BRIEF REPORT

# TRANSMITTED RESISTANCE IN HIV-1 OF PATIENTS FROM NINE DEPARTMENTS OF PERU

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## ABSTRACT

The main aim of this research is to identify the transmitted resistance (RT) of the Human Immunodeficiency Virus (HIV) in subjects from nine cities of Peru. For this, a descriptive and cross-sectional study was carried out in 135 adult subjects who agreed to participate through an informed consent. Blood samples were collected to perform the CD4 / CD8 cell count, viral load and HIV Genotyping. Socio-epidemiological information was collected from the participants through surveys. The results revealed a RT frequency of 9.8% (13/132). The information from this research might help improve the intervention and monitoring programs for antiretroviral resistance in the country.

**Keywords**: Genotype; Drug resistance; HIV (Source: MeSH NLM).

## INTRODUCTION

HIV/AIDS affects more than 36 million people worldwide; although the pandemic is still on the rise, the AIDS mortality rate has declined by as much as 34%, mainly due to increased antiretroviral therapy (ART) coverage [1].

It should be noted that when a resistant HIV genotype is transmitted to a healthy or previously infected person, it will result into transmitted resistance (TR) [2], which is related to the risk of virologic failure in patients that initiate ART [3]. In this regard, it is important to identify and perform surveillance of TR through HIV genotyping tests [2].

Regarding the prevalence of TR in Latin American and Caribbean (LAC) countries, a recent systematic review conducted on 81 studies between 2006 and 2015 revealed a frequency of 7.7% [4]. Likewise, a review conducted on 358 studies in 64 countries revealed that the prevalence of TR in LAC was 12%, higher than Asia (2%) and Africa (9%) [5].

Among the socioepidemiological factors related to TR, associations have been found between the population of men who have sex with men (MSM) [6], virological failure [7] and with sexually transmitted infections (STIs) [8], suggesting that there is not necessarily a common factor associated with TR.

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Most of the studies of TR in Peru were conducted in the city of Lima and showed that prevalence ranges from 1% to 14% [10-12]. These differences in the prevalence of TR could be related to the study period, methodological design, type of genotypic test used, size, origin and characteristics of the participants in each study.

Likewise, it is not known whether the frequency of TR in Lima is similar to that of other Peruvian departments, since the transmission dynamics in the capital city are different from those in the rest of the country [13]. In addition, socioepidemiological factors in Peruvian patients with TR have not been described. Therefore, the aim of this study was to estimate the frequency of TR in ART-naive HIV/AIDS patients in nine Peruvian departments. Additionally, the socioepidemiological factors found in the participants were described.

### KEY MESSAGES

**Motivation for the study:** The study resulted from the lack of information at the national level on the situation of transmitted resistance (TR) to antiretrovirals in the Peruvian population.

**Main findings:** This study showed that TR is moderate according to World Health Organization (WHO) classification.

**Implications:** Improvement of public policies for treatment and sex education campaigns, in order to help decrease TR cases throughout Peru.

## THE STUDY

A descriptive, cross-sectional study was carried out between July 2014 and December 2015 in 29 of the 79 public health facilities of the Peruvian Ministerio de Salud. These centers were selected because they cover 87.9% of patients that initiated ART nationwide [13] and correspond to nine Peruvian departments (Arequipa, Ica, Junín, Lambayeque, La Libertad, Lima, Loreto, Piura, and San Martín).

The sample size was calculated using the statistical program Epidat version 3.1, considering a prevalence of TR of 7.7% [4], assuming an absolute error of 5%, a 95% confidence level and a data loss rate of 20%, with which we established that at least 132 patients would be included. Table 1 shows the distribution of participants by department. The type of sampling applied was consecutive non-probabilistic, including patients of both sexes with at least 18 years of age, confirmed HIV diagnosis by ELISA, Western Blot, linear immunoblot assay (LIA) or indirect immunofluorescence (IFI), without previous ART. Patients with mental disorders and pregnant women were not considered.

