HIV IN MEXICO: A 10-YEAR POPULATION-BASED ANALYSIS TO EVALUATE POLICY CHANGES IN DIAGNOSIS, TREATMENT, AND EARLY MORTALITY ON PLWH 2008-2017

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Lay abstract

Health policies are designed, implemented, or changed to improve the population healthcare. Specifically, for the context of the HIV, policies also target to contain the global epidemic. Identify socio-economic determinants of People Living with HIV and the relationship with policy success is key to control and end with this public health concern. This doctoral thesis evaluates recent changes in HIV health policies in Mexico and identifies determinants of the three major HIV outcomes these policies affect: diagnosis, treatment, and early mortality in People Living with HIV.

Abstract

The last twenty years have been dynamic and relevant for the HIV/AIDS epidemic worldwide. Compared to the beginning of the HIV epidemic, People Living with HIV (PLWH) are living longer and better lives because of increased understanding of the disease, awareness, access to treatments and better quality of health care. In Mexico, since 2007 there was a major initiative that provided universal access to antiretroviral treatment and care for all PLWH, regardless their insurance status. The last two major health policy changes were implemented in 2013, and 2014. First expanding actions to increase early diagnosis and treatment. Second, modifying clinical guidelines (in 2014) to expand universal antiretroviral treatment access, irrespective of their baseline CD4 cell count and symptoms.

This dissertation examined the relationship of the two HIV policy changes in Mexico on diagnosis, treatment, and early mortality of people living with HIV using data from Mexican individuals receiving antiretroviral treatment from 2008 to 2017. The three original papers also identify the key determinants for the same three indicators. Results from the first study indicated that actions implemented in 2013 decreased the proportion of individuals with a late HIV diagnosis. The second article highlighted the importance of removing clinical indicators for treatment initiation, as this increases the number of PLWH initiating antiretroviral treatment and reduces the number of PLWH who develop virological failure. The last article showed that that being male, being older, showing worse biomarker levels at the time of diagnosis, and being diagnosed in a region other than Mexico City were factors associated with early mortality. While the descriptive data showed that the proportion of individuals experiencing early mortality decreased after the HIV policy changes implemented in Mexico in 2014. The entire work tells a complete story for understanding the HIV epidemic in Mexico, based on three main indicators.

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List of abbreviations

AIC: Akaike Information Criterion
ART: Antiretroviral treatment
BIC: Bayesian Information Criterion
CAPASITS: Ambulatory Centers for Prevention and Attention for HIV/AIDS and Sexually Transmitted Infections in Spanish
CENSIDA: National Center for the Prevention and Control of HIV
CI: Confidence Interval
HIV: Human immunodeficiency Virus
IQR: Interquartile
MSM: Men who have sex with Men
OR: Odds ratios
PLWH: People living with HIV
SALVAR: Antiretroviral therapy administration, logistics, and surveillance system in Spanish.
SDs: Standard deviations
SHPS: Social Health Protection System
SP: Seguro Popular
VF: Virological Failure
VL: Viral Load
WHO: World Health Organization

Declaration of Academic Achievement

This dissertation presents three original research studies (Chapters 2-4), an introductory chapter (Chapter 1) and a concluding chapter (Chapter 5). Chapter 2 has been published in BMC- AIDS research and therapy. Chapter 3 has been published in International Journal of STD & AIDS. I, Amilcar Azamar-Alonso, am the lead author of each co-authored chapter. I conceived of all research questions with input at various stages from committee members and colleagues, completed all data work and analysis, and wrote the manuscripts. Chapter 2-4 are co-authored with Jean-Eric Tarride. Andrew P. Costa. Lawrence Mbuagbaw, Fiona Smaill, and Sergio A. Bautista.

Chapter 1. Introduction

This dissertation comprises three original research studies that focus on progress and policy changes concerning the diagnosis, treatment, and health outcomes of people living with human immunodeficiency virus (HIV) in Mexico. Over the last few decades, Mexico has adapted its health policies to World Health Organization (WHO) guidance. In 2003, all People Living with HIV (PLWH) could freely access antiretroviral therapy (ART) regardless of their insurance status, as part of Seguro Popular –a public insurance covering all Mexican population independent of their employment situation (1). A few years later, the need to expand ART coverage and address inequalities in HIV treatment was acknowledged in the "*Plan de Acción Nacional*," which changed the focus of policies targeting only high-risk groups to include the broader population, such as women and people living in poverty (2,3).

Health policies are designed, implemented, or changed to improve the healthcare context and contain the HIV epidemic. This doctoral thesis evaluates recent changes in HIV health policies in Mexico and identifies determinants of the three major HIV outcomes these policies affect: diagnosis, treatment, and early mortality in PLWH. The first chapter summarizes the objectives, rationale, and contributions of the three original studies, which form the basis of this dissertation.

Objective

The three studies considered here examine the implications of the HIV policy changes in Mexico on PLWH in terms of diagnosis, treatment, and early mortality. This thesis contributes to a formal evaluation of the Mexican HIV policies implemented between 2008

and 2017. In addition, the third study offers a methodological contribution to the analyses of HIV survival data.

As such, the specific objectives for each study are to:

1. Identify the determinants of late HIV diagnosis (i.e., a diagnosis with a CD4 count of less than 200 cells/mm3) in Mexico from 2008 to 2017 and evaluate the impact of the 2013–2017 National HIV program, which aimed to increase HIV diagnoses.

2. Assess the determinants of virologic failure (VF) in Mexican PLWH on first-line ART between 2008 and 2017 and evaluate the effects of changes following the policy implemented in 2014 for expanding universal access to ART irrespective of CD4 count and symptoms.

3. Identify factors associated with early mortality of PLWH in Mexico from 2008-to 2017 and compare several statistic models to analyze early mortality.

The following section outlines the background and justification of each study included in this dissertation. It begins with an overview of the global HIV epidemic, progress, and challenges, followed by details about Mexico's health system and national HIV epidemic.

Global HIV trends: Challenges and opportunities

The past two decades have been transformative for the HIV/AIDS epidemic worldwide. Improvements in healthcare service delivery, innovation in treatment plans, and political commitment have changed the vision of the HIV epidemic from a crisis to the management of a chronic condition (4). Compared to the beginning of the HIV epidemic, PLWH are now living longer and have better lives due to increased access to effective treatments and better

quality of health care (5). For example, in Latin America and the Caribbean, AIDS-related deaths decreased by 19% from 2010 to 2016, and nearly 60% of all PLWH in the region are under treatment with ART. Nevertheless, the new infection rate in the region of 120,000 new diagnoses per year has remained constant since 2010 (6). This situation highlights the need for a sustained focus on the HIV epidemic from the scientific and public health sectors. Otherwise, the costs of fighting the epidemic will continue to increase and represent a significant burden on the region's public health systems and public finances.

To respond to the HIV epidemic, policymakers had to provide adequate resources to control HIV/AIDS while adapting public policies and programs due to a change in the demographics of the HIV epidemic over the past decade (5). One important example of health policy change is how countries shifted their HIV policies to include the WHO “treat all” policy, which stipulated the prompt initiation of ART following an HIV diagnosis regardless of CD4 cell count (7). This public health approach helps PLWH benefit from early treatment and reduces the risk of further transmission by lowering the viral load to undetectable levels, which in turn reduces the incidence of HIV.

“Treat all” is a set of efforts that aims to diagnose and treat all PLWH as soon as possible after diagnosis (8). Countries have responded to this guidance by implementing structural interventions such as increasing health system capacity for PLWH. These strategies have decreased the HIV transmission rate and increased HIV diagnosis and early referral to treatment in several countries. They have also increased life expectancy and health-related quality of life in PLWH (9). Despite these efforts, many individuals remain undiagnosed and therefore lack access to lifesaving ART and may continue to expose others to HIV (10).

The importance of early diagnosis

Timely diagnosis of HIV is the first step in ensuring optimal health outcomes and controlling the epidemic (11). Until 2015, late HIV diagnosis was defined worldwide as a diagnosis with a CD4 count lower than 350 cells/mm3 (12,13), but this definition was recently changed to a CD4 count lower than 200 cells/mm3 (14). Delayed diagnosis has been shown to affect patient prognosis, reducing the effectiveness of ART and increasing early mortality (i.e., within the first six months after treatment initiation) (11,15–17). Late diagnosis also has important consequences for public health due to an increased risk of transmission because precautionary measures may not be taken in the absence of an HIV diagnosis. (17,18), reducing the possibility of epidemic control, and triggering important economic concerns for national and international health systems. First, PLWH with a late diagnosis have a higher probability of opportunistic infections, AIDS, renal failure, and liver disease (18). From an economic point of view, individuals with a late HIV diagnosis incurred three times more healthcare expenditures than those with an early HIV diagnosis, both in the first and subsequent years following the diagnosis (17,19). Furthermore, late diagnosis increases HIV healthcare expenditure by adding new patients due to new infections traceable to PLWH with unknown status (20). In addition to early diagnosis, early treatment initiation is key in controlling the HIV epidemic.

The importance of early antiretroviral therapy (ART)

A key aspect of global HIV response is to increase ART coverage. The primary goal of ART is to achieve and maintain virologic suppression in PLWH to reduce disease progression and eliminate transmission (21,22). Recent clinical evidence has strongly determined that an

undetectable disease equals an untransmittable disease (U=U) (21). Although different countries are at different stages of ART coverage, and important research gaps still exist, there is a consistent global trend towards expanding access and achieving earlier ART initiation (23). Notably, evidence has shown that the combination of early diagnosis and timely access to ART reduces the probability of disease progression and improves health outcomes among PLWH (16,21,22,24,25).

Expanding access to ART involves significant technical, operational, programmatic, and ethical challenges to policymakers and implementers in many low- and middle-income countries (26). These challenges include implementing a strategic mix of approaches to ensure timely diagnosis of HIV infection in both health facility and community settings and effective referral networks among care settings to initiate early ART. Reliable, quality-assured, and affordable laboratory monitoring tools, an adequate health workforce, and uninterrupted drug supplies are also essential to improving ART coverage (27). Community- and health facility-based interventions to improve and sustain ART should accompany all previously mentioned efforts to ensure that people initiating treatment are retained in long-term care (28).

Global public health response to HIV

During the past decade, a relevant paradigm shifts central to the global HIV response has been the transition into a public health perspective that acknowledges how uneven HIV-related risks are distributed within the population. These inequities in the distribution of HIV-related risks spurred the new focus to include a set of interventions with the highest likelihood of impact the epidemic. Therefore, policies, interventions, programs, and initiatives must be tailored to risk profile. Implementing such interventions with finite resources has been, and

will continue to be, a major challenge for researchers, policymakers, and implementers, given the concurrent vulnerabilities that those at greater risk experience (among them poverty, food insecurity, depression, substance abuse, and barriers to health care access).

The Mexican Health System and HIV/AIDS public policies.

Historical overview of the Mexican health system

To provide financial protection for the most vulnerable Mexican families, the Mexican health sector underwent a major transformation in 2000 when it created the Social Health Protection System (SHPS), expanding care coverage to those without public insurance while guaranteeing more equitable and affordable access to healthcare services. The Mexican health system includes three parallel components which provide healthcare services: 1) employment-based (public or private sector) social insurance schemes, 2) a private sector composed of service providers, insurers, and pharmaceutical and medical device manufacturers and distributors; and 3) public assistance services for the uninsured supported by a financial protection scheme (29). The Mexican healthcare system had not changed substantially since 1959 when private-sector employees and federal workers were covered for all required health services (30). However, the segmented nature of the Mexican health system left informal sector workers (a term used for the non-salaried workers representing around 60% of the Mexican population) without any social security coverage. As such, informal workers had to incur out-of-pocket expenditures for health care (e.g., hospitalizations, doctors, and medications) (31).

These changes were a landmark in the recent history of the Mexican health system (32). Seguro Popular, the operating arm of the SHPS, was established in 2000 to offer financial protection to those excluded from social security (e.g., unemployed Mexicans). Since 2003, Seguro Popular has expanded substantially through increased enrollment (34–36) and guaranteed universal access to healthcare services, including the most vulnerable populations (31). A significant innovation of the SHPS was the creation of the Catastrophic Health Expenditure Fund in 2003 (33) (see figure 1), which covered the treatment of high-cost diseases, including HIV/AIDS, cancer, congenital malformations, and more (34).

HIV care in Mexico from 2000 to 2012

Alongside these health system reforms, in the early 2000s the Mexican government began to prioritize the HIV epidemic as a public health concern. Several programs were established to improve national HIV/AIDS indicators and PLWH health outcomes (35). Initially, efforts were focused on prevention initiatives such as promoting condom use among high-risk populations and communication campaigns to reduce stigma and increase HIV/AIDS awareness (1,36). In addition, the 2007 introduction of rapid HIV tests in some healthcare facilities was a significant policy aimed at increasing the diagnosis of PLWH (36–38).

In 2007, the Mexican government launched a major initiative to provide universal access to ART and free care for all PLWH irrespective of their insurance status (see fig. 1), but conditional on several clinical criteria such as CD4 counts (3). This initiative was implemented through the *Programa de Acción Específico*, Respuesta al VIH, SIDA e ITS 2007-2012 (Specific Action Program for HIV/AIDS and Sexual Transmission Infections), a five-year nationwide program. This program focused on prevention and treatment in key populations such as men who have sex with men (MSM), transgender populations, and sex

workers (36,37). The main objective of this 2007-2012 policy was to increase HIV diagnosis in these populations through prevention campaigns promoting the use of condoms, lubricants, and rapid tests. Consequently, HIV rapid tests offered and used in public institutions affiliated to Seguro Popular increased from 7.6% in 2007 to 22.7% in 2012 (36). In terms of treatment, enrolled patients (all PLWH regardless of their insurance status) could be treated in three types of facilities: 1) national institutes; 2) the specialty *Clínica Condesa* and 3) CAPASITS (HIV specialty clinics – "*Centro Ambulatorio para la Prevención y Atención en SIDA e ITS*"). The CAPASITS network was introduced in 2005 to treat HIV outside Mexico City and has since expanded. In 2017, 137 CAPASITS facilities were in operation compared to 49 in 2007 (39,40). The CAPASITS facilities are managed by the National Center for the Prevention and Control of HIV/AIDS (in Spanish, CENSIDA).

To monitor and evaluate the Mexican national HIV epidemic, the ARV Drug Management, Logistics and Surveillance System (in Spanish, SALVAR) was created in 2007. SALVAR is a national database designed to manage and monitor ART prescriptions and health outcomes among SHPS patients (41,42). The database contains information such as CD4 count, viral load, route of transmission, gender, age, and treatment plans of around 64% of all PLWH in Mexico (43), all covered by Seguro Popular without any other type of social insurance.

HIV policies in Mexico from 2013-2017

Following the changes implemented from 2007-2012, another major health policy change was implemented in 2013 when the Mexican government launched the National HIV program 2013-2017 (3). This new plan included a directive to expand actions beyond high-risk groups to include low-risk individuals (e.g., women and young heterosexual men) and

to increase early diagnosis and treatment even though the Mexican HIV epidemic remained concentrated in high-risk groups (e.g., MSM, transgender individuals, sex workers, and intravenous drug users) (see fig. 1). Since only 52% of PLWH knew their status in 2012 despite the implementation of the 2007-2012 HIV policies (3), increasing HIV diagnosis was one of the pillars of the 2013-2017 Mexican HIV program. From 2013 to 2017, the HIV budget doubled compared to the previous period, and additional resources were allocated to improve HIV care across Mexico. Although the only patients managed directly by the Ministry of Health (MoH) are those enrolled in Seguro Popular, the 2013-2017 HIV policies included all Mexicans, including those covered through employment-based public insurance plans. However, despite major efforts to address the epidemic in Mexico, more 208,000 people were living with HIV/AIDS in Mexico in 2021. Of the 19,000 individuals diagnosed with HIV in 2021, 5,300 individuals died of AIDS-related causes out of the (mortality rate of 4.2 per 100,000 habitants) (44).

In this context, the first study considered within this doctoral thesis evaluated the impact of the 2013 change in HIV policy in Mexico aimed at improving HIV diagnosis (45). In addition, it evaluated the determinants of late diagnosis in Mexican PLWH between 2008 and 2017. These two objectives are important to inform future HIV policies. Besides providing new information on the characteristics of PLWH diagnosed in Mexico between 2008-2017, the study – published in BMC AIDS Research and Therapy — found that the 2013 reform positively impacted the HIV diagnosis rate and that PLWHs were diagnosed at a younger age. Additionally, results indicated that a lower proportion of HIV was detected late (45).

The 2014 change in HIV guidelines in Mexico

Following the WHO recommendations for early initiation of HIV treatment as stated in the "Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV" presented in June 2013 (46), the Mexican HIV clinical guidelines were modified in 2014 to expand universal ART access in all PLWH, irrespective of their baseline CD4 cell count and symptoms (47,48) (see fig. 1). This contrasted with previous criteria, which required an individual to have a CD4 < 350 cells/mm3 before initiating ART. The rationale behind this change was previous evidence showing that early treatment initiation reduces the risk of disease progression and death and the risk of contracting tuberculosis as an opportunistic infection (49). Therefore, the cost of an earlier (generalized) treatment initiation would be balanced by long-term cost reduction in care for severe disease and fewer PLWH due to lower transmission (46).

The main objective of early ART initiation in PLWH is viral load suppression to reduce disease progression and increase life expectancy (50,51). Achieving viral load suppression is also an important HIV policy objective because virological failure (not achieving suppression or experiencing relapse) can be attributed to a combination of several factors, such as poor adherence, inadequate care, and contextual variables (52,53).

