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Zidovudine, a brief history before the first antirretroviral in Mexico

Zidovudina, una breve historia antes del primer antiretroviral en México

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Abstract

In the 1980s in Mexico, that of the «moral renewal», there was the opening to the market and the manifestation of human immunodeficiency virus (HIV) and AIDS. In this writing, the historical and therapeutic conditions are related to alleviate the syndrome until the arrival of the first antiretroviral. It is a reconstruction of the events, of which the medical-social, main clinical manifestations and of course the pharmacological therapy, until de the development zidovudina or azidotimidina of AZT, the first antiretroviral to be approved. Nevertheless, in the Mexican context, this event wasn't decisive to significantly change the morbility and the mortality.

Keywords: *AIDS. Antirretrovirals. AZT. Mexico. History of medicine.*

Resumen

En el México de la década de 1980, el de la «renovación moral», se vivió la apertura al mercado y la manifestación del virus de la inmunodeficiencia humana (VIH) y el sida. En este escrito se relatan las condiciones históricas y terapéuticas del síndrome en los pacientes mexicanos, hasta la llegada del primer antirretroviral. Se trata de una reconstrucción de los hechos, de los cuales se ha profundizado en aspectos médico-sociales, principales manifestaciones clínicas y terapéutica farmacológica, hasta que interviene en la patogenia del VIH/sida el desarrollo de la zidovudina o azidotimidina (AZT), primer antirretroviral en ser aprobado. No obstante, en el contexto mexicano este suceso no fue determinante para cambiar de manera significativa la morbimortalidad de los infectados.

Palabras clave: *Sida. Antirretrovirales. AZT. México. Historia de la medicina.*

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Introduction

The human immunodeficiency virus (HIV) and AIDS (acquired immunodeficiency syndrome), since their first report in 1981 in the United States of America and up to the present day, have become one of the most studied infections in the history of humanity. Knowledge has been generated through biomedical literature and the sexual behavior of human beings has been radically transformed.

Since then, the need to continue studying this virus has persisted, albeit with its nuances. In Mexico, the youth population remains a focal point of attention, highlighting the importance of having narratives that bring them closer to this historical reality.

Therefore, this work proposes to recount the historical and therapeutic conditions that, in Mexico, allowed the process of immunodeficiency to be addressed until the advent of monotherapy with the first antiretroviral: zidovudine or azidothymidine (AZT).

The Introduction of HIV/AIDS in Mexico

It is 1983, and the "moral renewal" dances to the rhythm of Blue Monday among the hip sways of hundreds of young people in Mexico. It is a pivotal moment in the country's history. In this time-space continuum, the economic sphere takes a leading role with Miguel de la Madrid Hurtado as the head of the Mexican state (1982-1988), amidst a severe economic crisis marked by factors such as increased public and private spending, the imbalanced relationship between internal and external inflation, and the strengthening of the overvaluation process (to name a few).

Neoliberalism, globalization, deregulation, free trade, openness, liberalization, and privatization are words used as lingua franca[1] to name and describe this new world erected by the rising Mexican technocracy based on an economy studied in the leading American colleges, now in the cabinet of the abovementioned Miguel de la Madrid[2].

The "McDonaldization of society," among other things, not only ensures a flow of goods through this commercial deregulation but also more actively allows the movement of people to spaces like the United States, the cradle of the massification of global popular culture and the epicenter of production and consumption[3]; aspects that, from a historical and epidemiological point of view, will be essential to determining the pathogenesis of HIV/AIDS in Mexico. As stipulated in *Diseases and Human Evolution* (2005)[4], the transformation of societies previously based on agriculture into an industrialized and globalized world has radically and definitively altered the patterns of infectious diseases.

Since June 5th, 1981, following the first reported cases of a strange illness in the United States, the alarm went off triggered by health authorities, the U.S. Centers for Disease Control and Prevention, through the epidemiological publication *Morbidity and Mortality Weekly Report*. In this journal, the patients showed an atypical condition: 5 previously healthy young men, aged 29 to 36, from Los Angeles County, CA, who, after lab tests, were all reactive for pneumonia caused by the agent *Pneumocystis jirovecii*, with infections from cytomegalovirus and mucosal candidiasis; furthermore, it was established that 2 of the 5 had succumbed within a short period.

Regarding mortality rates, from the beginning it was warned that a severe deficiency of the immune system was a key indicator (in a count, fewer CD4 lymphocytes or 200 cells per cubic millimeter, now CD4 < 200), causing these immunocompromised individuals to be exposed to various infections[5].

