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Impact of ART on HIV disease under the "*Universal antiretroviral treatment program for uninsured population*" in Mexico: analysis of an open cohort, 2004-2011

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Master of Public Health

Global Health

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Committee Chair

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Universidad Nacional Autónoma de México

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Abstract

Impact of ART on HIV disease under the "*Universal antiretroviral treatment program for uninsured population*" in Mexico: analysis of an open cohort, 2004-2011

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In Mexico, universal health care coverage began in 2003 with the legislation of the "*Seguro Popular*" (SPS) law. Through SPS all outpatient care and antiretroviral therapy (ART) for the treatment of the Human Immunodeficiency Virus (HIV) is provided. However, the scale-up of ART has not been homogeneous throughout the country. Using a monitoring system designed for the surveillance of the distribution of ART at a national level, we studied the cascade of HIV care and the demographic and geographic inequalities linked to HIV care for patients enrolled in care under SPS from 2004 to 2011. The objectives of the study where to describe the immune status of patients at first presentation to care, to assess the quality of care by estimating the time between treatment initiation and achieving a suppressed viral load and to quantify loss to follow-up. Between 2004 and 2011, 63,403 patients entered care under SPS. The male to female ration significantly increased from 3:1 in 2004 to 4:1 in 2011 ($p<0.01$). The median CD4+ T-lymphocyte (CD4+) count at presentation to care increased from 154 copies/μl in 2004 to 227 copies/μl in 2011. Important differences were observed between states; Mexico City had a median CD4+ count of 289 copies/μl in 2011, while other high prevalence states such as Veracruz and Chiapas had a median CD4+ of less than 200 copies/μl. Time from initiation of treatment to achieving a suppressed HIV-1 RNA viral load significantly decreased from a mean of 10 months in 2004 to 4 months in 2011 ($p<0.01$). In total, 25% of the cohort was lost to follow-up from 2004 to 2011, and ranged from >30% in some states to 15% in others. There has been an important increase in ART coverage in Mexico through the government funded SPS. However, many challenges remain, including late presentation to care and retention in care. This suggests that programs to improve early diagnosis, linkage to and retention in care need to be implemented in order to achieve better outcomes of ART in Mexico.

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Table of Contents

Introduction:

In its 2011 HIV/AIDS report, the World Health Organization (WHO) indicated substantial progress in achieving universal access to antiretroviral therapy (ART) in Low and Middle income countries (LMIC). Chile, Cambodia, Cuba, Rwanda and Botswana have already achieved universal access to ART (i.e. coverage of 80% of the population infected with the Human Immunodeficiency Virus (HIV) in need of treatment), and successful scale-up of ART programs has been documented in Malawi, Thailand, Brazil and South Africa (1-8). With increase in ART availability and distribution worldwide, early diagnosis, prompt linkage and entry to care, and both optimal engagement and retention in care are now seen as the major barriers to overcome if the HIV/AIDS epidemic is to be reversed(9).

In Mexico universal access to ART is close to being achieved. In 2011, ART coverage ranged from 70-85% and no stock-out[1] of antiretroviral drugs (ARV) was recorded (8, 10, 11). Achievements in the expansion of coverage were due to the legislation of the System of Social Protection in Health (SSPH) and to the subsequent implementation of the '*Seguro Popular de Salud*' (SPS) in 2004. SPS is a public health insurance program offered under SSPH that offers universal access to a comprehensive package of health services and guarantees financial protection to its members (12). SPS thus allowed previously uninsured individuals, including people living with HIV/AIDS (PLWHA), to access comprehensive care and treatment. In addition, the inclusion of HIV/AIDS

[1] A stock-out is a situation in which a product cannot be dispensed due to the lack of stock and which causes the forced interruption of treatment in at least one patient.

into the catastrophic expenditure fund (CFE) [2] in 2005 marked the beginning of universal access to ART for the previously uninsured population(13, 14).

Since 2005 and through 2011 more than 70,000 HIV-infected patients have been provided care under SPS. Currently, of the 65,000 patients (estimated to be 24% of PLWHA) in Mexico receiving ART; 60% are currently enrolled in SPS, and approximately $842 million dollars have been invested in both treatment and care for SPS patients from 2005 to 2011 (12, 13, 15).

At the end of 2011, it was estimated that approximately 147,137 people were infected with HIV in Mexico (10) and although overall HIV prevalence has remained stable between 0.2 - 0.3% in the general population since 1990, there are specific risk groups that are disproportionately affected. The main route of HIV transmission in Mexico is through sexual contact (16). The epidemic is concentrated among men, which represent 82% of cases and HIV prevalence is highest among men who have sex with men (MSM) and male sex workers (MSW) who have HIV prevalences around 17 - 18% (17, 18). Among women, 87% of infections occurred through heterosexual contact. Individuals aged 25-29 account for 30% of all HIV+ cases, 20% are aged 20-24 and 20% over 30 years of age (10). Geographically Mexico City (*Distrito Federal*; DF) accounts for 22% of all HIV cases, the state of Veracruz 13%, the state of Mexico 6% and the state of Chihuahua 5%.

With the introduction of Highly Active Antiretroviral Therapy (HAART) in 1996, a steep decline in mortality was observed for HIV-infected individuals who had health insurance, especially those living in Mexico City (19). The provision of ART under SPS has not yet provided robust evidence to

[2] CFE was legislated by SSPH and is a trust fund that provides financial resources to provide care and treatment for high cost/low incidence diseases including, but not limited to breast cancer, cervical cancer, neonatal intensive care and HIV/AIDS. In the specific context of HIV/AIDS, CFE covers all ambulatory and outpatient care, thus HIV-infected individuals do not have to pay for ART.

conclude the same at a national level. Despite increased funding and having close to universal access to ART, overall mortality due to HIV has not decreased as expected after 8 years of ART scale-up (20). National mortality estimates continue to fluctuate between 4.9 and 4.7 deaths per 100,000 and there continue to be strong geographical disparities among states, with rates ranging from 1.6 to 10.6 per 100,000 (15).

Experience from other countries' expansion of ART availability and coverage has shown significant decreases in both mortality and incidence. Spain halved HIV incidence in only 4 years and total mortality decreased by 60% in only 2 years after universal access to ART was implemented (21). Other countries such as Brazil and Thailand have also achieved similar results by up-scaling of treatment and prevention funding for HIV(3, 22). Brazil averted 60,000 AIDS cases, 90,000 deaths and 358,000 AIDS related hospital admissions from 1996 to 2002 with a large-scale universal anti-retroviral distribution program (22).

The effectiveness of ART in highly specialized settings and in general hospitals of Mexico City has been documented, thus it is not likely that lack of ART effectiveness is the cause for excess mortality (23, 24). In order to understand the factors contributing to excess mortality in the context of universal access to ART, a thorough evaluation of the cascade of HIV care must take place.

The cascade of care is derived from the spectrum of engagement in care (Figure 1), which holistically defines the different elements related to the treatment and care of HIV, and ranges from being unaware of HIV to infection to being fully engaged in HIV care. The cascade of care is a dissection of this spectrum and clearly defines the stages of care, which include: HIV diagnosis, linkage to care, retention in care, identifying patients needing ARV, ensuring all patients needing treatment get it and finally, having patients achieve virologic suppression. Thus, the cascade of care

provides researches with the opportunity to understand not only the magnitude of the epidemic, but also to define where along the cascade interventions are needed the most (Figure 2) (25, 26).

Problem statement

Lags in the cascade of care have serious individual, social and economical repercussions and early diagnosis, and prompt linkage and entry to care are crucial in reducing complications and decreasing mortality associated to HIV. Patients who enter care with a CD4+ T-lymphocyte count <350 cells/μl have been shown to have increased hospitalizations and premature deaths(27). In addition, patients with delayed initiation of treatment will have high HIV-1 RNA concentrations in blood and genital secretions which are associated with increased HIV transmission (28). Inadequate retention and engagement in care does not only result in increased transmission and mortality, but can also contribute to increased drug resistance. All of the above contribute to increased disability as well as financial instability for PLWHA and their families. A suboptimal cascade of care also has strong policy implications due to the strain that financing universal access of ART puts on government health expenditure. There are multiple competing health priorities that require funding; an inefficient ART program consumes a large portion of resources that could be used for other crucial public health interventions. Thus inadequate care is not only directly detrimental to PLWHA and their livelihoods, but damaging to a country's social and economical well-being.

Published data examining the cascade of care in Mexico is scarce. Most published studies are based on cross-sectional data and sample only a small portion of patients seeking care in highly specialized institutions in Mexico City. No studies have quantified geographical inequalities in HIV care. Furthermore, although data suggests delayed diagnosis, no nation-wide studies have been published

to know what the CD4 count at entry into care is and its variability across institutions and across states. Finally, no retention in care has been published to indicate how well states and institutions are performing with regards to ensuring adherence to treatment and continuing care.

Before the creation of SPS, epidemiological surveillance systems gathered information on HIV detection and mortality; however, information on the process of care of HIV patients was virtually non-existent. With the rapid expansion of ART scale-up in Mexico, a monitoring system to administer distribution, storage and use of ARV was created. Starting in 2007, the Administration System for Antiretrovirals (*Sistema de Administración y Vigilancia de Antiretrovirales*; SALVAR) was established in order to optimize the acquisition and distribution of ARV for the treatment of HIV-infected patients. This monitoring system allows to evaluate treatment outcomes and patients' immunologic and virologic response to treatment (10).

SPS finances HIV care on a per case basis and data is collected on each individual patient at every visit, thus allowing SALVAR to serve as a dynamic open cohort for study. In 2009 SPS began to finance both CD4+ T-lymphocyte cell counts and HIV-1 RNA measurements as important laboratory tests to adequately monitor ART outcomes (29). Although it does not serve as an epidemiologic surveillance tool, SALVAR provides an opportunity to analyze the cascade of care for this cohort and permits us to address the geographical heterogeneity in the process of care.

The identification of areas where the cascade of care could be improved will lead to the development of focused interventions that will not only benefit HIV-infected patients, but will optimize the government's current investment in ART. Furthermore, by increasing monitoring and evaluation, individual states and institutions could be held accountable for poor outcomes and projects to improve the cascade of care could be incentivized. With evidence-based strategies

focused on early diagnosis, proper linkage to care, engagement in care and retention in care, the reversal of the AIDS epidemic in Mexico could be achieved.

In the context of universal access to ART a distinction must be made between coverage and efficacy. Just because patients are started on antiretroviral therapy does not mean that they will achieve an undetectable viral load and the desired clinical outcomes. Not understanding where in the cascade of care patients are being lost, the conditions in which they start treatment or their level of engagement in care will result not only in the waste of valuable public resources but also in poor outcomes and an increased transmission of HIV. In order to close the gap on suboptimal quality of care and ultimately reduce mortality, effective coverage must be achieved. The former cannot be completed without looking at the different processes involved in HIV care. Describing and analyzing the cascade of care is paramount to stopping the epidemic.

Purpose Statement

The goal of this project is to describe some elements of the cascade of care and its change over time for patients currently receiving care under SPS and monitored through the SALVAR. We will examine the period 2004-2011 and our main outcomes will be the following:

1) CD4+ T-lymphocyte cell counts and HIV-1 RNA concentration at entry into care
2) Time in months from initiation of ART to achieving a suppressed viral load[3] (30)
3) Overall change in population CD4+ T-lymphocyte cell count and HIV-1 RNA concentration test results reported

[3] Suppressed viral load is the primary outcome indicator for the effectiveness of ART. For this study it is defined as a serum HIV-1 RNA concentration < 200 copies/μl. An optimal time in achieving viral suppression after initiation of ART is less than 6 months.

