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RESEARCH ARTICLE

Highly active antiretroviral therapy discontinuation time is associated with therapeutic failure among human immunodeficiency virus (HIV)-infected immigrant adults: A cohort study from a Peruvian referral hospital during the Venezuelan exodus

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Abstract

Objective: To evaluate the association between Highly Active Antiretroviral Therapy (HAART) discontinuation time and therapeutic failure (TF) in Venezuelan immigrants with HIV that restart HAART.

Methods: We carried out a retrospective cohort study in a large hospital in Peru. We included Venezuelan immigrants who restarted HAART and were followed over at least 6 months. The primary outcome was TF. Secondary outcomes were immunologic (IF), virologic (VF) and clinical (CF) failures. The exposure variable was HAART discontinuation, categorised as no discontinuation, less than 6 months, and 6 months or more. We applied generalised linear models Poisson family with robust standard errors to calculate crude (cRR) and adjusted (aRR) relative risks by statistical and epidemiological criteria.

Results: We included 294 patients, 97.2% were males, and the median age was 32 years. Out of all the patients, 32.7% discontinued HAART for less than 6 months, 15.0% discontinued for more than 6 months and the remaining 52.3% did not discontinue. The cumulative incidence of TF was 27.9%, 24.5% in VF, 6.0% in IF and 6.0% in CF. Compared with non-discontinued HAART patients, the discontinuation for less than 6 months (aRR = 1.98 [95% CI: 1.27–3.09]) and from 6 months to more (aRR = 3.17 [95% CI: 2.02–4.95]) increased the risk of TF. Likewise, treatment discontinuation of up to 6 months (aRR = 2.32 [95% CI: 1.40–3.84]) and from 6 months to more (aRR = 3.93 [95% CI: 2.39–6.45]) increased the risk of VF.

Conclusions: HAART discontinuation increases the probability of TF and VF in Venezuelan immigrants.

KEYWORDS
emigrants and immigrants, highly active antiretroviral therapy, HIV, Peru, treatment failure

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a public health problem, particularly in low- and middle-income countries (LMICs) [1, 2]. In Peru, 143,732 cases of HIV infection were reported between January 1983

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and September 2021 [3]. HIV infection increases the morbidity and mortality burden in healthcare services [1, 2, 4, 5]. In this sense, infection control is a priority in the health agendas of the LMICs, where highly active antiretroviral therapy (HAART) plays a crucial role [5, 6]. Although HAART has led to considerable improvements in several clinical outcomes, failure can occur, leading to therapeutic resistance [7]. Consequently, the study of HAART failure in these patients is highly relevant [7].

Therapeutic failure (TF) is one of the negative outcomes in the comprehensive management of HIV. It is composed of three elements: clinical (CF), immunological (IF) and virologic failure (VF) [8]. Variables that may be associated with TF include individual, social and clinical variables [4]. Among the individual factors, having psychiatric comorbidity, coinfection with tuberculosis, anaemia and substance use, among others, increases the risk of failure [9]. In addition, a critical component is socioeconomic factors, including lack of social support, unstable housing and migratory status [10]. Within the clinical characteristics, the TF is associated with tuberculosis coinfection, late-stage HIV, low CD4 levels and high viral load (VL) levels, poor adherence and treatment discontinuation stand out [9–11]. Added to these conditions, having immigrant status worsens the outcome [12]. Even in high-income countries, immigrants face several barriers that are translated into poor adherence to treatment, late presentation and loss of follow-up, situations that pose an increased risk of TF [13, 14]. Consequently, the discontinuation of HAART arouses a particular interest that requires an even more unique approach to the migrant population.

The discontinuation of HAART has a detrimental impact on the evolution of HIV infection. It has been described that the migrant population has a higher probability of developing TF associated with various factors, among which discontinuation is one of the most significant [15, 16]. Most migrant populations are considered vulnerable owing to discrimination, linguistic and cultural barriers, and lack of access to HIV-related information [12]. Indeed, migration in Latin America (LATAM) has increased considerably in recent years for political, economic and social issues [17]. The Venezuelan humanitarian exodus has been the largest ever reported in LATAM, encompassing over 6 million Venezuelans who have left their country due to economic and political crises [18]. Hence understanding their health needs is relevant not only to Peru but to the LATAM region as a whole [18, 19]. Nonetheless, Peru has been one of the main final destinations of this immigration [20]. In that sense, as of September 2019, 850,000 Venezuelan foreigners were residing in Peru [21], thereby impacting the country's healthcare system. Hence, our study aimed to assess the association between HAART discontinuation time and TF in Venezuelan immigrant HIV-infected adult patients in a large referral Peruvian hospital.

METHODS

Study design and setting

We carried out a retrospective study based on a cohort of Venezuelan patients who attended the Hospital Nacional Arzobispo Loayza (HNAL, from the Spanish acronym) outpatient department between January 2014 and December 2018, after which they restarted HAART. The HNAL is a reference healthcare centre of the Ministry of Health (MINSA, from the Spanish acronym) located in Lima, Peru. This hospital is one of the national reference centres in terms of HAART and treats patients affiliated with the Integrated Health Assurance. The programme for HIV encompasses 4959 patients. It is also one of the hospitals that provide access to health services to Venezuelan immigrants.

