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ORIGINAL ARTICLE

# Increased Rate of Protease Inhibitor-resistance Associated Mutations in Human Immunodeficiency Viruses Infecting Mexicans who had Been Living Abroad

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*Background.* Migrants face multiple barriers to accessing health services and antiretroviral therapy (ART). We tested the hypothesis that HIV-infected ART-experienced Mexicans with a history of residence in the U.S. have a higher rate of viral drug-resistance associated mutations (RAMs) versus those without such a history.

*Methods.* Viral genotypic resistance tests obtained from 336 HIV-infected Mexican patients throughout the country were analysed for the presence of viral-RAMs and its rate was compared between migrants and non-migrants. Adjustment for potential confounders was done though a multivariate analysis.

*Results.* Eighty-four Mexicans who had lived for at least 3 months in the U.S. were more likely to have three or more protease inhibitor (PI)-major RAMs (aOR = 2.47; 95% CI = 1.06–5.76; $p < 0.05$) than in 252 individuals without this background, independently of the time spent on ART.

*Conclusions.* A migration background is associated with a higher likelihood of the emergence of HIV variants with decreased susceptibility to several PI. 

*Key Words:* HIV, Protease inhibitors, Drug resistance, Transients and Migrants, Mexico.

## Introduction

Today, human immunodeficiency virus (HIV) infection is still a major global health issue; ending the epidemic by 2030 is one of the targets of the Sustainable Development Goals (1). Universal access to antiretroviral therapy (ART) prolongs survival among HIV-infected individuals and averts new infections (2). However, the increasing emergence of HIV strains with antiretroviral drug resistance is among the main challenges that countries are facing to fully reach such goals. A World Health Organization (WHO) study conducted in 14 countries found that in seven of these, the primary resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) was above 10% and that 68% of ART-experienced patients (with a history of at least one previous antiretroviral treatment) presented with one or more drug resistance-associated mutations (RAMs) in the viral reverse transcriptase gene (3).

Lack of adherence to the proper use of ART is the major determinant driving the selection and dissemination of HIV variants harbouring RAMs, which in turn lead to a loss of antiviral activity, seriously compromising the potential benefits of ART for viral control and survival among HIV-infected individuals. Several vulnerable subpopulations, including migrants, have been identified as being more prone to the suboptimal adherence to ART.

Migrants face multiple organizational, cultural, and individual barriers to accessing health services during all five stages of the migratory process (preparation, transit, desti-

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nation, interception, and repatriation); such barriers likely contribute to a lack of continued access to ART (4–10). A study identified that individuals who had migrated at least three times were 1.7 times more likely to be non-adherent to ART and had a 6.6 fold increase in the rate of loss to follow-up compared to non-migrants (8). However, few studies have investigated the prevalence of acquired resistance to ART in migrant populations; those that have been performed have identified the rate of this type of resistance between 21% in Spain and 61.5% in Portugal among HIV-infected migrants living in these countries (11,12).

In Mexico, one-third of HIV-positive individuals live in a state with high migration rates, and 10% of the people with HIV have lived, at least temporarily, in the U.S. (13,14). Until now, there have been no studies assessing whether there is a higher prevalence of acquired RAMs in HIV-infected returned Mexican migrants (individuals who were born in Mexico, lived for at least three months in the United States and returned voluntarily or involuntarily to Mexico) compared with Mexicans without a migratory background. In 2008, the Mexican Ministry of Health created a national board of clinicians with several years of ART experience to assist physicians from all over the country in the prescription of ART, particularly the prescription of salvage regimens for patients after the loss of viremia control (15,16). Data from these individuals, including their international migration history and infection with HIV variants harbouring RAMs, provided a unique opportunity to address whether an association between these two sets of information exists.

This study was conducted to test the hypothesis that there is a higher prevalence of RAMs, conferring reduced antiviral activity of NRTIs and of PIs, in HIV-infected ART-experienced returned Mexican migrants than in non-migrant controls matched for the time spent on ART.