4) CD4+ T-lymphocyte cell count and HIV-1 RNA concentration at last visit for deceased and lost to follow-up patients
5) Time from entry into care to death

Research Questions:

1) How have the demographic characteristics of patients receiving care under SPS changed from 2004 to 2011?
    a) We expect that the median age at entry into care will have decreased over the study period due to increased HIV testing and greater access to care earlier in the course of HIV infection. In addition, we expect the male to female ratio to have increased over time. Most cases will be observed in state with large urban and sub-urban areas such as Distrito Federal, Jalisco, Mexico, Baja California and Veracruz.
2) Has immunologic status of new patients entering care changed from 2004 to 2011?
    a) We expect that median CD4+ T-lymphocyte cell counts at entry into care would have increased over time. However, we expect to find strong geographical and sex disparities in levels of CD4+ cells at entry into care.
3) Has time from initiation of treatment to viral suppression changed?
    a) With the increase in availability of ART and greater potency of the available drugs we expect to see a decrease in the time from ART initiation to achieving a viral load for patients starting treatment from 2006 to 2011[4].
4) Population biomarkers

[4] The first recorded date of initiation of treatment for patients in the SALVAR monitoring system is 01/01/2006, thus the evaluation of time from initiation to treatment to viral suppression will only take place for the 2006-2011 period.

a) We expect both the number of CD4+ and HIV-1 RNA test to have been reported to have increased each year, especially since 2008. In addition, we expect that the proportion of tests with a CD4+ T-lymphocyte cell count >350 cells/μl to have increased over time and tests with a suppressed HIV-1 RNA concentration to have increased over time.

5) CD4+ T-lymphocyte cell counts and HIV-1 RNA concentration at last visit for deceased and lost to follow-up

   a) We expect to observe significantly lower CD4+ T-lymphocyte count and a higher HIV-1 RNA concentration at the last measurement for those deceased when compared to those remaining in the cohort. Similarly those lost to follow-up will present with lower CD4+ and higher HIV-1 RNA at the last visit than those remaining in the cohort.

6) Time from entry into care to death

   a) Most deaths will occur within one year of entry into care and we expect strong geographical differences in the survival of patients after entry into care. Urban areas with highly specialized hospitals such as Distrito Federal will have a higher survival than resource poor areas such as the southern state of Chiapas.

Significance Purpose

The availability of potent antiretroviral therapy in the mid-nineties dramatically improved the outcome of patients with HIV infection. With the scale-up of ART treatment in low and middle income countries, lives have been prolonged and the economic productivity of HIV-infected individuals has increased. The challenge now is to make effective use of the existing resources, namely ART, and achieve universal effective coverage.

In the context of universal access to HIV care, understanding the cascade of care and how it shapes both HIV transmission and mortality has imminent implications for public policy. Firstly, it will increase the transparency and accountability of local governments and institutions responsible for distribution of ART and clinical monitoring and care of patients. States with burgeoning epidemics will be under more pressure to ensure that clinical guidelines are followed and that utilization of resources is timely and effective. Secondly, it will provide a chance to evaluate health workers outcomes. This will provide an opportunity to develop programs to incentivize quality of care among physicians including pay-for-performance models, among others. Thirdly, quantifying quality of care indicators will allow an indirect estimation of transmission risk within the population. Special attention may be needed in certain areas of the country where the proportion of patients achieving viral suppression is low. Finally, this analysis will serve as a platform for hypothesis generation and will increase the information available to epidemiologists, economists and politicians invested in the HIV epidemic in Mexico and the world.

Definition of terms

HIV: Human Immunodeficiency that can lead to acquired immunodeficiency syndrome, or AIDS (31)

AIDS: Acquired Immunodeficiency Syndrome – stage of HIV infection that occurs when the immune system is damaged and the infected individual becomes vulnerable to opportunistic illnesses. A CD4 count below 200 cells per cubic millimeter of blood (200 cells/mm3) is also considered AIDS (31)

Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule (32).

CD4+ T-lymphocyte: important component of the human immune system and a biomarker used to assess the state of the immune system in the HIV infected host (31)

HIV-1 RNA: biomarker to assess HIV viral replication in the HIV infected host (31)

Engagement in care: embodies the distinct but interrelated process of linkage and retention in care (25)

Linkage to care: the process of engaging newly diagnosed HIV-infected persons into HIV primary care (33)

Entry into care: the first visit with an HIV care provider authorized to prescribe ART (34)

Retention in care: HIV patient being seen twice annually at least 60 days apart by a physician.(30)

Late Initiation of HAART: Initiation of ART in patients with a CD4+ count <200 cells/mm^3 or an AIDS defining event (35)

Late presenter: Late initiator of HAART who initiates ART therapy after 6 months of diagnosis of HIV (35)

Late tester: Diagnosis of HIV infection at a CD4+ T-cell count of < 200 cells/μl (35)

Literature Review:

In the context of universal access to ART, the cascade of care and its different components have emerged as a crucial component of achieving good health outcomes. There is a vast body of evidence supporting the need for strategies to improve the cascade of care, which has become the backbone of a focused US National HIV Strategy. This review intends to provide the reader with the current state of evidence regarding the different elements of the cascade of care and their repercussions. Specifically, evidence from Mexico and other LMIC will be highlighted.

Model of care for HIV-infected individuals under SPS in Mexico

The expansion of ART coverage under SSPH and SPS was accompanied by an increase in points of care. The Centers for Ambulatory Care of Acquired Immunodeficiency Syndrome (AIDS) and Sexually Transmitted Disease (STD) (*Centros Ambulatorios de Prevención y Atención en SIDA e ITS;* CAPASITS) are the operational unit of these public policies where both prevention and integral care is offered to patients. Since 2006, 66 CAPASITS have become fully functional and provide standardized care to patients throughout Mexico (29).

CAPASITS deliver comprehensive and integral care to HIV-infected individuals. Each center consists of a physician specialized in internal medicine or infectious diseases, one or two primary care physicians, nursing staff, a dentist, a laboratory technician, a psychologist and social workers. This ensures that patients received integral care, including mental health assessments and specialized counseling for MSM and women. Preventive programs such as STD detection, condom distribution, programs focused on increasing adherence to treatment and community campaigns focused on reducing stigma and discrimination are also a cornerstone of the role of CAPASITS. (36)

In 2011, a non-governmental organization called "Fundación Mexicana para la Salud" launched a project to strengthen national prevention and harm reduction strategies for MSM, transgender and IDUs that will span over 3 years. There are 4 main subject areas, which involve promotion, primary prevention, secondary prevention and detection/counseling. Specifically the implementation of Voluntary Counseling and Testing (VCT) areas and the training of counselors seek to address the current gap in linkage to care. Through these VCT modules patients will receive information on public health insurance and be linked to the nearest CAPASITS in order to begin treatment if necessary. (37)

Cascade of care

The "blueprint" for HIV treatment success includes making the diagnosis of HIV infection, linking infected individuals to outpatient care and retaining patients in care (38). Additionally, initiation of and adherence to ART leading to viral suppression are paramount to improving health status of PLWHA and decreasing HIV transmission (39). The underlying assumption of studying the cascade of care is that there is an opportunity to move patients forward at each point of the cascade of care. In addition, there is strong interplay between the environment, patients characteristics, health behavior and intended outcomes, which must be taken into account when understanding care seeking and retention for PLWHA (40). Factors such as transportation to clinics, unstable housing, poverty and perceived stigma have been shown to be barriers in linkage, retention and adherence to care. (41, 42).

In the Unites States only 79% of HIV-infected individuals are aware of their infection and only 50% of those aware they are HIV-positive are engaged in care. Thus, 60% of all HIV-infected individuals

are not receiving regular care. Of the remaining 40%, 80% need ART but only 75% receive it. The proportion of treated patient attaining reaching an undetectable viral load is only 80%, meaning that of the estimated 1.1 million PLWHA roughly 210,000 (19%) are adherent to treatment and reach an undetectable viral load. (26) In Mexico, approximately 67% of the estimated 147,000 PLWHA have been diagnosed and only 25% of those (65,000) are currently on ARV. Of that 25% on ART, 72% have had a reported HIV-1 RNA concentration $\leq$400 copies/μl after 6 or more months on treatment (10).

In order to assess the impact of improving each of the stages of the cascade of care on achieving an undetectable viral load, Gardner et al. modeled the effect of the following: a) increasing the number of diagnosed individuals to 90%; b) increasing engagement to care to 90%; c) increasing ART coverage to 90%; d) having 90% of patients on treatment achieving an undetectable viral load and e) all of the above. Option a) would only increase the number of undetectable HIV-infected patients from 19-22%; b) had the greatest individual impact by increasing the proportion of undetectable patients from baseline to 34%; c) derived in an increase from 19 – 28% and d) had the lowest impact with an increase of only 2 percentage points. Taken all together (e) resulted in an increase of 19% to 66%, thus showing that multiple strategies and points of impact are necessary in order to achieve better outcomes. (26)

Engagement in care

Engagement in care is the overarching theme ranging from linkage to care, followed by retention in care and ending in achieving an undetectable viral load. Several studies have shown that better engagement in care increases receipt to ART, results in higher treatment adherence and increases

viral suppression as well as survival (43-45). Better engagement in care also resulted in a reduction of ethnic, racial and socioeconomic inequalities in reaching good outcomes, and provided evidence of a reduction of risk behaviors (46, 47). However, poor engagement to care is still disproportionate among groups where the HIV epidemic is concentrated such as minorities and low-income individuals.

The 4 main barriers to engagement in care as indentified by Gardner et al., are: 1) a delay or failure to initiate therapy; 2) lack of persistence with therapy; 3) poor adherence to therapy and 4) viral resistance to medication (26). Interventions that focus specifically on linkage to or retention in care have shown better outcomes than more broad interventions that have multiple goals (33).

HIV diagnosis, linkage and entry to care

Only 3 studies from Mexico have been published regarding late testing (LT) or late presentation (LP) to care and their associated risk factors. A study in Tijuana seeking to identify perceptions of HIV that were linked with LT, defined LT as participants who had at least one of: (1) an AIDS-defining illness within 1 year of first positive HIV test; (2) a date of AIDS diagnosis within 1 year of first positive HIV test; or (3) an initial CD4 cell count <200 cells/μl within 1 year of first positive HIV test. Prevalence of late testing was 43% (n=342). Of 275 patients included in multivariate analyses, statistically significant variables included: "I preferred not to know I had HIV" (OR=2.78; CI 1.46–5.31); clinic of recruitment (OR 1.90; CI 1.06–3.41); exposure to peers engaging in high-risk sexual behavior (OR=1.14; CI 1.02–1.27); stigma regarding HIV-infected individuals (OR=0.65; CI 0.47–0.92); and stigma regarding HIV testing (OR=0.66; CI 0.45–0.97)(48). Individuals recruited

from health insurance clinics were more likely to be late testers, and contrary to the authors' hypotheses, stigma acted as a protective factor against LT.

Crabtree-Ramirez et al., reported that 61% of those presenting at the "National Institute of Nutrition and Medical Science" (*Instituto Nacional de Nutrición y Ciencias Médicas;* INNCM) were late presenters. Late presentation was defined as entering care with a CD4+ <200 cells/μl or an AIDS defining illness. Predictors of late presentation included older age (OR=2.4; CI 1.2-4.7), less than 9 years of education (OR=2.44; CI 1.37-4.33) and unemployment (OR=1.75; CI 1.12-2.75)(49). A comparative cohort study from Latin America also provided evidence of widespread LP. In Argentina median (IQR) CD4+ at entry into care was highest for Argentina, 181 (56-309), followed by Mexico, 147 (54-254). In addition, the proportion of Late ART initiation, defined as initiation of ART 6 or more months after diagnosis, was 79.1% in Mexico compared to 55.7% in Argentina (35).

In the United States, a retrospective study of 567 patients entering care from 2000-2005 at the 1917 HIV/AIDS clinic in Alabama estimated that 45.6% of patients entered care with a CD4+ <200 cells/μl, 17.5% entered care with a CD4+ 201-350 cells/μl, and 36.9% with a CD4+ >350 cells/μl. In addition 30.4% had a HIV-1 RNA concentration > 100,000 copies/μl. Significant predictors of delayed linkage to care were older age (OR=1.31 per 10 years; CI 1.06-1.62) and African American race (OR=2.45; CI 1.60-3.74) (38). In a study of the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) CD4+ levels at entry into care were estimated for 44,491 patients enrolled in the cohort. Median CD4+ at entry into care changed significantly over time ($p<0.01$) and increased from 256 (IQR: 96-455) in 1997 to 317 (IQR: 135-517) in 2007. The percentage of patients entering care with a CD4+ >350 cells/μl also significantly increased from 38% in 1997 to 46% in 2007 ($p<0.01$).