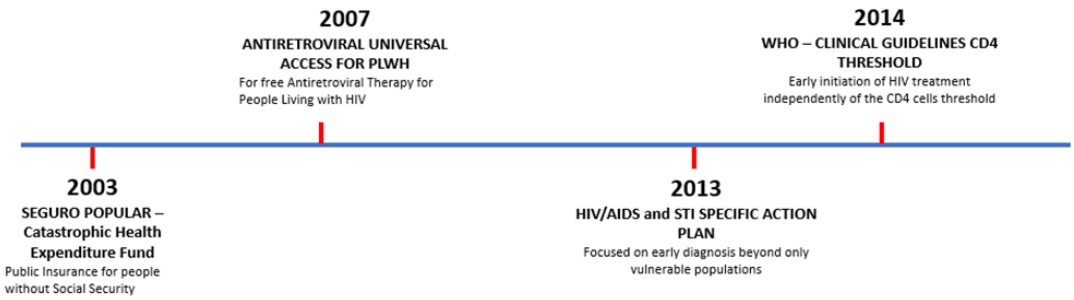
To generate evidence for future policy design and implementation, the objective of the second study was to document the change in rates of VF following the implementation of the 2014 HIV clinical guidelines in Mexico (54) and to identify the determinants of VF in Mexico between 2008 and 2017. Key results showed positive changes, as the percentage of PLWH with virological failure decreased from 50% to 33% after the 2014 guideline change after controlling for individual and contextual variables. Other results indicated that

removing the CD4 threshold for treatment initiation combined with the expansion of ART led to a higher proportion of PLWH who initiated treatment and a lower proportion who developed virological failure after these changes (54). This study was recently published in the International Journal of STD and AIDS (54).

The final goal: reducing early mortality

Reducing HIV mortality is one of the main goals of international and national HIV policies. Mortality rates among PLWH are higher in the first six months following treatment initiation and are often referred to as early mortality (55–57). The first two studies of this doctoral thesis evaluated the impact of two HIV policies in Mexico to control the national HIV epidemic: improving HIV diagnosis and decreasing virological failure (through timely access to ART). The third study of this doctoral thesis evaluates the impact of 2013 and 2014 HIV policies in decreasing early HIV mortality using a ten-year cohort from 2008 to 2017. In addition, this study also compared different statistical methods to analyze HIV early mortality. Key findings from the study showed a higher probability of early mortality in older patients and patients who started treatment in regions other than Mexico City or began ART with a viral load above 100,000 copies/mL. However, the results indicated that there was no difference in early mortality before and after the 2013 and 2014 policy changes. The study also showed that parametric models were preferred over the traditional Cox-regression models when analyzing early mortality survival.

Figure 1. Major HIV policies in Mexico 2000-2017



Thesis contributions

Study approaches

This sandwich thesis, composed of three main papers, uses quantitative methodologies to evaluate the impact of recent HIV policies in Mexico and better understand factors contributing to the early diagnosis, ART initiation, and mortality, thus providing evidence for future HIV health policies in Mexico and elsewhere. The three studies applied descriptive and regression analyses using the Mexican SALVAR database as the main data source for the years 2008-2017. As described previously, SALVAR is the primary source for understanding and analyzing the Mexican HIV epidemic and contains all relevant information on PLWH treated as part of Seguro Popular (around 64% of PLWH). The first two studies employed logistic regressions to predict changes in baseline odds for different factors and their association with the main outcome. The main advantage of this method is to provide easy interpretation of results (changes in odds/probabilities of an event). These results can be translated into policy, discourse, action, and improving decision-making. The third study used a survival analysis but compared different methodologies within the same approach. Unlike logistic regression, survival analysis incorporates "time-to-event" and is appropriate when data are collected prospectively. One of its main advantages is the

possibility of adjusting and selecting the shape of the distribution of survival times based on the data and therefore allowing more accurate estimation (58). Like logistic regression, results are easy to interpret and apply to policymaking, but estimations and model adjustments require specific data characteristics (i.e., follow-up time and time to event).

Study contributions

As the only study to have evaluated the impact of HIV policies in Mexico, this dissertation makes important contributions that could be used to inform future HIV health policies. Specifically, this dissertation focused on the three main elements to understand, control, and end the HIV epidemic: diagnosis, treatment, and mortality. Study one presented the first step to achieving global goals: improving HIV diagnosis strategies. It analyzed the effect of changing policy from addressing only high-risk populations to addressing all possible sources of transmission and demonstrated that these approaches expanded diagnosis, especially in younger populations. This paper indicated that the 2013–2017 National HIV program in Mexico has successfully decreased the proportion of individuals with late HIV diagnosis in Mexico and provided a set of key determinants of late diagnosis, which could help establish more accurate health policies. The second study followed the same approach but evaluated the last indicator of the WHO 95-95-95 goals: viral load suppression. This was achieved by eliminating the CD4 threshold to start ART in clinical guidelines. Like study one, this work provides evidence of how recent clinical strategies reduced the probability of virological failure, generating evidence that the combination of an early diagnosis and timely treatment initiation improves treatment effect and improves the health of PLWH in Mexico. Finally, study three established the factors associated with early mortality (using different

methodological approaches). This study finds that late treatment initiation and older age influence early mortality in PLWH; another factor is having initiated treatment with ART different than EFV+TDF/FTC. In conclusion, it was demonstrated that HIV reforms successfully increased diagnosis at an early period, ART initiation, lower VF, but no change in mortality rates.

This dissertation reveals the role of HIV-policy changes in national statistics and creates a narrative useful for understanding the three main indicators used to evaluate progress and improvements in the HIV epidemic. It also provides quantitative research findings to strengthen an evidence base that can be translated into policy on new directions in HIV strategies regarding prevention, diagnosis, and treatment. This dissertation is the first in recent years to use longitudinal data from the SALVAR dataset and the first to use ten years of data to evaluate the impact of HIV policies in Mexico. This opens the door to further similar research to continue monitoring the studied (and other) indicators. Methodologically this dissertation provides evidence towards using survival analysis in HIV/AIDS data.

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Chapter 2. Patient characteristics and determinants of CD4 at diagnosis of HIV in Mexico from 2008 to 2017: a 10-year population-based study

Declaration.

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I was responsible for conceptualizing the research question, study design, and methods, through consultations with Dr. Jean-Eric Tarride. I was responsible for all the data cleaning and analysis. Drs. Fiona Smaill, Lawrence Mbuagbaw, Andrew P. Costa, and Sergio A. Bautista each provided feedback on the drafts, which were incorporated into the final version of the chapter.

Original research paper

Title: Patient characteristics and determinants of CD4 at diagnosis of HIV in Mexico from 2008 to 2017: a 10-year population-based study

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Patient characteristics and determinants of CD4 at diagnosis of HIV in Mexico from 2008 to 2017: a 10-year population-based study

Abstract

Background: In 2007-2012 the Mexican government launched the National HIV program and there was a major change in HIV policies implemented in 2013-2018, when efforts focused on prevention, increase in early diagnosis and timely treatment. Still, late HIV diagnosis is a major concern in Mexico due to its association with the development of AIDS development and mortality. Thus, the objectives of this study were to identify the determinants of late HIV diagnosis (i.e., CD4 count less than 200 cells/mm^3) in Mexico from 2008 to 2017 and to evaluate the impact of the 2013-2017 National HIV program.

Methods: Using patient level data from the SALVAR database, which includes 64% of the population receiving HIV care in Mexico, an adjusted logistic model was conducted. Main study outcomes were HIV late diagnosis which was defined as CD4 count less than 200 cells/mm^3 at diagnosis.

Results: The study included 106,830 individuals newly diagnosed with HIV and treated in Mexican public health facilities between 2008 and 2017 (mean age: 33 years old, 80% male). HIV late diagnosis decreased from 45% to 43% (P <0.001) between 2008-2012 and 2013-2017 (i.e., before and after the implementation of the 2013-2017 policy). Multivariable logistic regressions indicated that being diagnosed between 2013-2017 (odds ratio [OR]= 0.96 [95% Confidence interval [CI]: [0.93, 0.98]) or in health facilities specialized in HIV care (OR=0.64 [95% CI: 0.60, 0.69]) was associated with early diagnosis. Being male, older than 29 years old, diagnosed in Central East, the South region of Mexico or in high-marginalized locality increased the odds of a late diagnosis.

Conclusions: The results of this study indicate that the 2013-2017 National HIV program in Mexico has been marginally successful in decreasing the proportion of individuals with late HIV diagnosis in Mexico. We identified several predictors of late diagnosis which could help establishing health policies. The main determinants for late diagnosis were being male, older than 29 years old, and being diagnosed in a Hospital or National Institute.

Keywords: HIV, Late diagnosis, Mexican *SALVAR*.

Background

Worldwide, more than 37.9 million people are living with HIV (PLWH) of which it was estimated that around 230,000 live in Mexico but only 79% know their status (1–3). In Mexico and elsewhere, the number of individuals diagnosed with HIV has increased during the last decade due to more transmission as well as disease awareness and the implementation of programs aimed to identify people at the early stage of the disease (4). In 2019, approximately 17,000 Mexicans were diagnosed with HIV, most of them were male (85%), between the ages of 25-39 years (70%) and contracted HIV due to sexual contact (71%) (5). Recognizing the problem as a public health matter, the Mexican government established twenty years ago different programs to improve HIV national indicators and the overall health of PLWH. In the beginning, efforts were focused on prevention for high risk populations (6), and the implementation of rapid testing aimed at pregnant women (2). An important improvement in HIV policies happened in 2003 when the Mexican government expanded the coverage of HIV treatment and care in public health facilities to people who were unemployed and individuals from the informal sector (7,8). In 2007, the National HIV program targeting prevention of HIV transmission in key high-risk populations -e.g. men who have sex with men , sexual workers- was launched and was in effect for 5 years (2,6).

A major change in HIV policies in Mexico was observed in 2013 when the 2013-2018 National HIV program was implemented with the mandate to expand efforts beyond the prevention of HIV transmission among high-risk populations to include populations at a lower risk (e.g. young people and women) and to increase early diagnosis and timely treatment (9). In 2014, the Mexican clinical guidelines were changed to recommend ART initiation regardless of baseline CD4 count and symptoms (9,10). One of the key objectives

of the 2013-2018 National HIV program was to decrease the percentage of individuals diagnosed with late HIV to 30% in 2017. With prevalence rates reported of 61% between 2001-2008 (11) and 49% between 2008-2013 (12), late HIV diagnosis is a major public issue due to its association with the development of complications (e.g. AIDS) and mortality (11–13). To support these efforts, the HIV budget also doubled and additional resources were allocated to improve HIV care across Mexico (14,15). For example, the number of HIV facilities outside of Mexico City increased from 49 in 2007 to 137 in 2017 (4,16).

Timely diagnosis and initiation of antiretroviral therapy are crucial to ensure optimal health outcomes among PLWH (17). However very few studies have been conducted to evaluate the impact of Mexican HIV policies on outcomes. For example, one study reported that in 2012 (5 years after the implementation of 2007-2012 HIV national program), more than half of patients died within six months after diagnosis, and the main factor associated with death was a late diagnosis (18). More recent government reports have documented that the percentage of individuals diagnosed with less than 200 CD4 cells/mm^3 decreased from 50% to 40% between 2015 and 2018 (19,20), suggesting a positive impact of the HIV policy in Mexico. However, only one study has examined the predictors of late diagnosis in Mexico using data from 2007 to 2014. While results indicate that men and older adults (more than 50 years old) were at a higher likelihood of late diagnosis (17) compared to the general population, this situation may have changed following the modifications in HIV policies that happened in Mexico after 2013. To better identify people at high-risk for a late diagnosis, and to inform further policies and strategies in Mexico to reach these people early, the main objectives of this study were to identify the determinants of late HIV diagnosis in Mexico between 2008 and 2017 and to evaluate the impact of the 2013-2017 National HIV Program.

Methods

Study design

The design was a retrospective population-based cohort study using Mexican administrative health data from the antiretroviral therapy administration, logistics, and surveillance system (*Sistema de Administración, Logística y Vigilancia de Antirretrovirales* - *SALVAR* for its acronym in Spanish).

Data source

The *SALVAR* database is an electronic system created in 2006 by the National Center for the Prevention and Care of HIV/AIDS to manage the clinical information of PLWH enrolled in the HIV/AIDS program led by the Mexican Ministry of Health (approximately 64% of all PLWHs in Mexico). While *SALVAR* was developed in 2006, it was not until 2008 that it was operational across Mexico. Currently, the system contains linked information on more than 172,000 Mexicans living with HIV (e.g. baseline characteristics, treatment regimens) receiving treatment (20).

Study population

The study population includes adults (18 years or older) diagnosed with HIV between January 1st, 2008, and December 31st of 2017 in health facilities affiliated to the Ministry of Health. Children, people who are incarcerated, and people receiving antiretroviral prophylaxis were excluded from the analyses. Individuals with incomplete information on gender, age, date of diagnosis, and results of the first measurement of Viral Load (VL) and CD4 were also excluded.

Study outcomes

The primary outcome of the study was HIV late diagnosis, which was defined as CD4 count less than 200 cells/mm^3 closest to the date of diagnosis reported in *SALVAR* (21). As the dataset does not specifically contains a variable for CD4 at moment of diagnose, it was considered that the measurement closest to the date of diagnosis (or with the same date), was the key measurement. Secondary outcomes included CD4 cell count at time of diagnosis, CD4 cell count stratified based on WHO recommendations: less than (<) 200, 200-349, 350-499 and, equal or more than (≥) 500 cells/mm^3 (22), and VL at time of diagnosis stratified as VL ≤100,000 units by milliliters of blood (u/ml) and more than 100,000 u/ml (23) for descriptive proposes. For CD4, a lower limit of zero and an upper limit of 2,000 cells/mm^3 was established based on clinical literature (17,24,25).

Independent variables

Age was described as a continuous variable reporting the mean and median, also age was categorized in groups (18-29, 30-39, 40-49, 50-59, and ≥60 years old). Gender was stratified as male, female, and transgender. Characteristics related to health facilities were also included. For the purpose of the study, Mexico was divided into five regions (18,26) (Central West, Central East, Northwest, Northeast, and South) and Mexico City was also counted as an additional region due its large population (25% of Mexicans live in Mexico City) and distinct structural characteristics. In addition, marginalization indices (11,17) grouped into three categories (high/ very high, medium and very low/low) were used to capture social and economic differences by locality of the health facilities where care is provided. Health facilities in which diagnosis and care are provided were described in terms of 1) Hospitals

and National Institutes that provides primary and specialty care in a tertiary level hospital; 2) Ambulatory Centers for Prevention and Attention for HIV/AIDS and Sexually Transmitted Infections (*CAPASITS* in Spanish) facilities which are specialized, stand-alone centers that provide ambulatory care for HIV and STI; and 3) Condesa, a specialized clinic for HIV located in Mexico city and which provides HIV ambulatory care for more than 15,000 PLWH in Mexico City.

Statistical analysis

Key characteristics of the study population were divided and compared in two periods according to policies changes, between 2008-2012 and 2013-2017. Student t-test and Welch test were presented for normally and non-normally distributed continuous variables while Chi-square tests were used for categorical variables. Due to expected skewness of some variables, mean values along with standard deviations (SDs) as well as median values and interquartile ranges (IQR) were used to summarize continuous variables (e.g. age, CD4 levels). Discrete variables were presented using percentages. Patients' and healthcare facilities' characteristics as well as outcomes (i.e. CD4 and VL) were presented for the periods of analysis to illustrate trends over time.

Logistic regressions were conducted to identify the determinants of late HIV diagnosis (i.e., CD4 < 200 cells/mm^3). All models were adjusted by the covariates mentioned above. In addition, a dummy variable corresponding to the period when diagnosed (2008-2012; and 2013-2017) was used to estimate the impact of the 2013-2018 HIV policies implemented in Mexico. To have a better understanding of the determinants of late HIV diagnosis before and after the implementation of the National HIV program in 2013, separate models were estimated for the period 2008-2012 and 2013-2017. Logistic models were

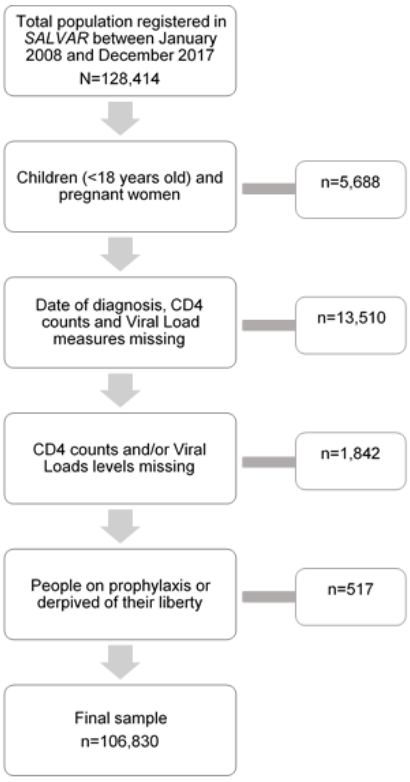
reported using Odds Ratios (OR) and associated confidence interval. Models' goodness of fit was evaluated with Receiver Operating Characteristic (ROC) curves and C-statistic (27), where a C-statistic value of 0.70 or greater indicates good discrimination.

Results

Study population characteristics

From the initial 128,387 individuals included in the *SALVAR* database for the period 2008-2017, 4,759 were children, 13,802 did not have information on diagnosis, CD4 counts or VL results' date, 2,254 patients did not have information about CD4 and VL, 23 people were on prophylaxis, and 531 were people deprived of their liberty. After excluding these groups (Figure 1), the study population consisted of 107,018 individuals.

