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ANTIRETROVIRAL THERAPY FOR HIV/AIDS: STATE OF THE ART

TERAPIA ANTIRRETROVIRAL PARA HIV/AIDS: O ESTADO DA ARTE

TERAPIA ANTIRRETROVIRAL PARA VIH/SIDA: EL ESTADO DEL ARTE

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ABSTRACT

Objective: to describe the historical evolution of HIV/AIDS therapy, the changes, and current protocols. ***Method:*** descriptive and informative study with analysis of the clinical protocols of therapeutic guidelines and search in the LILACS and MEDLINE databases, assessing full articles published from 1996 to 2017. ***Results:*** access to treatment in some countries has promoted survival increase and improvement. The strategy of linking three drugs in just one tablet, one of the most recent, among other benefits, seeks to strengthen compliance with antiretroviral therapy. ***Conclusion:*** the history of compliance with antiretroviral therapy and its impact on HIV/AIDS prevention remains a major challenge, the goal of which is to control and eradicate the epidemic. In this sense, it is necessary to increase the awareness of health professionals to be part of this fight, in which nursing has an important participation. ***Descriptors:*** Acquired Immunodeficiency Syndrome; Human immunodeficiency virus; Potent antiretroviral therapy (HAART); Nursing; Clinical evolution; Protocols.

RESUMO

Objetivo: descrever a evolução histórica da terapêutica para o HIV/AIDS, as mudanças ocorridas e protocolos atuais. ***Método*:** estudo descritivo, informativo, com análise dos protocolos clínicos de diretrizes terapêuticas e busca nas bases LILACS e MEDLINE, abrangendo artigos na integra, publicados de 1996 a 2017. ***Resultados*:** O acesso ao tratamento em alguns países permitiu o aumento e melhoria da sobrevida. A estratégia de unir três drogas em apenas um comprimido, uma das mais recentes, dentre outros benefícios, busca fortalecer a adesão à terapia antirretroviral. ***Conclusão*:** a história da adesão à terapia antirretroviral e seu impacto na prevenção do HIV/AIDS continua sendo um grande desafio, cuja meta é o controle e erradicação da epidemia. Nesse sentido, faz-se necessário uma maior conscientização dos profissionais de saúde para fazer parte desta luta, na qual a enfermagem tem importante participação. ***Descritores:*** Síndrome da imunodeficiência adquirida; Vírus da imunodeficiência humana; Terapia antirretroviral potente (HAART); Enfermagem; Evolução clínica; Protocolos.

RESUMEN

Objetivo: describir la evolución histórica de la terapia para el VIH/SIDA, los cambios ocurridos y los protocolos actuales. ***Método:*** estudio descriptivo e informativo con análisis de los protocolos clínicos de directrices terapéuticas y búsqueda en las bases LILACS y MEDLINE, analizando artículos completos publicados de 1996 a 2017. ***Resultados:*** el acceso al tratamiento en algunos países permitió el aumento y mejora de la sobrevida. La estrategia de unir tres drogas en un sólo comprimido, una de las más recientes, entre otros beneficios busca fortalecer la adhesión a la terapia antirretroviral. ***Conclusión:*** la historia de la adhesión a la terapia antirretroviral y su impacto en la prevención del VIH/SIDA sigue siendo un gran desafío, cuyo objetivo es el control y erradicación de la epidemia. En ese sentido, se hace necesaria una mayor concientización de los profesionales de salud para formar parte de esta lucha, en la cual la enfermería tiene una importante participación. ***Descriptores:*** Síndrome de Inmunodeficiencia Adquirida; Virus de la Inmunodeficiencia Humana; Terapia antirretroviral altamente activa (HAART); Enfermería; Evolución clínica; Protocolos.

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INTRODUCTION

Since the end of the 20th century, the human immunodeficiency virus (HIV), which causes the acquired immunodeficiency syndrome (AIDS), has caused an epidemic that has rapidly spread across the five continents and is a serious public health problem due to health problems and number of deaths, in addition to its strong impact on the economies of the countries. This epidemic emerged during an era when the world health authorities assumed that infectious diseases were controlled by technologies and modern medical knowledge.[1]

The AIDS virus belongs to the retrovirus group and causes chronic and progressive immune dysfunction in the body due to the decline in the levels of T-cell differentiation molecules (CD4+ T lymphocytes). CD4+ T lymphocytes, the main targets of HIV, are defense cells that memorize, recognize, and destroy foreign microorganisms that enter the human body. As a result, they change the defense capacity, making the body vulnerable to opportunistic infections, cancers, and neurological changes with high degree of lethality. The lower the rates, the greater the risk of developing AIDS.[2-3]