Geographically, regarding the dissemination of AIDS, it was initially believed that it had originated in places like California and then New York, as that is where the alarm went off. However, due to future phylogenetic research, a pattern in the distribution of the emerging pandemic would be established: in the United States, HIV/AIDS became visible in New York state, then spread to Georgia, and simultaneously appeared in Pennsylvania and California, and subsequently in New Jersey. However, before it reached American soil, AIDS was already present in Haiti and even earlier on the African continent[6].

Regarding the validity of what has been mentioned, now in reverse, it is explained that from the nascent Democratic Republic of Congo, with its bustling progress, both through its decolonization and the wave of Congolese workers moving to sugar cane plantations in Haiti, the virus reached the Caribbean island[7] and from there, with a certain prevalence, traveled to the United States through the booming sex tourism industry[8].

As for the introduction of HIV/AIDS in Mexico, there is evidence supporting the fact that it was an imported disease, when the first Mexican patients reported having lived or traveled outside the country for a time, particularly in the United States. In other cases, the infection occurred while they were in Mexico, and they

reported having engaged in risky sexual practices with American tourists[8]. In any case, what transpired was something that López and Van Broeck (2015)[9] would later explain regarding the BH (bisexual and homosexual) foreign man, noting that "outside their everyday conditions, [the traveler] feels freer to expand certain social, physical, or intellectual limitations. [and consequently] enhance their sexual interaction.".

Thus, *de vita et morbidus*, health authorities gathered information, sometimes sensitive, other times profound; enough to establish a profile, a pattern in the transmission of AIDS among Mexicans, and as expected, sexual activity and identity were part of it. Compared to what was reported in the United States, few studies have been found in Mexico, 2 of which serve the present writing and are primary sources.

It was, therefore, an epidemiological profile sketched mainly by young Mexican men, with a mean age of 34.8 years, corresponding to a middle to high economic classification; just over half identified as homosexual and to a lesser extent as bisexual; around 92% were single. Concerning their place of residence, there was a higher distribution between Mexico City, followed by the State of Mexico, Jalisco, and Monterrey, the states of the Mexican Republic with the highest industrial activity[10,11].

Regarding the most common initial sign of the syndrome, Dr. Ponce de León (2011)[11], a pioneer in patient care, recalls that they were "those of a young man with significant weight loss, chronic diarrhea, purplish skin lesions, oral candidiasis, and pneumonia with respiratory disease."

From outside to inside

It didn't take long for the combination of an epidemiological profile, plus the early signs and symptoms, to make it decisive to have guidelines that presumptively guided the diagnoses for AIDS. How? Through a more or less homogenized case criterion and adopted in major hospitals and centers across the country. Additionally, noting that, according to the economic limitations at the time, an AIDS diagnosis without lab test was an urgent reality[10].

Cases such as those seen in the first anamneses at Salvador Zubirán National Institute of Medical Sciences and Nutrition (the first to register the first HIV/AIDS case in Mexico) and hospitals from the Mexican Institute of Social Security[10,12] (Table 1) were noted.

In Mexico, clinical signs were primarily treated through therapy with antifungals, antivirals, and antibiotics, whether as therapeutic or prophylactic interventions[10,13,14] (Table 2).

Table 1. In contrast, the Ministry of Health and IMSS hospitals reported modest differences in the first Mexican patients

INCMNSZ	IMSS
Diarrhea	Chronic diarrhea
Weight loss	Candidiasis
Fever	Respiratory disorders
Weakness	Tuberculosis
Lymphadenopathy	Lymphadenopathy
Oral candidiasis	Headache
Anorexia	Fever
"Dermatitis"	"Dermatosis"
Paresthesias	

IMSS, Instituto Mexicano del Seguro Social; INCMNSZ, Instituto Nacional de Ciencias Médicas y de la Nutrición Salvador Zubirán.

The first antiretroviral

The history of the first antiretroviral does not begin in the late 1980s, or at least not with the intention of treating HIV/AIDS, but rather dates back several years earlier, when in 1964, at the Wayne State University School of Medicine (located in Detroit, MI, United States), American scientist Jerome Phillip Horwitz et al. first synthesized the drug AZT, expressly for the purpose of treating cancers caused by retroviruses (family Retroviridae), but with poor results, which left AZT "waiting for the right disease," as Dr. Horwitz said.

And so, many more years passed until this situation led to the involvement of one of the most recognized and controversial figures in the history of the first antiretroviral, American oncologist and researcher Samuel Broder, who at that time was working for the U.S. National Cancer Institute (NCI) in Michigan, United States.