Figure 1. Sample Flow for Analysis



SALVAR: *Sistema de Administración, Logística y Vigilancia de Antirretrovirales - SALVAR* for its acronym in Spanish

Table 1 summarizes the patients' characteristics at diagnosis over the period 2008-2017 and for each of the two periods of the analysis (2008-2012 and 2013-2017). The median age of the population was 31 years old (IQR=25, 39) and 80% were males. Almost two thirds of the study population were diagnosed in *CAPASITS* facilities, one third in the Central East region and 94% in regions with low marginality index (less deprived areas). Most of the health facilities were in regions of low marginalization index. Several changes were observed over the two periods of analysis (i.e. 2008-2012 and 2013-2017). For example, the median age decreased from 32 (IQR: 26, 40) to 31 (IQR: 25, 39) years old between 2008-2012 and 2013-2017 (*P<0.001*) while the proportion of individuals aged 18 to 29 years of age at diagnosis increased from 40% in the period 2008-2012 to 45% in 2013-2017 (*P<0.001*). During the same period, the proportion of male individuals at diagnosis increased from 77% to 81% (*P<0.001*). More individuals were diagnosed in the South of Mexico over time (*P<0.001*) and less in the Northwest region (*P<0.001*). Table 1 provides the details.

CD4 cells and Viral Load levels over time

Table 1 also presents the data on CD4 and VL (log10) for the whole population over 2008 and 2017 and for each of the two periods of analysis (2008-2012 and 2013-2017). Overall, the number of individuals with a late diagnosis (CD4<200 cells/mm^3 decreased significantly from 45% in 2008-2012 to 43% in 2013-2017 (*P<0.001*)). In parallel, the percentage of individuals diagnosed with a VL>100,000 u/ml increased from 35% to 38% in the same period (*P<0.001*).

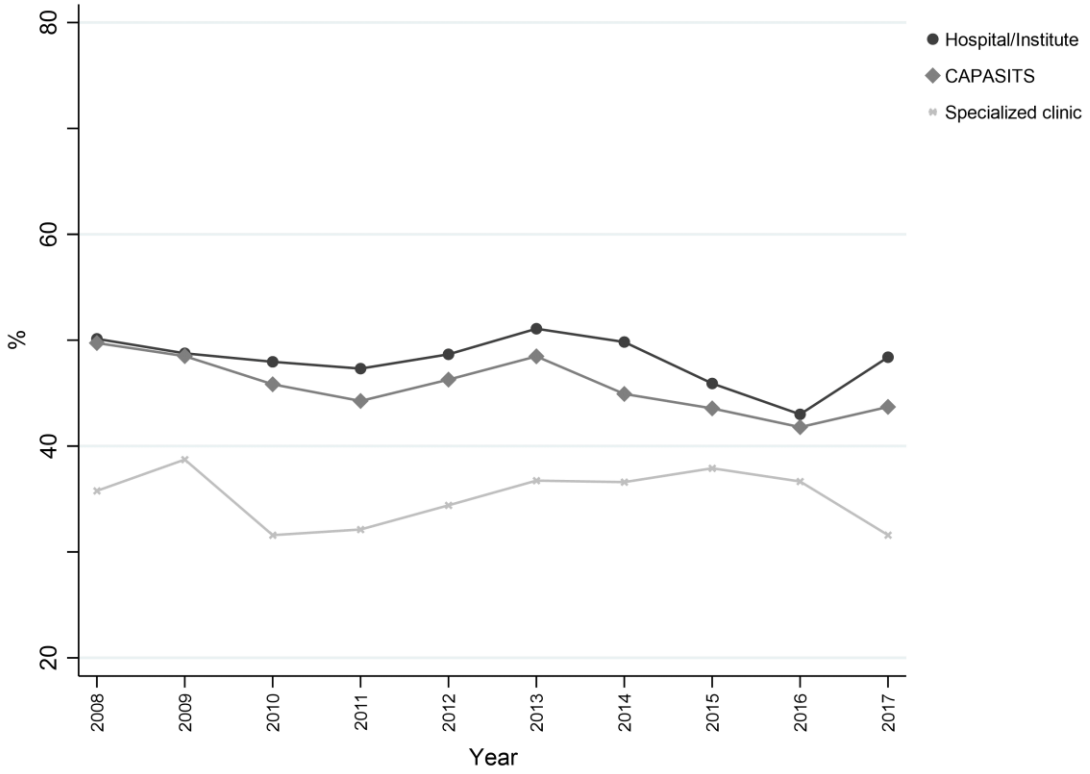
Table 2. Summary Statistics and Patients' Characteristics, CD4 and Viral Load at Diagnosis, 2008-2017

	Total	2008-2012	2013-2017	*P*-value
Sample	107,018	47,702 (44.58%)	59,313 (55.42%)	
Age				
Mean (SD)	33.09 (10.46)	33.50 (10.34)	32.53 (10.50)	<0.001
Median (IQR)	31 (25, 39)	32 (26, 40)	31 (25, 39)	
%				
18-29 yo	43.28	40.04	45.72	
30-39 yo	32.12	34.38	30.39	
40-49 yo	16.77	17.88	15.94	<0.001
50-59 yo	6.03	5.92	6.14	
≥60 yo	1.8	1.79	1.81	
Gender (%)				
Male	79.80	77.78	81.4	
Female	19.79	21.82	18.16	<0.001
Transgender	0.41	0.40	0.41	
Health facility (%)				
Hospital/ National Institute	20.59	21.12	19.38	<0.001
CAPASITS	66.46	66.32	66.31	
Specialized clinics	13.1	12.57	14.31	
Region (%)				
Mexico City	16.85	16.68	17.27	
Central East	30.89	31.60	31.14	
Central West	13.10	13.61	13.18	<0.001
Northeast	13.10	13.89	11.84	
Northwest	8.49	8.61	8.39	
South	16.85	15.61	18.17	
Marginality Index (%)				
High	2.05	1.85	2.21	
Medium	1.20	1.13	1.26	<0.001
Low	93.61	97.02	96.53	
CD4 cells				
Mean (SD)	289 (254)	286 (256)	291 (252)	<0.001
Median (IQR)	233 (88, 417)	226 (88, 410)	238 (89, 422)	<0.001
%				
<200	44.93	45.58	43.8	
200-349	22.47	22.44	22.36	<0.001
350-499	15.91	14.84	16.01	
>=500	17.79	17.14	17.83	
Viral Load (log10)				
Mean (SD)	4.28 (1.39)	4.15 (1.42)	4.38 (1.36)	<0.001
Median (IQR)	4.67 (3.56, 5.27)	4.59 (3.13, 5.19)	4.73 (3.80, 5.32)	
%				
≤100,000 u/ml	62.72	64.76	61.35	<0.001
>100,000 u/ml	37.44	35.24	38.65	

SD: Standard Deviation. Yo: years old. IQR: Interquartile. CAPASITS: Ambulatory Centers for Prevention and Attention for HIV/AIDS and Sexually Transmitted Infections in Spanish. Source: Authors' creation with information of SALVAR

Figure 2 presents over time the proportion of individuals diagnosed with CD4 <200 cells/mm^3 according to the type of facilities where they were diagnosed. Considering both periods, less individuals were diagnosed with a late diagnosis in Condesa compared to the population diagnosed in *CAPASITS* or other Hospitals/Institutes (*P<0.001*).

Figure 2. Percentage of individuals with a late diagnosis (CD4 < 200cells/mm^3) by health facility and year



Source: Authors' creation with information of *SALVAR*

Determinants of late diagnosis

The results of the multivariable logistic regression for CD4 at diagnosis are shown in Table 2. For CD4, being diagnosed during the period 2013-2017 compared to the previous period was associated with lower odds of late diagnosis (0.96 [95% CI: 0.93, 0.98]). Other factors

associated with lower odds of late diagnosis were being diagnosed at *CAPASITS* facilities (0.89 [95% CI: 0.86, 0.93]) or specialized clinics (0.64 [95% CI: 0.60, 0.69]), compared to Hospitals. The variables that significantly increased the odds of a late diagnosis were being male compared to female (1.28 [95% CI: 1.24, 1.33]), being older than 29 years old (1.85 [95% CI: 1.79, 1.90], 2.24 [95% CI: 1.79, 1.90], 2.423 [95% CI: 2.30, 2.56], 2.34 [95% CI: 2.13, 2.57] respectively for each age group), being diagnosed in a Central East (1.16 [95% CI: 1.08, 1.26]) or South region (1.21 [95% CI: 1.12, 1.31]) compared to Mexico City, and in a high marginalized locality (1.23 [95% CI: 1.12, 1.35]). However, as shown by the stratified analyses by time period (Table 2), being diagnosed outside Mexico City became a factor associated with lower odds during the period 2013-2017, while it increased the odds of a late diagnosis when diagnosed before 2013. The odds associated with a diagnosis at a later age were also greater for the period 2013-2017. Table 2 provides the details including the coefficients difference test across periods (Hausman test). As shown in these tables the C statistics in all models were below 0.70.

Table 2. Multivariate Logistic Regression for CD4 at Diagnosis, 2008-2017

Variable	OR CD4 (1: <200 cells/mm^3) All periods	OR CD4 (1: <200 cells/mm^3) 2008-2012	OR CD4 (1: <200 cells/mm^3) 2013-2017
Period of diagnosis (reference 2008-2012)			
2013-2017	0.96** (0.93, 0.98)		
Gender (reference female)			
Male	1.28** (1.24, 1.33)	1.33** (1.27, 1.40)	1.26** (1.20, 1.32)
Transgender	0.94 (0.77, 1.15)	1.09 (0.81, 1.47)	0.84 (0.64, 1.10)
Age group (reference 18-29)			
30-39	1.85** (1.79, 1.90)	1.66** (1.59, 1.73)	2.00** (1.92, 2.08)
40-49	2.24** (1.79, 1.90)	1.87** (1.78, 1.97)	2.59** (2.47, 2.72)
50-59	2.43** (2.30, 2.56)	1.98** (1.82, 2.1)	2.83** (2.63, 3.04)

>60	2.34** (2.13, 2.57)	1.79** (1.56, 2.05)	2.87** (2.53, 3.25)
Region (Mexico City)			
Central East	1.16* (1.08, 1.26)	1.50** (1.34, 1.67)	0.90 (0.80, 1.01)
Central West	0.89* (0.82, 0.96)	1.16* (1.04, 1.29)	0.68** (0.61, 0.76)
Northwest	0.97 (0.89, 1.05)	1.28** (1.14, 1.43)	0.74** (0.66, 0.86)
Northeast	1.06 (0.97, 1.16)	1.49** (1.32, 1.68)	0.77** (0.68, 0.86)
South	1.21** (1.12, 1.31)	1.55** (1.39, 1.74)	0.94 (0.84, 1.05)
Type of health facility (reference hospital/National Institute)			
CAPASITS	0.89* (0.86, 0.93)	0.84** (0.80, 0.89)	0.93* (0.89, 0.99)
Specialized clinics	0.64** (0.60, 0.69)	0.70** (0.63, 0.78)	0.56** (0.50, 0.62)
Index of marginalization (reference low)			
Medium	1.07 (0.95, 1.20)	0.92 (0.77, 1.10)	1.17** (1.00, 1.37)
High	1.23** (1.12, 1.35)	0.99 (0.86, 1.15)	1.43** (1.27, 1.62)
Observations	*107,018*	*47,705*	*59,313*
C-Statistics	*0.6158*	*0.6009*	*0.6165*

*** p<0.01, * p<0.05, +p<0.10. (95% Confidence Interval). OR: Odds Ratio. CAPASITS: Ambulatory Centers for Prevention and Attention for HIV/AIDS and Sexually Transmitted Infections in Spanish*

Discussion

By analyzing 10 years of data this study has provided new information to better understand the characteristics of the individuals diagnosed with HIV in Mexico between 2008 and 2017 and the impact of HIV policies implemented since 2007. Compared to the 2008-2012 period, more individuals were diagnosed at a younger age, less women were identified HIV positive, and more individuals were diagnosed in the South of Mexico in the period 2013-2017. Our univariate and multivariable analyses indicate that the actions implemented during the period 2013-17 reduced late diagnosis of HIV (17) in Mexico by 4% during that time period compared to 2008-2012. Although this difference was statistically significant the reduction is marginal and unlikely to be clinically meaningful (9). In terms of VL, we observed in parallel an increase in the population's levels of VL after 2013, which could be the result of

the 2013-17 initiatives aimed at non-high-risk individuals (such as massive testing, increasing awareness in heterosexual populations) with an advanced stage of the disease (28).

The increase in VL between the two time periods could also be the result of the 2013-2017 policies to improve early diagnosis as some individuals may have been diagnosed with high levels of VL due to a recent infection, which is often associated with a peak, although this is an unlikely theory (29). Still 42% of Mexicans are being diagnosed with CD4 <200 cells/mm3, compared to a governmental objective of 30% late diagnosis in 2017. Our stratified analyses also showed a strong regional effect during the period 2013-2017, with living outside of Mexico City decreasing the odds of a late diagnosis. These results could be explained by an increase in HIV health facilities (i.e. *CAPASITS*) outside Mexico City (from 49 in 2007 to 137 in 2017) (4,16) and the change from a decentralized to an integrated approach to HIV treatment and care in all HIV facilities in Mexico (9) as a result of the implementation of the 2013-17 National plan.

It is difficult to compare our results to other studies conducted in Mexico due to different study designs or period of analysis. However our results are similar to the findings of Carrizosa et al. (30) who reported a late diagnosis rate of 43.2% in 2010. Findings are also aligned with the results presented by Hernandez Romieu et al.(17) who reported using data from 2007 to 2014 that being male and being older increased the odds of a late diagnosis. Compared to this study, we also showed that being diagnosed in *CAPASITS* or Condesa reduced the risk of a late diagnosis compared to being diagnosed in non-specialized HIV hospitals, which could be explained by the organization of the HIV testing centers within the Mexican Health System. As opposed to *CAPASITS* which are the main HIV treatment

centers, many individuals are referred to hospitals or Institutes because they present a complicated health profile and many of them will be diagnosed with AIDS in that context.

Furthermore, Mexico City has the largest hospitals and expertise to treat individuals with very advanced HIV, which could explain some of the results. Another study among women using 2012-13 data from 4 clinics in Mexico also found that being older increased the risk of late diagnosis (31). On the other hand, while we found that being male increased the risk of a late diagnosis, a study conducted in 2011-12 in Mexico city, reported that women were more likely to be diagnosed later given that they have no suspicious of risk of infection due to their cultural and social disadvantage (16,31). These results could indicate that the prevention programs and early diagnosis policies no longer exclusively target high-risk populations (men who have sex with men and transgender population) and are consistent with the objectives established in the National Program in 2013 (9). Similarly, belong to the younger group represents a protective factor for a late diagnosis, which could be explained for a higher perception of risk and, therefore routinely testing, or because the treatment is free, even unemployed and unsecured young people could access care (11,17). Compared to the studies previously conducted in Mexico around HIV, our study provides new information as we also evaluated the impact of the 2013 National Specific Action program. We also showed that determinants of late diagnosis changed before and after the implementation of the 2013-2017 HIV policies and found important differences at the regional level.

When interpreting the results some limitations should be noted. First it was assumed that the closest measure to diagnosis observed in *SALVAR* database for CD4 and VL was the first measure taken at moment of diagnosis of HIV, which may not be always accurate. While we conducted regression analyses to identify the determinants of late diagnosis and VL

levels, we were constrained by the list of variables available in the database and there may be unmeasured confounders such as the increase in number of health facilities and distribution across Mexican regions, or some risk factors (such as no use of condom, multiple sexual partners) associated with self-perception of risk systematically differentiating the population reaching heath care. In addition, this analysis was limited by the design of SALVAR. At first the database was conceived to only capture ART logistic, and administration; however, in 2008 the systems allow to incorporate and track information about biomarkers such as CD4 and VL receiving treatment (32). Although SALVAR's strongest section is still treatment and only patients receiving are enrolled, we believe that eventually those patients diagnosed, but not immediately incorporated to the system, will eventually get ART, and then the database capture both dates: date of diagnosis, and date of treatment initiation. Also, while the *SALVAR* database contains a variable to document the transmission route, we could not include this variable in our models as more than 80% of the data were missing. As it is well known, transmission route is a key determinant for a self-perception of risk, and late diagnosis (33)). This could explain why our logistic regression models had moderate discrimination. Moreover, *SALVAR* does not account for the whole PLWH in Mexico, only for those registered in the Ministry of Health receiving treatment. As such, some individuals (e.g., diagnosed with an advanced AIDS-defining event that never received treatment or with a high CD4 without the need for immediate treatment) may not be registered in SALVAR. Although this proportion is unknown, we believe that this population is not large due to the existence and expansion of *CAPASITS* after 2013 and the push for a decentralized and universal access to HIV care in Mexico. Unfortunately, it is not possible to account for any correlation between testing and late diagnoses because Mexican records

only capture positive diagnosis and treatment linkage. Moreover, given the design of the models, we cannot claim that policy was completely responsible for changes in levels of late diagnosis, these could be also part of an increasing awareness and readiness for HIV testing and the disease in general, and a reduction of discrimination and stigma. However, we adjusted the model by possible trend with a period variable. Finally, a proportion of individuals were missed because of lack of complete information, this proportion represented a higher proportion of males, diagnosed in the Northwest region, in CONDESA, and after 2013. However, the study still has a large population, and we cannot evaluate the direction of magnitude of a possible bias. The study represents a first approach to associate measurable factors with late diagnosis and provide evidence for further research. Despite these limitations, our study has several strengths including the use a population-based cohort representing approximately 64% of the population receiving HIV care in Mexico. This is also the first study using and analyzing data later than 2014.

As it was mentioned before, some hypotheses can be formulated with all the information presented. We have identified key indicators, trends, and predictors of CD4 and VL levels at diagnosis to inform about the HIV/AIDS epidemic in Mexico. Although we observed a decrease in the number of individuals with a late diagnosis after the implementation of the 2013 National Specific program, this proportion is still high regarding the objective set in the 2013-2018 national plan (30%), and efforts should continue to improve HIV outcomes at diagnosis and reduce HIV transmission. Future research is also required to continue to evaluate the effectiveness of prevention programs such as increasing the HIV diagnosis rates and reaching broader populations for early detection, Furthermore, the information from SALVAR database could be analyzed to identify time from diagnosis

to treatment, and what can be improved to ensure access to antiretroviral therapy through the universal access program in Mexico. Finally, additional research should be made to measure the specific differences in economic resources and possible improvements to lead changes in national programs to reduce inequalities across health facilities and Mexican regions.