Population, sample and sampling

We included HIV-infected Venezuelan immigrant patients who attended outpatient consultation in HNAL between 2014 and 2018 to restart HAART with a minimum of 1 year of follow-up and with two measurements of CD4 and VL levels. We excluded pregnant women and patients who had clinical records with incomplete data, did not return to the outpatient clinic for follow-up or had clinical records of cognitive impairment. Venezuelan nationality was verified through the hospital register in which patients carried either a passport, foreigner's card or temporary residence permit.

We employed a non-probabilistic sampling method, using consecutive cases and proportionally allocating them by year of study. The sample size was calculated with OpenEpi Version 3® (Andrew G. Dean and Kevin M. Sullivan, Atlanta, GA). Based on the report of 44.9% migrants with HIV that had TF, found by Saracino et al. [12], an adjusted risk ratio for tuberculosis of 1.51, a frequency of 20%, and an incidence of failure of 44.9%; we calculated a required minimum sample size of 264 patients. Yet, considering 10% of administrative error, the final estimated sample size requirement was 294 patients.

Outcome variable

The primary outcome variable was a TF, a binary variable that indicates whether the patient experienced one or more of the three independent secondary outcomes. CF, VF and IF, all of which were measured 6 months after restarting HAART. We evaluated them according to the definitions provided by the World Health Organisation (WHO) [8]. The secondary outcomes were defined as follows:

- IF was defined as persistent CD4 levels below 50 cells/mm^3 or CD4 levels decreased by 50% [8].

- VF was defined as plasma VL levels that are not suppressed to <1000 copies/mL 6 months after initiation of HAART or plasma VL levels, which have been undetectable, higher than 1000 copies/mL in two measurements taken at an interval of 4 weeks [8].
- CF was defined as the presence of a new event indicating immunodeficiency after 6 months of HAART [8].

Exposure variable

Therapeutic discontinuation was defined as the condition when the patient does not comply with treatment for more than 30 consecutive days or when transferred to another health facility without confirmation of receipt [2, 22]. We obtained it through the patients' self-reporting and categorised it into three groups: no discontinuation, discontinuation for less than 6 months and discontinuation for 6 months or more. Furthermore, such information was confirmed using medical records.

Control variables

We included demographic characteristics such as sex (male or female), age (18–29, 30–39, 40–49, 50–59), sexual orientation (heterosexual, homosexual or bisexual), education (complete primary, complete secondary, higher technical or university); also clinical variables such as comorbidities presented at the time of HAART restarting such as anaemia (yes/no), depression (yes/no), diabetes (yes/no), hypertension (yes/no) and BMI (low weight < 18.5, normal 18.5–24.9, overweight 25–29.9 or obesity ≥30). In addition, we collected information on the previous HAART regimen and restart regimen (first-line, second-line or other regimens).

Data collection

We obtained a list of all immigrant patients who attended the infectious disease department for HAART between 2014 and 2018. We requested and reviewed the clinical records and HAART records of each patient. In addition, we identified all Venezuelan immigrant patients who initiated consultation in the study period and had two CD4 and VL records. We collected the data between December 2018 and March 2019.

Statistical analysis

By double entry, we generated a database in Microsoft Office Excel 2016® (Microsoft Corporation, CA). After a quality control evaluation, the database was exported to STATA version 14.0® (Stata Corporation, College Station, TX) for further analysis.

We described categorical variables as absolute and percentages, and quantitative variables using median and interquartile ranges according to the normality evaluated by Shapiro–Wilk test. Moreover, we estimated the cumulative incidence of TF, VF, FI and CF in the entire sample between the years 2014 and 2018. The Person chi-square test was used to test the association of the categorical variables and the outcome, based on the expected values. In considering the association between numerical variables and TF, we used Student's t and Kruskal–Wallis test, depending on the normality evaluated with the Shapiro–Wilk test and the homogeneity of variances assessed by Levene's test.

We applied generalised linear models (GLM) Poisson family with robust standard errors (due to unmeasured within-cluster variability) to estimate crude (cRR) and adjusted relative risks (aRR), with their respective 95% confidence intervals (95% CI), for both the primary and secondary outcomes assessed. We considered a p-value of <0.05 statistically significant for the primary outcome and <0.025 for the secondary outcomes. We performed the adjusted statistical model with variables with a marginal association with a $p < 0.2$ in the bivariate analysis. Furthermore, we adjusted for epidemiological criteria, controlling for variables that met the classic confounding criteria: hypertension, diabetes mellitus and depression [23]. We used the Bonferroni correction for exploratory analyses.

Ethical considerations

The protocol was approved by the Ethics Committee of the Universidad Peruana de Ciencias Aplicadas (UPC) and the Teaching and Research Office of HNAL. During the design and execution of the study, we considered the ethical principles in research [24].

RESULTS

Study population

Of the 4959 patients in the programme of HIV attended between 2014 and 2018, 9.04% ($n = 399$) were Venezuelan. We sampled 298 of them, of which we excluded 4 because they were outside the age range. Therefore, we included 294 patients, which represents 73.6% of all Venezuelans living with HIV from the hospital registries (Figure 1).