There have been significant efforts in the United States to develop strategies to improve linkage to care and decrease late presentation. The Antiretroviral Treatment Access Study (ARTAS-I), a linkage model incorporation multiple sources of clients and testing locations funded by the CDC, was a Randomized Control Trial (RCT) testing strengths-based case management (SBCM) as an intervention. It compared SBCM to standard of care referral in recently diagnosed HIV-infected individuals to primary care. Successful linkage to care was defined as attending at least one HIV medical care visit within 6 months after enrollment. The study population included 93% people of color or gay, 73% of study participants reported an income ≤$10,000, 77% were diagnosed with HIV in the last 6 months and 85% public insurance. After a 3 month intervention, 78% of those receiving SBCM attended at least one visit compared to 68% in the control arm and 64% of the intervention versus 49% of controls had a second visit ($p<0.01$) (50, 51) .

ARTAS-II was designed to evaluate the feasibility of implementing SBCM in local and health department as well as in non-profit community-based organizations (CBOs) for the same target population. This study yielded similar results with 79% of all participants having at least one visit in the first 6 months, and identified best practices associated with improving linkage to care (33, 52, 53). Other programs include: the Client-Oriented New Patient Navigator to Encourage Connection to Treatment (CONNECT), which used personalized orientation an decreased no show-rates after diagnosis from 30% in the 2004-2006 period to 19% in 2007-2008 and the HRSA-SPNS Outreach Initiatives, which through intensive outreach programs achieved similar results (33).

Retention in care

Missed visits are common after initial linkage to care and are associated with late initiation of ART as well as increased resistance to ARV and subsequently virologic failure (38, 44, 54). In the United States, a study conducted by Mugavero et al. found that 60% of patients missed visits during the first year after initial linkage to care. Missed visits were associated with younger age (OR=0.68 per 10 years; CI 0.56-0.83) higher baseline CD4 (>350 cells) and substance abuse (OR=1.67; CI 1.02-2.71) (38). Another study estimated that mortality rates per 100 persons were 2.3 times higher comparing those with missed visits compared to those engaged in care (40, 55). Other factors associated with low retention in care identified in a recent review included: female sex, belonging to an ethnic or racial minority, lack of social support, competing caregiver responsibilities, mental health or substance abuse issues, the misperception that health insurance is needed, stigma and negative perceptions about the health care system (52).

In Mexico retention in care after 1 year was estimated to be 87.9%. Additionally 91.3% of patients had had a CD4+ measurement and 91.8% had a viral load measurement in the last year (10). No studies were found evaluating the predictors of loss to follow-up for patients receiving care in Mexico. A systematic review of HIV cohorts in Sub-Saharan Africa estimated retention after 12 months of 70% and of 65% after 24 months, but did not identify any significant predictors of loss to follow-up (56). In Thailand loss to follow-up was estimated at only 8.8% after 1 year (3).

A recent systematic review analyzed the effectiveness of different interventions in improving retention in cares. The use of patient navigators by Bradford et al., increased the proportion of participants that had 2 or more clinic visits in the last 6 months from 64% to 87% in a pre-post design ($p<0.001$) and 79% had a visit in the last year. The intervention consisted in accompanying

clients to appointments, coordinating appointments, addressing barriers to care, providing referrals and developing skills (behavioral modeling, rehearsing conversations) among others(57). Enriquez et al., improved the number of visits per year from 2.81 to 5.3 ($p<0.05$) by using a bilingual health team when treating a sample Hispanic population (58). Finally, Gardner et al., provided evidence that SBCM also had a positive impact on retention. After a month intervention, 64% of the RCT intervention arm visited HIV clinicians at least twice in 12 months compared to 49% for the control ($p=0.006$) (50).

Interventions designed to improve linkage to and retention in care have led to the creation of clinical guidelines to improve these processes. The recommendations include: Systematic monitoring of successful entry into HIV care for all individuals diagnosed with HIV; Brief, strengths-based case management for individuals with a new HIV diagnosis; Intensive outreach for individuals not engaged in medical care within 6 months of a new HIV diagnosis may be considered; and the use of peer or paraprofessional patient navigators may be considered (59).

ART Outcomes:

Achieving an undetectable viral load is the main objective of providing timely and uninterrupted ART. Not only does an undetectable viral load facilitate immune recovery, but it also decreases transmission (28). Thus, impact of universal access to ART is many times measured through the percent achieving an undetectable viral load within 1 year of beginning ART. In Mexico, it was estimated in 2012 that, at a national level, approximately 72% of patients achieved a viral load <400 copies/μl in 6 or more months of treatment. Results from a review of general hospitals, HIV/AIDS specialized clinics and institutes in Mexico City during 2001-2006, provided evidence of adequate

ARV prescription as well as increased survival time. In this cohort, the percentage achieving an undetectable viral load within the first year was between 70-75%; estimates from similar studies in developed countries put the percentage of achieving an undetectable viral load at 90% in the first year (24, 60, 61).

In Georgia, among a cohort of 752 patients of which 76 % were men and 60% IDUs 86% of patients had VL <400 at last visit (62). In the United States, a cohort of 3,973 persons diagnosed from 2004-2010 in San Francisco showed a decrease in median time from HIV diagnosis to suppression from 32 months in 2004 to 10 months in 2009 ($p<0.0001$) (63). Another study identifying predictors of ARV success (achieving undetectable viral load within 24 weeks) in a treatment naïve population, found that higher CD4 count (> 100 geometric mean) (OR 3.96; CI 1.19-13.15), low Viral load (<100,000 copies/μl) (OR= 3.55; CI 1.29-9.81) and education higher than high-school at 48 weeks (OR=4.98; CI 1.11-22.4) were associated with treatment success (64).

Summary

Late diagnosis, inadequate linkage to care and poor retention in care are widespread problems. Current evidence demonstrates that there are still large gaps in knowledge regarding the different elements of the cascade of care. This is particularly true for Mexico, where current data is limited. Late presentation to care is common, however it has only been qualified in highly specialized hospitals and results may not be applicable to HIV-infected individuals receiving outpatient care. Furthermore, ART effectiveness has been assessed at a population level, yet discrepancies between states have not been addressed nor the change of achieving viral load suppression over time. In

addition, although approximately 87% of patients continue in care after a year, little is known about patient attrition after that time.

Existing data from the United States has demonstrated significant progress in developing adequate strategies to improve short-term linkage to and retention in care. Moreover, no long-term evaluations have been done of these interventions. The current framework in which outpatient care is delivered in Mexico is amenable to many of the evidence-based recommendations to improve the cascade of care. Closing the gaps on knowledge regarding the cascade of care is the first step towards understanding the epidemic in the context of universal access to ART.

Methods:

SALVAR provides longitudinal data on >70,000 individual patients enrolled in HIV care insured under SPS. Specialized ambulatory care centers and hospitals affiliated to the Ministry of Health transmit well-defined data elements captured from point-of-care electronic systems using standardized methodology and format. Informed consent is mandated by law for all HIV-infected patients enrolled in care under SPS and included in the SALVAR database (29, 65). The authors were granted access to the information by the Board of Directors of CENSIDA and the Mexican Ministry of Health. The Emory Institutional Review Board approved the study.

Study participants and variables of interest:

Patients included in the analysis were all HIV-infected adults (≥18 years of age) with a recorded entry into care between January 1st 2004 and December 31st 2011. Demographic characteristics of patients included: sex, age at entry into care, date of HIV diagnosis, date of entry into care, date of initiation of treatment, ethnicity (defined as belonging to an indigenous ethnic minority), incarceration status, state of residence and point-of-care. Immunologic variables included serum CD4+ T-lymphocyte cell count results counts (CD4+), date of the test and the laboratory where the test was performed. Virologic variables included serum HIV-1 RNA concentration (VL), date and laboratory of the performed test. All CD4+ measurements whose reported value was >2,500 cells/μl were excluded from the analysis. If two different measurements were reported for either CD4+ or VL on the same date, an average of the two results was taken. The VL results were transformed using a base 10 logarithmic scale in order to report population means and medians.

To address the objective of quantifying immunological status at entry into care, the first recorded CD4+ measurement was used. In order to minimize the inclusion of patients having received care before their reported entry into care, HIV-infected individuals whose first recorded CD4+ measurement was ±3 months (34, 66) from their reported date of entry to care were excluded from the analysis. Loss to follow-up was defined as any patient entering care in 2004 that had the last reported CD4+ measurement before the year 2011 and was not reported as deceased in SALVAR.

In order to assess the effectiveness of ART in the population, VL was used. Patients with a reported VL ≤200 copies/μl were considered in viral suppression and those with a reported VL ≤50 copies/μl were considered undetectable. The time from reported initiation of treatment to the first reported undetectable VL was calculated in months. In order to minimize the number of non-treatment naïve patients in the analysis, those with a suppressed VL result reported before the date of initiation of treatment were excluded from the analysis. The first recorded dates for initiation of treatment in the SALVAR system began in January 2006, thus the analysis of time from treatment to suppression includes only patients whose date of initiation of treatment is known. In order to assess the change in immunological and infective status of the population over time CD4+ and VL were stratified into groups. CD4+ results were categorized as follows: ≤200 cells/μl, 201-349 cells/μl, 350-499 cells/μl and ≥500 cells/μl; VL measurements were categorized as: ≤200 copies/μl, 201-99,999 copies/μl and ≥100,000 copies/μl. Population and state measures were obtained for each category excluding the first reported CD4+ and VL measurement in order to control for new patients entering the cohort each year.

To address geographical heterogeneity, states of residence were categorized based on the proportion of HIV-infected patients receiving care reported in each state. States were individually analyzed if they had more than 2,000 patients and states with less than 2,000 patients were aggregated into one

category. This resulted in the following categories: Distrito Federal, Veracruz, Mexico, Jalisco, Chiapas, Baja California, Tabasco, Guerrero, Tamaulipas and Other States.

Statistical methods:

In order to test for the change of demographic characteristics of the cohort over time, the Cochran-Armitage trend tests and Chi-Square tests for categorical variables (e.g. sex, ethnicity, incarceration status and state of residence) and linear regression for continuous variables (e.g. age) were used. The median CD4+ at first entry into care was characterized for the entire cohort and stratified by demographic and geographic characteristics. Due to non-normality of CD4+ distribution, the median was used and a Kruskal-Wallis test for trends was used to test the change in CD4+ over time.

To study the predictors of Late Presentation (LP), bivariate and multivariate logistic regression models were used. LP was defined as having a CD4 count <200 cells/μl at the first measurement ±3 months of recorded entry into care. Predictor variables included sex, ethnicity, incarceration status, age (categorized as 18-29, 30-49, 50-69 and 70 or older), seeking care in a CAPASITS, $\log_{10}$ HIV-1 RNA at entry into care and year of entry into care. Interactions between sex and age, sex and state, and ethnicity and sex were evaluated. Collinearity between predictor variables was assessed prior to testing for interaction. Variables showing evidence of collinearity were dropped from the model, beginning with interaction terms. A Backwards Elimination modeling strategy was conducted and likelihood ratio tests were used to test interaction. Once a gold standard model was obtained, confounding and precision assessment were conducted. Confounding was considered present if

there was a change >10% of the Odds Ratios of the variables of interest. Odds Ratios and 95% Confidence Intervals were calculated for both crude and adjusted models.

The Kaplan-Meier estimator was used in order to assess the change in time from initiation of ART to achieving an undetectable viral load by year of initiation of treatment and tested using the log rank statistic. Time from entry into care to death was estimated using the same method and the probability of death was calculated by quartiles. The Log-Rank statistic was used to assess differences in mortality for patients presenting to care at different levels of CD4+.

To quantify loss to follow-up, the total number of patients in care at the end of 2011 was divided by the number of patients whose last CD4 count was reported in 2010 and were not reported as deceased in the cohort. Paired Wilcoxon signed rank tests were performed to assess whether any immunological difference was present between those who were lost to follow-up and those who remained in treatment. The median CD4+ and VL was determined for all patients whose last visit was recorded in a given year and compared to the results for every patient still active in that year. Patients with a first recorded CD4 in that year were excluded from this comparison. Statistical results with a p-value <0.05 were considered significant. All analyses were conducted using SAS, version 9.3 (SAS Institute; Cary, NC).

