

# Virologic failure in people living with HIV in 1st line ART: A 10-year Mexican population-based study

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Amilcar Azamar-Alonso, PhD(c)<sup>1,2</sup> , Lawrence Mbugbaw, MD, MPH, PhD<sup>1,3</sup>, Fiona Smail, MBChB<sup>4</sup> , Sergio A Bautista-Arredondo, MSc<sup>5</sup>, Andrew P Costa, PhD<sup>1,6,7</sup> and Jean-Eric Tarride, PhD<sup>1,6,8,9</sup>

## Abstract

**Background:** In Mexico, the number of people living with HIV (PLWH) receiving antiretroviral therapy (ART) has increased in the last 20 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 (Human immunodeficiency virus), Antiretroviral Therapy, Location, North America, Other, Prevention, Viral disease

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## 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.<sup>1,2</sup> 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.<sup>1–5</sup> 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.<sup>6,7</sup>

In Mexico, the number of PLWH receiving ART has increased in the last 20 years due to different public policies focused on expanding access to ART. Starting in 2007, Mexico launched a major initiative to provide universal

<sup>1</sup> Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

<sup>2</sup> Gilead Sciences Inc., Foster City, CA, United States

<sup>3</sup> Biostatistics Unit, Father Sean O'Sullivan Research Centre, Hamilton, ON, Canada

<sup>4</sup> ChB Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada

<sup>5</sup> Center for Health Systems Research, National Institute of Public Health, Cuernavaca, Mexico

<sup>6</sup> Centre for Health Economics and Policy Analysis, McMaster University, Hamilton, Ontario, Canada

<sup>7</sup> Department of Medicine, McMaster University, Hamilton, Ontario, Canada

<sup>8</sup> The Research Institute of St Joe's Hamilton, Hamilton, ON, Canada

<sup>9</sup> McMaster Chair in Health Technology Management Hamilton, Hamilton, ON, Canada

## Corresponding author:

Amilcar Azamar-Alonso, Department of Health Research Methods, Evidence, and Impact, CRL 201, McMaster University Main St West Hamilton, ON, Canada L8S 4K1.

Email: [azamaraa@mcmaster.ca](mailto:azamaraa@mcmaster.ca)

access to ART conditional on several clinical criteria including CD4 counts  $\leq 200$  cells/mm<sup>3</sup> and the presence of risk symptoms.<sup>8</sup> Following the World Health Organization (WHO) recommendations for early treatment initiation of PLWH in June 2013,<sup>9</sup> a major policy change 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.<sup>10,11</sup> 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<sup>12,13</sup> Clinical and observational studies have shown that maintaining VL under that threshold is a predictor of long-term health outcomes<sup>14</sup> Although VL is an important measure of disease progression, likelihood of transmission, and mortality,<sup>15</sup> as a policy measure, it is also important to document virologic failure (VF) following first 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.<sup>16–18</sup>

While an early study conducted in a third-level hospital in Mexico City in 2010 found that the probability of VF was 20% at 48 months after ART initiation and was higher among youth (individuals younger than 30 years old),<sup>14</sup> 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 first 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.<sup>15</sup> 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 not until 2008 that the system was fully implemented nationwide. Currently, it contains information on more than 140,000 PLWH on ART.<sup>16</sup>

### Study population

For this analysis, we included adults (18 years old and older) living with HIV who received their first ART after January 1<sup>st</sup>, 2008 and before September 1<sup>st</sup>, 2017. Given the purpose of the analysis, we only considered patients that had completed at least 12 weeks of follow-up,<sup>9,19</sup> 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 first line ART treatment initiation. As per the Mexican clinical guidelines definition,<sup>17</sup> VF was determined by one of the following two criteria: 1) individuals without a reduction of at least one log<sub>10</sub> of VL count at week eight compared to baseline information; and 2) individuals who had reduced at least one log<sub>10</sub> within the first 8 weeks, but after 6 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 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 as well as switches in ART treatments. Patients changing their first 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<sup>20</sup> 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<sup>21</sup> was assigned to the location of each health facility where PLWH were treated to reflect social and economic differences among health facilities.<sup>1</sup>

In terms of biologic measures, CD4 cell count at first line ART treatment initiation was divided into two groups by CD4 count lower than 200 cells/mm<sup>3</sup> and higher or equal to 200 cells/mm<sup>3</sup>, based on prior evidence of an association of CD4 count with VF.<sup>22</sup> 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.<sup>23</sup> We also grouped ART as the three most used and representative first 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 first line ART in SALVAR). Although today integrase inhibitors are an important treatment option for PLWH, their use represented less than 2% of total first line ART from 2008 to 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 (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-fit of the logistic models was estimated using the c-statistic.

