transplacental transmission, during labor, delivery or breastfeeding, has predominated markedly, with the first reported and confirmed case of seropositivity from this type of exposure being in 1985[24].

The most recent concern with issues related to HIV/AIDS is the change in the epidemiological profile of carriers of the syndrome , the increase in the number of infected women has resulted in an increase in the rates of vertical transmission of HIV. This situation has led to the infection of a considerable percentage of children worldwide with the HIV virus, since many of the infected women are of reproductive age[25,26]. A fact that raises doubts about the conduction of clinical studies with patients with HIV is the memory of studies conducted without ethics, such as the historic Tuskegee Untreated Syphilis Study, which it was a medical experiment held in Alabama, between 1932 and 1972 and which is still referred to as an example of scientific misconduct[27].

Thus, studies with HIV carriers generate many questions, some of them even in the 1990s, in the United States. These studies were often performed on individuals considered poor or vulnerable, and some with a control group using placebo. Until recently, many of these studies were conducted in underdeveloped countries, and a large proportion of these patients find themselves in these situations because they are infected with HIV[28].

In 1994, Protocol 076 proved that the use of AZT in HIV-positive pregnant women during prenatal care and at the time of delivery and, in the baby, during the first six weeks of life, reduced the transmission of the virus by 2/3 to the children. This study was considered one of the most important (and controversial) in the area of prevention of vertical transmission and showed the possibility of preventing infection in the baby, when pregnant women are identified and treated properly[29].

The controversy came from the use of a placebo-controlled group. The study was stopped when the first preliminary analysis was done and the efficacy and safety of the use of AZT was verified. All participants in the placebo group were offered the opportunity to be treated equally with AZT[29].

Although the implementation of research protocols such as Protocol 076 has faced dilemmas and debates, the results of these studies have promoted untold benefits in the choice of appropriate therapy for pregnant women with HIV.

In the clinical research carried out in the country, there are several publications of studies, in agreement with the national Research Ethics Committees, carried out with pregnant women with the syndrome, who continued treatment with ARV throughout their pregnancy. Although most of these studies are retrospective observational, they do support the safety of ARVs for babies. Such information can be evidenced in the studies by Cartaxo et al. (2013)[23], Araújo et al. (2008)[25].

After the study of protocol 076 carried out by Connor et al. (1994)[29], the MS proposed the inclusion of HIV counseling and diagnosis in the routine of prenatal care. It also adopted other measures such as the administration of zidovudine in combination with other antiretroviral drugs for infected pregnant women, administration of zidovudine during labor and postpartum for newborns and the substitution of breastfeeding[30].

Before the MS adopted prophylactic measures for vertical transmission, there was a great bioethical dilemma related to the treatment of pregnant women with the AIDS virus. The scarcity of publications made it difficult to choose a treatment capable of preventing vertical transmission to the fetus, without harm to the mother.

As a result of the growing number of children infected through vertical transmission, there was the publication of recommendations from the MS on assistance to pregnant women. Recent examples of these documents include the Treatment Guide Recommendations for Prophylaxis of Mother-to-Child Transmission of HIV and Antiretroviral Therapy in Pregnant Women, published in 2010[21], the Clinical Protocol and Therapeutic Guidelines for the Prevention of Mother-to-Child Transmission of HIV, Syphilis and Viral Hepatitis, 2015[19] and the Clinical Protocol and Therapeutic Guidelines – Prevention of Vertical Transmission of HIV, Syphilis and Viral Hepatitis published by the National Commission for the Incorporation of Technology in the SUS (CONITEC)[31].

These guidelines recommend that all treatment of pregnant women be carried out in a way that preserves confidentiality, voluntariness and consent for different treatments and approaches throughout the risk period - from pregnancy to breastfeeding[21,22,31].

Recommendations

Currently, there are adequate drugs for the management of pregnant women with HIV capable of preventing vertical transmission without harm to the mother. Each case

must be evaluated separately and the physician can make use of guidelines developed by the MS dealing with the use of ARVs in pregnant women with HIV/AIDS. The prescriber must use the available treatments for the benefit of the sick, according to their ability and judgment, according to the Hippocratic tradition, following the bioethical principle of beneficence, provided that the risks that such medicines can promote to the pregnant woman and the baby are adequately measured. Since during ARV treatment, physiological changes can occur during pregnancy and that can affect the kinetics of drug absorption, distribution, biotransformation and elimination, potentially altering the pregnant woman's susceptibility to toxicity to different drugs.

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