The Brazilian Journal of

INFECTIOUS DISEASES

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Original article

Geolocalization of HIV-1 subtypes and resistance mutations of patients failing antiretroviral therapy in Salvador – Brazil

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ARTICLE INFO

ABSTRACT

Background: Geographical distribution of HIV variants is an important way to understand the circulation and spread of such viral strains.

Objectives: To evaluate the spatial distribution of HIV-1 variants in patients failing antiretroviral therapy, in Salvador, Brazil.

Methods: We performed a cross-sectional evaluation of HIV resistance test reports of patients who underwent genotyping tests in a referral center in Salvador, Brazil, for the years 2008–2014. The laboratory database contains around 2500 resistance reports of patients failing antiretroviral therapy. Genotypic tests were performed by sequencing of HIV-1 POL region (TrueGene, Siemens). We assessed HIV-1 resistance mutations and subtype, as well as residential address, age, and gender of patients.

Results: We evaluated 1300 reports, 772 (59.4%) of them from male patients. As expected, subtype B predominated (79%) followed by subtypes F1 (6.7%) and BF (6.5%). The most frequent mutations in HIV-1 reverse transcriptase were 184V (79.1%), 41L (33.5%), 67N (30.4%), 103N (42.4%), and 108I (11.1%). Most frequent mutations in HIV-1 protease were 63P (52.4%), 36I (47.9%), 15 V (33.0%), 62 V (28.1%) and 13 V (25.8%). Some mutations (41L, 215Y, 210W) were significantly more frequent among men. We detected a significantly higher accumulation of 103N mutation in specific areas of Salvador. We identified a more restricted circulation pattern for subtype FB (more frequent in some regions), and F1 (almost absent in a specific region).

Conclusion: Our results suggest that specific subtypes/resistance mutations present a distinct frequency rate in specific areas of Salvador, probably due to a restricted circulation pattern. This trend to clustering was observed in regions covered by AIDS referral centers, suggesting that pattern of care for such patients can interfere in virological outcomes.

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Introduction

The estimated number of people infected with HIV worldwide exceeds 34 million cases.[1] Brazil has about 608,230 cases of infection (17.9/100,000 inhabitants).[2] The Northeast region reported 12.9% (78,686) of cases, 19,290 (24.5%) of them in Bahia state.[2] Salvador, state capital city, ranks third among Northeastern cities with the highest infection rate (28.9/100,000).[2]

One of the main obstacles to create a vaccine against HIV is the great genetic diversity presented by the virus, which varies according to different regions. These genetic mutations can be associated with different patterns of viral circulation and resistance to antiretrovirals.[3–5] The epidemic in Bahia is characterized by a high genetic variability, with circulation of subtypes B, F, D and its recombinant forms.[6,7] Social factors (population growth, urbanization, transportation, habits, and sexual behavior) contribute to the dispersion and to genetic diversity of the virus.[8,9] Molecular epidemiology can be used to determine the history of viral evolution, the spatial spread, to identify the focus of viral dynamics, and how it takes place in a specific population.[10–12]

There are few studies in Latin America and Brazil about spatial dispersion of HIV-1 variants. It is extremely important to identify the geographical distribution of the virus in these countries, to understand its genetic diversity, and to evaluate potential factors driving the epidemic in specific areas. The objective of this study was to assess the spatial distribution of genetic mutations and viral subtypes of HIV-1 strains detected among patients failing antiretroviral therapy, in Salvador, Brazil.

Methods

Study design, population, and settings

This was a cross-sectional study. Genotypic test reports were retrieved from the database of the Laboratório de Pesquisa em Infectologia (Infectious Diseases Research Laboratory, LAPI), located at the University Hospital Professor Edgard Santos (HUPES), Federal University of Bahia, in Salvador, Brazil. Until February 2016, LAPI was the only public reference laboratory in Bahia to perform free of charge HIV resistance testing. To guarantee sample consistency we collected data for the years 2008–2014, since most of currently used antiretroviral drugs were already available in that period of time.

The HUPES is located in a central area of Salvador and serves predominantly patients from Salvador and surrounding cities. Data were collected from the LAPI genotyping database (which contains information on approximately 2500 patients), and included only those living in Salvador, with a residential address that could be identified by a valid postal code. A final sample of 1300 patients was included. We collected data on age, sex, residential address, and genotyping test reports. Genotyping was performed through a commercially available platform (TrueGene, Siemens, USA), according to manufacturer's instructions. HIV-1 drug-resistance mutations for each antiretroviral drug were assessed according to the IAS list.[13]

Statistical analysis

The collected information was stored in a database, and analyzed by using SPSS version 18 package. Frequency of HIV-1 subtypes and resistance mutations were expressed in percent, and adjusted for age, sex, and spatial location. The comparison between frequency of HIV-1 mutations/subtypes by sex/origin was performed by *chi-square* test. Mean age was compared using Student's *t*-test.

Georeference of HIV-1 variants

Kernel density estimations and georeferencing was done using ArcGIS 10.3 (ESRI, 17 Redlands, CA, USA). Patients were grouped according to their informed postal code, in the different administrative regions of Salvador. Postal code was used to define patients geospatial localization.

Results

Population and setting

We collected data from 1300 genotyping reports from February 2008 to December 2014. All individuals fulfilling the requirements to participate in the study had the genotyping test performed at LAPI. Among participants, 772 (59.4%) were men (mean age 42 ± 9.4 years) and 528 (40.6%) were women (mean age 39 ± 9.6 years, $p = 0.002$, for comparison of mean age by sex).

We identified a total of 126 districts which were grouped according to the 16 administrative regions of the city of Salvador. We identified eight regions (listed in Table 1) as the origin of the majority (79%) of patients, while the remaining eight regions contributed to only 21% of the studied sample.

Frequency and distribution of HIV subtypes

The main subtypes identified were B (78.5%), F1 (6.7%), and FB (6.5%), while the other subtypes were present in less than 3% of the studied patients. Subtype B was the most common variant and was present in all regions, with no significant variation in its geographical distribution. However, subtype FB predominated in regions II, III, IV and XVI, and was less frequent in regions V, XI and XII, as it can be seen in Fig. 1 ($p = 0.008$).

On the other hand, subtype F1 was less frequent in region V, though this difference was only marginally non-significant as can be seen in Fig. 1 ($p = 0.064$).

Resistance mutations

The most frequent mutations associated with resistance to Nucleoside Reverse Transcriptase Inhibitors (NRTIs) were 184V (79.1%), 41L (33.5%), 67N (30.4%), 215Y (24.6%), 70R (24.5%), and 210W (22.3%). Other mutations had a frequency lower than 20%. The frequency of the thymidine-associated mutations (TAM) 41L and 210W was significantly higher among men than among women (34% vs 29%, $p = 0.04$, and 24% vs 17%, $p = 0.002$, respectively). Another TAM (215Y) showed a trend for a higher