Results:

Demographic characteristics

The study population included 63,403 adults who entered the cohort between 2004 and 2011. The total number of patients entering the cohort per year and their demographic characteristics are

shown in Table 1. The median age of patients entering care significantly decreased from 41 years in 2004 to 34 in 2011 ($p<0.01$), and the male to female ratio increased from 3:1 to 4:1 in the same period ($p<0.01$). The proportion of patients belonging to an indigenous ethnic minority (indigenous) significantly decreased over time (4% to 2%; $p<0.01$), as did the number of incarcerated patients entering the cohort (14% to 3%; $p<0.01$). Three states: Distrito Federal, Veracruz and Mexico accounted for 35% of the total number of patients entering care during the study period and approximately 63% of the total patients were located in only 9 of 32 states in the country.

Presentation to care

Only 37,374 (59%) patients in the final cohort had a first CD4+ measurement within 3 months of their reported date of entry into care. The number of reported CD4+ results increased from 614 in 2004 to 5,925 in 2008 and 8,418 in 2011. The overall median CD4+ and inter-quartile range at first presentation to care is shown in Figure 3. The median CD4+ at first presentation to care increased from 154 cells/μl in 2004 to 227 cells/μl in 2011 ($p<0.01$). The proportion of patients entering care with a CD4+ ≥350 cells/μl increased from 16% in 2004 to 33% in 2011 ($p<0.01$). The differences in CD4 + levels at presentation to care by demographic characteristics and state can be seen in Table 2. The Distrito Federal had the largest gain in CD4+ over the study period and increased from a median 154 cells/μl in 2004 to 298 cells/μl in 2011. The states of Veracruz and Jalisco had the lowest overall gain and median CD4+ at presentation was still below 200 cells/μl in 2011 (197 and 194 respectively). Chiapas had the lowest CD4+ at presentation to care in 2011 with 189 cells/μl.

Results from the bivariate and multivariate logistic models assessing late presentation are shown in Table 3. Being aged 18-29 when presenting to care (OR=0.49; CI 0.46-0.51) and seeking care in a

CAPASITS (OR=0.81; CI 076.-0.86) were associated with presenting with a CD4+ >200 cells/μl. Males had a higher odds of being late presenters (OR=1.43; CI 1.34-1.49) and a significant interaction between being indigenous and male provided evidence that males of this ethnic minority presented late to care (OR=1.24; CI 1.03-1.48). Being male proved to be a protective effect in Distrito Federal (OR= 0.62; CI 0.57-0.67); no other interactions between sex and state had a $p<0.05$.

ART outcomes

Only 20,519 patients had a recorded undetectable viral load after the reported date of initiation of treatment. Overall the mean time from initiation of antiretroviral treatment to achieving a suppressed viral load decreased from 21 months for those starting in 2006 to 4 months in 2011. Figure 4 presents results from the Kaplan Meier estimation including at risk population for each year. Time from initiation of treatment to achieving an undetectable viral load changed significantly from 2006 to 2011 ($p<0.001$). When stratified by CD4+ at presentation to care, significant differences were detected between those presenting to care with a CD4+ of 350 copies/μl or greater and the other groups ($p<0.001$). Approximately 50% of individuals with a CD4+ ≥350 copies/μl achieved an undetectable viral load at 4 months, while 50% of individuals with a CD4+ <200 copies/μl achieved an undetectable viral load at 7 months ($p<0.001$) (Figure 5). Trends of change for selected states can be seen in Figure 6.

A total of 216,845 CD4+ measurements took place for patients enrolled in SPS during the study period (2004 to 2011). The overall number of tests performed increased from 824 in 2004 to 25,902 in 2008 and 71,257 in 2011. The median (IQR) number of CD4 and VL tests in the cohort was 4 (2-6) and was equal for men and women. The cumulative proportions of CD4+ (left) and VL (right)

results are presented in Figure 7. The proportion of tests with a result <200 cells/μl significantly decreased from 21% in 2004 to 12% in 2011, and the group with ≥500 cells/μl increased from 29% in 2004 to 42% 2011 ($p<0.01$). There were 209,991 serum HIV-1 RNA tests among the same population between 2004 and 2011. A similar increase was observed with 673 tests reported in 2004, 24,186 tests in 2008 and 70,681 tests reported in 2011. The percentage of VL results ≥100,000 copies/μl decreased from 12% in 2004 to 4% in 2011. The number of tests with a suppressed viral load (≤200 copies/μl) increased from 14% in 2004 to 79% in 2011 ($p<0.001$).

Mortality and Loss to Follow-up

In total 5,426 death were recorded in the study period, however only 4,485 were recorded after the date of entry into care. Kaplan-Meier survival estimates are presented in Figure 8. Fifty-percent of deaths in the total cohort occurred in the first 7 months after entry to care and the mean time to death was 15 months. When stratified by CD4+ at entry to care mortality was higher for those presenting to care with a CD4+ <200 cells/μl. A difference was observed between patients entering care with 200-349 cells/μl and those with ≥ 350 cells/μl in the first 24 months, however, after this period differences were no longer significant (Figure 9). Table 4 shows demographic, immunologic and virologic characteristic of those deceased during the study period. The proportion of death was higher for males than for females (9% vs. 7%). Guerrero had the highest proportion of deaths with 18% followed by Baja California (13%) and Veracruz (12%). Jalisco had the lowest amount of recorded deaths (3%). The median (IQR) CD4+ at death was 83 (30-207) and was not significantly different among sexes ($p=0.35$).

Statistics regarding loss to follow-up are presented in Table 5. During the study period 25% of patients who had recorded CD4+ were lost to follow-up. The highest proportion of lost to follow-up was among incarcerated individual where 65% of those enrolled in the cohort were lost. The states with the highest proportion of loss to follow-up were Baja California (38%), Jalisco (31%), Tamaulipas (31%) and Veracruz (27%). The median (IQR) CD4+ for those lost to follow-up was 264 cells/μl and was significantly different from the median CD4 of those remaining in the cohort (354 cells/μl) ($p<0.01$). The states of Chiapas and Tabasco had the lowest median CD4 counts of those lost to follow-up (205 and 217 respectively) and also presented with the highest viral loads when they exited the cohort (log10 HIV-1 RNA of 4.56 and 4.25 respectively).

Discussion:

Since the creation of SPS approximately 52.6 million Mexicans have benefited from a comprehensive package of health interventions and been spared from financial strain from medical costs thanks to this social protection of health (12). Cumulatively more than 65,000 patients have benefited from ART since the implementation of SPS. In addition, efficient negotiations between government representatives and the pharmaceutical industry have reduced the bulk price of ART, thus contributing to increased access to treatment (67). This analysis provided evidence that although more patients are entering care, there are still important gaps to be addressed in the cascade of care, if resources are to be maximized.

Late presentation to care has been associated with increased risk of death and an increased cost of treatment and care per patient (27, 68, 69). In Mexico, no population estimates were available for CD4+ level at entry into care. This analysis demonstrated a significant increase in median CD4+ over time, and Odds Ratios obtained from multivariate logistic models indicate that patients presenting to care in 2011 had lower odds of being late presenters. However, due to the fact that CD4+ testing was not routinely done before 2009 it is difficult to evaluate whether presentation to care has improved over time. Moreover, the median CD4+ at entry into care still remains very low and is likely contributing to the excess mortality observed in the context of ART scale-up.

Strong state differences were also identified in the analysis. In the Distrito Federal where access to diagnosis, testing and quality of care is higher, the median CD4+ was close to 300 cells/μl. In other states more than 50% of HIV patients are still presenting to care with AIDS. The fact that seeking care in a CAPASITS was a protective factor for late presentation may be due to the fact that sicker patients access emergency care instead of primary care, thus patients being cared for in outpatient clinics are more likely to be healthy than those cared for in hospitals or national institutes. This also

supports the difference observed in the proportion of late presenters to care observed between the SALVAR cohort, estimated at 45% in 2011, and the results obtained by Crabtree-Ramirez et al., from INNCM where 63% of patients entering care in the clinic were late presenters, with a median CD4+ of 147 cells/μl (35).

Despite late presentation to care, outcomes of ART scale-up have improved for patients receiving care under SPS. The time from initiation of treatment to achieving an undetectable viral load decreased significantly over time and differences between states that were apparent for those beginning treatment in 2006 are now almost homogeneous in 2011. Although this may be due to improvement of patterns of prescription and improved patient adherence, this lag may also be due to the poor viral load monitoring taking place before 2009. The trends in laboratory testing clearly show a large increase both in the number of tests performed and reported as suppressed. Clearly with the addition of funding for CD4+ and HIV-1 RNA tests in 2009, not only did the amount of tests reported change, but more importantly it allowed physicians a more profound assessment of the effectiveness of the prescribed treatment.

Mortality and loss to follow-up continue to be important barriers. Approximately 50% of the deaths recorded in the cohort were within 7 months of entry into care and is associated with the proportion of patients entering care with a CD4 <200 cells/μl. This seems to indicate that late presentation is the main contributor to premature deaths in the cohort. Even with scale-up of ART, if patients continue to present late to care, mortality will not be reduced. Furthermore a quarter of the patients that entered care in 2004 were lost to follow-up by 2011 and strong geographical disparities were observed. It is worrying that those lost to follow-up had higher viral loads and lower CD4+ counts at their last visit suggests due to the possible contribution of these patients to the transmission of HIV.

The implications for public health are clear. Although significant scale-up of ART has been effective in improving outcomes for patients enrolled in SPS, late presentation to care is one of the main obstacles for achieving the full potential of universal access to ART in Mexico. Not only is late presentation related to increased mortality, it is also associated with an increased lag time between initiation of ART and achieving an undetectable viral load. Specific strategies must be focused on increasing HIV testing for HIV-infected but asymptomatic individuals and ensuring adequate linkage to care after HIV diagnosis. The current CAPASITS model is amenable to the evidence-based interventions currently recommended and should adapted to the Mexican context (59).

The factors contributing to late presentation to care and late diagnosis need to be studied more in depth. There is evidence that stigma among healthcare providers directed towards PLWHA is still present in Mexican hospitals and clinics (70). Stigma and discrimination are associated with lower rates of HIV testing and contribute to risky behaviors such as non-adherence to ART and increase in unprotected sex (71). Programs to decrease stigma and discrimination are crucial to increasing HIV testing and linkage to care for HIV-infected individuals. The use of economic incentives to increase preventive measure uptake and increased testing are currently being studied in Mexico. Bertozzi et al., found a positive effect of providing monthly monetary rewards, where acceptance probabilities for participation in preventive activities and repeat testing were 73.9% for a monthly model and 80.4% for a quarterly model. The Willingness to Accept was $288 per person per year and was lower for MSW $156 per year (72). Other interventions such as pay-for-performance for physicians providing care to HIV-infected individuals may also contribute to enhancing both quality of care and decreasing attrition.

Limitations

There are several limitations to the results obtained from the analysis. Because SALVAR is a monitoring database to evaluate the distribution and existence of ART, it is not optimal for epidemiologic study. The quality of the data is questionable and a large amount of missing values for the diagnosis date of patients entering the cohort made several elements of the cascade of care difficult to evaluate. The date of entry into care does not necessarily represent the true initiation of care for HIV-infected patients of SALVAR but rather represent the date where the patient's information was uploaded to the database. Although we did our best to minimize bias in terms of accurately measuring CD4+ count at entry into care and ART outcomes for treatment naïve patients, there is a possibility that the estimates may be underestimating CD4 levels at entry in to care . Furthermore, due to the large proportion of loss to follow-up, estimates of ART treatment effectiveness in the population may be overestimated as many of the patients lost to follow-up had initiated treatment, and patients remaining in the cohort may be healthier and more compliant with treatment. Information on mortality for patients may not be entirely accurate. Many patients lost to follow-up may already be deceased. This will not be known until a comprehensive cleaning and compilation effort to compare national death registries and the patients present in SALVAR has been done. Calculations of time from diagnosis to linkage to care were not available because of paucity of reliable diagnosis dates for the patients in the cohort. For this reason we are not able to conclude whether late diagnosis or late presentation to care plays a larger role in contributing to mortality in the cohort. Finally, the presence of risk factors such as MSM, IDU and MSW was not available for this cohort thus limiting the extent to which we can characterize risk for these patients and assess whether there is differential bias in the characterization of the cascade of care for these subgroups.