Indeed, the importance of Dr. Broder's intervention (a "dynamic figure" in the burgeoning history of the drug AZT) lies in his ability to merge 2 important events to create a strategic alliance between the private and the public industry. On one hand, Burroughs Wellcome (BW) was open to collaborating on a clinical trial, and on the other was Broder, who had been traveling across the country urging various pharmaceutical companies to study HIV/AIDS more, considering

Table 2. It is observed that, due to the lack of an effective drug against the virus, antibiotics, antivirals, and antifungals were used to treat the infections that emerged

Clinical signs	Infectious agent	Treatment
Oral candidiasis	*Candida albicans*	Fluconazole
Pneumonia caused by *Pneumocystis jirovecii*	*Pneumocystis jirovecii*	Trimethoprim-sulfamethoxazole/pentamidine
Tuberculosis	*Mycobacterium tuberculosis*	Isoniazid
Herpes simplex virus types 1 and 2	Herpes simplex virus	Acyclovir
Diarrhea in HIV/AIDS coinfection	*Cryptosporidium spp./Isospora belli*	Spiramycin/trimethoprim-sulfamethoxazole
Cytomegalovirus infection	Cytomegalovirus	Acyclovir (for cases with retinitis)
Cryptococcosis	*Cryptococcus neoformans* var. *neoformans* and *Cryptococcus neoformans* var. *gatti*	Fluconazole
Toxoplasmosis	*Toxoplasma gondii*	Azithromycin/trimethoprim-sulfamethoxazole

that at that time most of them were wary and distrustful of the topic. Broder even urged them to send their most promising compounds to the NCI.

Rise and fall of AZT

And so it happened, following the recommendation of scientist Jane Rideout, combined with the expertise gained from studying retroviruses (especially in antiviral drugs), that BW —neither slow nor idle— sent approximately 50 compounds to Broder's team by the end of 1984, all marked with a code of one or more letters, hoping that, in particular, the compound behind the inscription "S" would be chosen. Of course, that "S" corresponded to the code assigned to AZT while it sat on the shelf: 509US1. Therefore, by February 1985, Broder's team had identified AZT as the most effective of all the samples submitted, and in July 1985 it moved from being a test-tube investigation to human application, with results that appeared to be promising; by then, cases of HIV/AIDS had already been confirmed worldwide.

These circumstances —both the social climate surrounding the early cases treated with AZT and the hunger for life— served as a watershed for the development of a new clinical trial in March 1986, one that could concentrate on a larger population, combined with tests designed and directed entirely by BW's own scientists, not underestimating that this was the clinical trial that has sparked the most bitter discussions due to the ethical, procedural, and economic controversies it generated from within.

For example, there are cases such as BW not having the necessary infrastructure to fully conduct the research and care processes, as, according to consulted sources, this was still under construction. Additionally, it was necessary to find an alternative drug to AZT, as the standard procedure required another drug for comparison purposes; however, only AZT was available. Consequently, the situation resulted in the use of a placebo, something still controversial in the biomedical community, which would deem such a proposition as dishonest. Lastly, but no less important, the country faced a shortage of thymidine (hence the drug being named azidothymidine [AZT]), a raw material for its production, complicating the scenario as global reserves were insufficient.[15]

How were such challenges addressed? In the first case, it is believed that the solution came from Dr. Broder, who made the NCI (government agency) infrastructure available to conduct the necessary procedures. In the second case, regarding the dilemma of using a placebo, it is known that without an alternative drug, the order to administer this ineffective substance to some patients was maintained, while others were given AZT. Finally, on the supply of thymidine, a favorable outcome was achieved when BW's head of technical development, David Yeowell, declared in 1960 that a pharmaceutical company had produced considerable quantities of thymidine and managed to supply it throughout the AZT clinical trial. He even reached an agreement to ensure this supply in tons with future prospects. This pharmaceutical company was Pfizer.

In short, once everything necessary was gathered, and without ignoring the above-mentioned difficulties, the double-blind clinical trial involved 282 patients across a total of 12 medical centers in the United States. Among them, a profile of almost entirely Caucasian homosexual men who had had cases of pneumonia caused by *P. jirovecii* was shown. Of note that there were no data indicating the use of AZT in Latino men, although this was not an exclusion criterion for the research.

A total of 145 out of the 282 patients received AZT in doses of 1500 mg, while 137 received the placebo, and BW took note of what was happening, assuming they did not know who was receiving what, except for an external panel of doctors whose job was to monitor the results. Until, deliberately, the trial was closed due to the death of 19 patients who were on the placebo vs those who had received AZT, of whom only 1 had died. For the latter, the drug was described as having an impact on 3 basic aspects:

- Reduction of mortality in AIDS patients (vs those who received the placebo).
- Reduction of opportunistic infections (especially *P. jirovecii* pneumonia).
- Increase in the number of CD4 lymphocytes.