Conclusions

The results of this study indicate that the proportion of individuals with a late HIV diagnosis decreased marginally following the National HIV program implemented in 2013 in Mexico. However, the proportion of late HIV diagnosis remains much above the proposed levels in the National Specific Action Plan 2013-2018. Analyzing those factors that identify high-risk populations for a late diagnosis could expedite the achievement of policy objectives and improve national indicators of HIV in Mexico. Therefore, more efforts should be allocated to improve early detection and treatment of HIV.

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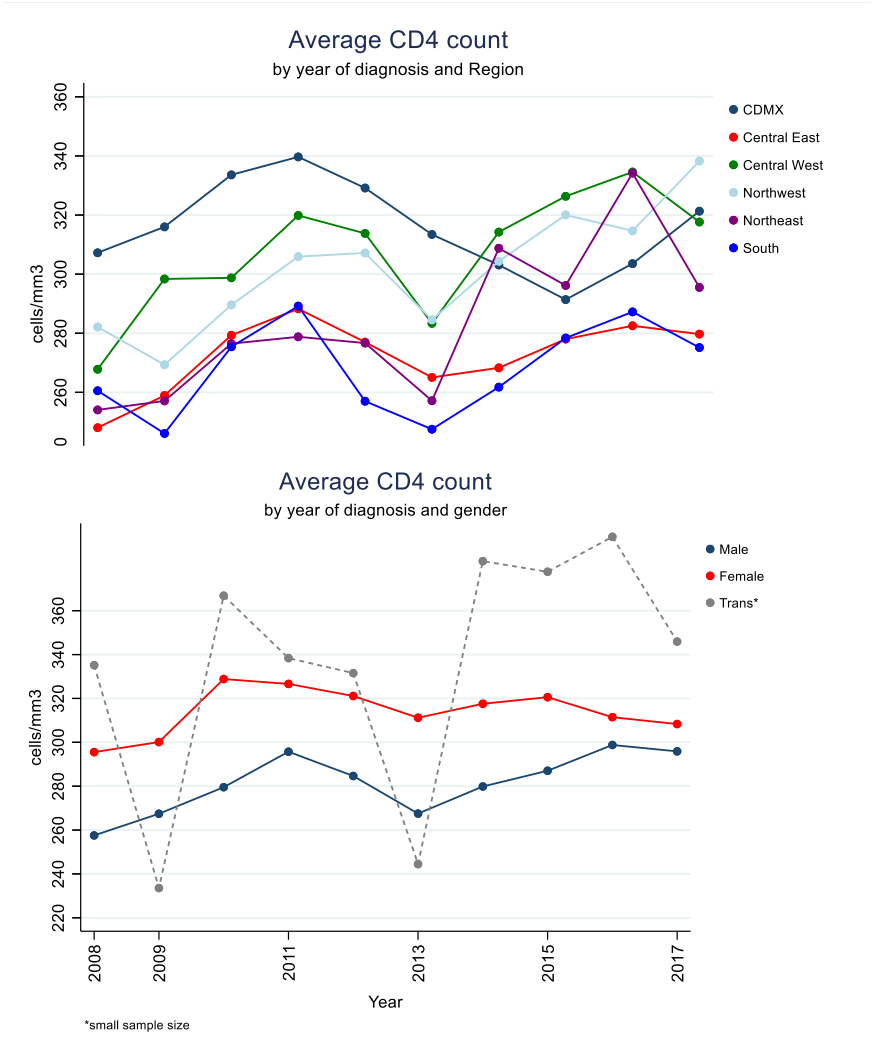
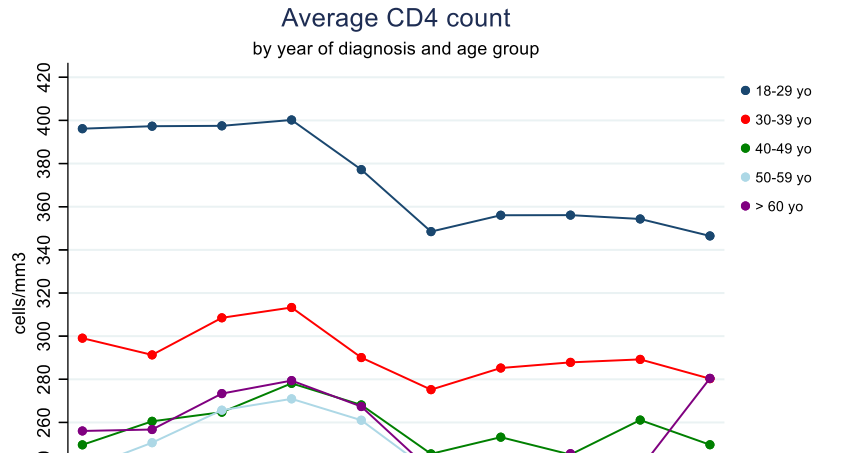
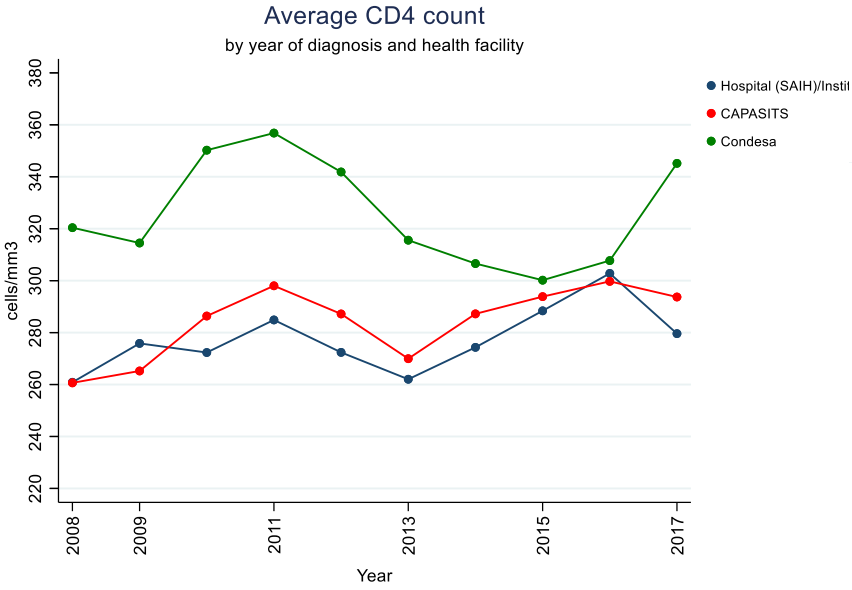
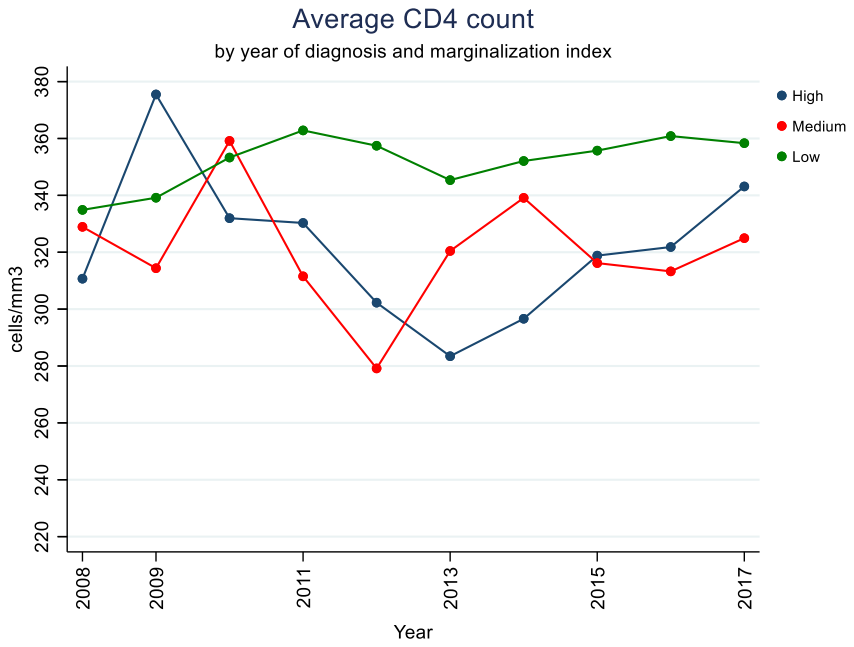
Appendix

Figure A1.




Average CD4 count
by year of diagnosis and age group
cells/mm3
420
400
380
360
340
320
300
280
260
18-29 yo
30-39 yo
40-49 yo
50-59 yo
> 60 yo


Average CD4 count
by year of diagnosis and health facility
cells/mm3
380
360
340
320
300
280
260
240
220
2008
2009
2011
2013
2015
2017
Year
Hospital (SAIH)/Instil
CAPASITS
Condesa


Average CD4 count
by year of diagnosis and marginalization index
cells/mm3
220
240
260
280
300
320
340
360
380
2008
2009
2011
2013
2015
2017
Year
High
Medium
Low

Declaration.

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I was responsible for conceptualizing the research question, study design, and methods, through consultations with Dr. Jean-Eric Tarride. I was responsible for all the data cleaning and analysis. Drs. Fiona Smaill, Lawrence Mbuagbaw, Andrew P. Costa, and Sergio A. Bautista each provided feedback on the drafts, which were incorporated into the final version of the chapter.

Original research paper

Title: Virologic failure in People Living with HIV in 1st line ART: a 10-year Mexican population-based study

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Key words
HIV, Antiretroviral Therapy, Mexican SALVAR.

Running title
VF in PLWH in Mexico

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Virologic failure in People Living with HIV on 1st line ART: a 10-year Mexican population-based study

Abstract

Background: In Mexico, the number of PLWH receiving ART has increased in the last twenty years. The elimination of a CD4 threshold to initiate publicly funded ART was a major policy implemented in 2014. The study objective was to assess the determinants of Virologic Failure (VF) in Mexican PLWH on first-line ART between 2008 and 2017 and to evaluate the effects of changes following the 2014 policy.

Methods: A 10-year patient-level data analysis was conducted using the Mexican SALVAR database. The main outcome was the proportion of PLWH with VF. A multivariable logistic regression was conducted to identify the association between covariates and VF before and after the 2014 policy implementation.

Results: We found a lower proportion of people with VF in 2014-2017 compared with 2008-2013 (50% vs 33%, $p<0.001$). The multivariable analysis showed a reduction in the odds of virologic failure after 2014 (Odds ratio: 0.50 [95% CI: 0.48 - 0.51]). Place of treatment and level of deprivation were significant predictors of VF in during 2014-2017, but not before.

Conclusion: This study indicates that, by lowering threshold levels of CD4 required for treatment initiation in Mexico, a higher number of PLWH initiated treatment during 2014-2017, compared to 2008-2013 and the odds of VF were reduced.

Keywords: HIV, Antiretroviral Therapy, Mexican SALVAR.

Introduction

The primary goal of Antiretroviral Therapy (ART) is to achieve and maintain virologic suppression in People Living with HIV (PLWH) and to reduce disease progression and eliminate transmission through the achieving and maintaining viral suppression (1,2). It has been shown that early diagnosis and full timely access to ART reduce the probability of disease progression and improve health outcomes among PLWH (1–5). In addition to timely diagnosis and treatment, adequate monitoring and timely identification and management of treatment failure are key to reducing the clinical impact of HIV (6,7).

In Mexico, the number of PLWH receiving ART has increased in the last twenty years due to different public policies focused on expanding access to ART. Starting in 2007, Mexico launched a major initiative to provide universal access to ART conditional on several clinical criteria including CD4 counts ≤ 200 cells/mm3 and the presence of risk symptoms (8). Following the World Health Organization (WHO) recommendations for early treatment initiation of PLWH in June 2013 (9), a major policy changed occurred when the Mexican HIV-clinical guidelines were modified in 2014 to expand universal access to ART to all PLWH irrespective of their baseline CD4 count and symptoms (10,11). The performance of the program is monitored quarterly by the government, and has shown that, on average 80% of the PLWH in Mexico show Viral Load (VL) counts below 50 copies/ml (virologic success) during their routine checkups (12,13). Clinical and observational studies have shown that maintaining VL under that threshold is a predictor of long-term health outcomes (14). Although VL is an important measure of disease progression, likelihood of transmission, and mortality (15), as a policy measure, it is also important to document virologic failure (VF) following 1st line ART treatment initiation (independently of the treatment option) at the

population level. This is because VF is the result of multiple and complex factors that go beyond treatment efficacy such as poor adherence, inadequate care or access to healthcare, and other sociodemographic factors and contextual variables (16–18).

While an early study conducted in a third-level hospital in Mexico City in 2010 found that that the probability of VF was 20% at 48 months after ART initiation and was higher among youth (individuals younger than 30 years old) (14), this study was published before the 2014 changes in clinical guidelines. In addition, the determinants of VF have not been explored in Mexico and the 2014 policy changes have not been evaluated. Providing information about the proportion of PLWH with VF in Mexico, as well as the influence of changes in clinical approach for treatment initiation following the 2014 Mexican policy change will generate evidence for further HIV-policy design and implementation in Mexico and elsewhere. Therefore, the objective of this study was to document the change in rates of VF and compare the determinants of VF in Mexico before and after the updated 2014 clinical guidelines.

Methods

Study design

We performed a retrospective population-based cohort study to assess virologic failure after receiving 1st line treatment in PLWH in Mexico. Data were accessed using the Mexican Administrative Health Data from the Antiretroviral Administration Logistics, and Surveillance System (SALVAR in Spanish).

Data source

SALVAR is an electronic system managed by CENSIDA (National Center for the Prevention and Care of HIV/AIDS in Spanish) and funded by the Mexican Ministry of Health. It contains

clinical, biometric, antiretroviral therapy and demographic information of individuals enrolled in the national HIV/AIDS program. All patients provide consent for the use of personal information (15). Data presented in this analysis was provided to the authors as a secondary anonymized dataset. Data in SALVAR began to be captured in 2006, however it was until 2008 that the system was fully implemented nationwide. Currently, it contains information on more than 140,000 PLWH on ART (16).

Study population

For this analysis, we included adults (18 years old and older) living with HIV who received their first ART after January 1st, 2008 and before September 1st, 2017. Given the purpose of the analysis, we only considered patients that had completed at least 12 weeks of follow-up (9,19), and at least three VL measures. Pregnant women, children, people who are incarcerated, and people receiving antiretroviral prophylaxis were excluded from the analyses. Individuals with incomplete information on gender, and age were also excluded.

Study outcomes

The primary outcome was the proportion of people with Virologic Failure following 1st line ART treatment initiation. As per the Mexican clinical guidelines definition (17), VF was determined by one of the following two criteria: 1) individuals without a reduction of at least one log10 of VL count at week eight compared to baseline information; and 2) individuals who had reduced at least one log10 within the first eight weeks, but after six months of ART initiation presented two continuous VL measures above 200 copies/ml at any further week.

However, considering WHO recommendation and in order to include more individuals in our study, we considered at least 12 weeks of follow-up instead of eight.

First line of treatment was defined as the first ART components prescribed to the patient based on the information reported in SALVAR. The database also provides the specific ART assigned at treatment initiation a well as switches in ART treatments. Patients changing their 1st line ART from a 3-pill regimen to fewer pills (i.e., a 2 or 1-pill scheme), but maintaining the same components (i.e., efavirenz/emtricitabine/tenofovir disoproxil fumarate [EFV/FTC/TDF)] and EFV+FTC+TDF) were not considered switching lines of ART treatment.

Independent variables

All variables such as gender (i.e., male, female and trans), age (as a continuous and categorical variable), year of ART initiation, geographic information of facility (region and type of health facility), baseline virologic measures, and type of treatment were collected at the time of treatment initiation. Region was grouped following previous analysis on Mexican HIV population (20) as Central East, Central West, Northwest, Northeast and South. For our analysis, Mexico City was stratified as another region (instead of being part of Central East) based on the number of people living and receiving treatment there. Health facilities were categorized by type as Specialized Clinic CONDESA (based on Mexico City), Tertiary level Hospitals or National Institutes of Health, and the Ambulatory Centers for Prevention and Attention for HIV/AIDS and Sexually Transmitted Infections (CAPASITS in Spanish). The marginalization index (high, medium and low) estimated by the Mexican government for

each Mexican municipality/location (22) was assigned to the location of each health facility where PLWH were treated to reflect social and economic differences among health facilities[1].

In terms of biologic measures, CD4 cell count at 1st line ART treatment initiation was divided into two groups by CD4 count lower than 200 cells/mm3 and higher or equal to 200 cells/mm3, based on prior evidence of an association of CD4 count with VF (22). Baseline VL was classified as lower or equal than 100,000 copies/mL and higher than 100,000 copies/mL and was used as an adjustment for ART allocation based on clinical guidelines to reduce bias due to treatment selection (23). We also grouped ART as the three most used and representative 1st line ART available in Mexico during the studied timeframe, reported in SALVAR database for the analysis: efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF), efavirenz + abacavir/lamivudine (EFV+ABC/3TC), Boosted Protease Inhibitors + backbone (Boosted PI), and other (including integrase inhibitors and all other regimens defined as a 1st line ART in SALVAR). Although today integrase inhibitors are an important treatment option for PLWH, their use represented less than 2% of total 1st line ART from 2008-2017 in the SALVAR database, and less than 1% before 2014. Therefore, they were included in the "other" category to avoid any estimation bias.