Conclusions and Recommendations:

Several recommendations stem from this analysis. Firstly, in order to adequately understand the spectrum of engagement in care in Mexico, the SALVAR monitoring database must be improved if the cascade of care is to be adequately described in Mexico. In the cohort 62% of patients had a missing diagnosis date. If linkage to care is to be evaluated, increased communication between SALVAR and other national HIV registries needs to take place. In addition, multiple entry dates are used in the current monitoring system, a unique date needs to be determined and used for programmatic purposes. Having a robust information system will enhance accountability of institutions and states regarding quality of care.

Secondly the indicators used to evaluate the HIV/AIDS program must change. The IOM recently released guidelines including core indicators of HIV care (30). These indicators include:

a. Proportion of people newly diagnosed with HIV with a CD4+ cell count >200 cells/mm3 and without a clinical diagnosis of AIDS
b. Proportion of people newly diagnosed with HIV who are linked to clinical care for HIV within 3 months of diagnosis
c. Proportion of people with diagnosed HIV infection who are in continuous care (two or more visits for routine HIV medical care in the preceding 12 months at least 3 months apart)
d. Proportion of people with diagnosed HIV infection who received two or more CD4 tests in the preceding 12 months
e. Proportion of people with diagnosed HIV infection who received two or more viral load tests in the preceding 12 months

f. Proportion of people with diagnosed HIV infection in continuous care for 12 or more months and with a CD4+ cell count ≥350 cells/mm3
g. Proportion of people with diagnosed HIV infection and a measured CD4+ cell count <500 cells/mm3 who are not on ART
h. Proportion of people with diagnosed HIV infection who have been on ART for 12 or more months and have a viral load below the level of detection
i. All-cause mortality rate among people diagnosed with HIV infection

The use of these indicators will allow for a better monitoring of both the cascade of care and specific outcomes related to ART therapy.

Thirdly increased HIV testing is necessary. This could be achieved by combining a mass media campaigns and with providing ambulatory centers with rapid HIV tests. This would allow HIV tests to be performed in primary settings that are not viewed as centers specifically for HIV infected individuals. In addition to increased promoting and availability of tests for HIV, community mobilization to address the issues of stigma, homophobia and discrimination is crucial component to increase testing uptake within the population. Initiative such as Scenarios from Africa, where people living with HIV/AIDS tell their stories through videos that are produced by top country directors and actors have shown that amplifying the voices of these HIV-infected individuals is enough to challenge and change social norms (73).

Finally linkage and retention in care need to be improved. There is evidence that peer navigators and strengths based counseling can increase patients' visits to centers and improve adherence to treatment. Currently the CAPASITS model in Mexico is amenable to such interventions; however,

investments must be made in order to provide incentives for both patients and health care workers to achieve good outcomes. Furthermore, incentives based programs should be explored given the successful nature of conditional cash transfer programs in the country.

This is the first attempt to describe the evolution of HIV-care for patients under SPS over time since universal access to ART was mandated by law in 2003. Although this study does not analyze every aspect of care, it provides an overview of the challenges that any country seeking to provide effective universal access to ART might face. Increasingly, as funding and in-country availability of ART have grown, focus is shifting from procurement of resources to optimization in the use of those resources. The results from this analysis indicate a favorable evolution of treatment outcomes overtime as quantified by both achieving viral suppression and restoring immune function at a population level. Moreover, important challenges remain, including late presentation to care and poor retention in care. Thus, programs to improve early diagnosis, linkage to and retention in care need to be implemented if better outcomes are to be obtained through the expansion of HIV care and treatment among the SP population.

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Tables and Figures:

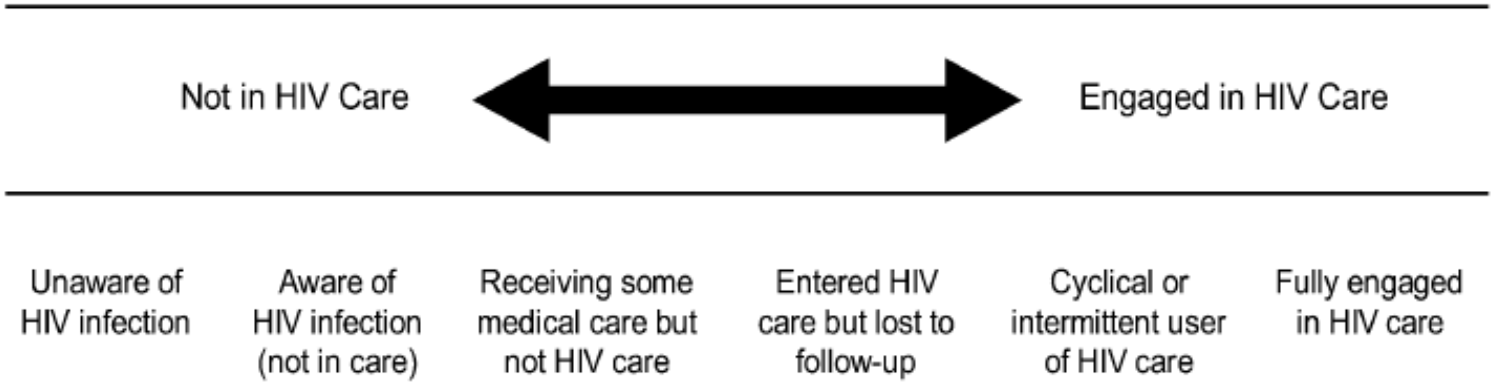

Figure 1. The Spectrum of Engagement in Care. Adapted from Cheever et al. 2007

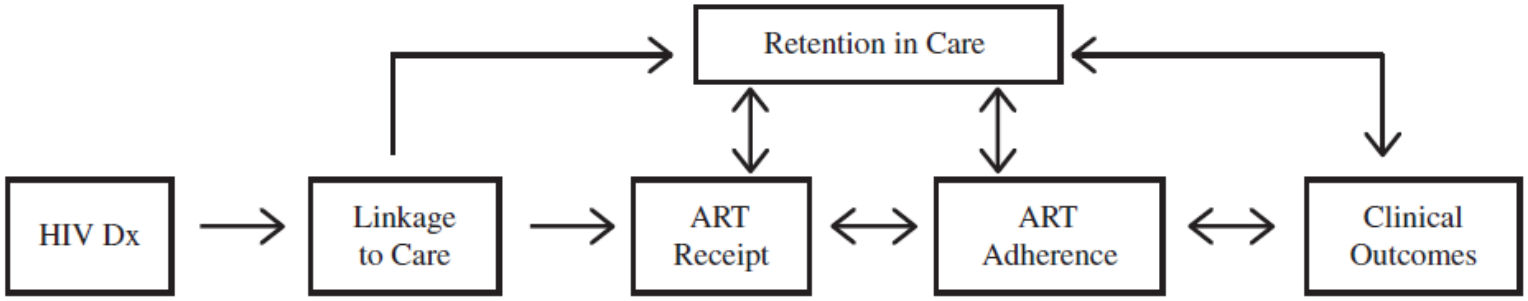

Figure 2. The Cascade of HIV Care

Source: Ulett K.B., et al., The Therapeutic Implications of Timely Linkage and Early Retention in HIV Care. AIDS patient care and STDs 2009;23 (1):41-49.

Table 1. Characteristics of HIV-infected patients enrolled in SPS by year, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2004-2011

Characteristic	Total (N=63,403)	2004 (n=3,378)	2005 (n=4,525)	2006 (n=6,854)	2007 (n=6,565)	2008 (n=10,280)	2009 (n=10,534)	2010 (n=10,535)	2011 (n=10,732)	Pa
Age, median (IQR) years	36 (30-44)	41 (35-48)	40 (34-47)	38 (33-45)	38 (32-45)	37 (31-45)	36 (30-43)	34 (28-42)	34 (27-41)	<0.01
Sex										
Male	48,804 (77)	2,525 (4)	3,442 (5.4)	5,036 (7.9)	4,884 (7.7)	7,820 (12)	8,274 (13)	8,282 (13)	8,541 (13)	<0.01
Male:Female ratio		2.9	3.1	2.7	2.8	3.1	3.6	3.5	3.8	
Ethnicity										
Indigenous	1,792(3)	118(4)	161(4)	371(5)	210(3)	236(2)	337(3)	222(2)	200(2)	<0.01
Incarcerated	4,394(7)	519(15)	717(16)	1,173(17)	732(11)	283(3)	251(2)	417(4)	302(3)	<0.01
State										
Distrito Federal	9,984 (16)	600(18)	711(16)	958(14)	663(10)	1474(14)	2612(25)	1504(14)	1462(14)	0.04
Veracruz	7,249 (11)	460(14)	551(12)	764(11)	1165(18)	1176(11)	981(9)	1052(10)	1100(10)	<0.01
Mexico	4,857(8)	219(6)	360(8)	480(7)	480(7)	910(9)	804(8)	937(9)	965(9)	<0.01
Jalisco	4,346 (7)	396(12)	428(9)	416(6)	428(7)	851(8)	626(6)	624(6)	577(5)	<0.01
Chiapas	2,982(5)	145(4)	174(4)	292(4)	228(3)	462(4)	487(5)	590(6)	604(6)	<0.01
Baja California	2,751(4)	124(4)	172(4)	218(3)	390(6)	506(5)	363(3)	478(5)	500(5)	<0.01
Tabasco	2,530 (4)	111(3)	166(4)	305(4)	234(4)	370(4)	300(3)	516(5)	528(5)	<0.01
Guerrero	2,349 (4)	71(2)	191(4)	239(3)	241(4)	366(4)	504(5)	336(3)	401(4)	0.02
Tamaulipas	2,332 (4)	76(2)	109(2)	219(3)	201(3)	435(4)	450(4)	376(4)	466(4)	<0.01
Other States	23,725 (37)	1176(35)	1663(37)	2963(43)	2535(39)	3730(36)	3407(32)	4122(39)	4129(38)	