HIV-infected individuals should exhibit equal or less clinical indices than 200 CD4 cells/ml for the development of AIDS. The higher the rate of these cells loss, the faster the progression of AIDS-related infections. Thus, the number of CD4+ cells present in blood is an indicator that can be used to measure the severity of the disease.[3]

Until the late 1980s, there was little knowledge about the pathogenesis and history of HIV infection. This fact made it difficult to provide care to persons living with HIV/AIDS (PLWHA), thus limiting the treatment of opportunistic infections. Since the beginning of the epidemic, Brazil recorded 842,710 AIDS cases from 1980 to June 2016, and there was an average of 40,600 new cases per year from 2010 to 2014. Regarding mortality, up to December 2015, there were 303,353 deaths, although a slight drop in the AIDS mortality rate was observed, which decreased from 5.9 per 100 thousand inhabitants in 2006 to 5.6 in 2015.[4] In 1987, with the advent of zidovudine (AZT), therapeutic hope and research on antiretroviral (ARV) drugs also emerged, opening up new perspectives for the treatment of AIDS.[5]

ARV drugs are used in the treatment of infections caused by retroviruses and for prophylaxis of opportunistic diseases, such as pneumocystosis. The use of this therapy has led to a profound reformulation in the clinical and epidemiological aspects of HIV/AIDS infection.[6] Since the emergence of the first ARV regimens, the goal was to define criteria and consensus for the initiation of treatment, based on estimates of risks of opportunistic infections, evolution to AIDS, and death.

After decades, since the onset of the epidemic, treatments provided to PLWHIV have undergone major changes. The first cases received palliative care, mainly involving nursing and the use of medication to control infectious complications. With the evolution of research, new combinations of drugs, known as antiretroviral therapy (ART), have been adopted, whose functions are: inhibition of virus replication in the body; preservation of the immune function; reduction of the likelihood of more resistant viral strains emergence; and increasing time and quality of PLWHA's lives.[3]

Over several decades of epidemic, Brazil has been concerned with healthcare quality provided to PLWHA. The country has been considered one of the model countries regarding AIDS treatment, control, and care, by promoting interventions, mainly due to the establishment of ART by the Unified Health System in November 1996 as part of the Brazilian health policy, including free universal access to health services and medicines.

Compared to other millennial and stigmatizing diseases, such as tuberculosis and leprosy, AIDS treatment has achieved a major breakthrough in a little more than 30 years, in which several drugs have been used and replaced. Treatment and control have been improved because ARV drugs are also used to decrease virus transmission, since regular use considerably reduces viral load and, in most cases, keeps it undetectable.[7]

Considering these rapid advances, our goal in the present study was to report the historical evolution of HIV/AIDS therapy, pointing out the main changes that have occurred, the related factors, and the current protocols that seek greater effectiveness, due to fewer adverse events and better therapeutic response, in addition to treatment compliance.

- **Evolution of HIV/AIDS treatment**

Few studies have reported the evolution of ARV drugs addressing the main factors that contributed to the changes in the world consensus. Each protocol is linked to the best immune response and fewer side effects, seeking to ensure 95% compliance with treatment as recommended by the World Health Organization (WHO).[7]

At the beginning of the epidemic, medical care for HIV patients was considered precarious and limited. Its unstable supply, due to the limited therapeutic resources available and the logistic fragility of the distribution and dispensation[8] was limited to address the signs and symptoms of opportunistic diseases, which were many.

In 1987, the Food and Drug Administration (FDA) of the United States approved zidovudine, or azidothymidine (AZT), for HIV patients. This medicine was initially developed for cancer treatment and, after a randomized clinical trial, it was demonstrated that this drug had some ability to control HIV. This way, it began to be used for this purpose, being considered the first ARV drug used in HIV/AIDS treatment.[9]

In the 1980s and to the mid-1990s, monotherapy with AZT followed by dual therapy were the only treatment options, however, with high cost, which limited the access to many patients. The mobilization of health professionals, activists, and the civil society to fight HIV/AIDS has made it possible to reduce the price of ARV drugs, the inclusion of treatment procedures in the Unified Health System table in 1992, and the national production of AZT in 1993.[10]