Statistical analysis

Population baseline characteristics were presented for the overall study period and separately for the periods between 2008-2013 (i.e., before policy change) and 2014-2017

[1] The marginalization index is constructed by the Mexican government and reported by locality or municipality. The index is constructed through a principal component analysis (PCA) indicating the level of deprivation by geographical area. It includes aggregated socio-economic variables (at locality or municipal level) such as proportion of individuals older than 15 years old without elementary school, proportion of houses without drinking water, electricity, or cement floor (21)

(i.e., after policy change). Discrete variables were presented as percentages, while continuous variables were described in terms of mean, standard deviation (SD), median and Inter-quartile range (IQR). Chi-Squared test for categorical variables and two-sample Welch tests for continuous variables, were used to compare the population characteristics and outcomes between the two time periods (e.g., before and after the change in policy). VF, our primary outcome, was also presented for the overall study period, by time period and by category of 1st line ART.

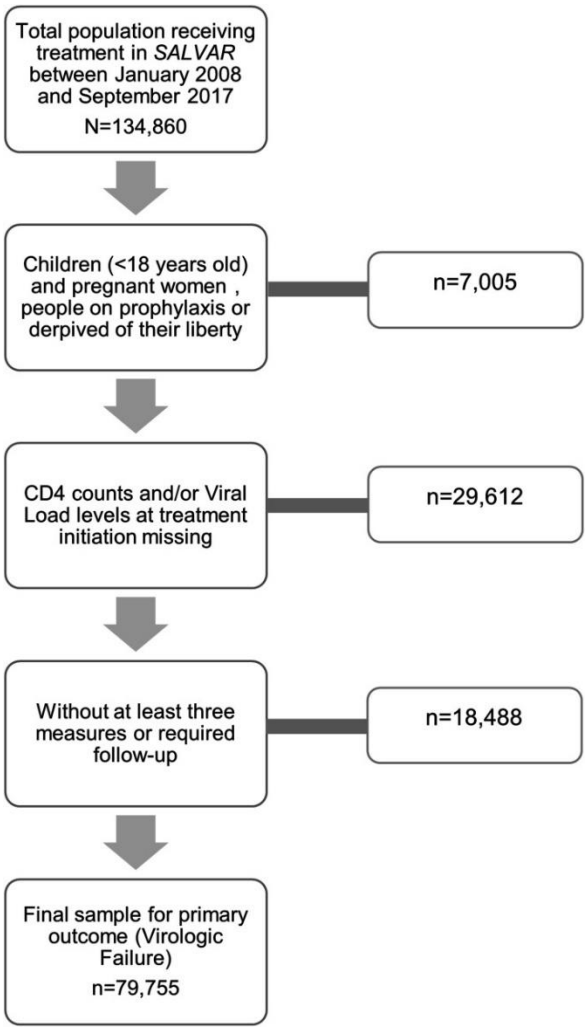
To identify the factors associated to VF, a multivariable logistic regression was conducted adjusting by previously mentioned variables in addition to a dichotomous variable indicating the period of policy change in 2014. Furthermore, two models were performed stratifying by time periods (2008-2013 and 2014-2017) allowing a deeper understanding of the association between covariates and the main outcomes before and after the introduction of the 2014 policy. Results are presented as Odds Ratios (OR) with a 95% confidence interval (CI). Goodness-of-fitness of the logistic models was estimated using the c-statistic.

Results

Study population

SALVAR data set contains information about 1st line ART of 134,860 individuals during January 2008 and September 2017. Of those, 7,005 were younger than 18 years old, pregnant women or deprived of their liberty. 29,612 did not have information about VL or CD4 at treatment initiation, and 18,488 did not have at least three VL measures or established time of follow-up. The final sample shown in Figure 1 consisted of 79,755 individuals.

Figure 1. Sample flow for analysis



Comparing both periods, the age at treatment initiation was lower after 2014 (mean 34.8 vs. 33.2yo), there were less female (20% vs 17%, p<0.001), a lower proportion initiated treatment in a Hospital or National Institute (24% vs. 18%, p<0.001) and more in a CAPASITS (62% vs. 67%, p<0.001), while proportionally less individuals were initially treated in Mexico City and more in the South region. Marginality index showed no difference between periods. The proportion of individuals diagnosed with CD4 <200 cells/mm^3 was

higher during 2014-2017 (12%) compared with 2008-2013 (7%). The same was seen for individuals with VL ≥ 100,000 copies/mL, although the mean log10 was lower before 2014 (4.06 vs 4.31). Treatment distribution was also different between periods: during 2008-2013 the proportion of patients with EFV/FTC/TDF was 64%, EFV+ABC/3TC was 9%, and 13% with Others; while, after 2014 this proportion changed to 68%, 15% and 8% respectively. Time from diagnosis to treatment was on average 1 week lower in 2014-2017 compared with 2008-2013 (median 6.98 vs 7.97 weeks). Details can be found in Table 1 for the full population and by period.

Table 1. Summary Statistics and Patients' Characteristics at treatment initiation, January 2008- September 2017

Variable	Total	2008-2013	2014-2017	P-value
Sample size	79,755	38,320	41,435	
Age				
Mean ± SD	33.99 ± 10.26	34.77 ± 10.21	33.24 ± 10.24	<0.001
Median (IQR)	32 [26-40]	33 [27-41]	31 [25-39]	
%				
18-29 yo	39	35	44	
30-39 yo	34	36	32	
40-49 yo	18	20	16	<0.001
50-59 yo	7	2	6	
≥60 yo	2	7	2	
Gender (%)				
Male	80	79	82	
Female	19	20	17	<0.001
Transgender	1	1	1	
Health facility (%)				
Hospital/Clinic/National Institute	21	24	18	
CAPASITS	65	62	67	<0.001
Specialized clinics CONDESA	14	14	15	
Region (%)				
Mexico City	19	20	18	
Central East	31	31	31	
Central West	14	15	13	<0.001
Northeast	12	12	11	
Northwest	8	8	9	
South	16	14	18	
Marginality Index (%)				
High	2	2	2	
Medium	1	1	1	0.135
Low	97	97	97	
Bio-markers				
CD4				
Mean ± SD	289.74 ± 230.78	268.80 ± 218.31	308.98 ± 240.07	<0.001
Median (IQR)	250 [110-407]	230 [104-372]	271 [117-442]	

<200 cells/mm^3 (%)	10	7	12	<0.001
≥200 cells/mm^3 (%)	90	93	88	
VL				
Mean ± SD	4.19 ± 1.42	4.06 ± 1.47	4.31 ± 1.35	<0.001
Median (log10) (IQR)	4.61 [3.3-5.2]	4.55 [2.6-5.2]	4.65 [3.7-5.2]	
<100,000 u/ml (%)	63	63	62	0.045
≥100,000 u/ml (%)	37	37	38	
Treatment (%)				
EFV/FTC/TDF	66	64	68	<0.001
EFV+ABC/3TC	12	9	15	
Boosted PI	12	14	9	
Other	10	13	8	
Time diagnose-treatment				
Mean ± SD	42.96 ± 97.9	44.09 ± 94.52	41.92 ± 100.93	0.007
Median (IQR)	7.27 [2.1-27.1]	7.97 [0.1 - 3]	6.98 [2.8-22.5]	

Source: Authors' contribution using SALVAR 2008-2017. Yo: years old. VL: Viral Load. EFV/FTC/TDF: Emtricitabine, Tenofovir, Efavirenz; EFV+ABC/3TC: Abacavir, Lamivudine, Efavirenz. P-value for differences between periods.

Virologic failure

The proportion of VF among adults who initiated treatment over the period of January 2008-September 2017 was 41%, while the proportion of PLWH with VF was lower after 2014 (50% vs 33%, p<0.001). Stratifying by ART, the regimens "Other" and Boosted PI presented the highest proportion of people with VF (43% and 47% respectively). However, differences were observed in the VF associated with each treatment regimens after 2014. While the "Other" category was the regimen with the highest proportion of people with VF in 2008-2013 and the lowest after 2014 (55% vs 25%, respectively, p<0.001) EFV/FTC/TDF had the lowest proportion before 2014 and the second highest after (47% vs 34%, p<0.001). Details can be found in Table 2.

	Period of analysis			
ART option	2008-2017	2008-2013	2014-2017	P-value
Total 1st line ART	41	50	33	<0.001
EFV/FTC/TDF	39	47	34	<0.001
EFV+ABC/3TC	38	49	33	
Boosted PI	47	54	37	
Other	43	55	25	

Authors' contribution using SALVAR 2008-2017. ART: Antiretoviral therapy. EFV/FTC/TDF: Emtricitabine, Tenofovir, Efavirenz; EFV+ABC/3TC: Abacavir, Lamivudine, Efavirenz

Table 2. Virologic failure (%) of adults in 1st line ART. 2008-2017

Determinants of VF

Results of the multivariate logistic regression show that initiating ART during the period 2014-2017 reduced by half the odds of VF (OR=0.50 [95% CI: 0.49, 0.52]), compared to initiating treatment between 2008-2013. Other factors associated with lower likelihood of VF were being male (0.88 [95% CI: 0.85, 0.91]), older than 29 years old (e.g., 0.91 [95% CI: 0.88, 0.94 for 30-39 yo], being diagnosed with CD4 ≥200 cells/mm^3 (0.89 [95% CI: 0.85, 0.94]). Contrary, having initiated treatment in a different region than Mexico City (1.48 [95% CI: 1.36, 1.62] compared to Central East, having a 1st ART other than EFV/FTC/TDF (e.g., 1.22 [95% CI: 1.16, 1.28] for EFV+ABC/3TC) increased the odds of having VF. Table 3 also presents the stratified analyses by time period and results indicated changes in the association with regions. Compared to Mexico City, all other Mexican regions increased the odds of VF before 2014 but this association was not statistically significant after 2014. Similarly, having started treatment with other regimen, reduced the likelihood of VF during 2014-2017 but not before. Finally, for CD4, the OR direction changed for being diagnosed with CD4 ≥200 cells/mm3, increasing marginally the odds of VF in the period 2014-2017 compared with 2008-2013 (See table 3).

Table 3. Multivariate Logistic Regression for Virologic Failure, 2008-2017

Variable	Virologic failure		
	OR All periods	OR 2008-2013	OR 2014-2017
Period of treatment initiation (ref: before 2008-2013)			
2014-2017	0.50** [0.487 - 0.517]		
Gender (ref: Female)			
Male	0.88** [0.847 - 0.914]	0.87** [0.829 - 0.919]	0.86** [0.809 - 0.907]
Transgender	0.84 [0.675 - 1.045]	0.8 [0.585 - 1.086]	0.85 [0.626 - 1.162]
Age (ref: 18-29)			
30-39	0.91** [0.880 - 0.942]	0.81** [0.772 - 0.852]	1 [0.955 - 1.052]
40-49	0.78** [0.747 - 0.812]	0.70** [0.657 - 0.737]	0.86** [0.808 - 0.913]
50-59	0.72** [0.680 - 0.770]	0.66** [0.607 - 0.721]	0.78** [0.709 - 0.851]
>60	0.72** [0.645 - 0.805]	0.67** [0.575 - 0.774]	0.77** [0.646 - 0.906]
Region (ref: Mexico City)			
Central East	1.48** [1.355 - 1.622]	1.91** [1.702 - 2.142]	0.83* [0.721 - 0.965]
Central West	1.76** [1.609 - 1.920]	2.09** [1.867 - 2.334]	1.09 [0.946 - 1.263]
Northwest	2.13** [1.933 - 2.337]	2.86** [2.528 - 3.230]	1.14+ [0.983 - 1.333]
Northeast	1.94** [1.756 - 2.150]	2.79** [2.445 - 3.190]	0.99 [0.843 - 1.160]
South	1.76** [1.608 - 1.935]	2.61** [2.315 - 2.939]	0.89 [0.765 - 1.030]
Type of health facility (ref: hospital/National Institute)			
CAPASITS	1.09** [1.041 - 1.140]	1.08* [1.013 - 1.149]	1.14** [1.066 - 1.218]
Specialized clinic	2.96** [2.723 - 3.225]	3.48** [3.128 - 3.880]	1.89** [1.652 - 2.172]
Index of marginalization (ref: low)			
Medium	1.17+ [0.986 - 1.380]	1.15 [0.903 - 1.459]	1.18 [0.921 - 1.520]
High	0.90+ [0.810 - 1.010]	0.83* [0.712 - 0.966]	1.02 [0.862 - 1.205]
Viral load			
At treatment (ref : VL≤100,000 u/ml)			
VL>100,000 u/ml	1.50** [1.453 - 1.547]	1.31** [1.257 - 1.371]	1.73** [1.648 - 1.805]
CD4			
At treatment (ref: CD4<200 cells/mm^3)			
CD4≥200 cells/mm^3	0.89** [0.849 - 0.937]	0.68** [0.629 - 0.738]	1.08* [1.011 - 1.149]
Treatment options			
ART (ref: EFV/FTC/TDF)			
EFV+ABC/3TC	1.22** [1.166 - 1.282]	1.16** [1.077 - 1.245]	1.34** [1.259 - 1.432]
Boosted PI	1.32** [1.260 - 1.381]	1.34** [1.263 - 1.426]	1.29** [1.203 - 1.387]
Other	1.19** [1.133 - 1.252]	1.61** [1.240 - 1.399]	0.67** [0.621 - 0.741]

Constant	0.62** [0.534 - 0.717]	0.76** [0.618 - 0.926]	0.37** [0.293 - 0.460]
Observations	79,755	38,320	41,435
C-Statistics	0.6368	0.6144	0.6013

*** p<0.01, * p<0.05, + p<0.1. (95% Confidence Interval). Authors' contribution using SALVAR 2008-2017. OR: Odds Ratio. CAPASITS: Ambulatory Centers for Prevention and Attention for HIV/AIDS and Sexually Transmitted Infections in Spanish. VL: Viral Load. ART: Antiretoviral therapy. EFV/FTC/TDF: Emtricitabine, Tenofovir, Efavirenz; EFV+ABC/3TC: Abacavir, Lamivudine, Efavirenz*

Discussion

Based on ten years of national data of PLWH in Mexico, this study has provided new information on the determinants of Virologic Failure and treatment success between 2008 and 2017 and clinical guideline changes for treatment initiation since 2014 eliminating the CD4 threshold previously established (CD4 ≤ 200 cells/mm3). Compared to the 2007-2013 period, individuals treated during 2014-2017 were younger, a higher proportion was male, mostly initially treated in CAPASITS, a higher proportion in the South of Mexico, and (as expected) with higher levels of baseline CD4, compared to the period 2008-2013. The proportion of individuals with VF decreased from 50% in 2008-2013 to 33% in 2014-17 suggesting that more adults were responding better to treatment. The multivariate analysis indicates that actions in 2014, eliminating the CD4 threshold for treatment initiation, reduced the odds of VF by 50%, after controlling for other variables. When analyzing VF by period, it was shown that being initially treated in another region than Mexico City or in a medium or highly deprived area was not a significant predictor of VF during 2014-2017. These could be explained by the national distribution of health facilities in the whole country which almost doubled from 2007 to 2013 (24,25) and changes into a more integrated and centralized approach to HIV treatment and care in Mexico (10), including testing for all high and not high-risk population was expanded, the CD4, lowering the threshold for treatment initiation,

and starting massive prevention campaigns as the result of the 2013 implementation of the National HIV plan (10,26).

It is difficult to compare our analysis with other studies conducted in Mexico given that this is the first study analyzing VF in these settings for all PLWH receiving care through the MoH. However, there is a governmental publication reporting that of all people enrolled in SALVAR living in Mexico City or the State of Mexico, 46.8% have acquired-resistance to Efavirenz (27). Our results showing a higher likelihood of VF among female are consistent with the results showed by Mata-Marín et al. (28) in a hospital in Mexico, who explained the findings because of a lower educational level and a higher probability of being unemployed for women as well as lower resources and social insurance to access ART compared to men. Regarding our findings for age, similar results were found in Latin American and Caribbean countries including Mexico (29–31), where the older population had a lower risk of VF, possibly explained by a higher adherence, lower risk behaviors, and general awareness of better health care. Also, consistent with international literature, studies in Latin America and Africa, show that to initiate treatment with CD4 ≥200 cells/mm3 reduces the odds of VF. These effects could be explained because CD4 count at treatment initiation is a biological predictor of a better immunological function and slower disease progression (32–35). However, our stratified analysis indicated that CD4 levels increase the odds of VF after 2013, but the association is marginal (OR of 1.08; 95% CI of 1.01 to 1.15). Although the association of CD4 levels and VF after 2014 is counterintuitive, it could be explained by a few reasons. First, as identified as one of our study limitations, SALVAR data do not include information on treatment adherence, which may create some bias. Second, in addition to eliminating in 2014 the CD4 threshold to initiate ART treatment, a year before

other measures were implemented including diagnosis and awareness campaigns, increasing access to HIV care by targeting low-risk individuals could partially explain this result as we were not able to control for these unmeasured confounders. For example, it has been shown that individuals with a lower perception of risk have a poorer adherence (36), which could be the case for those PLWH with higher CD4 count (fewer symptoms and warning signs for disease progression) (36,37). Besides the direct association of poor adherence and VF, intermittent ART adherence has also been associated with CD4 variability, which is also associated with VF (37). Contrary, lower VL levels at treatment initiation are associated with better prognosis and successful viral responses (32). This could be explained because VL is a predictor for disease progress. Patients with higher levels at treatment initiation presented a more complex and advanced disease than patients with lower levels (38,39). When observing the stratified analysis for VF, our results are similar to a previous analysis concerning Mexican regions and different periods (26). The effect of being treated in a region different than Mexico City losses significance after 2014. This could also be explained to changes in policies regarding diagnosis, where late testing is the main reason for a late and unsuccessful treatment (40), as well as an expansion of the Mexican health system (10). Compared to studies previously performed in Mexico around PLWH, our study gives information based on national-wide patient-data and evaluated changes in treatment initiation policies after modifications in international and national clinical guidelines.