General characteristics

The median age was 32 years, and 97.2% of the patients were male. In addition, 88.0% reported being homosexual or bisexual, and 54.7% had a university education. Of the patients who discontinued HAART, 32.7% did so for less than 6 months, 15.0% did so for more than 6 months, and

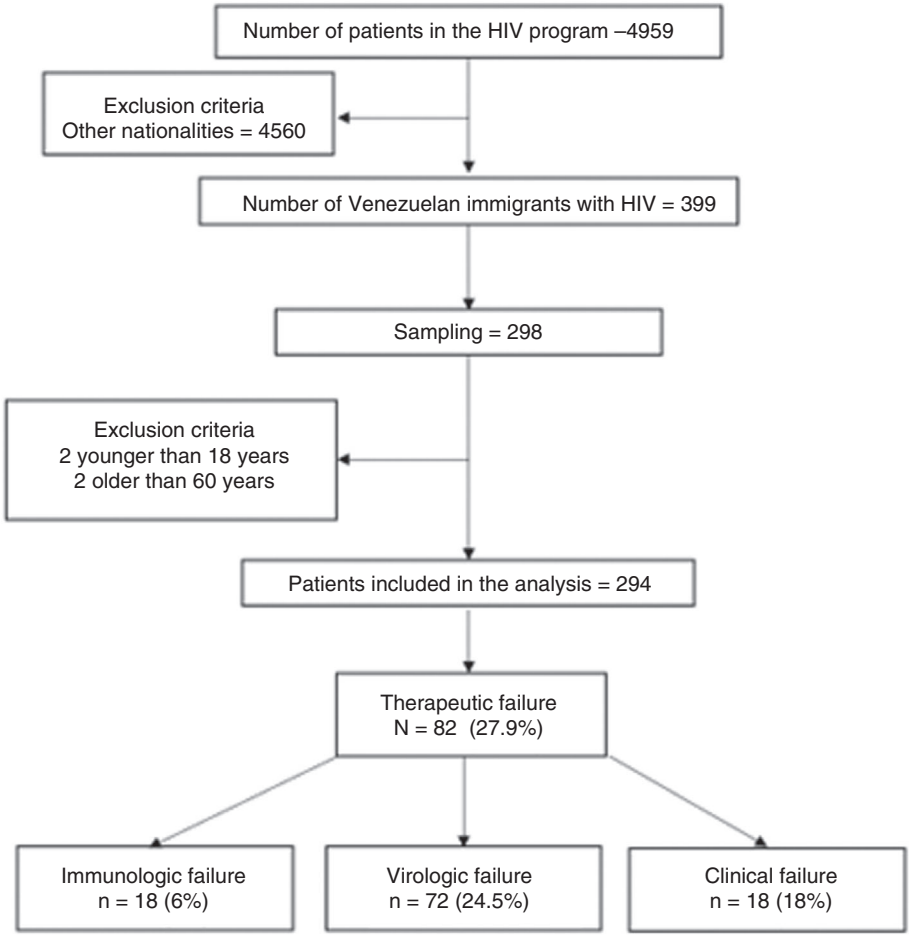

FIGURE 1 Flow chart of the patients included in the study.

the remaining 52.3% did not discontinue. At the time of analysis, all patients who had previously discontinued HAART had restarted their treatment. The cumulative incidence of TF in the entire sample was 27.9%, 24.5% in VF, 6.1% in IF and 6.1% in CF (Table 1).

Factors associated with treatment discontinuation

Of the patients who discontinued treatment, 32.8% of those who identified as homosexuals and bisexuals stopped treatment for less than 6 months, and 14.3% discontinued treatment for 6 months or more. More than half of the non-discontinued patients had a university education. The HAART scheme most frequently used by those who dropped out was the first-line scheme. The laboratory data analysis revealed that the baseline mean CD4 levels were significantly lower among individuals who discontinued HAART, either less than 6 months (415.2 cells/mm^3) or 6 months or more (428 cells/mm^3), in comparison to those who did not discontinue (558.8 cells/mm^3). VL levels were also significantly higher among those who stopped HAART than those who did not stop (Table 2).

Factors associated with therapeutic, virologic, immunologic and clinical failure

TF was significantly associated with the duration of discontinuation. TF occurred in 33.3% of patients who discontinued treatment for less than 6 months and 54.5% of those who stopped treatment for 6 months or more, while in those who did not discontinue treatment, it occurred in 16.9%. Moreover, TF was marginally associated with BMI and diabetes mellitus. Regarding VF, it was significantly related to the time of discontinuation and diabetes mellitus. VF occurred in 30.2% of patients who discontinued for less than 6 months and 52.3% of those who stopped for 6 months or more, and 13.0% of those who did not abandon. Baseline CD4 levels were marginally associated. The IF was significantly related to sexual orientation. IF was observed in 17.1% of homosexual or bisexual patients, whilst it occurred in 4.6% of heterosexual patients. The level of education and anaemia and the time of discontinuation were marginally associated with IF. CF was significantly related to the diagnosis of anaemia and BMI and marginally with depression. CF occurred in 20.0% of patients with anaemia, whereas 4.5% of patients without anaemia had CF (Table 3). Most of the patients with TF, VF and IF discontinued HAART. Nevertheless, half of the patients with CF did not discontinue the treatment (Figure 2).

TABLE 1 Characteristics of the HIV Venezuelan immigrants included in the analysis.