## Methods

### *Study Sample Population and Data Collection*

This was a cross-sectional comparison study using information from HIV-infected patients requiring a change in antiretroviral regimen in the ART roll-out programme run by the Mexican Ministry of Health. Patients requiring a change of regimen are reviewed by a National Peer Advisory Committee (CORESAR, its acronym in Spanish) (15). The sample was selected by exposure status (migration/non-migration background). Physicians caring for patients in HIV clinics complete a structured application form that collects data concerning sociodemographic data (including international migration history and time since HIV diagnosis), patient plasma HIV-1 viral load measurements, CD4+ T-cell counts, coinfections, clinical events, concurrent medications, and a complete history of ART including commencement date, regimens, and the reasons for antiretroviral regimen change (e.g., virologic failure, adverse events, regimen simplification, or pharmacologic interactions) since the HIV-infection diagnosis.

We created a database containing this information as well as the genotypic resistance tests (genRT) results from routine testing. The eligibility criteria required that patients: a) were Mexican, b) had specific information about their migration history, c) had one or more genRT under pharmacological pressure, and d) had a complete physical or electronic record from CORESAR. The enrolment period of the study was from November 5, 2008–March 28, 2018. The physician obtained patients' consent to register their personal information on the first visit. During the study enrolment period, CORESAR evaluated 2,790 individuals, of whom 210 were individuals who had lived for at least three months in the U.S. (migrants); 1,616 were non-migrants, and 964 individuals had no information about their migration background. The sample is comprised of 336 Mexican individuals, 84 with a migration background (40% of all migrants) who fulfilled the inclusion criteria, and 252 non-migrants randomly selected at a 3:1 ratio and matched by time spent on ART treatment (± one year) (Figure 1).

### *Analysis of Drug Resistance-associated Mutations*

As part of routine clinical care, genRT are obtained when a patient receiving ART experiences virological failure. The corresponding tests from all eligible patients were analysed. Major resistance mutations were defined according to the IAS-USA 2015 list (17). The ViroSeq HIV-1 Genotyping System (Abbott) method was used for the majority of the genRT, and no differential trend over time in the rate of use of this technique occurred during the study period. In patients with more than one genRT, all RAMs identified in all tests were pooled; thus, a single (pooled) test per patient was analysed (i.e., the numbers of genRT and individuals were the same).

Prevalence of NRTIs and protease inhibitor-major RAMs (PI-mRAMs) were calculated. There was an interest in specifically analysing darunavir (DRV)-RAMs, as this is the PI (second generation PI, with the highest barrier to resistance within this class) commonly used as the cornerstone of deep-salvage regimens in heavily treatment-experienced patients. Moreover, viral strains harbouring three or more PI-mRAMs are likely to become less susceptible to the antiviral effect of most of the first-generation PI, and viral strains harbouring three or more TAMs become less susceptible to the antiviral effect of the recommended NRTI backbone; thus, we chose these dichotomous events as our major outcomes. We did not analyse the presence of RAMs conferring resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs), as the great majority of genRTs were identified while the individual was not taking a drug within this drug class;

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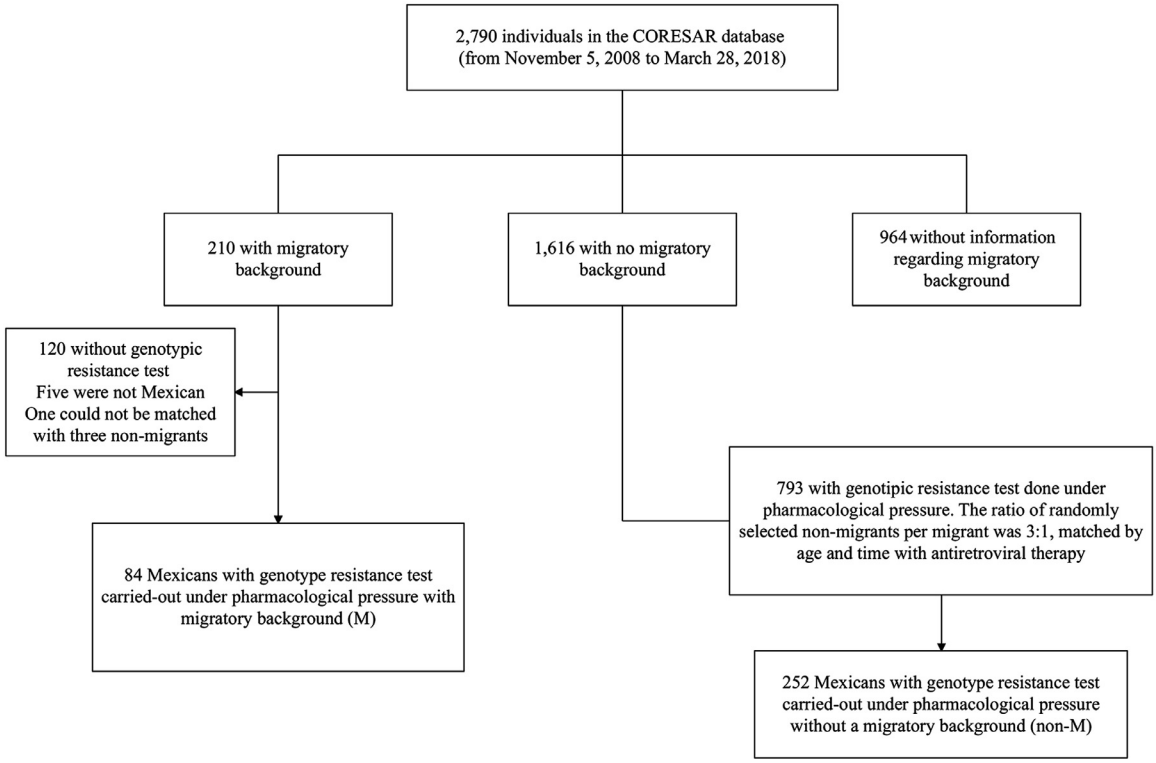