In 1995, the nucleoside pair (NRTI) zidovudine and lamivudine (3TC), associated with a non-nucleoside reverse transcriptase inhibitor (NRTIs), preferably efavirenz, was the first officially adopted and recommended therapeutic regimen.[11] The use of this pharmacological scheme led to the inhibition of HIV replication and decrease of viral ribonucleic acid (RNA) in plasma to undetectable levels.[12]

The approval of new classes of ARV drugs (protease inhibitors) in 1995 increased treatment options.[10] The emergence of this new drug represented an important scientific and technological milestone in the context of the epidemic. From the creation of this pharmacological class, it was possible to observe an increase in the survival of PLWHA.[13]

A study aimed at analyzing the action of this drug demonstrated that it was more effective in comparison to monotherapy regimens. This finding has determined a new treatment standard that has lasted for years.[14] This fact, since 1996, have given way to the use of highly active antiretroviral therapy (HAART) with the combination of three or more drugs.[15] In the same year, the first ARVT consensus regulated the prescription of ARV drugs in Brazil, adopting the triple ARV regimen, which combined two reverse transcriptase inhibitors and one protease inhibitor.[16]

Thus, from Law 9.313, dated 13th November 1996, the State was obliged to provide free universal ARVT.[17,18] At that time, there were already more than 22 thousand AIDS cases and the process of feminization, internalization, and pauperization of the epidemic was observed.[2]

The Clinical Protocol Guidelines for the Management of HIV Infection complied with the recommendations of the Brazilian Ministry of Health in accordance with WHO guidelines, in which ARVT was indicated for symptomatic or asymptomatic patients provided that they had a T-CD4+ cells counts below 200 cells/mm.[3] In addition, other factors should be considered, such as patients' characteristics (motivation, capacity for compliance, and other comorbidities) and assessment of the evolution of immunological and virological parameters.[19] This protocol was simplified in 2003 and updated in 2006. Through the use of HAART, it was possible to achieve significant success in the treatment provided to PLWHA, with a significant decrease in AIDS morbidity and mortality rates.[20,21]

As previously discussed, after the establishment of this protocol, there was immediate decrease in mortality, improvement of immunity indicators, and recovery of opportunistic infections. This fact made experts optimistic about the treatment, even thinking about cure. However, it was observed that the combined treatment only controlled the virus in the body but did not eliminate it.

The previous consensus was used until mid-2013, whose evaluation of the response to treatment used the reduction of viral load and the increase (or interruption of the fall) in the number of CD4+ cells. The desirable amount of undetectable viral load should be below 50 or 80 copies/ml over a six-month period. Recovery of CD4 lymphocyte counts usually occurs more slowly than the reduction of viral load.[8] It is worth noting that the pharmacological regimen of ARV drugs should be adjusted according to the specific situation of each patient, depending on several clinical and laboratory indicators.[3]

At the end of 2013, there was a change in the Clinical Protocol Guidelines for the Management of HIV Infection. The preferred regimen of first-line antiretroviral therapy with tenofovir (TDF) + lamivudine (3TC) + efavirenz (EFZ), used as monodrug therapy, i.e., separately administered, made their ingestion difficult. Therefore, they started to

be produced in combination, known as fixed dose or "three-in-one", in order to better meet the needs of PLWHA, promote better quality of life, and strengthen compliance with treatment.[22]

This therapy scheme began to be provided in June 2014 to new patients who had started ARVT in the two Brazilian states with the highest detection of HIV rate, i.e., Rio Grande do Sul and Amazonas.[5] In January 2015, the provision occurred gradually in Brazil. The proposal was to facilitate and contribute to strengthening compliance with ARVT, as well as to ensure therapeutic success, having a direct and positive impact on the ambitious goal of 90-90-90, namely: to achieve that 90% of PLWHA were aware of diagnosis; that 90% of persons who knew about their HIV status received ARVT; and that 90% of persons undergoing ARVT had their viral load suppressed, keeping them healthy and reducing their risk of HIV transmission.[23]

Since February 2017, a new proposal for first-line treatment has been adopted in Brazil, i.e., dolutegravir associated with tenofovir + lamivudine (two-in-one), firstly offered to patients who started ARVT for the first time. Subsequently, it will be gradually offered to all patients. The expectation is that 100,000 patients will be treated this year with this new treatment.[23]

For the WHO, this new protocol is the most appropriate for the treatment of HIV/AIDS, and Brazil has adopted this strategy as a way to promote greater efficiency in treatment with the Unified Health System involvement.[22] The historical evolution of ARV drugs in the last 30 years can be seen in Figure 1.