Characteristics	$n = 294$
Age (years)[a]	32 (10.0)
18–29	138 (46.9)
30–39	106 (36.1)
40–49	39 (13.3)
50–59	11 (3.7)
Sex	
Male	286 (97.2)
Female	8 (2.7)
Sexual orientation	
Heterosexual	35 (11.9)
Homosexual and bisexual	259 (88.0)
Level of education	
Secondary completed or incomplete	66 (22.4)
Superior technical	67 (22.7)
Superior university	161 (54.7)
Body mass index	
Low weight	41 (14.0)
Normal	167 (56.8)
Overweight or obesity	86 (29.0)
Comorbidities	
Anaemia	30 (10.2)
Hypertension	4 (1.4)
Diabetes mellitus	4 (1.4)
Depression	35 (11.9)
Baseline CD4	492 (337.5)
Baseline viral load	322,598 (29680)
Time of discontinuation	
No discontinuation	154 (52.3)
Less than 6 months	96 (32.7)
Six months or more	44 (15.0)
Therapeutic failure	82 (27.9)
Clinical failure	18 (6.1)
Virologic failure	72 (24.5)
Immunologic failure	18 (6.1)
Previous HAART scheme	
First-line scheme	206 (70.0)
Second-line scheme	55 (18.7)
Based on tenofovir	19 (6.5)
Based on abacavir	26 (8.8)
Based on zidovudina	10 (3.4)
Other schemes	33 (11.2)
Restart HAART scheme	
First line scheme	193 (65.6)
Second line scheme	62 (21.09)
Based on tenofovir	18 (6.0)
Based on abacavir	37 (12.6)
Based on zidovudina	7 (2.4)
Other schemes	39 (13.3)

[a]Medians with their respective interquartile ranges were used for numerical variables.

Regression models

Therapeutic failure

In the crude analysis, we observed a higher probability of TF in patients who discontinued treatment for less than 6 months (cRR = 1.96 [95% CI: 1.24–3.07]; $p = 0.003$) and in patients who discontinued it for 6 months or more (cRR = 3.20 [95% CI: 2.06–4.99]; $p = 0.001$), than among non-discontinued patients. This association was maintained in the adjusted model for statistical criteria for those who discontinued for less than 6 months (aRR = 1.98 [95% CI: 1.27–3.09]; $p = 0.002$) and 6 months or more (aRR = 3.17 [95% CI: 2.02–4.95]; $p = 0.001$). It was also maintained in the model adjusted for epidemiological criteria (Table 4).

Virologic failure

VF was associated with the discontinuation of fewer than 6months. (cRR = 2.31 [95% CI: 1.38–3.84]; $p = 0.001$) and of 6 months or more (cRR = 3.99 [95% CI: 2.83–6.57]; $p = 0.001$). The increased risk persists in the analysis adjusted for statistical and epidemiological criteria for those who discontinued for less than 6 months (aRR = 2.32 [95% CI: 1.40–3.84]; $p = 0.001$) and 6 months or more (aRR = 3.93 [95% CI: 2.39–6.45]; $p = 0.001$), compared to those who did not discontinue treatment (Table 4).

Immunologic failure

IF was associated in the crude analysis (cRR = 3.47 [95% CI: 1.05–11.4]; $p = 0.041$). In the adjusted model by epidemiological criteria, having discontinued HAART for 6 months or more was associated with a higher probability of IF than not discontinuing (aRR = 3.57 [95% CI: 1.09–11.66]; $p = 0.041$). However, when adjusted for statistical criteria, the association was lost (Table 4).

Clinical failure

Concerning CF, we found no association with discontinuation time in the crude model nor in the model controlled for BMI, anaemia and depression. We performed the model adjusted by statistical and epidemiological criteria, where minimal variation was observed (Table 4).

DISCUSSION

Main findings

Our findings show that HAART discontinuation increases the probability of TF and VF in young adult Venezuelan

TABLE 2 Patients' characteristics according to treatment discontinuation time.

Characteristics	*n*	No discontinuation, *n* = 154, *n* (%)	Discontinuation for less than 6 months, *n* = 96, *n* (%)	Discontinuation for 6 months or more, *n* = 44, *n* (%)	*p*-value
Age (years)					0.092
18–29	138	71 (51.5)	49 (35.5)	18 (13.1)	
30–39	106	58 (54.7)	34 (32.1)	14 (13.2)	
40–49	39	18 (46.2)	9 (23.1)	12 (30.7)	
50–59	11	7 (63.6)	4 (36.4)	0 (0)	
Sex					0.887
Male	286	149 (52.1)	94 (32.9)	43 (15.0)	
Female	8	5 (62.5)	2 (25.0)	1 (12.5)	
Sexual orientation					0.670
Heterosexual	35	17 (48.6)	11 (31.4)	7 (20.0)	
Homosexual and bisexual	259	137 (52.9)	85 (32.8)	37 (14.3)	
Level of education					0.899
Secondary completed or incomplete	66	33 (50.0)	23 (34.8)	10 (15.2)	
Superior Technical	67	33 (49.3)	22 (32.8)	12 (17.9)	
Superior University	161	88 (54.6)	51 (31.6)	22 (13.6)	
Body mass index					0.940
Low weight	41	22 (53.6)	12 (29.3)	7 (17.0)	
Normal	167	85 (50.9)	56 (33.5)	26 (15.5)	
Overweight or obesity	86	47 (54.6)	28 (32.5)	11 (12.7)	
Comorbidities					
Anaemia	30	17 (56.6)	9 (30.0)	4 (13.3)	0.883
Hypertension	4	2 (50.0)	2 (50.0)	0 (0)	0.812
Diabetes mellitus	4	2 (50.0)	1 (25.0)	1 (25.0)	0.636
Depression	35	18 (51.4)	9 (25.7)	8 (22.86)	0.325
HAART scheme					
Previous HAART scheme					0.762
First-line scheme	206	104 (50.4)	70 (33.9)	32 (15.5)	
Second-line scheme	55	32 (58.2)	17 (30.9)	6 (10.9)	
Other schemes	33	18 (54.5)	9 (27.3)	6 (18.2)	
Restart HAART scheme					0.776
First-line scheme	193	102 (52.8)	62 (32.1)	29 (15.0)	
Second-line scheme	62	34 (54.8)	21 (33.8)	7 (11.3)	
Other schemes	39	18 (46.2)	13 (33.3)	8 (20.5)	
Laboratory data					
Baseline CD4 (cells/mm^3)[a]		558.8 (340)	415.2 (256)	428 (277.5)	**0.0001**
Baseline viral load (copies/mL)[a]		10,684 (230)	119,504 (82,795)	1,826,917 (21,0697)	**0.0001**