## Results

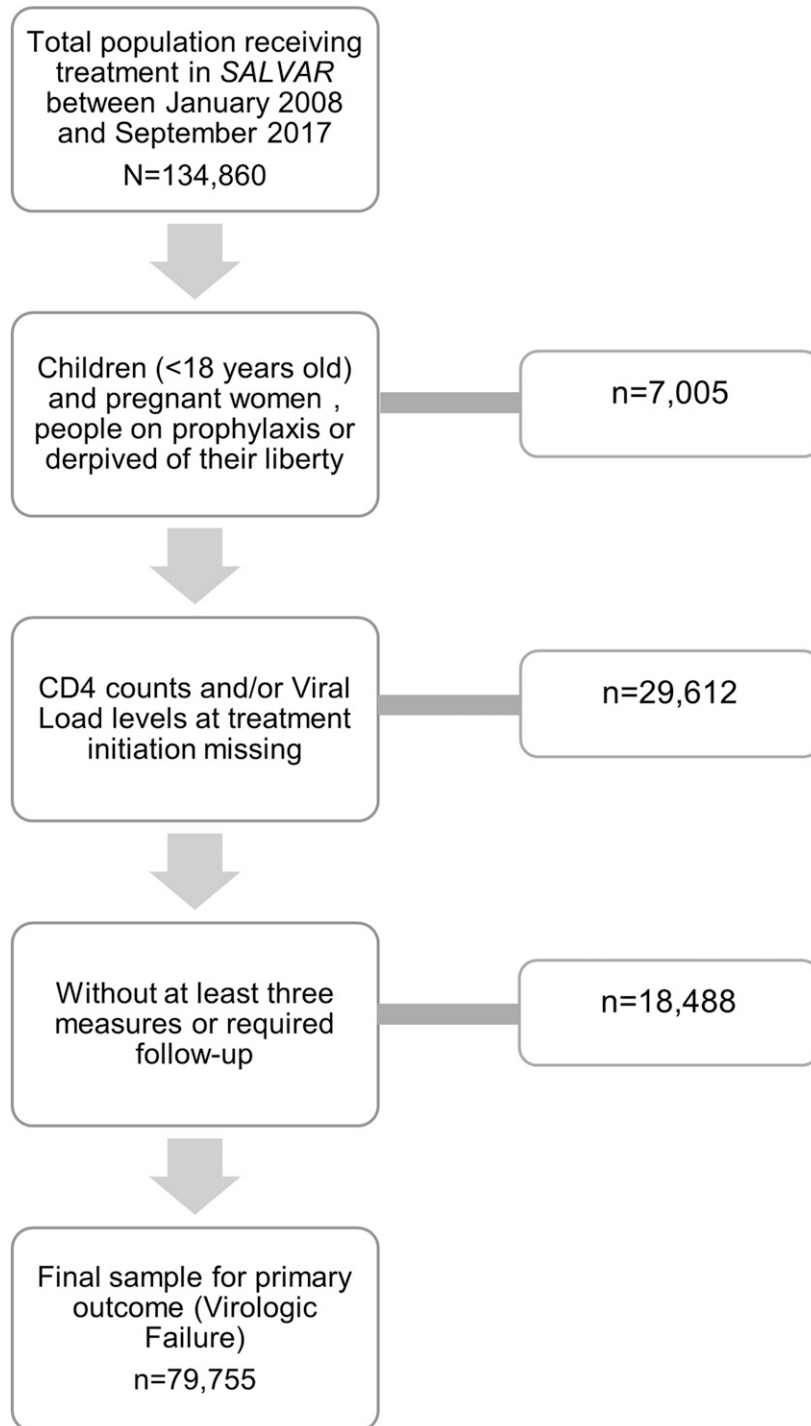
### Study population

SALVAR dataset contains information about first line ART of 134,860 individuals during January 2008 and September 2017. Of those, 7005 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.

Comparing both periods, the age at treatment initiation was lower after 2014 (mean 34.8 vs 33.2 yo), there were fewer females (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 fewer 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<sup>3</sup> was higher during 2014–2017 (12%) compared with 2008–2013 (7%). The same was seen for individuals with VL  $\geq 100,000$  copies/mL, although the mean log<sub>10</sub> 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 one 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.