The ethical principles established during the informed consent (IC) procedure followed during patient recruitment. In addition, participants completed a written survey to collect socio-epidemiological and clinical information about them. Peripheral blood samples were then collected and transferred to the National Referral Laboratory for STD/HIV-AIDS of the Instituto Nacional de Salud (INS) in Lima in sealed boxes labeled with the place of origin. Patient information was entered in an Excel database with restricted access and in charge of the principal investigator, while the ICs were archived under lock to ensure the confidentiality of the participants.

For HIV genotyping, a 1020 bp region was amplified by two rounds of PCR [14] and then, the sequence was determined by the Sanger method using the ABI 3500 XL genetic analyzer (Thermo Fisher Scientific®, United Kingdom). Samples that did not amplify by the In-House platform were handled using the commercial Trugene® method (Siemens Healthcare Diagnostics Inc. Deerfield, Illinois, USA). The consensus sequence was obtained using the RECall program (beta v3.05) [15].

To perform the analysis of resistance mutations, the sequences were entered into the HIVdb Program (https://hivdb.stanford.edu/hivdb/by-mutations/) of the Stanford University HIV Drug Resistance Database version 8.8, while the quality control of the sequences was performed with the World Health Organization (WHO) Quality Control Tool (https://pssm.cfenet.ubc.ca/who_qc).

Viral load was determined by an automated (Cobas) real-time PCR system using Taqman probes (Roche, Branchburg, USA), while CD4/CD8 count was performed by flow cytometry through the BD Multitest™ IMK kit and Facscanto II cytometer (BD).

The data collected were processed with the Stata v14.2 statistical package (Stata Corporation, College Station, Texas, USA). Descriptive results were obtained by using proportions for qualitative variables (department of residence, clinical status, sexually transmitted infection, type of STI and mutation identified) and mean with standard deviation for quantitative variables: age, time of diagnosis (years), number of sexual partners in the last year, number of sexual partners


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**Table 1.** Socio-epidemiological and virological characteristics of the study sample.

| Characteristics | n (%) / mean ± SD |
|---|---|
| Age | 35.1 ± 10.77 |
| Sex | |
| Female | 26 (19.3) |
| Male | 109 (80.7) |
| Department of residence | |
| Arequipa | 6 (4.4) |
| Ica | 3 (2.2) |
| Junín | 10 (7.4) |
| La Libertad | 7 (5.2) |
| Lambayeque | 16 (11.9) |
| Lima/Callao | 41 (30.4) |
| Loreto | 17 (12.6) |
| Piura | 3 (2.2) |
| San Martín | 32 (23.7) |
| Years with HIV diagnosis † | |
| Arequipa | 2.00 ± 1.79 |
| Ica | 4.00 ± 5.66 |
| Junín | 1.40 ± 1.26 |
| La Libertad | 1.86 ± 1.86 |
| Lambayeque | 2.56 ± 1.41 |
| Lima/Callao | 1.90 ± 2.35 |
| Loreto | 1.25 ± 2.14 |
| Piura | 1.67 ± 1.15 |
| San Martín | 0.90 ± 0.49 |
| Total | 1.67 ± 1.89 |
| Clinical status | |
| AIDS | 45 (33.3) |
| Not AIDS | 78 (57.8) |
| Not established | 12 (8.9) |
| Sexually Transmitted Infection | |
| Yes | 43 (33.1) |
| No | 81 (62.3) |
| Not specified | 6(4.6) |
| Virological and immunological status | |
| Viral load (copies/mL) | 247,150.8 ± 39,194.7 |
| CD4 cell count (cells/μL) | 282.6 ± 222.7 |

† Time since HIV infection was first detected to enrollment in the study.
n: number of participants; SD: standard deviation.

in the last six months, CD4, CD8 and CD3 cell counts, viral load (copies/mL), viral load (log10). Resistance, viral load and CD4/CD8 results were reported in the INS NetLab system (https://www.netlab.ins.gob.pe/FrmNewLogin.aspx) for the treatment of participants by their treating physicians.