**Figure 1.** Study Profile. Selection of the 336 study individuals.

this lack of pharmacologic selective pressure leads to the underestimation of the true prevalence of such RAMs.

### *Data Analysis*

We divided the patients into two groups according to their migratory background: group 1 included patients who had lived for at least three months in the U.S., and group 2 comprised those who did not have a migratory background. We compared the rates of the development of various specific NRTIs, PIs, and DRV-RAMs between the two groups. We report the data as absolute values and percentages or medians and interquartile ranges. We tested the differences between these groups in the percentage of genRT with RAMs, presence of $\geq$3 thymidine analogue mutations (TAMs), presence of $\geq$3 PI-mRAMs, and presence of $\geq$3 DRV-RAMs with a chi-square test or Fisher's exact test. We used multivariate logistic regression modelling to estimate the association between a migratory background as a binomial variable and the presence of $\geq$3 TAMs, $\geq$3 PI-mRAMs, and $\geq$3 DRV-RAMs, adjusting for potential confounders (gender, age, $\geq$10 years since HIV diagnosis, number of prior ARV regimens, number of genRT, and nearest [before genRT] vRNA plasma level and T-CD4$^+$ cell count). These potential confounders were selected based on previous studies that showed that these variables are associated to treatment failure and the emergence of resistance associated mutations (18–20). We also used the bootstrap method as a resampling technique to estimate the statistics for this population, generating potential confounder-adjusted odds ratios (aORs) and the attendant 95% confidence intervals (95% CIs). We selected a sample size of 83 per group and 1,500 replicates because the bootstrap standard error did not change significantly between 1,500 and 2,000 replications. We did not adjust *p*-values for multiple comparisons. The Research Ethics Committees of the Instituto Nacional de Salud Pública (registration number: 17CEI00420160708) and the Instituto Nacional de Ciencias Médicas y Nutrición, Salvador Zubirán (registration number: 1602) approved this study.

## Results

We obtained data regarding the demographics, migratory background, and genRT from all 336 eligible HIV-infected patients: 84 Mexican migrants and 252 non-migrants (Figure 1). Since one of our inclusion criteria was that participants had their physical or electronic CORESAR records complete, we did not have missing data when carrying out the data analysis.

Table 1 shows the characteristics of the whole sample as well as the comparisons of diverse features between the two groups. For all subjects in the study, the median age was 41 years (IQR = 33–48); the median time since HIV-infection diagnosis was 11.85 years (IQR = 6.50–16.60); the median time on ART was 9.9 years (IQR = 5.80–