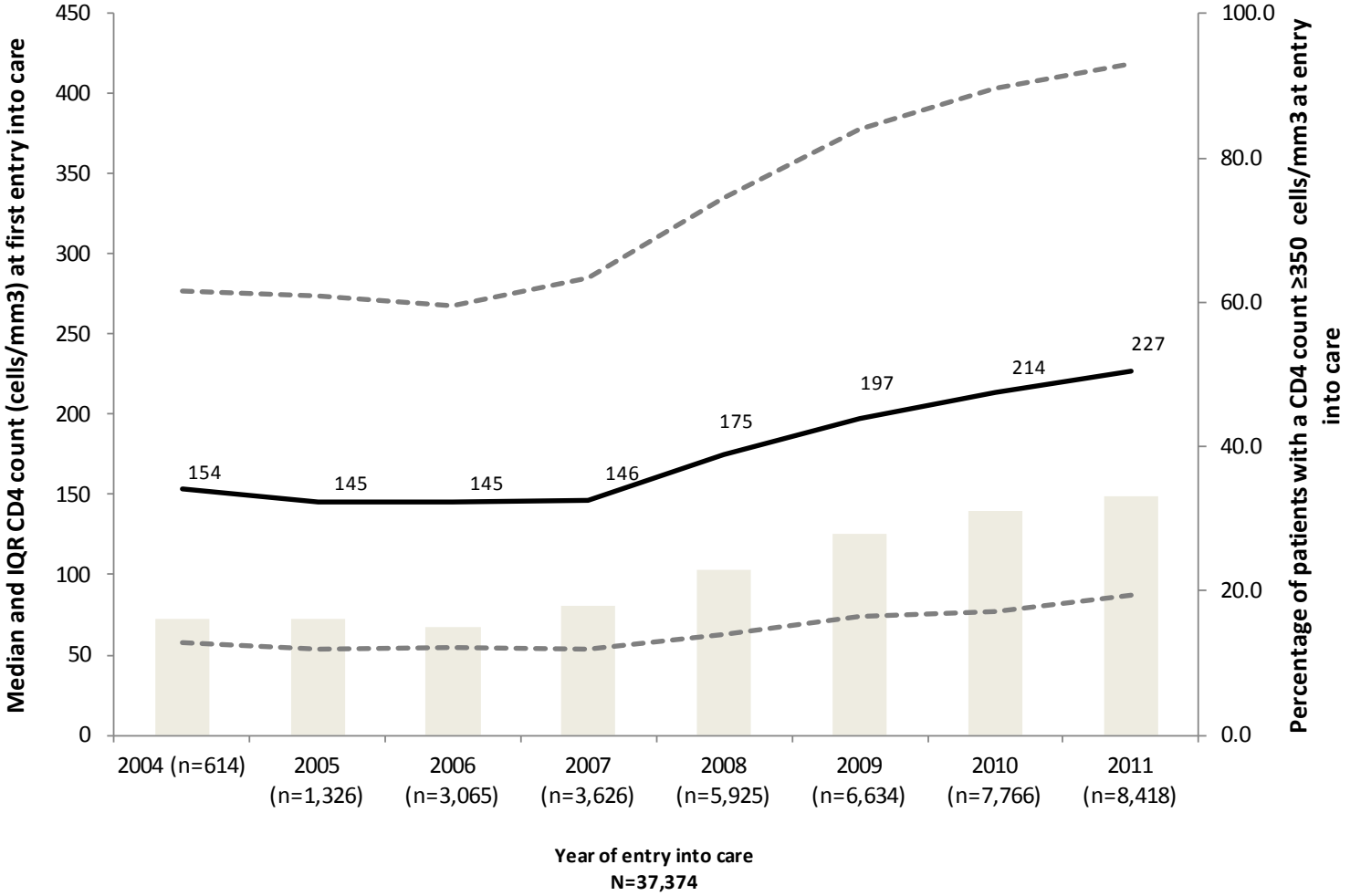

Figure 3. Median CD4+ and Interquartile Range at first entry into care and proportion of patients entering care with a CD4+ count >350 cells/µl, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2004-2011.

Table 2. Data on CD4+ T-Lymphocyte (CD4+) count at first presentation to care, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2004-2011

Characteristic	2004 (n=614)	2005 (n=1,326)	2006 (n=3,065)	2007 (n=3,626)	2008 (n=5,925)	2009 (n=6,634)	2010 (n=7,766)	2011 (n=8,418)	p - value
Total	154 (58-277)	145 (54-274)	145 (55-268)	146 (54-285)	175 (63-335)	197 (74-378)	214 (77-403)	227 (87-419)	<0.001
Sex									
Male	133 (51-270)	141 (48-274)	129 (49-252)	124 (47-258)	162 (56-315)	188 (70-368)	201 (71-387)	219 (83-413)	<0.001
Female	207 (137-296)	162 (79-278)	186 (76-308)	199 (87-367)	214 (94-388)	230 (89-409)	251 (109-461)	246 (103-445)	<0.001
Ethnicity									
Indigenous	205 (74-328)	202 (56-276)	157 (72-244)	148 (49-289)	145 (64-303)	142 (75-272)	147 (78-318)	204 (95-359)	0.21
Incarcerated	95 (43-271)	92 (28-213)	106 (33-235)	107 (26-243)	157 (62-324)	301 (107-499)	309 (167-444)	353 (174-518)	<0.001
State									
Distrito Federal	154 (63-263)	152 (67-279)	160 (70-284)	150 (60-272)	214 (88-346)	264 (114-452)	278 (114-449)	289 (126-488)	<0.001
Veracruz	161 (56-282)	121 (44-222)	109 (34-192)	112 (46-211)	146 (49-293)	181 (60-345)	180 (66-361)	197 (63-372)	<0.001
Mexico	302 (111-472)	131 (46-261)	82 (38-208)	115 (37-262)	150 (49-315)	209 (79-368)	202 (73-389)	211 (91-432)	<0.001
Jalisco	127 (35-265)	147 (51-296)	123 (49-248)	165 (63-284)	203 (71-393)	167 (56-395)	182 (64-409)	194 (76-378)	<0.001
Chiapas	222 (152-342)	188 (86-299)	142 (67-283)	150 (83-259)	136 (57-277)	139 (55-272)	167 (58-343)	189 (75-357)	<0.001
Baja California	120 (58-142)	194 (110-268)	200 (56-359)	199 (87-341)	176 (77-335)	191 (74-421)	250 (81-465)	200 (75.5-378)	0.42
Tabasco	164 (48-340)	231 (92-472)	208 (51-543)	172 (99-371)	164 (45-287)	130 (46-278)	205 (87-357)	254 (108-465)	<0.001
Guerrero	306 (244-368)	302 (175-412)	200 (85-310)	178 (92-311)	216 (99-371)	261 (128-445)	306 (154-524)	304 (161-502)	<0.001
Tamaulipas	142 (13-271)	211 (48-360)	186 (64-290)	162 (68-255)	164 (87-323)	200 (60-381)	202 (76-377)	208 (68-404)	0.34
Other States	105 (44-253)	131 (44-254)	157 (59-281)	149 (51-321)	181 (65-353)	184 (69-364)	205 (73-398)	219 (80-412)	<0.001

CD4+ results indicate median (IQR) unless otherwise specified
p-values were obtained using the non-parametric Kruskal-Wallis test for trend

Table 3. Predictors of Late Presentation (CD4+ <200 cells/µl), Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2004-2011

Predictors of LP	cOR (95% CI)	aOR (95% CI)	p-value
Age (30-49 referent)			
18-29	0.48 (0.46-0.50)	0.49 (0.46-0.51)	<0.001
50-70	1.1 (1.02-1.17	1.13 (1.05-1.22)	<0.001
70 or older	0.84 (0.63-1.20)	0.71 (0.52-0.97)	0.03
Sex			
Male	1.41 (1.34-1.49)	1.43 (1.31-1.56)	<0.001
Ethnicity			
Indigenous	1.31 (1.14-1.49)		
Incarcerated			
	1.12 (1.02-1.23)	0.78 (0.69-0.86)	<0.001
Period of entry to care (referent=2011)			
2004	1.81 (1.53-2.14)	1.63 (1.35-1.98)	0.07
2005	1.91 (1.70-2.15)	1.7 (1.49-1.95)	0.001
2006	1.98 (1.8-2.16)	1.86 (1.69-2.04)	<0.001
2007	1.91 (1.76-2.06)	1.71 (1.57-1.86)	<0.001
2008	1.41 (1.32-1.51)	1.37 (1.28-1.47)	0.37
2009	1.9 (1.12-1.18)	1.2 (1.1-1.8)	<0.001
2010	1.08 (1.01-1.5)	1.07 (1-1.15)	<0.001
Viral Load			
Log10 HIV-1 RNA	1.64 (1.6-1.67)	1.68 (1.65-1.72)	<0.001
Institution			
CAPASITS	0.79 (0.74-0.80)	0.81 (0.76-0.86)	<0.001
State			
Distrito Federal	0.73 (0.69-0.78)		0.004
Veracruz	1.37 (1.28-1.46)	1.21 (1.05-1.4)	0.009
Mexico	1.09 (1.01-1.17)	1.07 (0.89-1.28)	0.46
Jalisco	1.08 (0.99-1.18)	0.92 (0.73-1.17)	0.5
Chiapas	1.23 (1.11-1.36)	1.14 (0.94-1.38)	0.18
Baja California	0.89 (0.80-0.99)	0.88 (0.7-1.1)	0.25
Tabasco	0.95 (0.86-1.06)	0.78 (0.62-0.98)	0.03
Guerrero	0.58 (0.51-0.65)	0.66 (0.51-0.85)	0.001
Tamaulipas	0.94 (0.84-1.06)	1.11 (0.88-1.4)	0.37
Interaction			
Indigenous-Male		1.24 (1.03-1.48)	0.02
Indigenous-Female		0.84 (0.65-1.08)	0.17
DF-Male		0.62 (0.57 - 0.67)	<0.001
DF-Females		1.35 (1.1-1.66)	0.0043

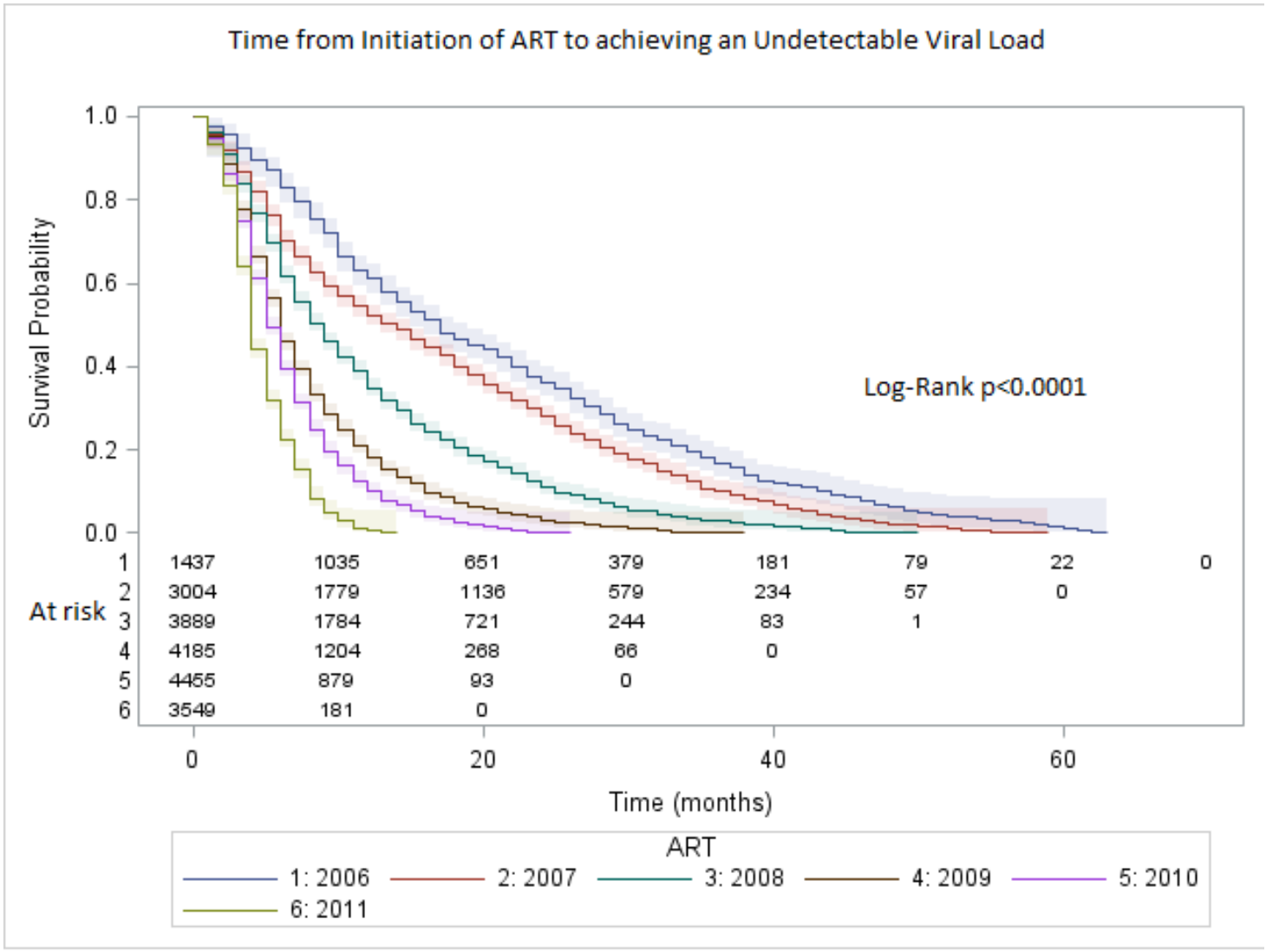

Figure 4. Kaplan Meier survival estimates from initiation of ART to achieving a serum HIV-1 RNA <50 copies/µl by year of treatment, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2006-2011.