The project was approved by the Institutional Research Ethics Committee of the INS with code OI-094-13.

## FINDINGS

A total of 135 participants with HIV diagnosis were recruited from different regions of the country (Table 1). The population was characterized by being mostly male (80.7%) with a mean age of 35.1 ± 10.8. We also found that patients residing in Ica had HIV diagnosis for the longest time (4.00 ± 5.66 years) while those from San Martin had a more recent time of diagnosis (0.90 ± 0.5 years). The virological and immunological status of the participants revealed 247 150.8 ± 39 194.7 RNA copies/mL and CD4 lymphocyte count of 282.6 ± 222.7 cells/mL, with 33.3% of patients in the AIDS phase and 90.7% of STIs in the male population.

The genotype of 132 participants was analyzed. Three HIV samples were excluded because they were not reactive to RT-PCR and sequencing tests, both in-house and commercially available. The frequency of TR in the studied population was 9.8% (13/132), with five cases in Lima, four in San Martín, two in Lambayeque and one each in La Libertad and Piura.

Analyzing TR by department and according to the type of antiretroviral (ARV), a higher frequency was observed for the non-nucleoside reverse transcriptase inhibitor (NNRTI) group (6.1%, 8/132), with Lima and San Martín reporting the highest rates (Table 2). ARV resistance mutations were mainly associated with NNRTI (n = 10; 7.6%), predominantly the E138A mutation (2.3%), which confers a low level of resistance to rilpivirine (RPV) (Table 3). Likewise, we also observed the K103N mutation (1.5%), which is associated with a high level of resistance to efavirenz and nevirapine. The analysis of socio-epidemiological factors revealed that the mean number of sexual partners in the last year was higher in those patients who presented TR (10.8 ± 27.5) (Table 4).

## DISCUSSION

According to our findings, the frequency of TR in Peru (9.8%), corresponds to a moderate level of resistance according to WHO [16], similar to what other LAC countries (from 8.2% to 12.8%) reported between 2014 and 2016 [4].In contrast to our study, Lama *et al.* [9] reported a TR frequency of 3.3%, despite the fact that the study population corresponded to MSM, which is characterized by high-risk sexual behavior for HIV/STI transmission [17]. This value is probably related to the period in which the study was conducted,

**Table 2.** Frequency of antiretroviral-resistant HIV genotype according to department and according to the antiretroviral group used.

| Department | n | Resistance to anyARV n (%) | Resistance to PI n (%) | Resistance to NRTI n (%) | Resistance to NN-RTI n (%) |
|---|---|---|---|---|---|
| Arequipa | 6 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Ica | 3 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Junín | 10 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| La Libertad | 7 | 1 (14.3) | 0 (0.0) | 0 (0.0) | 1 (14.3) |
| Lambayeque | 15 | 2 (13.3) | 0 (0.0) | 0 (0.0) | 2 (13.3) |
| Lima/Callao | 40 | 5 (12.5) | 1 (2.5) | 0 (0.0) | 4 (10.0) |
| Loreto | 17 | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Piura | 3 | 1 (33.3) | 1 (33.3) | 0 (0.0) | 0 (0.0) |
| San Martín | 31 | 4 (12.9) | 2 (6.5) | 1 (3.2) | 1 (3.2) |
| Total | 132 | 13 (9.8) | 4 (3.0) | 1 (0.8) | 8 (6.1) |

n: number of participants; ARV: antiretroviral; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor.

when ART in Peru was just beginning to be implemented, shortly after WHO began monitoring the drug resistance emergency [16].

On the other hand, the mutations identified in this study were mostly related to NNRTI resistance, in concordance with the resistance recently described in MSM and transgender population in Lima [12] and with different reports in LAC countries [5,6]. Likewise, TR compared with NNRTIs could be related to acquired resistance in the Peruvian population, where we recently identified a high prevalence of NNRTI resistance [18].