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**Table 1.** Demographic, virologic and antiretroviral therapy (ART) characteristics of the study participants stratified by migratory background

| | All participants ($n$ = 336) | Mexican migrants ($n$ = 84) | Non-migrant Mexicans ($n$ = 252) | $p$ |
|---|---|---|---|---|
| Age in years median (IQR)[a] | 41 (33-48) | 42 (36-47.5) | 40 (31-48) | 0.07 |
| Sex $n$ (%)[b] | | | | |
| Men | 273 (81.3) | 75 (89.3) | 198 (78.6) | 0.02 |
| Women | 63 (18.8) | 9 (10.7) | 54 (21.4) | |
| Region of residence n (%)[b] | | | | 0.02 |
| South | 89 (26.5) | 23 (27.4) | 66 (26.2) | |
| Central | 180 (53.6) | 36 (42.9) | 144 (57.1) | |
| North | 67 (19.9) | 25 (29.8) | 42 (16.7) | |
| Time since HIV-infection diagnosis in years median (IQR)[c] | 11.9 (6.5-16.6) | 13.1 (6.2-18.2) | 11.3 (6.5-15.4) | 0.18 |
| Time with ART in years median (IQR)[c] | 9.9 (5.8-14.2) | 9.8 (5.6-13.9) | 9.9 (5.8–14.3) | 0.95 |
| Late HIV diagnosis $n$ (%)[b] | | | | 0.62 |
| Yes | 240 (72.5) | 57 (70.4) | 183 (73.2) | |
| No | 91 (27.5) | 24 (29.6) | 67 (26.8) | |
| Adherence to ART $n$ (%)[b] | | | | 0.72 |
| Good (>94%) | 133 (39.6) | 34 (40.5) | 99 (39.3) | |
| Average (75–94%) | 108 (32.1) | 29 (34.5) | 79 (31.4) | |
| Poor (<75%) | 95 (28.3) | 21 (25.0) | 74 (29.4) | |
| Previous ART schemes median (IQR)[c] | 3 (2–5) | 3 (2–4) | 3 (2–5) | 0.73 |
| Comorbidities (yes) $n$ (%) | | | | |
| Hepatitis B[b] | 14 (4.2) | 5 (6) | 9 (3.6) | 0.35 |
| Hepatitis C[d] | 10 (3) | 7 (8.3) | 3 (1.2) | 0.003 |
| Tuberculosis[b] | 16 (4.8) | 6 (7.1) | 10 (4) | 0.23 |

[a]IQR: interquartile range
[b]$\chi^2$ test;
[c]$U$ Mann-Whitney test;
[d]Fisher's exact test.

14.15), and the median number of prior ARV regimens was three (IQR = 2–5). Most of the individuals were diagnosed with fewer than 200 T-CD4$^+$ cells/mL of blood, and there were significantly larger proportions of men, individuals living in the northern states of Mexico, and subjects co-infected with hepatitis C virus among the migrants than among the non-migrants ($p$ <0.05).

A significantly higher proportion of Mexican migrants than non-migrants had genRT showing several RAMs. Proportionally more migrants had genRT with certain major PI-mRAMs (V32I, I47V, I54M, and L90M), DRV-RAMs (V11I, V32I, I47V, and I54M; $p$ <0.05), and three or more DRV-RAMs (19.1% and 4%, respectively; $p$ <0.001) (Table 2).

In contrast, the proportion of migrants with genRT showing NRTI-RAMs, including thymidine analogue-associated mutations (TAMs), was like the proportion of non-migrants, except for L74V (6 and 17.9%, respectively; $p$ <0.01) (Table 3).

After adjusting for potential confounders (age, sex, ≥10 years since HIV diagnosis, number of prior ARV regimens, number of genRT, and most recently obtained previous to genRT-vRNA plasma level and T-CD4$^+$ blood cell count), we found that having lived at least three months in the U.S. was associated with a higher likelihood of having a genRT showing ≥3 PI-mRAMs (aOR = 2.47; 95% CI = 1.06–5.76; $p$ <0.05). The result for ≥3 DRV-RAMs was not strictly statistically significant but had a $p$-value close to 5% (aOR = 7.21; 95% CI = 0.88–59.07; $p$ = *0.06*).

## Discussion

There is evidence that migrants are more likely to be non-adherent to ART and to be lost to follow-up compared to non-migrants, and a few other studies have shown a prevalence of acquired viral resistance to antiretrovirals ranging from 21–34% in certain migrant populations (8,11,12). However, to the best of our knowledge, there is no published study testing the hypothesis that a migration background is associated with a higher rate of infection with RAM-harbouring HIV strains. In this study, we show that under similar conditions of time spent on ART and number of prior regimens, heavily antiretroviral-exposed Mexicans with a migration background are more likely to have resistance tests showing diverse genetic determinants of reduced PI antiviral activity compared with individuals without such a history.