### 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.



**Figure 1.** Sample Flow for Analysis.

### 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  $CD4 \geq 200$  cells/mm<sup>3</sup> (0.89 [95% CI: 0.85, 0.94]). In contrast, having initiated treatment in a different region than Mexico City (1.48 [95% CI: 1.36, 1.62] compared to Central East, having a first ART other than EFV/FTC/TDF (e.g., 1.22 [95% CI: 1.16, 1.28] for EFV+ABC/3TC)

**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 $\pm$ SD	33.99 $\pm$ 10.26	34.77 $\pm$ 10.21	33.24 $\pm$ 10.24	<0.001
Median (IQR)	32 [26–40]	33 [27–41]	31 [25–39]	
%				
18–29 yo	39	35	44	<0.001
30–39 yo	34	36	32	
40–49 yo	18	20	16	
50–59 yo	7	2	6	
$\geq$ 60 yo	2	7	2	
Gender (%)				
Male	80	79	82	<0.001
Female	19	20	17	
Transgender	1	1	1	
Health facility (%)				
Hospital/Clinic/National institute	21	24	18	<0.001
CAPASITS	65	62	67	
Specialized clinics CONDESA	14	14	15	
Region (%)				
Mexico City	19	20	18	<0.001
Central East	31	31	31	
Central West	14	15	13	
Northeast	12	12	11	
Northwest	8	8	9	
South	16	14	18	
Marginality index (%)				
High	2	2	2	0.135
Medium	1	1	1	
Low	97	97	97	
Bio-markers				
CD4				
Mean $\pm$ SD	289.74 $\pm$ 230.78	268.80 $\pm$ 218.31	308.98 $\pm$ 240.07	<0.001
Median (IQR)	250 [110–407]	230 [104–372]	271 [117–442]	
<200 cells/mm <sup>3</sup> (%)	10	7	12	<0.001
$\geq$ 200 cells/mm <sup>3</sup> (%)	90	93	88	
VL				
Mean $\pm$ SD	4.19 $\pm$ 1.42	4.06 $\pm$ 1.47	4.31 $\pm$ 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
$\geq$ 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 $\pm$ SD	42.96 $\pm$ 97.9	44.09 $\pm$ 94.52	41.92 $\pm$ 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

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

ART option	Period of analysis			p-value
	2008–2017	2008–2013	2014–2017	
Total 1 <sup>st</sup> 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: Antiretroviral therapy. EFV/FTC/TDF: Emtricitabine, tenofovir, efavirenz; EFV+ABC/3TC: Abacavir, lamivudine, efavirenz

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 regimens, reduced the likelihood of VF during 2014–2017 but not before. Finally, for CD4, the OR direction changed for being diagnosed with CD4  $\geq 200$  cells/mm<sup>3</sup>, increasing marginally the odds of VF in the period 2014–2017 compared with 2008–2013 (See Table 3).

## Discussion

Based on 10 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  $\leq 200$  cells/mm<sup>3</sup>). Compared to the 2007–2013 period, individuals treated during 2014–2017 were younger, a higher proportion was male, more were initially treated in CAPASITS, a higher proportion were in the South of Mexico, and (as expected) with baseline CD4 was higher, compared to the period 2008–2013. The proportion of individuals with VF decreased from 50% in 2008–2013 to 33% in 2014–2017, 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<sup>24,25</sup> and changes into a more integrated and centralized approach to HIV treatment and care in Mexico,<sup>10</sup> 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.<sup>10,26</sup>

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.<sup>27</sup> Our results showing a higher likelihood of VF among female are consistent with the results showed by Mata-Marín et al.<sup>28</sup> 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,<sup>29–31</sup> where the older population had a lower risk of VF, possibly explained by 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  $\geq 200$  cells/mm<sup>3</sup> 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.<sup>32–35</sup> 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 1.01–1.15). 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<sup>36</sup> which could

**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 <sup>3</sup> )			
CD4≥200 cells/mm <sup>3</sup>	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]

(continued)



**Table 3.** (continued)

Variable	Virologic failure		
	OR All periods	OR 2008–2013	OR 2014–2017
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: Antiretroviral therapy. EFV/FTC/TDF: Emtricitabine, tenofovir, efavirenz; EFV+ABC/3TC: Abacavir, lamivudine, efavirenz.

be the case for those PLWH with higher CD4 count (fewer symptoms and warning signs for disease progression)<sup>36,37</sup> 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.<sup>37</sup> In contrast, lower VL levels at treatment initiation are associated with better prognosis and successful viral responses.<sup>32</sup> 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.<sup>38,39</sup> When observing the stratified analysis for VF, our results are similar to a previous analysis concerning Mexican regions and different periods.<sup>26</sup> 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,<sup>40</sup> as well as an expansion of the Mexican health system.<sup>10</sup> 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 29,000 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.<sup>41,42</sup> Some studies have shown that two of the main determinants of non-adherence are access to ART and financial constraints.<sup>43,44</sup> However, the Mexican government started providing free treatment to all PLWH in 2003.<sup>40</sup> 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 first 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.<sup>45</sup> 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 a 10 year 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 deeper understanding of VF determinants.

## Conclusion

This study indicates that, by removing threshold levels of CD4 required for treatment initiation in Mexico, combined with an expansion of ART access through provision of 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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## ORCID iDs

Amilcar Azamar-Alonso  <https://orcid.org/0000-0002-0398-3896>  
Fiona Smail  <https://orcid.org/0000-0002-1305-6260>

## Notes

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)

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