Our study has some limitations. The analysis was constrained by the list of variables captured in SALVAR, which do not include possible confounders, such as employment situation, risk behaviors and access to HIV healthcare (e.g., some individuals in remote areas could never know their HIV status). Second, there was some missing information from 29

thousand adults, which might not be random. However, we did not find any differences on gender, age or region between those with complete information and those without CD4 and VL measures. The data did not allow for capturing adherence to treatment, which could be a determinant of treatment success, and therefore VF (41,42). Some studies have shown that two of the main determinants of non-adherence are access to ART and financial constraints (43,44). However, the Mexican government started providing free treatment to all PLWH in 2003 (40). Besides, to our knowledge, no widespread or national programs to improve adherence were implemented during the time of analysis. Therefore, we assumed that adherence rates did not change significantly from one period to another. Finally, the 1st line ART used for the analysis are mainly based on a backbone + EFV, which does not reflect current treatment options and ART use in Mexico where integrase inhibitors are the preferred ART option in clinical guidelines (45). However, this work presents the Mexican situation during 2008-2017 and evaluates the modification on national clinical guidelines after 2014. The findings of our study could also increase awareness, improvement of HIV-specific health care, and changes in treatment options by informing decision-makers about trends and outcomes of the current HIV program. Despite the limitations, our study has several strengths. We performed a national-wide analysis with a large sample of patient-data representing 64% of PLWH in Mexico and a long follow-up period. This is the first analysis studying determinants of Virological Failure in Mexico with this sample size and 10 years study period.

Derived from our analysis, some hypotheses can be made. We identified key indicators and determinants of treatment success that could inform future policies and programs targeting PLWH in Mexico. Further research is required to evaluate the association

between early treatment initiation, time from diagnosis to treatment, and virologic outcomes. Furthermore, this analysis highlights the need to record adherence in the SALVAR database for a deep understanding of VF determinants.

Conclusions

This study indicates that, by removing threshold levels of CD4 required for treatment initiation in Mexico, combined with an expansion of ART access through a more clinics country-wide, a greater number of PLWH initiated treatment and fewer had virologic failure. Identifying sociodemographic determinants of VF could enhance policy development and facilitate the achievement of policy objectives, improving national indicators of the Mexican epidemic of HIV.

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Chapter 4. Early mortality and survival analysis after 1st line ART in PLWH in Mexico: a 10-year population-based study

Declaration.

This paper has been submitted to International Journal of STD & AIDS. It is waiting for revisions.

I was responsible for conceptualizing the research question, study design, and methods, through consultations with Dr. Jean-Eric Tarride. I was responsible for all the data cleaning and analysis. Drs. Fiona Smaill, Lawrence Mbuagbaw, Andrew P. Costa, and Sergio A. Bautista each provided feedback on the drafts, which were incorporated into the final version of the chapter.

Original research paper

Title: Early mortality and survival analysis after 1st line ART in PLWH in Mexico: a 10-year population-based study

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Key words
HIV, early mortality, Antiretroviral Therapy, Mexican SALVAR.

Running title
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Early mortality and survival analysis after 1st line ART in PLWH in Mexico: a 10-year population-based study

Abstract

Background: Several factors are associated with AIDS-related early mortality including CD4 count, high viral load (VL) at ART initiation, male sex, and age >40 years old. Different studies have compared Cox regression models with parametric models for survival analysis but not specifically for AIDS-related early mortality. The objectives of this study were to identify factors associated with early mortality of PLWH in Mexico from 2008-2017 and to compare semi-parametric Cox regression models and parametric survival models.

Methods: A 10-year retrospective population-based cohort study was conducted to assess AIDS-related early mortality defined as death <6 months after ART initiation between 2008 and 2017. A comparison of Cox regression and three parametric survival models was evaluated based on AIC and BIC parameters to identify the association between covariates and early mortality during 2008-2017.

Results: Factors found in all four models with a higher probability of early mortality were being older than 29 years, treatment initiated in a region other than Mexico City, treatment started with VL≥ 100,000 copies/mL, and received boosted PI, or "other" ART. The Gompertz distribution had the best fit, while Cox regression had the worst fit and the proportional hazard assumption was not met. All models shown parallel results.

Conclusions: Consistent with international studies, late diagnosis was identified as a critical factor for early mortality showing that regardless of the efforts that have made to improve timely diagnosis and treatment access, therefore endeavours should continue. We found that parametric methods are preferred to Cox regression models.

Introduction

With the development and widespread use of Antiretroviral Therapy (ART), AIDS-related deaths have decreased by around 61% over the last 20 years (1,2). However, differences are observed among low, middle and high-income countries with higher mortality rates in low-income countries due to different factors such as access to care, access to information or social determinants (e.g., religion, stigma, fear) (1,3). Mortality rates among people living with HIV (PLWH) have also been shown to be higher in the first six months after ART initiation and then decrease over time (4–6). Timely diagnosis and ART initiation have been recognized as crucial elements for improving health outcomes among PLWH and several countries have implemented policies to improve access to ART treatment (7). In Mexico, since 2007, all PLWH can receive treatment and care for free, independent of their insurance status. Another major reform occurred in Mexico in 2014 when all PLWH could initiate ART treatment regardless of their disease stage, baseline CD4 count or symptoms (10,11). Still, out of 19,000 individuals diagnosed with HIV in Mexico in 2019, 5,300 died due to AIDS-related causes (mortality rate of 4.2 per 100,000 habitants) (12).

Several factors are associated with AIDS-related early mortality, which is generally defined as death within either the first six months or the first 12 months following ART initiation, including CD4 cell count and a high viral load (VL) count at ART initiation, male sex, and age greater than 40 years. (13–19). Despite considerable international literature on factors associated with early mortality in PLWH (13,15,16,20),

only one Mexican study has explored early mortality trends from 2008 to 2012 and the factors associated with early mortality were not presented (21).

From a methodological point of view, most studies evaluating the determinants of AIDS-related early mortality have relied on using a semi-parametric Cox model (13,15,22). Compared to other types of models, Cox regression models do not require a pre-defined data distribution or a baseline hazard function. However, the Cox regression model assumes proportional hazards and if this assumption is violated, Cox models should not be used (23). Studies have, however, indicated that few analyses using Cox regression (<5%) document whether the proportional hazard assumption (PHA) is met (24,25). In other areas of medical research, several studies have compared the Cox regression model with parametric models for survival including exponential, Weibull, Log-Logistic, Log-Normal, Gompertz or Generalized Gamma models. Based on goodness of fit tests, these studies have shown that parametric models are often preferred to the Cox regression models (25–27). To our knowledge, there are no studies that have compared different survival models to identify the determinants of AIDS-related early mortality. Therefore, the objectives of this study were to identify factors associated with AIDS-related early mortality of PLWH in Mexico from 2008 to 2017 and to compare semi-parametric Cox regression models and parametric survival models.

Methods

Study design

SALVAR is a Mexican electronic system managed by the Ministry of Health through the National Center for the Prevention and Care of HIV/AIDS (CENSIDA in Spanish). Its

aim is to monitor all PLWH enrolled in the national HIV/AIDS program (excluding people receiving care through social security, or the Mexican Navy and Army), their treatment, and related health outcomes. The database contains information about clinical, biometric, antiretroviral therapy (ART) and demographic characteristics of individuals (26). SALVAR began to capture data in 2006, but it was not until 2008 when the system was fully implemented nationwide (26). Patients provide consent for the use of personal information at the moment of enrollment (27), although data presented in this analysis was provided to the authors as a secondary anonymized dataset. Currently, it contains information on more than 140,000 PLWH on ART (28).

Data source

SALVAR is a Mexican electronic system managed by the Ministry of Health through the National Center for the Prevention and Care of HIV/AIDS (CENSIDA in Spanish). Its aim is to monitor all PLWH enrolled in the national HIV/AIDS program (excluding people receiving care through social security, or the Mexican Navy and Army), their treatment, and related health outcomes. The database contains information about clinical, biometric, antiretroviral therapy (ART) and demographic characteristics of individuals (28). SALVAR began to capture data in 2006, but it was not until 2008 when the system was fully implemented nationwide (28). Patients provide consent for the use of personal information at the moment of enrollment (29), although data presented in this analysis was provided to the authors as a secondary anonymized dataset. Currently, it contains information on more than 140,000 PLWH on ART (30).

Study population

For this analysis, we included adults (18 years old and older) living with HIV who received their first dose of ART after January 1st, 2008, and before July 1st, 2017. Individuals with incomplete information on key variables such as gender, age, CD4, VL, and date of treatment initiation were excluded. Pregnant women, people who are incarcerated, and people receiving antiretroviral as prophylaxis were also excluded.

Outcome

The dependent variable was AIDS-related early mortality. Consistent with a previous Mexican study (21), early mortality was defined in our base case analysis as AIDS-related mortality within the first six months following ART treatment initiation.

Exposures

Independent variables included an individual's socio-economic information as well as variables regarding the health facilities where ART treatment was provided. All the information was collected at treatment initiation. An individual's information was gender defined as male, female and trans, age categorized as 18-29, 30-39, 40-49, 50-59, and 60 or more years old, and year of ART initiation. Based on previous studies (29), CD4 cell count at treatment initiation was divided into two groups: lower than 200 cells/mm3 and higher or equal to 200 cells/mm3. Similarly, baseline VL was classified as lower or equal than 100,000 copies/mL and higher than 100,000 copies/mL (30). ART alternatives were grouped based on the three most used and representative 1st line ART available in

SALVAR database during the period of analysis: efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF), efavirenz + abacavir/lamivudine (EFV+ABC/3TC), Boosted Protease Inhibitors (PI) and others (including Integrase Inhibitors + backbone and all other regimens defined as a 1st line ART in SALVAR).

Several variables were used to describe the health facilities where ART treatment was initiated. First, Mexico was divided into six geographical regions: Mexico City, Central East, Central West, Northwest, Northeast and South (31,32). Mexico City was classified as another region because of the significant number of PLWH receiving treatment there compared to other regions of Mexico. Health facilities were also categorized as Specialized Clinic CONDESA (based in Mexico City and providing specialized care to prevent HIV and take care of PLWH), Tertiary level Hospitals or National Institutes of Health, and the Ambulatory Centers for Prevention and Attention for HIV/AIDS and Sexually Transmitted Infections (CAPASITS in Spanish). A marginalization index –estimated by the Mexican government (categorized as high, medium and low) was assigned to reflect socio-economic context for location of the health facility where PLWH were treated (33). Finally, a variable accounting for time period (2008-2013, and 2014-2017) was included to capture the HIV policy changes introduced in Mexico in 2014 (34).

Statistical analyses

Population baseline characteristics and heath care facilities information were presented for the overall population and separately by early mortality and non-early mortality (those

who died after six months or remained alive). Discrete variables were presented as percentages, while continuous variables were described in terms of mean, standard deviation (SD), median and Inter-quartile range (IQR). Chi-Squared test for categorical data and two-sample Welch tests for continuous variables were used to compare the population characteristics and outcomes between the two categories.

Early mortality data was first presented using a Kaplan-Meier curve for the overall study period and descriptively for each year of the analysis. Factors associated with AIDS-related early mortality were evaluated using a semi-parametric Cox regression, and three parametric survival models commonly used for HIV-mortality analysis (35–38) (Weibull, Gompertz, and Exponential). All models were adjusted for the above-mentioned variables. The proportional hazard assumption of the Cox regression model was evaluated by calculating the correlation between the ranking of individual failure times and the Schoenfeld residuals. When the correlation is close to 0, then PHA assumption is met and the results of the Cox-regression model are valid (39).

Results from the Cox regression and the parametric models were presented as hazard ratios (HRs), with 95% confidence intervals (CIs). Goodness of fit of models was tested with Akaike information criterion (AIC) and Bayesian information criterion (BIC) for all models, choosing the best-fitted model by the lowest scores in both criteria. In addition, a visual inspection of the fit of the models was also done using Cox-Snell Residual Plots. Due to different definitions of HIV-related early mortality used in the literature (11), sensitivity analyses were conducted by early mortality defined as death within 3-months (17) or death 12-months (14) after ART initiation.

Results

Cohort description

SALVAR database contained 134,860 patients enrolled for the period 2008-2017. Of these, 128,387 were adults (18 years and older) at moment of treatment initiation, 21,722 did not have information about VL or CD4 at treatment initiation, and 954 people were on prophylaxis, deprived of their liberty or pregnant women. After excluding these groups, the study population consisted of 105,711 individuals (See Appendix).

Table 1 presents the baseline characteristics for the overall population and by early mortality status. The average age of our population was 33.7 years old (standard deviation; SD 9.8) 80% were male, 68% were treated in a CAPASITS, 33% started ART treatment in the Central West region of Mexico, 15% in Mexico City, and 9% in the Northwest region of Mexico. Most health facilities were in low marginalized areas. For the biomarkers, 55% of our population initiated treatment with CD4 ≥200 cells/mm3 and 63% with VL< 100,000 copies/mL. The median follow-up period was 115 weeks (IQR: 34; 248).

Table 1. Summary Statistics and Patients' Characteristics at treatment initiation, January 2008- September 2017

	Total	Early mortality	No early mortality	P-value
Sample	**105,711**	**4,980**	**100,731**	
Age (%)				
Mean ± std	33.76 ± 9.86	37.09 ± 9.79	33.60 ± 9.83	<0.001
Median [IQR]	32 [26, 40]	36 [29, 44]	32 [26, 40]	
18-30 yo	39.64	25.57	40.36	
31-40 yo	33.18	36.31	33.01	
41-50 yo	18.4	24.22	18.12	<0.001
51-60 yo	6.85	11	6.65	
>60 yo	1.93	3.2	1.86	
Gender (%)				
Male	79.66	83.65	79.46	<0.001

Female	19.93	16.31	20.11	
Transgender	0.41	0.04	0.43	
Health facility (%)				
Hospital/Clinic/National Institute	19.13	20.45	19.06	
CAPASITS	67.14	73.05	66.85	0.678
Specialized clinics	13.73	6.5	14.09	
Baseline biomarkers				
CD4 cells (%)				
Mean ± std	288.29 ± 253.95	100.54 ± 158.62	297.47 ± 253.97	<0.001
Median [IQR]	232 [88, 416]	48 [20, 111]	244 [99, 426]	
<200	44.76	86.95	42.68	<0.001
≥200	55.24	13.05	57.32	
Viral Load (%)				
Mean ± std	4.29 ± 1.39	5.06 ± 1.08	4.26 ± 1.38	<0.001
Median [IQR]	4.68 [3.61, 5.27]	5.25 [4.72, 5.73]	4.64 [3.54, 5.24]	
<100,000 u/ml	62.63	35.19	63.95	<0.001
≥100,000 u/ml	37.37	64.81	36.05	
Last measure biomarkers				
CD4 cells (%)				
Mean ± std	443.55 ± 296.59	92.81 ± 141.29	460.72 ± 291.31	<0.001
Median [IQR]	410 [222, 617]	48 [20, 107]	426 [247, 630]	
<200	22.33	88.03	19.08	<0.001
≥200	77.67	11.97	80.92	
Viral Load (%)				
Mean ± std	2.22 ± 1.64	4.82 ± 1.36	2.09 ± 1.54	<0.001
Median [IQR]	1.59 [0, 2.99]	5.19 [4.46, 5.70]	1.59 [1.49, 2.47]	
<100,000 u/ml	89.33	39.88	91.76	<0.001
≥100,000 u/ml	10.67	60.12	8.24	
Marginality Index (%)				
High	2.29	2.81	2.26	
Medium	1.01	1.1	1	0.980
Low	96.71	96.09	96.73	
Region (%)				
Mexico City	15.57	7.23	16.01	
Central East	33.08	39.29	32.71	
Central West	12.78	10.2	12.91	<0.001
Northeast	13.51	18.66	13.27	
Northwest	9.39	7.7	9.5	
South	15.66	16.92	15.61	
Follow-up (weeks)				
Mean ± std	154.65 ± 141.22	8.31 ± 6.76	160.54 ± 138.80	<0.001
Median [IQR]	114.7 [34.05, 248.03]	6.27 [2.70, 12.67]	123.23 [43.42, 254.7]	

Compared to individuals alive or dying six months after ART treatment initiation, PLWH dying within six months of initiating ART treatment were older (37 years old [SD: 10] versus 34 [SD: 34], p<0.001), more likely to be male (84% versus 79%, p<0.001), to have

a lower CD4 count at baseline (87% had a CD4 cell less than 200 versus 43%, p<0.001) or higher VL (65% had a VL>100,000u/ml versus 36%, p<0.001). The details are presented in Table 1.

PLWH early mortality description

Over the study time-period, the 6-month mortality rate among PLWH in Mexico was 4.7% as shown in Figure 1. However, differences were seen over time and early mortality increased from 3.6% in 2008 to 5.7% in 2011 before plateauing in 2012 and 2013 and decreasing from 5.6% in 2014 to 2.8% in 2017 as shown in Figure 2.

Factors associated with PLWH early mortality

Table 2 presents the results of our survival regression model and the AIC and BIC values. Although the PHA was not met in the Cox regression (p-value <0.05 for the overall test), all models' results are presented in Table 2 for comparison purposes. The best survival model utilized the Gompertz distribution, and has a lower AIC and BIC, as well as a better adjustment for the Cox-Snell residual. The model with the highest AIC and BIC was the Cox model.