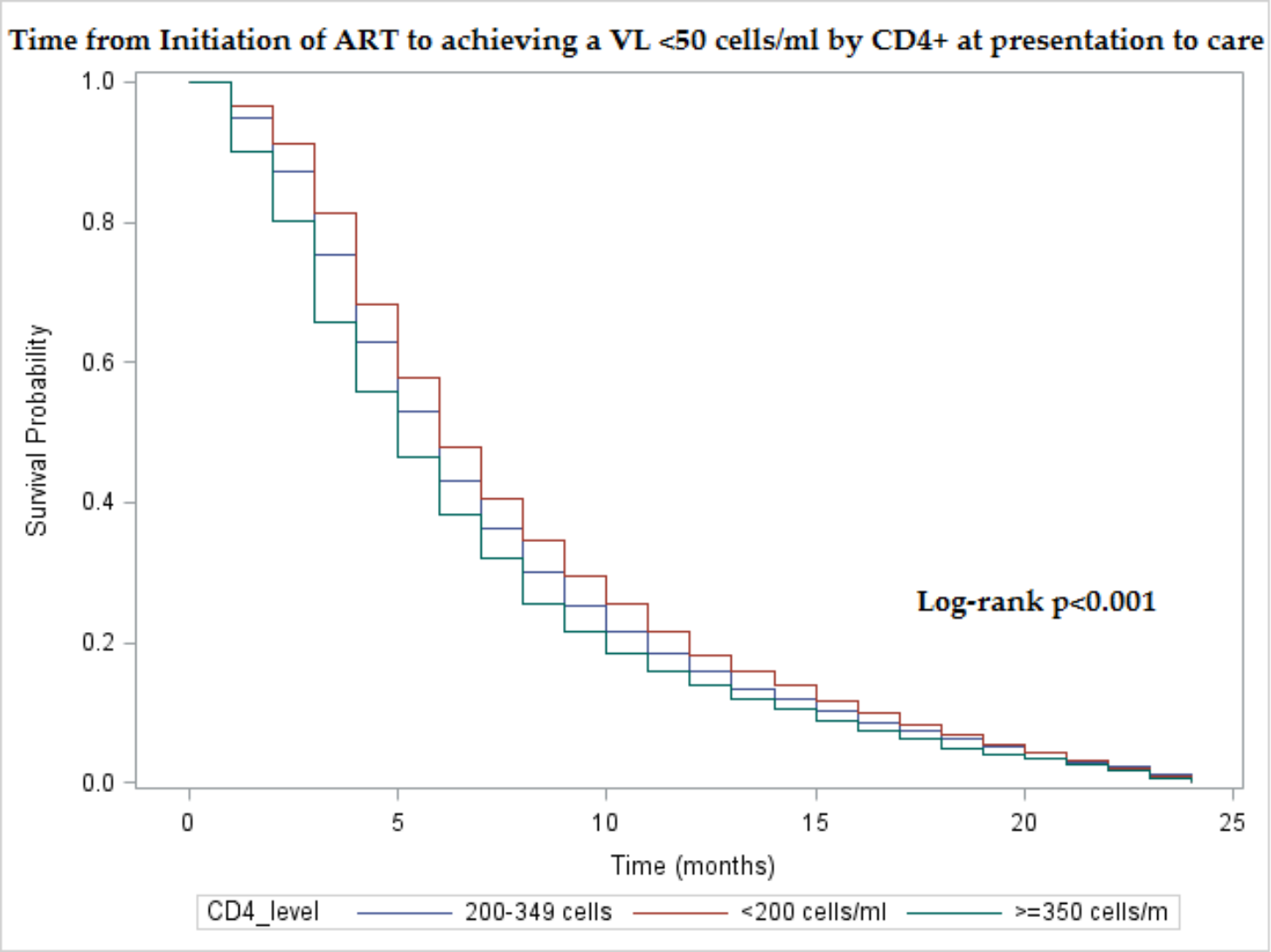

Figure 5. Time (months) from initiation of ART to achieving a serum HIV-1 RNA <50 copies/µl by CD4+ at entry into care, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2006-2011.

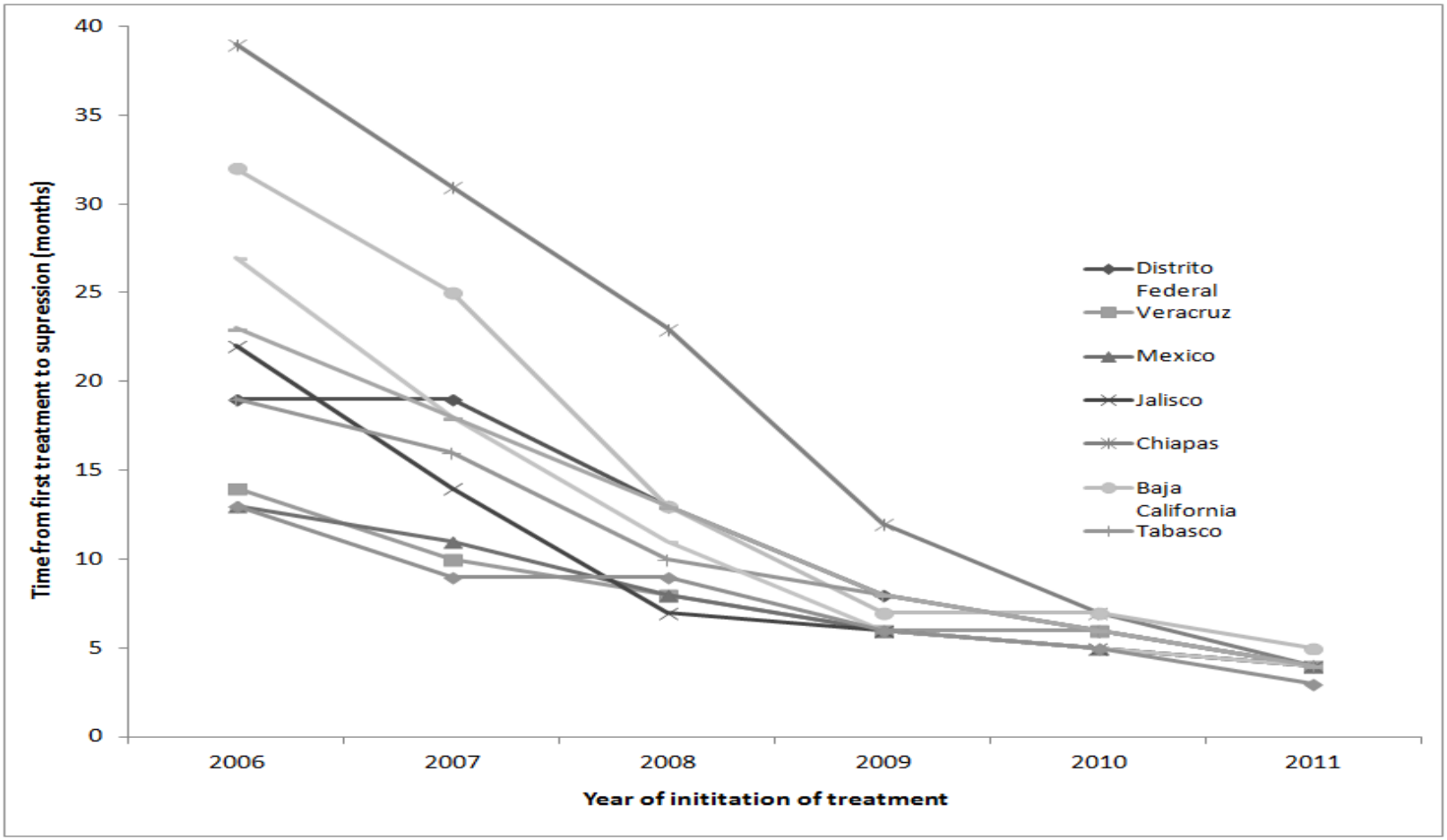

Figure 6. Mean time (months) from initiation of ART to achieving a serum HIV-1 RNA <200 copies/µl by year of treatment, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2006-2011.

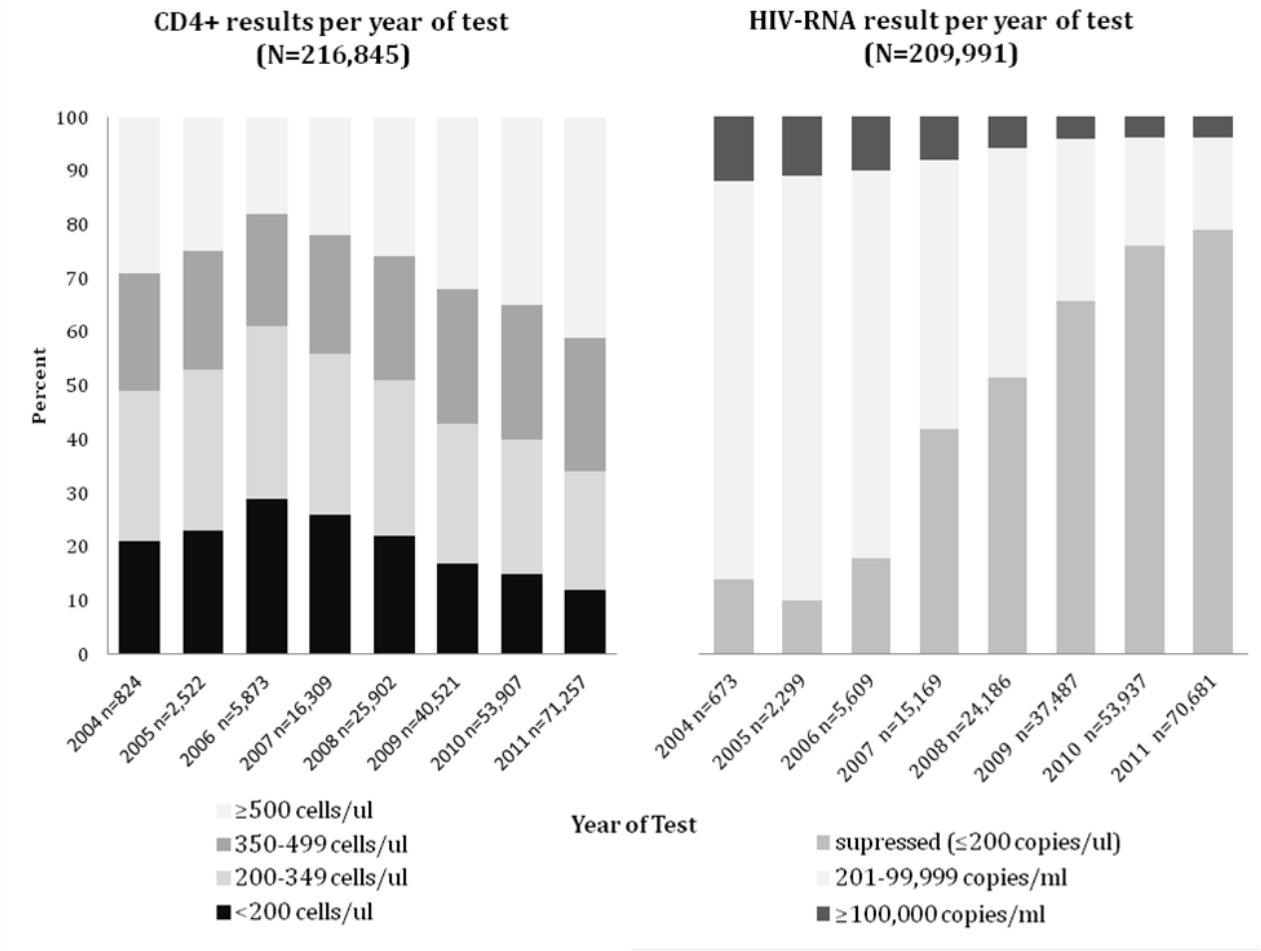

Figure 7. CD4+ and HIV-1 RNA test results per year excluding new patients, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2006-2011.