In general, in individuals undergoing ART, the main drivers of the selection, emergence and dissemination of HIV-quasispecies harbouring drug-RAMs are: a) insufficient compliance with taking all medicines at the proper dosage and daily schedule; b) the prescription of an inappropriate drug combination (i.e., omission of 3 fully antiviral-active drugs or the prescription of regimens with

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**Table 2.** Rate of HIV-genotypic resistance tests with protease inhibitor major (and darunavir-) resistance-associated mutations stratified by migratory background

| Substitutions | All participants ($n$ = 336) | Mexican migrants ($n$ = 84) | Non-migrant Mexicans ($n$ = 252) | $p$ |
|---|---|---|---|---|
| V11I $n$ (%)[a,b] | 10 (2.3) | 6 (7.1) | 4 (1.6) | 0.01 |
| V32I $n$ (%)[b,c] | 25 (7.4) | 12 (14.3) | 13 (5.2) | 0.006 |
| L33F $n$ (%)[b,c] | 46 (13.7) | 14 (16.7) | 32 (12.7) | 0.36 |
| M46I $n$ (%)[c] | 80 (23.8) | 20 (23.8) | 60 (23.8) | 1.00 |
| M46L $n$ (%)[a] | 8 (2.4) | 3 (3.6) | 5 (1.2) | 0.41 |
| I47V $n$ (%)[b,c] | 20 (6) | 11 (13.1) | 9 (3.6) | 0.001 |
| I50V $n$ (%)[a,b] | 10 (2.3) | 3 (3.6) | 7 (2.8) | 0.71 |
| I54L $n$ (%)[a,b] | 5 (1.5) | 2 (2.4) | 3 (1.2) | 0.60 |
| I54M $n$ (%)[a,b] | 10 (3) | 7 (8.3) | 3 (1.2) | 0.003 |
| Q58E $n$ (%)[c] | 28 (8.3) | 7 (8.3) | 21 (8.3) | 1.00 |
| T74P $n$ (%)[a,b] | 2 (0.6) | 0 (0.0) | 2 (0.8) | 1.00 |
| L76V $n$ (%)[a,b] | 8 (2.4) | 1 (1.2) | 7 (2.8) | 0.68 |
| V82A $n$ (%)[c] | 55 (16.4) | 14 (16.7) | 41 (16.3) | 0.93 |
| I84V $n$ (%)[b,c] | 41 (12.2) | 15 (17.9) | 26 (10.3) | 0.06 |
| L89V $n$ (%)[a,b] | 9 (2.7) | 4 (4.8) | 5 (2) | 0.23 |
| L90M $n$ (%)[c] | 75 (22.3) | 26 (31) | 49 (19.4) | 0.02 |
| Number of PI-mRAMs median (IQR[(d)])[e] | 0 (0–2) | 0 (0–2) | 0 (0–2) | 0.06 |
| Number of DRV-RAMs (median (IQR)[e] | 0 (0–1) | 0 (0–1.5) | 0 (0–1) | 0.06 |
| ≥3 PI-mRAMs $n$ (%)[c] | 40 (11.9) | 15 (17.9) | 25 (9.9) | 0.05 |
| ≥3 DRV-RAMs $n$ (%)[c] | 26 (7.7) | 16 (19.1) | 10 (4) | < 0.001 |

[a]Fisher's exact test;
[b]Darunavir-resistance-associated mutations;
[c]$\chi^2$
[d]IQR, interquartile range
[e]$U$ Mann-Whitney test.

**Table 3.** Rate of HIV-genotypic resistance tests with nucleos(t)ide reverse transcriptase inhibitors-resistance-associated mutations stratified by migratory background