Note: Numbers presented in bold font indicate statistically significant results at the specified level of significance ($p < 0.05$).
[a]Medians with their respective interquartile ranges were used for numerical variables. CD4 and viral load were only described because they are part of the outcome definition.

immigrant patients with HIV, regardless of the other demographic and clinical variables measured. In addition, we have found a gradient in the magnitude of the association where the longer the withdrawal time, the greater the probability of presenting TF. The results are of great importance in the public health arena since they highlight the need to restart HAART early as a strategy to prevent TF [25]. This is all the more relevant because of the association between TF and HAART resistance [11, 16, 25]. However, no association was found between discontinuation and IF and CF. The above leads to a reflection on the importance of early restart of HAART in these patients in the context of the Peruvian health system, even more so in a situation of the massive migration of the Venezuelan population amid the COVID-19 pandemic [21]. Despite the large increase of patients, HAART is provided free-of-charge to all immigrants as part of the national HIV strategy. Overall, migrants are part of a vulnerable population that is at risk of acquiring HIV or having worse access to care and outcomes due to persistent structural and social determinants. Faced with

TABLE 3 Factors associated with therapeutic, virologic, immunologic and clinical failure in HIV Venezuelan immigrants included in the analysis.

		Therapeutic failure			Virologic failure			Immunologic failure			Clinical failure		
	n	Failure, *n* (%)	No failure, *n* (%)	*p*-value	Failure, *n* (%)	No failure, *n* (%)	*p*-value	Failure, *n* (%)	No failure, *n* (%)	*p*-value	Failure, *n* (%)	No failure, *n* (%)	*p*-value
Age (years)													
18–29	138	39 (28.3)	99 (71.7)	0.718	35 (25.4)	103 (74.7)	0.704	8 (5.8)	130 (94.2)	0.580	8 (2.8)	130 (942)	0.368
30–39	106	32 (30.2)	74 (69.8)		28 (26.4)	78 (73.5)		8 (7.5)	98 (92.5)		6 (5.6)	100 (94.3)	
40–49	39	8 (20.5)	31 (79.4)		7 (17.9)	32 (82.1)		1 (2.5)	38 (97.4)		2 (5.0)	37 (94.8)	
50–59	11	3 (27.3)	8 (72.7)		2 (18.2)	9 (81.8)		1 (9)	10 (90.9)		2 (18.2)	9 (81.8)	
Sex													
Male	286	81 (28.3)	205 (71.7)	0.296	71 (24.8)	215 (75.2)	0.377	17 (5.9)	269 (94.0)	0.401	18 (6.3)	268 (93.7)	0.599
Female	8	1 (12.5)	7 (87.5)		1 (12.5)	7 (87.5)		1 (12.5)	7 (87.5)		0 (0)	8 (100.0)	
Sexual orientation													
Heterosexual	35	11 (31.4)	24 (68.6)	0.619	8 (22.8)	27 (77.0)	0.811	6 (17.1)	29 (82.8)	**0.004**	3 (8.6)	32 (91.4)	0.364
Homosexual and bisexual	259	71 (27.4)	188 (72.5)		64 (24.7)	195 (75.3)		12 (4.6)	247 (95.3)		15 (5.7)	244 (94.2)	
Level of education													
Secondary completed or incomplete	66	17 (25.7)	49 (74.2)	0.146	14 (21.2)	52 (78.7)	0.103	9 (13.6)	57 (86.3)	0.025	4 (6.1)	62 (93.9)	0.852
Superior technical	67	25 (37.3)	42 (62.6)		23 (34.3)	44 (65.6)		3 (4.4)	64 (95.5)		5 (7.4)	62 (92.5)	
Superior university	161	40 (24.8)	121 (75.1)		35 (21.7)	126 (78.2)		6 (3.73)	155 (96.2)		9 (5.5)	152 (94.4)	
Body mass index													
Low weight	41	16 (39)	25 (60.9)	**0.173**	13 (31.7)	28 (68.3)	0.338	3 (7.3)	38 (92.6)	0.832	8 (19.5)	33 (80.5)	**0.002**
Normal	167	41 (24.5)	126 (75.5)		36 (21.5)	131 (78.4)		9 (5.4)	158 (94.6)		6 (3.6)	161 (96.4)	
Overweight or obesity	86	25 (29)	61 (70.9)		23 (26.7)	63 (73.2)		6 (6.9)	80 (93)		4 (4.6)	82 (95.3)	
Anaemia													
Yes	30	11 (36.6)	19 (63.3)	0.258	10 (33.3)	20 (66.6)	0.235	4 (13.3)	26 (86.6)	0.098	6 (20.0)	24 (80.0)	**0.001**
No	264	71 (26.8)	193 (73.0)		62 (23.4)	202 (76.5)		14 (5.3)	250 (94.7)		12 (4.5)	252 (95.5)	
Hypertension													
Yes	4	0 (0)	4 (100.0)	0.268	0 (0)	4 (100.0)	0.323	0 (0)	4 (100.0)	0.776	0 (0)	4 (100.0)	0.776
No	290	82 (28.3)	208 (71.7)		72 (24.8)	218 (75.2)		18 (6.2)	272 (93.8)		18 (6.2)	272 (93.8)	
Diabetes mellitus													
Yes	4	3 (75.0)	1 (25)	**0.067**	3 (75)	1 (25)	**0.047**	0 (0)	4 (100.0)	0.776	1 (25.0)	3 (75.0)	0.224
No	290	79 (27.2)	211 (72.8)		69 (23.7)	221 (76.32)		18 (6.2)	272 (93.8)		17(6.0)	273 (94.0)	
Depression													
Yes	35	9 (25.7)	26 (74.3)	0.760	8 (22.8)	27 (77)	0.811	1 (3)	34 (97)	0.342	4 (11.4)	31 (88.6)	0.152
No	259	73 (28.2)	186 (71.8)		64 (24.7)	195 (75.3)		17 (6.5)	242 (93.4)		14 (5.4)	245 (94.6)	
Baseline viral load[a]	294	222222.6 (97492)	361687.5 (5146)	0.793	251903.8 (109690)	345623.6 (5520)	0.866	552,846 (564676)	307,305 (23880)	0.804	4,415,253 (95780)	316,807 (28980)	0.922
Baseline CD4[a]	294	460 (295)	504 (350)	0.214	442 (250)	508 (350)	**0.072**	521 (613)	490 (336)	0.637	496 (385)	492 (338)	0.946
Time of abandonment													
No discontinuation	154	26 (16.9)	128 (83.1)	**0.001**	20 (13.0)	134 (86.9)	**0.001**	5 (3.3)	149 (96.7)	0.079	9 (5.8)	145 (94.0)	0.253