Onset of epidemic	**1987**	**1995**	**1996-1997**	**2013**	**2014**	**2017**
Palliative care	Azidothym-idine or Zidovudine (AZT o ZDV)	Reverse transcript ase inhibitor	Highly active antiretroviral therapy – HAART	**Two-in-one** (tenofovir and lamivudine)	**Three-in-one**	Dolutegravir
Alternative methods		Lamivudin e (3TC)	Combination of two reverse transcriptase inhibitors and one protease inhibitor		Triple- dose combination (Tenofovir, lamivudine and efavirenz)	Two-in-one (Tenofovir and lamivudine)
Control of infectious complications						

Figure 1. Evolution during 30 years in HIV/AIDS treatment. São Paulo, SP, Brazil, 2017.
*1996 – 1997: Free universal provision of antiretroviral drugs, Unified Health System.
*2013: International guidelines recommend the use of three drugs, and at least two of those different three drugs.

OBJECTIVE

- To describe the historical evolution of HIV/AIDS therapy, changes, and current protocols.

METHOD

This is an informative article aimed to describe the historical evolution of HIV/AIDS therapy, the changes that have occurred, and the current protocols. We analyzed the clinical protocols of therapeutic guidelines, and performed a search in the Latin American and Caribbean Health Science Literature (LILACS) and Medical Literature Analysis and Retrieval System Online (MEDLINE) databases, accessed through the Virtual Health Library (VHL). The following descriptors were used: Acquired immunodeficiency syndrome; Human immunodeficiency virus; Potent antiretroviral therapy (HAART); and Nursing. The inclusion criteria for the search were abstracts and full articles published from 1996 to 2017.

RESULTS AND DISCUSSION

In these thirty years of epidemic, science has advanced rapidly in this area. Currently, there are several types of ARV drugs for the medication regimen. They are available in five classes: nucleoside reverse transcriptase inhibitors (NRTIs); non-nucleoside reverse transcriptase inhibitors (NNRTIs); protease inhibitors (PI); fusion inhibitor; and integrase inhibitor (Figure 2).

Class	Action	Antiretroviral drug
Nucleoside reverse transcriptase inhibitors	They act in the reverse transcriptase enzyme, incorporating themselves to the DNA chain created by the virus. They make this chain defective, preventing the virus from reproducing itself.	Abacavir, Lamivudine, Tenofovir, Zidovudine, Didanosine EC, and Lamivudine/Zidovudine combination.
Non-nucleoside reverse transcriptase inhibitors	They directly block the enzyme action and the multiplication of the virus.	Efavirenz, Neviparine, Efavirenz, and Etravirine.
Protease inhibitors	They act on the protease enzyme, blocking its action and preventing the production of new copies of HIV-infected cells.	Atazanavir, Darunavir, Lopinavir/, Ritonavir, and Tripanavir.
Fusion inhibitors	They prevent the virus from entering the cell and, therefore, it cannot reproduce itself.	Enfuvirtide and Maraviroc.
Integrase inhibitors	They block the activity of the integrase enzyme responsible for the integration of HIV DNA into human DNA, thereby inhibiting virus replication and its ability to infect new cells.	Rategravir and dolutegravir.

Figure 2. Characterization of antiretroviral drugs, expected action, and type of antiretroviral drugs. São Paulo, SP, Brazil, 2017.
Source: Ministry of Health/Sanitary Vigilance Secretariat/Department of Sexually Transmitted Infections, AIDS, and Viral Hepatitis.

This variety of ARV drugs allows greater adequacy of treatment to the needs of each patient, always seeking the best therapeutic response. It is currently agreed that the use of ARVT has proven effectiveness in improving quality and expectancy of HIV/AIDS patients' lives, being able to change the natural evolution of the disease and radically reduce the morbidity and mortality rate. The success of therapy, however, depends on other factors, such as: adverse effects; viral resistance; drug toxicity; and compliance with treatment.[8]

Survival of HIV-positive patients observed in 1989 was only five months, increasing to ten months in 1995. The following year, a decrease in mortality was observed, given that, after diagnosis, the patients had an increase of 58 months in their survival rate.[25,26]

This increase in PLWHA's life expectancy since 1996 was mainly related to the establishment of ARVT in November of the same year, as part of the Brazilian policy of free universal access to health services and medicines.[26] This policy made Brazil a worldwide reference in AIDS treatment and care.[27] The risk of dying in the first year was significantly lower for those patients that used two reverse transcriptase inhibitors or HAART.[28]