| Substitutions | All participants ($n$ = 336) | Mexican migrants ($n$ = 84) | Non-migrant Mexicans ($n$ = 252) | $p$ |
|---|---|---|---|---|
| M41L $n$ (%)[a,b] | 86 (25.6) | 20 (23.8) | 66 (26.2) | 0.66 |
| K65R $n$ (%)[a] | 65 (19.4) | 12 (14.3) | 53 (21.0) | 0.17 |
| D67N $n$ (%)[a,b] | 87 (25.9) | 25 (29.8) | 62 (24.6) | 0.35 |
| K70R $n$ (%)[a,b] | 55 (16.4) | 17 (20.2) | 38 (15.1) | 0.26 |
| K70E $n$ (%)[a] | 18 (5.4) | 8 (9.5) | 10 (3.4) | 0.05 |
| L74V $n$ (%)[c] | 50 (14.9) | 5 (6) | 45 (17.9) | 0.008 |
| M184V $n$ (%)[a] | 252 (75.0) | 65 (77.4) | 187 (74.2) | 0.56 |
| L210W $n$ (%)[a,b] | 50 (14.9) | 9 (10.7) | 41 (16.3) | 0.21 |
| T215F $n$ (%)[a,b] | 41 (12.2) | 13 (15.5) | 28 (11.1) | 0.29 |
| T215Y $n$ (%)[a,b] | 83 (24.7) | 19 (22.6) | 64 (25.4) | 0.60 |
| K219E $n$ (%)[a,b] | 40 (11.9) | 10 (11.9) | 30 (11.9) | 1.00 |
| K219Q $n$ (%)[a,b] | 28 (8.3) | 11 (13.1) | 17 (6.8) | 0.06 |
| Total number of TAMs median (IQR)[d,e] | 0 (0–3) | 1 (0–3) | 0 (0–3) | 0.43 |
| ≥3 TAMs $n$ (%)[a] | 94 (28) | 23 (27.4) | 71 (28.2) | 0.88 |

[a]$\chi^2$
[b]Thymidine analogue mutations (TAMs)
[c]Fisher's exact test
[d]IQR: interquartile range
[e]Mann-Whitney $U$ test.

components with low barriers to developing resistance, or with non-ritonavir-boosted PI); c) adverse drug-drug interactions; and/or d) gastrointestinal malabsorption.

Based on these various potential determinants, we postulate two factors as the more plausible explanations for the increased rate of PI-mRAMs in the HIV strains infecting migrants. First, differences in the use of proper regimens are one explanatory factor, as it is possible that migrants more frequently receive suboptimal therapies. Second, it is likely that migrants' access to and intake of antiretrovirals during the complex migration and repatriation process is more inconsistent than those of their non-migrant counterparts; the suboptimal intake of antiretrovirals is likely due to the presence of diverse barriers to accessing HIV health services, leading to sub-dosing, incomplete regimens, and/or temporal (short course) treatment interruptions.

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Unfortunately, we were unable to test both hypotheses due to several factors mentioned in the following limitation acknowledgment section of the present study.

Hence, there is no clear explanation as to why the proportion of migrants infected with HIV variants with less susceptibility to antiretroviral drugs is higher. Reasonably, it can be assumed that both groups (migrants and non-migrants) were a) heavily antiretroviral-experienced individuals and equally exposed to these drugs in the past (as both samples had a similar time on ART and a similar number of prior drug regimens); b) patients with a suboptimal adherence in terms of drug intake, as this is the basic determinant of a history of multiple regimen changes; and, c) individuals who had received similar drug combinations, as the Mexican Health System tends to follow the recommendations of formal and universally accepted guidelines (such as the US-DHHS guidelines). We postulate that irregular drug intake is the main phenomenon leading to the selection and emergence of drug-resistant HIV variants. It could be that most non-migrant Mexicans show virologic failure secondary to abrupt abandonment of all the components of the ART regimens due to side effects, therapy fatigue, and/or misconceptions and negative behaviours vis á vis the disease. In contrast, suboptimal adherence among migrants may occur mostly secondary to a lack of uninterrupted access to antiretrovirals, leading to the intake of sub-therapeutic dosages and/or incomplete regimens (mono-, bi-therapy) for long periods of time. In this latter scenario, continuous pharmacologic selective pressure during persistent viremia becomes the strongest determinant of the selection and emergence of RAM-harbouring HIV variants, as opposed to the scenario of an abrupt and complete drug interruption, in which case this outcome is less likely to occur.

Ritonavir-boosted darunavir is a second-generation PI with the highest genetic barrier to the development of resistance and constitutes the cornerstone of deep-salvage ART regimens. The susceptibility of HIV to darunavir is significantly decreased in viral strains harbouring three or more of the 11 DRV-RAMs (21,22). In a study of a sample of PI-experienced Mexican patients (with a history of being exposed to a median of two PIs), the prevalence rate of genRT showing three or more DRV-RAMs was 4.4% (23). In contrast, we found that 19% of subjects from the same population of that study but with a migration background had an infection with viral strains showing three or more DRV-RAMs. Similarly, viral strains harbouring three or more PI-mRAMs are generally less susceptible to the antiviral effect of most PIs. Thus, salvage regimens might be less effective in patients with virologic failure and an international migration history.