(Continues)

TABLE 3 (Continued)

		Therapeutic failure			Virologic failure			Immunologic failure			Clinical failure		
	n	**Failure, *n* (%)**	**No failure, *n* (%)**	***p*-value**	**Failure, *n* (%)**	**No failure, *n* (%)**	***p*-value**	**Failure, *n* (%)**	**No failure, *n* (%)**	***p*-value**	**Failure, *n* (%)**	**No failure, *n* (%)**	***p*-value**
Less than 6 months	96	32 (33.3)	64 (66.7)		29 (30.2)	67 (69.7)		8 (8.3)	88 (91.7)		4 (4.2)	92 (95.8)	
Six months or more	44	24 (54.5)	20 (45.5)		23 (52.3)	21 (47.7)		5 (11.3)	39 (88.6)		5 (11.4)	39 (88.6)	
Previous HAART scheme													
First-line scheme	206	56 (27.1)	150 (72.9)	0.858	49 (23.8)	157 (76.2)	0.867	10 (4.8)	196 (95.0)	0.175	12 (5.8)	194 (94.1)	0.926
Second-line scheme	55	17 (30.9)	38 (69.0)		15 (27.3)	40 (72.7)		4 (7.3)	51 (92.7)		4 (7.3)	51 (92.7)	
Other schemes	33	9 (27.3)	24 (72.0)		8 (24.2)	25 (75.7)		4 (12.0)	29 (87.8)		2 (6.0)	31 (93.9)	
Restart HAART scheme													
First-line scheme	193	53 (27.5)	140 (72.5)	0.912	46 (23.8)	147 (76.7)	0.844	10 (5.2)	183 (94.8)	0.435	14 (7.3)	179 (92.7)	0.583
Second-line scheme	62	17 (27.4)	45 (72.6)		15 (24.2)	47 (75.8)		4 (6.5)	58 (93.5)		2 (3.2)	60 (96.7)	
Other schemes	39	12 (30.7)	27 (69.2)		11 (28.2)	28 (71.8)		4 (10.3)	35 (89.7)		2 (5.0)	37 (94.8)	

Note: Numbers presented in bold font indicate statistically significant results at the specified level of significance ($p < 0.05$).
[a]Medians with their respective interquartile ranges were used for numerical variables.

severe inequalities in health, migrants can present challenges to achieve the 95–95–95 target throughout LATAM, especially in countries with limited access to healthcare [26].

In the context of the ongoing pandemic, it has become evident how it has affected HIV diagnostic services; however, the administration of HAART has not been significantly affected [27]. Patients with HIV are deemed very likely to experience therapeutic abandonment due to restrictions in patient care, delay of controls to receive HAART and limitations with the implementation of telehealth [27]. Furthermore, immigrants have a higher risk of contracting infectious diseases, including COVID-19 [28]. According to WHO, only five countries reported a decrease in the number of people receiving HAART monthly [27, 28]. One of these countries was Peru, which in July 2020 reported that slightly more than half of the HIV population received treatment [29]. In these patients who discontinue treatment, whose disease is uncontrolled or who are in a TF situation, there is an increased risk of SARS-CoV-2 infection, severe disease and death [27, 28, 30].