From that moment onwards, the approval time by the U.S. Food and Drug Administration for AZT to come to light has been one of the shortest in the history of antiretrovirals. Thus, it was marketed on March 19th, 1987, under a new patent name: Retrovir®.

However, the urgency with which the drug was approved, in "high priority" status, triggered a bunch of questions that could not be resolved at that time, such as possible side effects or the cost of the drug. The toxicity caused bone marrow suppression, with subsequent cases of anemia accompanied by neutropenia, situations that patients reported with symptoms such as nausea, headaches, insomnia, and fatigue at the beginning of the treatment, and if they reached a year with it, myopathy[15,16]. Otherwise, they assured, it allowed a survival period of 21 months, enough time for patients to put their affairs in order.

This goes without mentioning the high cost of Retrovir®, which ranged from $8000 up to $12,000 per patient, which, at the time, was considered the most expensive drug in history[16]. It was practically unaffordable for the average person or for the coverage of some health systems around the world.

For all these reasons, and under a lot of pressure, BW had to face government hearings to try to reduce the cost. Nine months later, it was reduced by 20%, and it was explained that this decision was due to decreased manufacturing costs. But that would not be enough to mitigate the public's anger and media coverage, as controversies continued to mount, questioning every aspect of the drug, starting with the clinical trial and its fundamental deficiencies, such as the masking of AZT and the placebo, since it was claimed that patients always knew what they were taking, either by the taste, smell, or because some took their pills to chemists for analysis, which undermined the double-blind trial[15].

Another aspect was the cost reduction and the assistance that BW received to conduct their research at the NCI and the lack of recognition later given to university and government researchers (by not categorically considering them as co-inventors). However, the most criticism was directed at the way the drug was administered, often in high doses, which ensured repeated purchases, without overlooking the medical difficulties faced by those "on AZT"[15,16].

In Mexico, meanwhile, the possibility of acquiring Retrovir® was almost remote from the beginning, as its approval was only achieved in February 1990, although by 1988 it was possible to obtain it through a written request issued by the Ministry of Health, requesting the sale of Retrovir® in BW laboratories or through involvement in some clinical trials that were conducted sparingly by certain institutes. However, to be honest, there was much skepticism around this, either because of the internal struggles being fought on American soil or because it was claimed that the drug was so cytotoxic that it killed you before the syndrome itself did; inventions and creations of the so-called "iatrogenic vampires"[16]. The decision-makers in medical matters in Mexico were also notably absent, as they rarely spoke out and allowed speculation and misinformation to flourish[17]. Dr. Gustavo Terán, founder of the Center for Research on Infectious Diseases *(Centro de Investigación de Enfermedades Infecciosas)*, merely commented that Retrovir® had "marginal" and "short-lived" effects, and that survival among Mexicans reached only about 6 or 8 months.

It wasn't long before didanosine (ddI) emerged as a substitute for Retrovir®, and then zalcitabine (ddC) eclipsed AZT, until in 1996, the results from the use of highly active antiretroviral therapy (HAART) arrived from Vancouver, Canada, demonstrating convincingly that the combination of three or four antiretrovirals reduced morbidity and mortality, allowed a degree of HIV suppression, and provided greater tolerance; for these reasons, it is still used today[18].

Conclusions

The emergence of HIV/AIDS, with all its vicissitudes, marked an advance in the biomedical field. These advances included attempts to explain the pathogenesis as well as aspirations to mitigate the disease.

Such advances (understand pharmacological therapy) were possible thanks to certain conditions, but others did not favor them. In Mexico, the financial aspect played a fundamental role, as it allowed the use of antifungal, antibiotic, and antiviral therapy as the basis for treating HIV/AIDS signs, but not for purchasing the first antiretroviral, either due to the consequences of the neoliberal policies facing the country or the weakening of the welfare state, but even more so due to the high cost of AZT. In this sense, it is understandable that the use of the above-mentioned drugs was more financially functional.

Equally important were the tests conducted in the United States, which did not provide conclusive information about the use of AZT in the Latino population and left a ring of questions, because for the Caucasian population it was significant in terms of longer survival and reduced morbidity and mortality, especially from *P. jirovecii* pneumonia, which was not the main cause of death among Mexican cases.

In conclusion, we should mention that the delay in acquiring AZT and the increased cost of its use in clinical trials at some institutes were largely due to the silence from authorities regarding the presence of HIV/AIDS in Mexico, which hindered and obscured a "lost generation" that did not see the dawn of the future.

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Conflicts of interest

None declared.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

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