There are several barriers to accessing HIV health services among undocumented migrants, such as lack of health insurance, fear of discrimination and deportation, educational level, and lack of social networks, among others. These barriers, which may occur throughout all five phases of the migratory process, preclude continued access to proper ART and raise the probability of selecting resistant HIV strains (5,7–9). In the U.S., García et al. found that the HIV-infected Latino population was not receiving appropriate care, with only 54% retained in care, 44% receiving ART, and 36% achieving viral suppression (24). Acknowledging that migrants, mainly undocumented, are highly vulnerable to discrimination, criminalization, and health care inequality, international, bilateral, and humanitarian efforts to eradicate these practices are urgently needed.

We also observed a higher prevalence of HCV infection among persons with a background of stay in the United States. A possible explanation for this is that migrants, as part of their transit on their way to the United States, commonly have a temporary stay in cities located on the international border, such as the city of Tijuana, Mexico. Tijuana is positioned along a major drug trafficking route and is also a city with a high risk of acquiring blood-borne viral infections (such as HCV) due to high-risk injection behaviors (limited access to sterile syringes and needle sharing among injection drug users). It is likely that some migrants could have had a higher exposure to HCV acquisition, as opposed to non-migrants, by having lived in places with a more frequent illegal drug-injection and commercial-sex practices as compared to other parts of the country. However, this is just a hypothesis since the information available in our database does not allow a further inquiry into the higher prevalence of HCV among migrants compared to non-migrants.

Our study had several limitations related to incomplete or unreliable information (of variables not included in the analysis) retrieved from questionnaires filled out by treating physicians (secondary information). The level of adherence to ART was not measured with a validated tool, such as the Adult AIDS Clinical Trials Group (AACTG) questionnaire; this precluded us from comparing drug-intake behaviours between groups and testing the hypothesis of more inconsistent access to (and intake of) antiretroviral drugs in migrants. Additionally, because our data were collected retrospectively (by a recall strategy), complete and reliable ART histories are lacking, particularly among migrants. Inaccurate data on the ART regimen histories of the individuals impeded us from assessing the hypothesis that migrants more frequently received suboptimal regimens than non-migrants. Last, we had no data about access to health care services during the stages of the migratory process, which prevented us from testing the hypothesis that the lack of access to healthcare is one of the major determinants of the inconsistent intake of antiretroviral drugs in migrant populations. Moreover, we were unable to measure and control for various other potential confounders, such as: migration features,

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socioeconomic status, and route of transmission. Finally, our results are not generalizable to all HIV-infected Mexican migrants and non-migrants, since the source of patients in our study was a referral site characterized by heavily antiretroviral-exposed individuals during a median of 10 years and a median of three previous ART schemes.

Our data support the following recommendations: a) in HIV-infected individuals showing virologic failure to ART who have a migration background, a viral resistance test is mandatory, a peer-advisory strategy needs to be offered to their physicians, and access to deep-salvage antiretroviral regimens ought to be assured; and b) the barriers to HIV health care need to be urgently addressed, and strategies aimed at reversing them should be implemented.

## Conclusions

This is the first epidemiological study in ART-experienced HIV-infected individuals showing that an international migration background is associated with an increased rate of persons infected with HIV-quasispecies harbouring multiple protease inhibitor RAMs, regardless of time spent on ART and number of regimens of prior antiretroviral exposure. We hypothesize that this could be driven by a more inconsistent intake of ART during migration and repatriation compared with the level of adherence among ART-non-adherent Mexicans without such a background. This finding is relevant in the clinical approach to migrants with virologic failure, highlighting the importance of inquiring the migratory background and treatment experience of patients, and supports multidisciplinary strategies aimed at offering continuous and effective health care services during all stages of the migratory process.

## Declaration of Competing Interest

JJC has served as consultant on advisory boards for Janssen Pharmaceutical and Merck and reports personal honoraria from Gilead, Bristol-Myers Squibb, and GlaxoSmithKline. SL, CH, RL-F, JMS-D, and JPR-H have nothing to declare.

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