Comparison with previous studies

Evidence regarding the association evaluated is controversial; however, studies suggest that dropout impacts TF. They also conclude that TF is related to mortality, which represents a cost to the local health system, and to the development of therapeutic resistance, which has global implications [31, 32]. Genet et al. analysed the risk factors associated with TF. They found that being in a rural area, having a clinical HIV stage III/IV, poor adherence to treatment, coinfection with tuberculosis and treatment discontinuation were associated with treatment failure in adult patients initiating HAART [31]. Conversely, Saracino et al., in an analysis of the ICONA study, described that immigrants have a higher rate of TF and VF than non-immigrants. However, this was not found to be associated with treatment abandonment [12]. The authors mentioned that TF is associated with other comorbidities such as tuberculosis and situations of vulnerability immigrants suffer [12]. Pérez-Molina et al., in a retrospective Spanish cohort study, associated the development of VF with the late restart of HAART and higher discontinuation of HAART, but found no association with immigrant status [33]. Thus, the association of TF with HAART discontinuation is clear, but not with the fact of being an immigrant [34].

Explanation of findings, geopolitical context and public health implications

The recent humanitarian crisis in Venezuela has resulted in massive immigration of its population [19]. It seeks the resolution of its needs, one of which is health [19, 22]. Due to the situation of such a country, its health system is fragmented, with a shortage of medicines and human resources [35, 36]. For this reason, Venezuelans migrate to

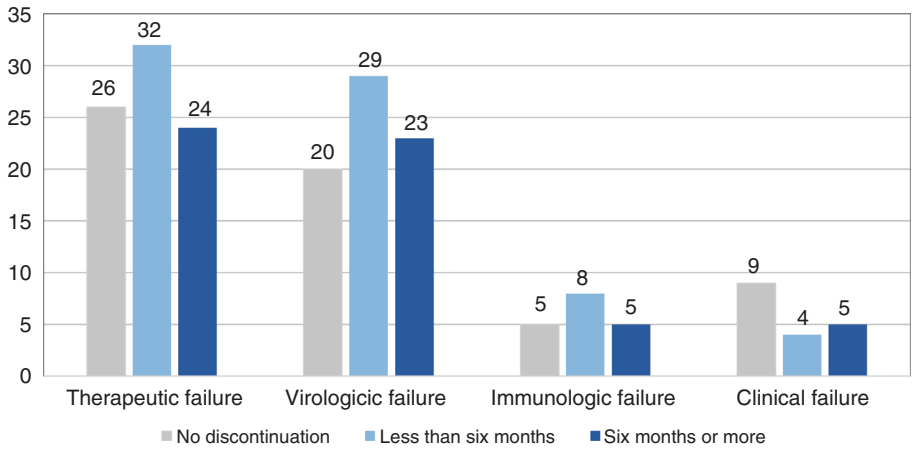

FIGURE 2 Frequency of discontinuation duration according to therapeutic failure.

TABLE 4 Association between discontinuation HAART time and therapeutic, virologic, immunologic and clinical failures (crude and adjusted generalised linear models Poisson family).

	Crude model			Statistical-adjusted model*			Epidemiological-adjusted model**		
	cRR	(95% CI)	*p*-value	aRR	(95% CI)	*p*-value	aRR	(95% CI)	*p*-value
Therapeutic failure[a]									
No discontinuation	Base			Base			Base		
Less than 6 months	1.96	1.24–3.07	**0.003**	1.98	1.27–3.09	**0.002**	1.96	1.25–3.08	**0.003**
Six months or more	3.20	2.06–4.99	**0.001**	3.17	2.02–4.95	**0.001**	3.18	2.05–4.93	**0.001**
Virologic failure[b]									
No discontinuation	Base			Base			Base		
Less than 6 months	2.31	1.38–3.84	**0.001**	2.32	1.40–3.84	**0.001**	2.31	1.39–3.85	**0.001**
Six months or more	3.99	2.83–6.57	**0.001**	3.93	2.39–6.45	**0.001**	3.96	2.42–6.49	**0.001**
Immunologic failure[c]									
No discontinuation	Base			Base			Base		
Less than 6 months	2.55	0.85–7.58	0.092	2.40	0.82–6.99	0.107	2.53	0.85–7.51	0.093
Six months or more	3.47	1.05–11.4	**0.041**	2.99	0.87–10.30	0.081	3.57	1.09–11.66	**0.035**
Clinical failure[d]									
No discontinuation	Base			Base			Base		
Less than 6 months	0.70	0.22–2.24	0.557	0.73	0.25–2.08	0.557	0.73	0.22–2.34	0.602
Six months or more	1.93	0.68–5.47	0.216	1.96	0.67–5.79	0.219	1.77	0.70–4.49	0.227

Note: Numbers presented in bold font indicate statistically significant results at the specified level of significance ($p < 0.05$).
Abbreviations: aRR, adjusted relative risk; base, comparison base category; cRR, crude relative risk.
[a]Model adjusted by diabetes mellitus and body mass index.
[b]Model adjusted by diabetes mellitus.
[c]Model adjusted by educational level, sexual orientation and anaemia.
[d]Model adjusted by depression, body mass index and anaemia.
*Model adjusted by statistical criteria.
**Model adjusted by epidemiological criteria: arterial hypertension, diabetes mellitus and depression.

neighbouring countries in LATAM, whose health systems also have severe limitations, including Peru, which has a fragmented, segmented and partially decentralised health system [35]. Among them are HIV-infected patients waiting to receive HAART free of charge according to the MINSA, which has recognised HAART as a therapy that should be provided to all HIV-positive patients without discrimination [4]. In this line, other LATAM countries should guarantee timely and universal access to HAART.