**Table 3.** Frequency of resistance mutations identified according to type of antiretroviral.

| Associated mutation | n (%) | ARV | RL |
|---|---|---|---|
| PI | | | |
| Q58E | 3 (2.3) | FPV | Low |
| L10F | 1 (0.7) | TPV | Low |
| Total | 4 (3.0) | | |
| NRTI | | | |
| T215N | 1 (0.7) | AZT, D4T | Low |
| Total | 1 (0.7) | | |
| NNRTI | | | |
| E138A | 3 (2.3) | RPV | Low |
| K103N | 2 (1.5) | EFV, NVP | High |
| V106I | 2 (1.5) | DOR | Low |
| V108I | 2 (1.5) | NVP | Low |
| A98G | 1 (0.8) | DOR, EFV, RPV | Low |
| Total | 10 (7.6) | | |

PI: protease inhibitors; NRTI: nucleoside reverse transcriptase inhibitors; NNRTI: non-nucleoside reverse transcriptase inhibitors; n: total number of mutations; ARV: antiretroviral affected by mutation; RL: resistance level according to HIV db classification of the HIV Drug Resistance Data Base Program of Stanford University; FPV: fosamprenavir; TPV: tripnavir; AZT: zidovudine; D4T: stavudine; NVP: nevirapine; RPV: rilpivirine; EFV: efavirenz; DOR: doravirine;.

On the other hand, the studies reported by Soria *et al.* [10,11] conducted in the city of Lima revealed considerable differences in TR in two time periods, from a low level (1% between 2007 and 2009) to a high level (14% between 2014 and 2015), which suggests that TR is experiencing an increase over time, as has been reported in other countries, where TR rose from low to moderate in only six years [16]. These data suggest the need for longitudinal studies or periodic national surveillance to identify changes in TR over time, in order to take appropriate prevention measures and reduce HIV transmission in the population.

It should be noted that among the socio-epidemiological factors studied, we identified that the mean number of sexual partners in the last year was higher in the group that presented TR. Although these findings are descriptive, they suggest that sexual promiscuity could be playing an important role in the transmission of resistant strains of HIV, which could explain the high prevalence of TR found in MSM and transgender population in Lima [12] and in other related studies [4,5].

The main limitation of this study is the time elapsed since the samples were collected (>5 years). However, we consider that the findings described in this article will help to better understand the phenomenon of TR in Peru, which


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**Table 4.** Transmitted resistance to antiretrovirals in HIV-1 according to socio-epidemiological, virological and immunological characteristics.

| Characteristics | No resistance | | With resistance (n=13) |
|---|---|---|---|
| | n | Mean ± SD | Mean ± SD |
| Age | 116 | 35.4 ± 10.9 | 32.9 ± 9.5 |
| Time to diagnosis (years) | 114 | 1.7 ± 2.0 | 1.3 ± 0.9 |
| Number of sexual partners in the last year | 111 | 6.7 ± 29.9 | 10.8 ± 27.5 |
| Number of sexual partners in the last 6 months | 111 | 3.7 ± 17.6 | 0.8 ± 1.3 |
| CD4 cell count (cells/μL) | 117 | 274.0 ± 220.3 | 274.7 ± 170.4 |
| CD8 cell count (cells/μL) | 117 | 1,054.9 ± 561.9 | 804.9 ± 573.8 |
| CD3 cell count (cells/μL) | 117 | 1,380.4 ± 693.2 | 1,141.5 ± 718.2 |
| Viral load (copies/mL) | 118 | 259,740.2 ± 407,699.8 | 151,753.7 ± 199,932.0 |
| Viral load (log10) | 118 | 5.0 ± 0.7 | 4.8 ± 0.7 |

n: number of participants; SD: standard deviation.

will allow us to propose new public health policies focused on generating changes in first-line ART strategies through early identification of the resistant genotype.

In conclusion, our study shows that TR in Peru is moderate, mainly to NNRTI, highly prevalent in coastal and jungle departments, and in people with multiple sexual partners. Consequently, further surveillance studies are required to determine the current situation of TR in Peru, as well as its associated factors.

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