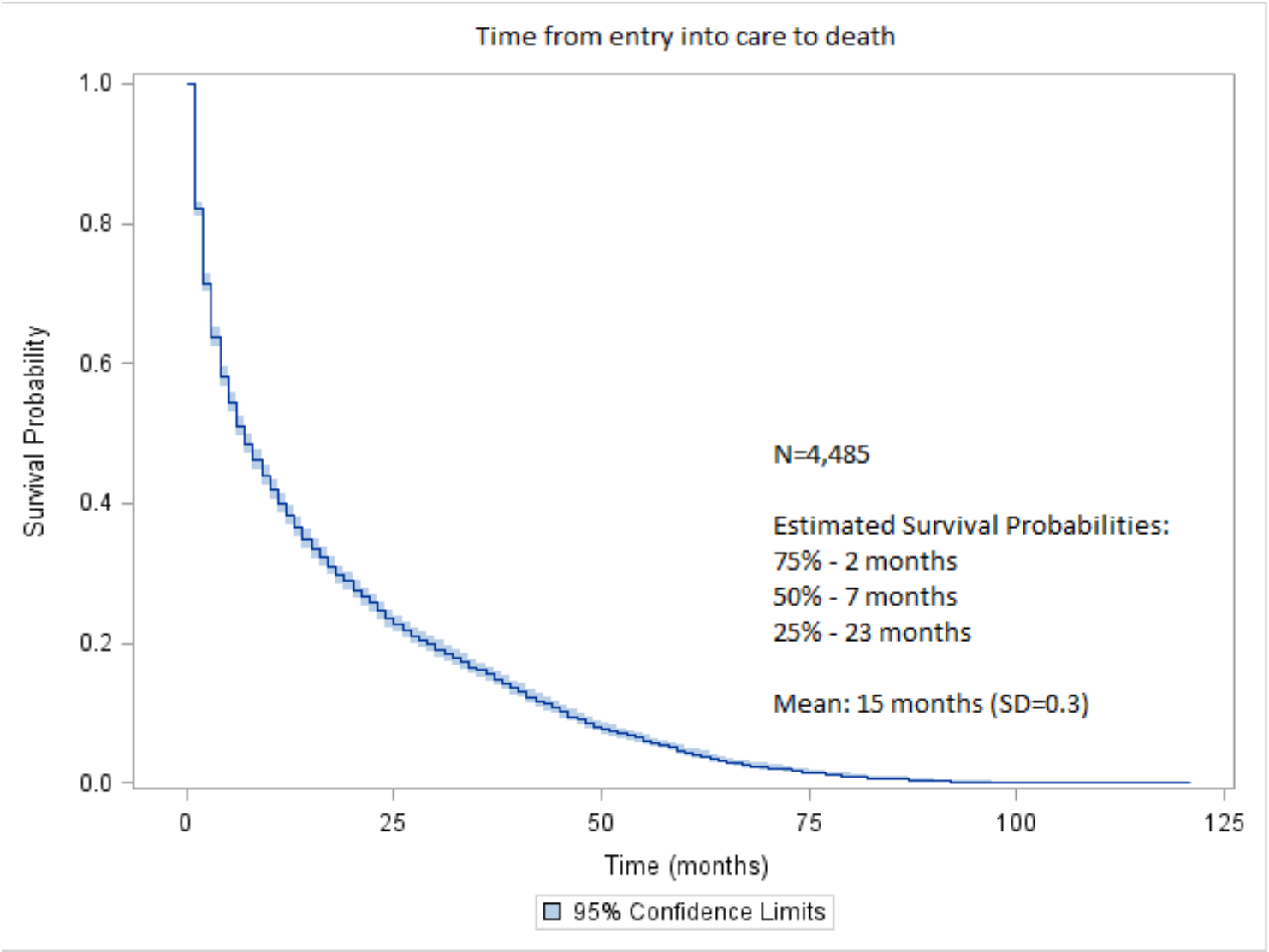

Figure 8. Time from entry into care to death, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2006-2011.

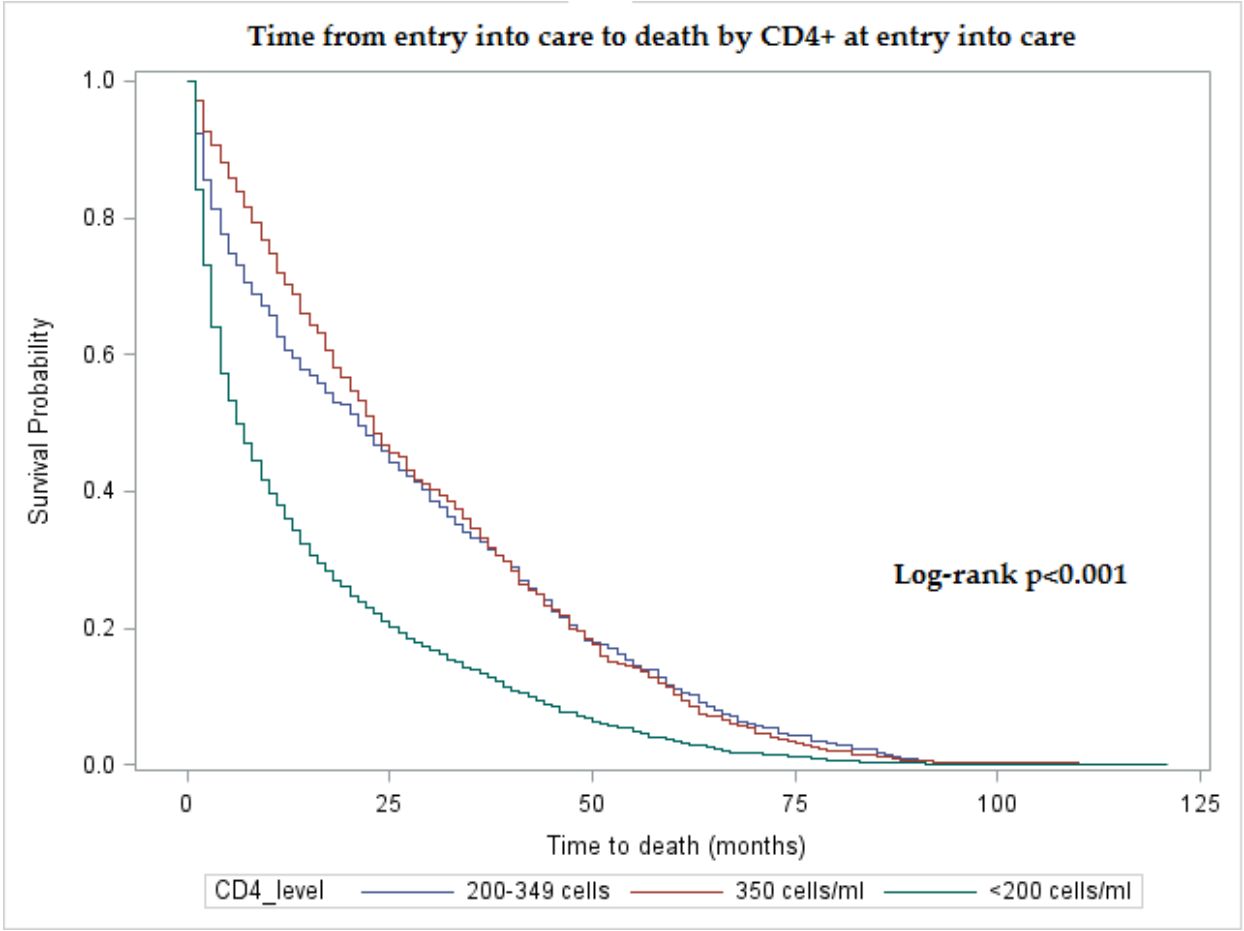

Figure 9. Time from entry into care to death by CD4+level at entry into care, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2006-2011.

Table 4. Immunologic and Virologic characteristics of deceased patients at last visit, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2006-2011.

Characteristics	n (%)	CD4+ T-lymphocyte cells/µl, Median (IQR)	Log10(HIV-1 RNA) copies/µl, Median (IQR)
Total	5,426 (9)	83 (30-207)	4.87 (2.85-5)
Sex			
Male	4,416 (9)	84 (30-205)	4.87 (2.81-5)
Female	1,010 (7)	83 (30-209)	4.85 (3.11-50)
Ethnicity			
Indigenous	129 (7)	77 (38-234)	5 (2.85-5)
Incarcerated	96(2)	108 (30-206)	4.85 (2.83-5)
State			
Distrito Federal	771 (8)	108 (42-245)	4.89 (2.6-5)
Veracruz	834 (12)	67 (22-170)	4.68 (3.05-5)
Mexico	312 (6)	75 (29-194)	4.98 (2.38-5)
Jalisco	117 (3)	84 (36-240)	4.59 (2.12-5)
Chiapas	273 (9)	68 (29-189)	5 (3.27-5)
Baja California	354 (13)	122 (36-214)	4.87 (2.91-5)
Tabasco	164 (7)	103 (41-246)	4.86 (3.11-5)
Guerrero	415 (18)	124 (56-264)	4.10 (2.13-5)
Tamaulipas	206 (9)	79 (31-223)	4.89 (2.83-5)
Other States	1980 (8)	74 (27-194)	4.96 (3.19-5)

Table 5. Data on CD4+ T-Lymphocyte (CD4+) count stratified by follow-up status, Administration, Logistics and Surveillance System of Antiretroviral Drugs (Sistema de Administracion, Logistica y Vigilancia de Medicamentos ARV; SALVAR), 2004-2011

	Lost to follow-up			Cohort			p-value
Characteristic	n (%)	CD4+ T-lymphocyte cells/μl	log10(HIV-1 RNA) copies/μl	n (%)	CD4+ T-lymphocyte cells/μl	log10(HIV-1 RNA) copies/μl	
Total	12,999(25)	264 (107-454)	3.81 (2.18-4.98)	39,744(75)	354 (214-529)	1.90 (1.7-3.76)	<0.001
Sex							
Male	9890 (25)	252 (98-442)	3.88 (2.07-4.78)	30,526(75)	345 (207-518)	1.85 (1.7-3.78)	<0.001
Female	3109 (25)	298 (144-491)	3.64 (2.48-4.78)	9,218(75)	383 (238-562)	2.12 (1.7-3.7)	<0.001
Ethnicity							
Indigenous	395 (26)	272 (119)	4.18 (2.04-5)	1,131(74)	386 (238-539)	1.7 (1.7-3.25)	<0.001
Incarcerated	2232 (65)	180 (60-352)	4.28 (2.6-5)	1,210(35)	359 (214-529)	2.49 (1.7-4.18)	<0.001
State							
Distrito Federal	1803 (22)	310 (131-500)	4.16 (2.42-5)	6,529(78)	386 (247-556)	1.84 (1.7-4.04)	<0.001
Veracruz	1557 (27)	229 (82-406)	3.7 (2.45-4.8)	4,280(73)	317 (186-489)	1.81 (1.7-3.61)	<0.001
Mexico	848 (19)	252 (87-428)	4.06 (1.7-5)	3,692(81)	361 (222-525)	1.7 (1.7-3.65)	<0.001
Jalisco	1200 (31)	240 (89-459)	2.75 (1.7-4.84)	2,639(69)	368 (215-552)	1.7 (1.7-2.7)	<0.001
Chiapas	618 (25)	205 (76-346)	4.56 (2.6-5)	1,855(75)	286 (173-444)	2.6 (2.6-4.35)	<0.001
Baja California	810 (38)	312 (164-495)	3.4 (2.55-4.75)	1,309(62)	371 (219-559)	2.6 (1.7-3.98)	<0.001
Tabasco	509 (24)	217 (81-418)	4.25 (2.45-5)	1,597(76)	338 (199-515)	1.77 (1.7-4.29)	<0.001
Guerrero	252 (14)	365 (173-509)	3.27 (1.7-4.48)	1,546(86)	438 (294-636)	1.7 (1.7-3.08)	<0.001
Tamaulipas	569 (31)	242 (115-423)	3.89 (2.22-4.48)	1,289(69)	316 (188-473)	2.11 (1.7-4.05)	<0.001
Other States	4833 (24)	271 (112-462)	3.73 (2.49-4.93)	15,008(76)	350 (210-526)	2.29 (1.7-3.76)	<0.001
p-value shows significance values for the comparison of CD4 values using the Wilcoxon rank test							