HIV is a chronic disease in which the beneficial effect of HAART adherence on the patient's immunological and virological status has been proposed [16, 25]. Contrarily, if the patient abandons the treatment, the antiretroviral effect will be diminished, which will cause an insufficient suppression of viral replication [4, 5]. In the absence of optimal HAART therapy concentrations, the virus can initiate persistent replication [25], possibly triggering TF, therapeutic resistance, AIDS and death [25]. The HIV-positive

immigrant community is more likely to drop out of treatment because of the lack of treatment in pharmacies in their country, the journey made when leaving their country, restricted access to medical care, poverty, limited knowledge about the host healthcare system, and stigma [37, 38].

Limitations and strengths

Our study has limitations that could potentially affect its internal and external validity. First, the data source was extracted from the physician's clinical records so that measurement biases could occur. However, an electronic record in the hospital's HIV programme was used to compare the information. Second, while the non-probabilistic consecutive cases sampling design used in this study enabled to recruit a sample that met the criteria for testing the hypothesis under analysis, it may not be representative of the entire population of Venezuelan immigrants with HIV. This is because the sampling method may have excluded individuals who were not seeking care, were unable to attend the hospital, or were not diagnosed with HIV. As a result, the findings of this study may have limited generalizability beyond the sample that was studied. Nonetheless, the sample size was sufficient for testing the hypothesis under investigation. Third, when measuring the time to discontinuation as expressed by the patients, there could be a risk of recall bias and social desirability bias. Therefore, we categorised the variable to facilitate data collection. We excluded those histories with incomplete or incorrectly filled-out data in these scenarios. Fourth, as we only studied patients from HNAL, it will be difficult to extrapolate our results. Nevertheless, it is a national reference centre in managing HIV. Furthermore, according to official data, the most significant number of Venezuelan immigrants infected with HIV are receiving HAART in Lima and are treated at MINSA reference centres. Fifth, no IF and CF data were obtained, which is counterbalanced by the time defined for measurement is 6 months, a criterion that was met in all patients included in the study. Given that our study had multiple outcomes, we considered one as the primary outcome (TF) and three others as exploratory in nature (VF, CF, IF). It is possible that having few observations with the outcomes IF and CF could affect the precision of the estimates, which reinforces our initial position of leaving it as exploratory. Sixth, our study was focused on Venezuelan migrants who effectively accessed to the health system, but it does not inform on needs, barriers or health outcomes related to HIV of those who did not access. In addition, focusing on Venezuelan is relevant but misses other migrant communities that could be important. Furthermore, the novel knowledge of the paper is with regards to migrant HIV patients only, not how different or similar they are to local HIV patients. Seventh, information on the specific time and place where patients were diagnosed with HIV was not available, limiting our ability to explore possible variations in treatment outcomes based on these factors. Beyond the above limitations, our study constitutes primary evidence that could serve as a basis for planning public health policies and developing special evidence-based programmes for the evaluation of immigrant HIV patients [39]. Despite the development in recent years of studies on Venezuelan immigration in Peru, this is the first to associate treatment discontinuation with TF in the Venezuelan immigrant population with HIV.

Recommendations for future research and policy planning

We recommend researching to evaluate the health conditions and needs of Venezuelan and other immigrant patients with HIV in Peru and, consequently, in LATAM, to make a situational diagnosis that will allow the formulation of informed interventions based on the best available scientific evidence, which seeks to avoid therapeutic discontinuation and promote greater surveillance of these patients. The approach of this study did not contemplate the analysis of other comorbidities or concomitant infections associated with TF; however, it is necessary to improve the registry of immigrant patients with HIV and opportunistic infections, and to expand the clinical record, considering other factors associated with TF. It is also necessary to evaluate the impact of the migratory process through health indicators such as HIV infection and its repercussion on the country's health system [40]. Considering the current situation of antiviral susceptibility and resistance in Latin America, further studies on HIV genotypification are necessary to assess the need for recommending it among migrants who have discontinued HAART. On the other hand, to the best of our knowledge, no study has evaluated HAART discontinuation and TF among Peruvian patients. Hence, we recommend that further studies should be conducted to evaluate the effects of HAART discontinuation and TF in Peruvian patients living with HIV. By evaluating the impact of HAART discontinuation and TF in Peruvian patients, we can improve our understanding of the challenges facing HIV-positive individuals in Peru and develop more effective strategies to address these issues.

CONCLUSION

Based on a retrospective cohort in a large referral public hospital in Perú, HAART discontinuation increase the probability of developing TF and VF in Venezuelan immigrant patients. Treatment discontinuation should be explored as a variable of high importance in assessing patients with HIV.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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