Table 2. Survival analysis for early mortality 2008-2017

	Cox	Weibull	Exponential	Gompertz
Covariables Hazard ratio [95% CI]				
Gender (ref: Male)				
Female	0.78**	0.77**	0.74**	0.78**
	[0.720 - 0.839]	[0.711 - 0.828]	[0.690 - 0.803]	[0.721 - 0.840]
Transgender	0.10**	0.09**	0.08**	0.10**
	[0.025 - 0.398]	[0.023 - 0.364]	[0.020 - 0.314]	[0.025 - 0.398]
Age (ref: 18-29)				
30-39	1.36**	1.35**	1.33**	1.36**
	[1.271 - 1.466]	[1.259 - 1.452]	[1.237 - 1.426]	[1.270 - 1.465]
40-49	1.60**	1.58**	1.55**	1.60**
	[1.479 - 1.732]	[1.457 - 1.707]	[1.434 - 1.680]	[1.477 - 1.730]
50-59	1.95**	1.93**	1.95**	1.94**
	[1.757 - 2.155]	[1.743 - 2.138]	[1.764 - 2.164]	[1.752 - 2.149]

>60	2.18** [1.860 - 2.553]	2.18** [1.858 - 2.550]	2.21** [1.884 - 2.586]	2.17** [1.855 - 2.546]
Region (ref: Mexico City)				
Central East	3.11** [2.208 - 4.371]	3.12** [2.220 - 4.395]	3.32** [2.356 - 4.664]	3.10** [2.201 - 4.359]
Central West	2.07** [1.464 - 2.921]	2.10** [1.483 - 2.960]	2.25** [1.594 - 3.181]	2.06** [1.461 - 2.915]
Northwest	3.61** [2.562 - 5.092]	3.73** [2.644 - 5.253]	4.13** [2.931 - 5.824]	3.60** [2.555 - 5.077]
Northeast	2.10** [1.478 - 2.997]	2.15** [1.509 - 3.059]	2.32** [1.631 - 3.307]	2.10** [1.475 - 2.991]
South	2.73** [1.930 - 3.855]	2.80** [1.979 - 3.952]	3.07** [2.174 - 4.343]	2.72** [1.926 - 3.848]
Type of health facility (ref: hospital/National Institute)				
CAPASITS	0.98 [0.909 - 1.061]	0.99 [0.921 - 1.075]	1.01 [0.935 - 1.090]	0.98 [0.910 - 1.061]
Specialized clinic	1.38+ [0.971 - 1.950]	1.39+ [0.980 - 1.969]	1.43* [1.011 - 2.032]	1.38+ [0.972 - 1.952]
Index of marginalization (ref: high)				
Medium	0.87 [0.632 - 1.185]	0.84 [0.611 - 1.145]	0.79 [0.578 - 1.083]	0.87 [0.633 - 1.187]
Low	0.88 [0.738 - 1.057]	0.86+ [0.716 - 1.025]	0.80* [0.667 - 0.954]	0.88 [0.738 - 1.057]
CD4 Levels at diagnose (ref: <200 cell/mm3)				
≥ 200 cells/mm3	0.16** [0.145 - 0.172]	0.16** [0.144 - 0.172]	0.16** [0.143 - 0.170]	0.16** [0.145 - 0.173]
VL level at diagnose (ref: <100,000 u/mL)				
≥ 100,000 u/mL	1.82** [1.713 - 1.939]	1.82** [1.708 - 1.933]	1.82** [1.714 - 1.939]	1.82** [1.710 - 1.936]
Treatment options				
ART (ref: EFV/FTC/TDF)				
EFV+ABC/3TC	1.08 [0.963 - 1.219]	1.1 [0.979 - 1.239]	1.13* [1.003 - 1.269]	1.08 [0.963 - 1.218]
Boosted PI	1.32** [1.206 - 1.446]	1.29** [1.176 - 1.410]	1.21** [1.104 - 1.323]	1.32** [1.205 - 1.444]
Other	1.58** [1.476 - 1.687]	1.56** [1.457 - 1.665]	1.53** [1.426 - 1.631]	1.57** [1.469 - 1.679]
Period (ref: 2008-2013)				
2014-2017	1.06+ [0.995 - 1.119]	1.40** [1.316 - 1.482]	2.80** [2.640 - 2.969]	1.05+ [0.992 - 1.116]
Observations (individual/week)	105,711	105,711	105,711	105,711
ciEform in brackets ** p<0.01, * p<0.05, + p<0.1. Shape= 0.323 for Weibull, and gamma= -0.110 for Gompertz.				
AIC	108866.7	55864.96	67687.32	48365.17
BIC	109067.7	56085.02	67897.81	48585.23

Models showed that factors associated with a higher probability of early mortality were being older than 29 years old (e.g., belong to the 30-39 years old group, HR:1.36 [CI 95%:

1.27, 1.47] for the Gompertz and Cox model, 1.35 [CI 95%: 1.26, 1.45] using Weibull, and 1.33 [CI 95%: 1.24, 1.42] using Exponential distribution), initiating treatment in a region different than Mexico City (e.g., receiving care in the South region, HR: 2.72 [CI 95%: 1.93, 3.85] using Gompertz, 2.73 [CI 95%: 1.93, 3.85] with Cox regression, 2.80 [CI 95%: 1.98, 3.95] with Weibull, and 3.07 [CI 95%: 2.17, 4.34] using Exponential distribution. Factors associated with a lower probability of early mortality were being female (HR: 0.78 [CI 95%: 0.72, 0.84] with Gompertz and Cox, 0.77 [CI 95%: 0.71, 0.83], and 0.74 [CI 95%: 0.69, 0.80] using Weibull and Exponential, respectively), and individuals who have started their first line ART treatment with CD4≥ 200 cells/mm3 (HR: 0.16 [CI 95%: 0.14, 0.17] in all models). As shown, most results were consistent among all models with a few exceptions. Compared to the Gompertz model, the results of the Exponential model indicated than having started treatment in a Condesa clinic statistically increased the risk of early mortality by 43% ($p<0.05$) while being treated in facility from a low marginality municipality statistically reduced the risk 20% ($p<0.05$). Although all the multivariable models indicated that initiating treatment after 2014 increased the probability of early mortality, the association was only statistically significant for the Exponential (2.80 [CI 95%: 2.64, 2.97], $p<0.001$) and Weibull (HR: 1.40 [CI 95%: 1.32, 1.48], $p<0.001$) distributions.

Sensitivity analyses

Models using either a 3-months or a year cut-off were not different from the model with six-months for almost all variables except for the period of which treatment was initiated (2008-2013 and 2014-2017). With a 3-months cut-off this variable ranges from HR 1.12

($p<0.01$) in the Gompertz model, to HR 3.05 ($p<0.01$) in the Exponential model. Conversely, using a year as a cut-off, the variable is mostly seen as a protective factor (HR: 0.71, $p<0.01$) in both Cox, and Gompertz), but not in the Exponential model (HR: 1.82, $p<0.01$). See Appendix.

Discussion

This study identified several factors associated with early mortality in PLWH in Mexico between 2008 and 2017 including gender, age and biomarkers at time of diagnosis, which shows the importance to adjust for baseline characteristics when analyzing HIV early mortality. While results were relatively similar among the different models, our results show that the Cox PH regression model should be used with caution as the proportional hazard assumption may not hold as shown here and, in this case, that parametric methods fit the data better.

Some authors have shown that the Gompertz function is known to show a better fit when analyzing all-cause mortality, the Weibull function works better for single causes (40), and the Exponential function assumes a constant hazard ratio independent of age, or follow-up time (41). However, all distributions are equivalent when the risk has a linear relation with time (42), which is the case for most of the follow-up time of this study. Also, in our analysis the only time-dependant variables were the year of treatment initiation, the distribution of health facilities, and weeks of follow-up. Regarding the semi-

parametric approach, one of the key advantages is that it is a flexible model without need for a baseline hazard function. However, the main disadvantage of this approach is that if the proportional hazard assumptions are not met, this may lead to a biased effect on the model (23,24). In this sense, other studies, especially in Oncology, have found that semi-parametric Cox model often reports the highest AIC and BIC, and violates the PHA (23–25,43). Fitting distributions depend on the data's nature but similar to evidence from oncology, a few HIV-mortality analyses have shown that parametric models may represent better alternatives than the widely used cox-regression models (35–38). In our analysis, PHA were not achieved by the semi-parametric model, and exploring goodness of fit, the Cox models also reported the poorest fit, and the highest AIC and BIC, while the lowest was shown by the Gompertz function, followed by Weibull.

Individuals dying within six months after treatment initiation were older, a higher proportion were male, more were treated in a CAPASITS, in the Central West region, and a substantial higher proportion initiated treatment with CD4<200 cells/mm3, and VL≥100,000 copies/mL than those who remained alive after six months. The type of clinic or the marginalization index of the clinic´s location had no effect on the event. Results from the different models were consistent with most of the descriptive results and across methodological approaches. Accounting for changes in health policies regarding treatment guidelines and ART access in 2014, descriptively this study found that after those changes, the proportion of people with early mortality decreased, but these changes varied in effect across different model definitions when adjusting for factors such as patient's age, gender, or distribution of health facilities.

Our results are difficult to compare to other studies in Mexico. Even though there is one related study, it was entirely descriptive and did not explore associated factors to early mortality (19). However, our findings are consistent with international studies. For example gender and age differences have been widely explained in different contexts (11,13,14,20,44,45). Evidence suggests that both males and older individuals have been found to have a higher probability of early mortality because of risk behaviors leading to delayed healthcare seeking, and poor adherence (11,14,15,20). Another important factor to predict early mortality has been late diagnosis (generally defined by CD4<200 cells/mm3 (46)) (11,13,14,14,19) which is associated with a weakened immune system, the existence of opportunistic diseases, or an advanced stage of the disease (36, 41). Although we cannot compare results regarding regional, and type of health facilities, the fact that being in a region different than in Mexico City increases the risk of early mortality could be explained by cultural differences such as a higher stigma and discrimination and promotion of gender-related behaviors, limiting diagnosis and treatment (49), as well as differences in access (shorter distance to services) and quality of care (REF)

This analysis presents some limitations to be considered when interpreting the results. First, there could be a lag between the time of death and the time when the event is reported to SALVAR. This could underestimate the rate, especially for the last year of observation, but there is no evidence to date that this could represent a high proportion and alter the results. Another assumption of the analysis is that all deaths reported in SALVAR are HIV-related, because the cause of death is not reported in the database

which could lead to an overestimation, however this issue could be constant across all time and does not generate a bias. Another limitation is that we were constrained by the list of variables available in SALVAR and there may be unmeasured confounders such as indigenous self-reported status, risk behaviors (i.e., use of condom, attendance to risk encounter sites, substance abuse or intravenous drug use), or treatment adherence. Also, we were limited by the design of SALVAR, but other authors have used this database to analyse the same outcome (19), and the database allows the documentation of key information for almost 70% of PLWH in Mexico.

Despite these limitations, to our knowledge, this is the first study analysing early mortality in PLWH in Mexico, after 2012 and using different approaches to test robustness. Some conclusions can be made. First, it was explored how different modeling approaches can either corroborate or contradict results, therefore the selected method should be part of the evaluation design process. Second –and regarding the HIV epidemic in Mexico – late diagnosis was identified as a critical factor for early mortality showing that regardless of the efforts that have made to improve timely diagnosis and treatment access, efforts should continue.

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Appendix

Table A1. Survival analysis for early mortality 2008-2017. Three months cut-off

Early mortality (3-months)	Cox	Weibull	Exponential	Gompertz
Covariables				
Gender (ref: Male)				
Female	0.78**	0.76**	0.74**	0.78**
	[0.713 - 0.849]	[0.701 - 0.835]	[0.679 - 0.809]	[0.713 - 0.850]
Transgender	0.13**	0.12**	0.10**	0.13**
	[0.033 - 0.532]	[0.030 - 0.485]	[0.026 - 0.419]	[0.033 - 0.532]
Age (ref: 18-29)				
30-39	1.32**	1.31**	1.29**	1.32**
	[1.219 - 1.436]	[1.211 - 1.426]	[1.189 - 1.400]	[1.218 - 1.435]
40-49	1.60**	1.58**	1.55**	1.59**
	[1.460 - 1.748]	[1.444 - 1.729]	[1.414 - 1.693]	[1.457 - 1.745]
50-59	1.98**	1.98**	2.03**	1.97**
	[1.767 - 2.224]	[1.766 - 2.223]	[1.806 - 2.273]	[1.759 - 2.215]
>60	2.00**	2.02**	2.09**	1.99**
	[1.664 - 2.411]	[1.681 - 2.435]	[1.734 - 2.512]	[1.656 - 2.400]
Region (ref: Mexico City)				
Central East	3.33**	3.37**	3.66**	3.31**
	[2.239 - 4.942]	[2.265 - 4.999]	[2.466 - 5.442]	[2.229 - 4.921]
Central West	2.10**	2.14**	2.36**	2.09**
	[1.407 - 3.136]	[1.432 - 3.191]	[1.578 - 3.517]	[1.402 - 3.126]
Northwest	3.89**	4.03**	4.59**	3.87**
	[2.616 - 5.796]	[2.708 - 6.000]	[3.082 - 6.829]	[2.602 - 5.767]
Northeast	2.12**	2.17**	2.41**	2.12**
	[1.409 - 3.201]	[1.442 - 3.276]	[1.601 - 3.636]	[1.405 - 3.191]
South	2.80**	2.88**	3.24**	2.79**
	[1.877 - 4.186]	[1.928 - 4.299]	[2.168 - 4.836]	[1.869 - 4.169]
Type of health facility (ref: hospital/National Institute)				
CAPASITS	0.97	0.98	1	0.97
	[0.884 - 1.054]	[0.899 - 1.071]	[0.914 - 1.089]	[0.886 - 1.056]
Specialized clinic	1.44+	1.45+	1.53*	1.44+
	[0.963 - 2.163]	[0.971 - 2.179]	[1.023 - 2.296]	[0.964 - 2.164]
Index of marginalization (ref: high)				
Medium	0.98	0.95	0.91	0.98
	[0.690 - 1.397]	[0.666 - 1.349]	[0.638 - 1.292]	[0.690 - 1.397]
Low	0.92	0.9	0.84+	0.93
	[0.751 - 1.140]	[0.729 - 1.107]	[0.679 - 1.029]	[0.751 - 1.140]
CD4 Levels at diagnose (ref: <200 cell/mm3)				
≥ 200 cells/mm3	0.14**	0.14**	0.14**	0.14**
	[0.130 - 0.160]	[0.129 - 0.158]	[0.127 - 0.156]	[0.130 - 0.160]
VL level at diagnose (ref: <100,000 u/mL)				
≥ 100,000 u/mL	1.93**	1.93**	1.94**	1.92**
	[1.795 - 2.072]	[1.796 - 2.073]	[1.807 - 2.084]	[1.791 - 2.067]
Treatment options				
ART (ref: EFV/FTC/TDF)				
EFV+ABC/3TC	1.08	1.1	1.11	1.08

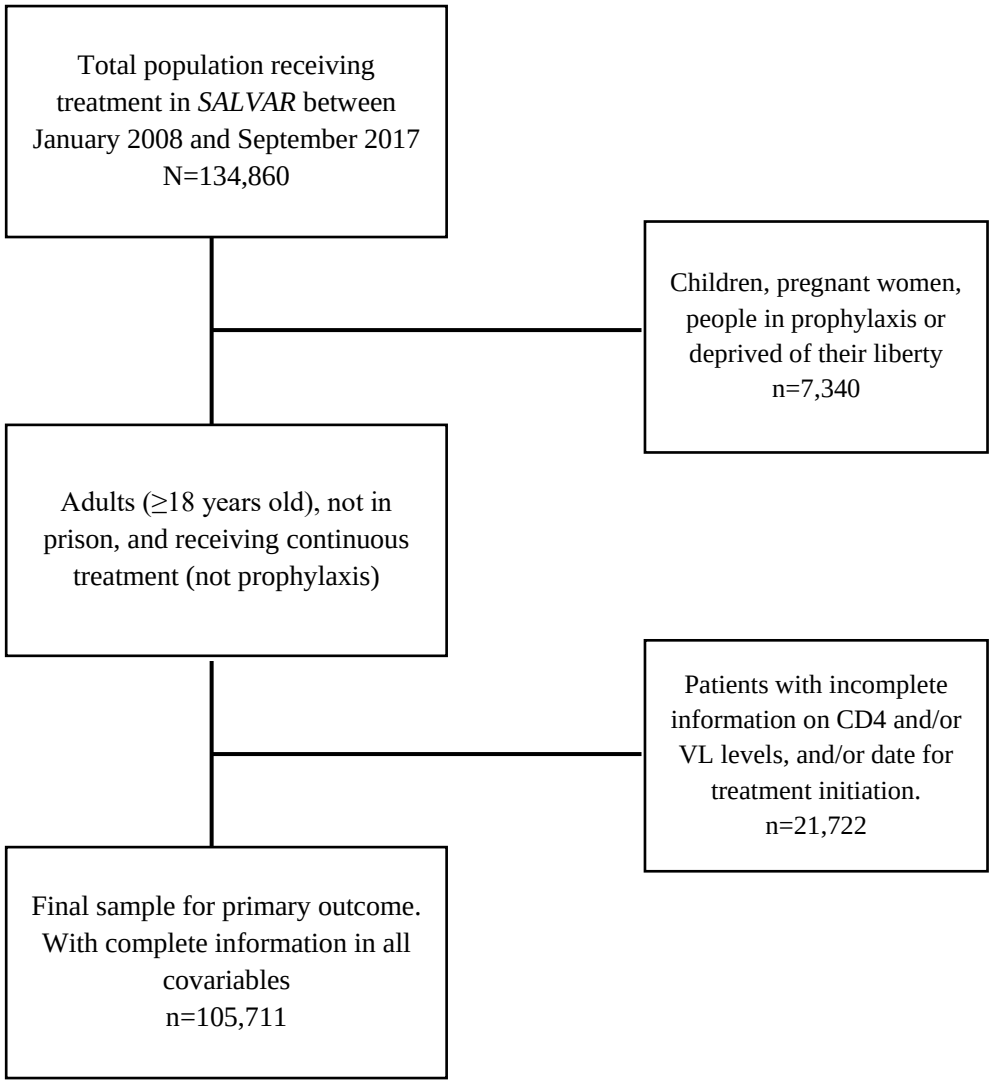
	[0.939 - 1.235]	[0.956 - 1.257]	[0.972 - 1.277]	[0.940 - 1.236]
Boosted PI	1.34**	1.31**	1.22**	1.34**
	[1.206 - 1.486]	[1.178 - 1.450]	[1.098 - 1.352]	[1.205 - 1.483]
Other	1.62**	1.62**	1.59**	1.61**
	[1.500 - 1.748]	[1.504 - 1.752]	[1.472 - 1.717]	[1.491 - 1.737]
Period (ref: 2008-2013)				
2014-2017	1.13**	1.48**	3.05**	1.12**
	[1.056 - 1.207]	[1.383 - 1.583]	[2.850 - 3.260]	[1.051 - 1.201]
Observations (individual/week)	105,711	105,711	105,711	105,711
ciEform in brackets ** p<0.01, * p<0.05, + p<0.1				
AIC	83004.21	45193.85	56113.06	38096.87
BIC	83205.13	45413.91	56323.55	38316.93