New methods of drug combinations and the development of drugs that are increasingly potent and have less side effects have not only provided a better quality of life for PLWHA, but also reduced morbidity and mortality due to AIDS. This fact was demonstrated by a population study that revealed the improvement in survival of PLWHA, with an average life expectancy of 32.5 years from the beginning of treatment.[29]

ARV drugs have had an important positive impact on the lives of PLWHA. The continuous and correct use provides PLWHA with a favorable immune condition, preventing the occurrence of infections caused by opportunistic diseases, AIDS development, and, consequently, death. However, complications related to long-term use of ARV drugs (lipodystrophy, cardiovascular diseases, gastrointestinal disorders), some of which are still unknown, must be taken into consideration. This way, there is a need to develop programs for the continuous updating of the teams that provide healthcare to PVWHA.[1]

Another factor that requires experience and knowledge for proper management is ARVT in HIV-infected women. Even though the recommendations for therapy are similar for men and women, there are inherent peculiarities of women that deserve special attention, such as contraception, drug tolerability, and compliance with treatment. An important point in this discussion is the low representativeness of women in most clinical trials with new drugs used to treat HIV infection, which reduces our possibility of assessing the specific effects of these drugs on women.[30]

It is worth noticing that, despite the acknowledged advances made in terms of public health policies in Brazil, there is a long and difficult path to be pursued in the quest for the quality of healthcare provided to PLWHA. Overcoming inequities and inequalities poses a challenge, because, in the day-to-day healthcare, there are several barriers to the implementation of

individualized and comprehensive care aimed at health promotion, either by the enormous regional diversity, or by the lack of dialogue in different government spheres.[1] Figure 3 shows the changes in ARVT protocols that have occurred over the years.

Onset of epidemic	**1980s - Mid-1990s**	**1995**	**1996**	**2013**	**2014**	**2017**
Little knowledge of the pathogenesis of HIV infection.	Consolidation of research on ARV drugs.	Supply of AZT in the public network.	HAART	Daily ingestion of many tablets in the previous scheme.	Strengthening compliance by reducing intake to only one daily tablet.	Side effects related to the central nervous system in the previous scheme.
Only limited attention to the control of infectious complications.	New perspectives in the treatment of AIDS.	Virus control.	First consensus.	Decreased side effects.	Many side effects in the previous scheme.	Current: Higher potency, less possibility of emergence of resistant strains, and less side effects.
		New treatment standard.	Simplified in 2003.			
		Increased possibilities of virus transmission.	Updated in 2006.			
			Emergence of several side effects.			
			Increase in transmission.			

Figure 3. Evolution of protocols and factors related to changes. São Paulo, SP, Brazil, 2017.

CONCLUSION

Currently, being HIV-positive is a chronic and treatable condition, due to advances in the discovery of increasingly potent ART drugs with fewer side effects. The control of virus replication and the consequent improvement in the immune system of PLWHA through ARVT led AIDS to be characterized by its current chronic disease profile.

Universal access to treatment in some countries has led to increased survival and improved life quality of PLWHA. To ensure the expansion of access impact, it is necessary to provide early diagnosis and timely treatment. This behavior will have an impact on prevention, increasing not only the expectation but also the quality of life of the patients by reducing their morbimortality.

Countries have sought to produce new medicines in order to minimize costs and, in some of them, as in Brazil, guarantee free universal access to treatment. Therapeutic regimens have been adopted to ensure better quality and expectancy of PLWHA's lives, as well as the minimization of side effects related to the prolonged use of ARV drugs, which is considered an important factor leading to the abandonment of treatment and the emergence of resistant viral strains, thus increasing the level of replication and, consequently, resistance to medications currently available.

The history of compliance with ARVT and its impact on HIV/AIDS prevention remains a major challenge. The goal is to control and eradicate the epidemic, ensuring treatment continuity and developing strategies to measure, monitor, increase, and maintain compliance. In this sense, it is necessary to promote greater awareness and commitment of health professionals so that they can be part of this fight towards maximum compliance with ARVT, in which nursing has important participation.

Although we still face problems, including the rising incidence of HIV infection in some groups and stigma and discrimination of patients, advances continue to occur, allowing us to view the future with optimism.

In this new scenario, we are already discussing the end of the epidemic and the strategies needed to achieve this goal. The establishment of new prevention methods, new and improved antiretroviral drugs, the prospect of vaccines, and the gradual progress towards eradication of infection have been the focus of most international events.

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