Table A2. Survival analysis for early mortality 2008-2017. A year cut-off

Early mortality (A year)	Cox	Weibull	Exponential	Gompertz
Covariables				
Gender (ref: Male)				
Female	0.79**	0.78**	0.76**	0.79**
	[0.745 - 0.842]	[0.737 - 0.833]	[0.719 - 0.812]	[0.746 - 0.842]
Transgender	0.22**	0.20**	0.18**	0.22**
	[0.103 - 0.456]	[0.096 - 0.422]	[0.084 - 0.370]	[0.104 - 0.456]
Age (ref: 18-29)				
30-39	1.31**	1.29**	1.26**	1.31**
	[1.235 - 1.384]	[1.220 - 1.367]	[1.195 - 1.339]	[1.235 - 1.384]
40-49	1.43**	1.41**	1.37**	1.43**
	[1.344 - 1.529]	[1.320 - 1.502]	[1.287 - 1.464]	[1.343 - 1.528]
50-59	1.78**	1.76**	1.78**	1.78**
	[1.639 - 1.942]	[1.622 - 1.921]	[1.633 - 1.934]	[1.638 - 1.940]
>60	2.13**	2.13**	2.17**	2.13**
	[1.873 - 2.428]	[1.872 - 2.425]	[1.905 - 2.468]	[1.871 - 2.425]
Region (ref: Mexico City)				
Central East	2.79**	2.83**	3.04**	2.79**
	[2.102 - 3.700]	[2.134 - 3.757]	[2.289 - 4.030]	[2.100 - 3.698]
Central West	2.14**	2.19**	2.37**	2.14**
	[1.613 - 2.852]	[1.648 - 2.916]	[1.781 - 3.150]	[1.612 - 2.850]
Northwest	3.48**	3.63**	4.09**	3.48**
	[2.618 - 4.621]	[2.734 - 4.824]	[3.075 - 5.427]	[2.616 - 4.617]
Northeast	2.17**	2.24**	2.46**	2.17**
	[1.623 - 2.908]	[1.677 - 3.003]	[1.840 - 3.295]	[1.623 - 2.907]
South	2.75**	2.84**	3.14**	2.75**
	[2.065 - 3.660]	[2.136 - 3.785]	[2.360 - 4.183]	[2.064 - 3.657]
Type of health facility (ref: hospital/National Institute)				
CAPASITS	1.01	1.02	1.03	1.01
	[0.945 - 1.072]	[0.955 - 1.083]	[0.970 - 1.100]	[0.945 - 1.072]
Specialized clinic	1.36*	1.39*	1.47**	1.36*
	[1.018 - 1.812]	[1.042 - 1.854]	[1.098 - 1.954]	[1.020 - 1.814]
Index of marginalization (ref: high)				
Medium	0.9	0.87	0.82	0.9
	[0.698 - 1.157]	[0.673 - 1.117]	[0.637 - 1.056]	[0.698 - 1.158]
Low	0.86+	0.84*	0.79**	0.86+
	[0.744 - 1.000]	[0.723 - 0.971]	[0.678 - 0.911]	[0.745 - 1.001]
CD4 Levels at diagnose (ref: <200 cell/mm3)				
≥ 200 cells/mm3	0.25**	0.25**	0.25**	0.25**
	[0.240 - 0.270]	[0.240 - 0.271]	[0.238 - 0.268]	[0.240 - 0.270]
VL level at diagnose (ref: <100,000 u/mL)				
≥ 100,000 u/mL	1.50**	1.50**	1.52**	1.50**
	[1.432 - 1.580]	[1.429 - 1.576]	[1.443 - 1.591]	[1.431 - 1.579]
Treatment options				
ART (ref: EFV/FTC/TDF)				
EFV+ABC/3TC	0.97	0.99	1.01	0.97
	[0.882 - 1.071]	[0.896 - 1.088]	[0.920 - 1.116]	[0.882 - 1.071]

Boosted PI	1.35**	1.31**	1.24**	1.35**
	[1.251 - 1.447]	[1.223 - 1.414]	[1.151 - 1.330]	[1.251 - 1.446]
Other	1.52**	1.48**	1.44**	1.51**
	[1.437 - 1.601]	[1.406 - 1.565]	[1.362 - 1.517]	[1.435 - 1.598]
Period (ref: 2008-2013)				
2014-2017	0.71**	0.94*	1.82**	0.71**
	[0.678 - 0.749]	[0.898 - 0.993]	[1.727 - 1.908]	[0.678 - 0.749]
Observations (individual/week)	105,711	105,711	105,711	105,711
ciEform in brackets ** p<0.01, * p<0.05, + p<0.1				
AIC	165369.3	78302.63	92666.81	69251.34
BIC	165570.3	78522.69	92877.3	69471.39

Figure A1. Sample flow for analysis



Chapter 5. Conclusions

Through this dissertation, I have examined the impact of recent HIV policy changes in Mexico on the diagnosis, treatment, and early mortality of people living with HIV (PLWH) using data from Mexican individuals receiving ART from 2008 to 2017. Three original scientific articles were written to generate evidence for policy evaluation within the Mexican health system context. This final chapter summarizes the main findings of each of the three studies and their policy implications, then discusses their limitations and recommends avenues for further policy research and evaluation.

Main findings and contributions

Over the last 15 years, two major policies linked to universal health coverage were implemented in Mexico to improve health outcomes for PLWH. The three articles presented in this dissertation evaluate the impact of these national HIV policies. The first article analyzes the impact of the 2013-2017 national HIV policy aimed at increasing HIV screening and detection and identifies the determinants of late HIV diagnosis in Mexico (1). Results indicate that actions implemented through the 2013–2017 national HIV program in Mexico decreased the proportion of individuals with a late HIV diagnosis, as compared to the 2008-2012 period. Moreover, several factors were identified as predictors of late diagnosis, such as being male and aged 29 years or older.

These study findings are important for several reasons. First, they show that the 2013 HIV policy implemented in Mexico was successful in decreasing the percentage of people with late diagnosis, especially in younger and more vulnerable populations.

Therefore, focusing efforts to expand programs targeted to PLWH –not only in high-risk population, but among youth and non-high-risk populations—should continue to be a priority on the government agenda. A second main contribution of this chapter is the identification of factors influencing late HIV diagnosis in Mexico, which in turn has crucial implications for patients, policy design, and the entire health system, as early HIV detection reduces healthcare expenditures, morbidity and mortality. Identifying predictors of late HIV diagnosis allows for the design of tailored interventions which are likely to have a larger impact on Mexico's HIV epidemic such as developing interventions to promote HIV testing among those at lower perceived risk of infection (who are not routinely offered testing) and sexually active youth or women in vulnerable situations.

Early diagnosis, however, is only the first established step to achieving the WHO 95-95-95 goals to end the global HIV epidemic by 2030. The second article of this sandwich thesis moves beyond HIV diagnosis to evaluate the impact of the 2014 HIV policy change in Mexico (2). This policy change aimed to promote universal ART access, irrespective of CD4 count. The study also identified determinants associated with virologic failure (VF). Results highlighted the importance of removing the consideration of CD4 count as a threshold for ART initiation, as this increases the number of PLWH initiating ART and reduces the number of PLWH who develop VF. This, in combination with nationwide expansion of ART access, has positively impacted Mexico's response to the HIV epidemic. As for the predictors of VF, place of treatment and level of deprivation were shown to be important predictors from 2014 to 2017, but not before. Also, it is important to consider that in the 2014-2017 period new and more efficacious treatments

like integrase inhibitors started to be used which could positively impact health outcomes (i.e., VF).

These findings are also important for policymakers and HIV advocates as they provide evidence on the benefits of policy aimed at expanding ART access irrespective of CD4 counts. Combining timely diagnosis and early treatment initiation improves treatment effectiveness and overall health outcomes of PLWH in Mexico. The characterization of VF determinants (place of treatment and level of deprivation) can also inform the development of tailored interventions to improve Mexico's HIV epidemic indicators. For example, PLWH with the highest risk of VF might benefit from closer virological monitoring, as they likely experience higher rates of social vulnerabilities (such as food insecurity, housing vulnerability or substance use disorders) (3,4). Nonetheless, these strategies should be accompanied by interventions to increase risk awareness, and to reduce stigma and discrimination.

The last article of this thesis completes this path by evaluating a final health outcome related to HIV: AIDS-related early mortality in Mexico after 2012 (5). The objectives were to identify factors associated with early mortality of PLWH in Mexico from 2008-2017 and to compare semi-parametric Cox regression models and parametric survival models using Weibull, Exponential, and Gompertz distribution. This study also showed that while results were relatively similar among the different multivariate statistical models used to fit the mortality data, Cox PH regression model should be used with caution as the proportional hazard assumption was not met. In this case, parametric methods fitted the mortality data better. As for the factors associated with AIDS-related early mortality in Mexico from 2008 to 2017, this study revealed that being male, being

older, showing worse Viral Load levels and CD4 cells count at the time of diagnosis (such as CD4 count and viral load), and being diagnosed in a region other than Mexico City were factors associated with early mortality. While the descriptive data showed that the proportion of individuals experiencing AIDS-related early mortality decreased after the HIV policy changes implemented in Mexico in 2014, this association was only seen in the Gompertz and Weibull multivariable models.

Implications

Overall, this dissertation highlights the importance of evaluating health policies on diverse health outcomes. It contributes to understanding the influence that HIV-policy changes have had on the epidemic in Mexico. It also helps illustrate how recent HIV policy changes have impacted HIV outcomes in terms of early HIV diagnosis, treatment initiation and early mortality. The results suggest that actions aimed to promote early HIV diagnosis, early treatment initiation, and strategies for effective monitoring of HIV indicators should continue to be prioritized. It is important to acknowledge that most HIV-health-related outcomes in Mexico such as early diagnosis, early treatment initiation and reduction on virologic failure of PLWH have improved significantly over the last 15 years – except for early mortality where the trend and changes are not as clear as other health-related outcomes.

Second, key indicators and determinants derived from the three articles could inform future policies targeting PLWH in Mexico. As previously mentioned, identifying key elements in policy success will not only help improve outcomes, but also increase resource allocation. The three articles highlighted several relevant factors across different

phases of the HIV care pathway, namely early diagnosis (the first step towards initiating care), timely diagnosis and treatment initiation, and early mortality. To our knowledge, this is the first analysis evaluating the impact of the two major policy changes developed in Mexico over the last 15 years on HIV diagnosis, treatment, and early mortality. As such the totality of this work provides important information to understand the HIV epidemic and the impact of HIV policies on key outcomes, which could be used to guide future policies. Other Latin American countries have previously published studies on indicators of the HIV epidemic (6–8), however, to our knowledge, no study encompasses the impact of health policies on all three components addressed by this study: diagnosis, treatment, and early mortality.

Methodological strengths and Limitations

Together, the studies presented in this dissertation have three main strengths. First, the results were based on large population-based cohorts representing approximately 64% of the population receiving HIV care in Mexico through the MoH, including employed and unemployed individuals, sex workers, and vulnerable populations. We also used 10 years of data from the SALVAR database to evaluate the impact of recent HIV policy reforms in Mexico on population outcomes. This dissertation emphasizes the relevance of robust national databases to evaluate policy changes over time and the use of alternative methodological approaches for health policy analysis. It also opens the door for further (and improved) policy design and implementation.

Methodologically, the three papers use different quantitative approaches to evaluate the impact of recent HIV policies in Mexico. Given the methods used, in addition

to being easy to interpret, the papers are part of the few pieces of quantitative evidence evaluating HIV policies adopted in Latin America. Most of the previous publications focus on narrow populations (e.g., pregnant women (9) or indigenous population (10)), or are based on qualitative research (11,12), which could be explained by the lack of reliable, long-term population-based records in many countries in the Latin America region (13). Finally, from a methodological point of view, the study has shown that the "gold standard" cox proportional-hazards model (PH) models use to model mortality should be used with caution.

Some limitations must be acknowledged. First, this is not an impact evaluation of the interventions that the Mexican government has implemented for improving outcomes in PLWH. The findings from the analysis in this thesis provide an overview of some of the factors and determinants that affect PLWH health outcomes. However, it is not possible to completely attribute our findings to the policies evaluated in the studies presented here. Another limitation to bear in mind is that we did not consider the possibility of a change of insurance coverage (i.e., from CENSIDA to IMSS) in our analyses due to the limitations associated with our data (only individual covered in CENSIDA). This should not however be a major concern for two reasons: 1) individuals that failed to 1st line ART before a change in insurance coverage are included in the analyses; and 2) less than 4% of PLWA moved from CENSIDA to other Social Insurance before presenting virological failure. Unfortunately, given the limitations of the dataset, we were not able to have access to outcome data outside of CENSIDA. Since the analyzed data included information from the initial years of the SALVAR database, there was missing information from a significant number of PLWH during the analyzed years–that

was not imputed— which may not be randomly missing. However, the remaining sample size was big enough to draw important conclusions. Second, the three papers focused only on first-line treatment, which covers only one part of the PLWH treatment path. Nonetheless, it provides relevant information for improving current and future health policies aimed at increasing diagnosis rate, first-line ART treatment and decreasing early mortality. Another limitation is that the SALVAR database does not begin collecting patient information at diagnosis, but rather when first-line ART treatment is initiated. In addition, information on CD4 cells count at diagnosis is not collected as time of diagnosis but instead is entered retrospectively in the database by the treating physician. However, it should be expected that all PLWH requiring treatment should receive first-line ART treatment under the universal coverage policy. Therefore, the number of PLWHs that are included in SALVAR and who are diagnosed but who are not receiving ART treatment should be few. In addition, the dataset does not compile information regarding treatment compliance or adherence. Another limitation to consider is that some individuals may be lost from follow-up because they died. However, there is not a way to account for this Also, despite the SALVAR data set is the biggest repository of HIV indicators in Mexico, it only captures information on PLWH that are enrolled and receive HIV care through the Seguro Popular in public institutions (approximately 64% of the Mexican population). Without information on the population not enrolled in Seguro Popular (e.g., around 36%), our results may not be generalizable to all PLWH in Mexico. Finally, since the analyses used data from 2008 to 2017, it is important to mention that the period of analysis in this study does not consider the most recent HIV programs and policies implemented in Mexico. For example, a national rollout strategy using integrase inhibitors as the preferred

regimen for ART initiation was implemented in 2019. Considering that the integrase inhibitors are considered the most effective ART for first line patients, the results generated in this thesis which used data from 2008 to 2017 may not reflective of the current ART landscape and this could be an additional factor to explain Virological Failure results in the second study. t. However, this work portrays a "before and after" study around recent HIV policy changes in Mexico and illustrates the type of analysis which may help effectively track the country's HIV-health-related indicators.

Implications for Policy and Practice

This dissertation presents implications for HIV policy and practice in Mexico and elsewhere. First, it provides evidence on which factors should be considered when designing tailored interventions for expanding HIV screening and treatment. It provides policymakers and advocates with evidence around public health policies proven to improve the health of PLWH in Mexico, and around tailored interventions to improve HIV care. Also, the results of these articles mark future research avenues for improving PLWH care practices. Although this study was conducted with Mexican data of PLWH, the results can help other countries (e.g., Latin America, Low- and Middle-income countries) to design or implement their policies based on our outcomes and evaluation.

To our knowledge, this dissertation is unique in evaluating the changes of recent HIV policies in Mexico, which will help inform future health policy design and implementation. This doctoral work focused on diagnosis, treatment, and early mortality, which are the three key elements to understanding, controlling, and ending the HIV epidemic. In general, this dissertation describes how HIV reforms successfully increased

early diagnosis, ART initiation, and lower VF, though mortality rates have remained unchanged.

This dissertation not only provides an overview of the path for PLWH from diagnosis to death, but it also contributed to policy evaluation methods in the country. This work reveals the importance of constant monitoring and evaluation of HIV-related policies, as well as general health policies. For example, design interventions focusing on adherence with closer virological monitoring among PLWH at the highest risk of VF or improving the current patient records to expand the scope of SALVAR including other key features such as adherence. Besides, to record virological failure (as a rutinary outcome) and change of regimen due to drug resistance to improve health indicators at patient and national level, as well as acquire and provide the most effective ART. Also, the complete work tells a useful story for understanding the three main indicators to evaluate progress and advancements in the HIV epidemic. This opens the door for similar research to continue monitoring the studied indicators, as well as others contextual and socioeconomic factors such adherence to ART, income, education, place of residency among others. To understand the multifactorial approaches when evaluating HIV diagnosis in Mexico, it is also critical to consider the work that Community Lead Organizations do to improve access among those most vulnerable and at risk of HIV infection . This is left for future research.

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