Resistance to protease inhibitors and HIV-1 genetic variability in V3 region in people living with HIV/AIDS

Resistência aos inibidores de protease e variabilidade genética do HIV-1 na região V3 em pessoas vivendo com HIV/AIDS

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Dear Editor

One of the main characteristics of HIV-1 is its high genetic variability and the occurrence of resistance mutations to antiretroviral therapy (ART), particularly in individuals who use these medications for prolonged periods[1]. In addition, HIV-1 has a high mutation rate in the env gene, particularly in the variable region 3 (V3 region), which has implications for viral infectivity, virus neutralization by antibodies, and host coreceptor tropism[2]. Therefore, this study described the genetic variability of HIV-1, regarding the protease and V3 region of the env gene, as well as the profile of protease inhibitors (PIs) resistance mutations in people living with HIV/AIDS (PLWHA) using ART, over more than 10 years in the city of Belém, Pará, Northern Brazil.

Blood samples were collected from 17 PLWHA at two time points, the first between 1996 and 2001 and the second in 2017. DNA isolation, amplification of the protease and C2V3 regions of HIV-1, and nucleotide sequencing were performed in both periods (accession numbers in GenBank: PP333467 a PP333484). In 17 PLWHA, 58.8% were male and 41.2% female. The average age in 2017 was 56.2 years, ranging from 41 to 73 years. The majority identified as heterosexual (52.9%), and most individuals had completed high school education (35.3%). They received the diagnosis of HIV-1 infection between 1996 and 1999 (41.17%) and initiated ART between 1998 and 1999 (35.29%).

About the profile of resistance mutations in the nucleotide sequences of the protease, two samples (BRPA_26865 and BRPA_26967) presented the mutations D30N and M46I in the first time, and only one sample (BRPA_26898) displayed the accessory resistance mutation G73S in the second time. One sample (BRPA_26888) was non-functional due to G/A-type hypermutations. About the amino acid sequence in the V3 segment region of the HIV-1 envelope, the most frequent variant was GPGR (52.9%) followed by GWGR (35.3%), and one sample with the GFGR variant (5.9%) and one with the GWRR variant (5.9%). According to the determination of the tropism for the coreceptor, most of the samples showed tropism for the R5 coreceptor (76.4%), and only 23.6% obtained tropism for the X4 coreceptor.

A retrospective cohort study in Minas Gerais, Southeastern Brazil, also found a decrease in the rate of resistance mutations for PIs and nucleoside reverse transcriptase inhibitors (NRTIs), despite the doubling of the number of patients initiating ART in Brazil from 2002 to 2014[3]. A study conducted in Manaus, Northern Brazil, in 2018–2019 found a high rate of drug resistance mutations (DRMs) in PLWH with treatment failure. The most common mutations were M184I/V to NRTIs and K103N/S to non-NRTIs (NNRTIs)[4].

In our patients, we found the accessory DRMs G48R and G73S to PIs in one isolate of subtype B. The mutation G48V is a non-polymorphic mutation selected by the drug saquinavir (SQV) and, less frequently, by LPV. The mutation in this position can confer high-level resistance to SQV and intermediate-level resistance to atazanavir (ATV). Similarly, the mutation G48M is also a non-polymorphic mutation selected in highly resistant PI viruses. However, other mutations such as G48A/R/S/T/Q are considered rare non-polymorphic mutations, selected in viruses with multiple PI resistance mutations.

Finally, this is the first study on the genetic variability of HIV-1, regarding the protease and V3 region of the env gene, over more than 10 years in the city of Belém, Pará, Northern Brazil. Our findings agree with previous studies that have shown that the most frequent circulating variants of subtype B in Brazil are GPGR and GWGR[5]. Thus, a low genetic variability of HIV-1 was observed for both regions, among individuals, in the two study periods. No major DRMs to PIs were found, and only one sequence had an accessory mutation.

Approval by the Human Research Ethics Committee

Not required for this type of article.

Participation of each author

MESA: Conceptualization. DLAP: Writing – original draft. MSB: Writing – original draft. HNFE: Writing – original draft. FBF: Writing – review & editing. RRSF: Writing – review & editing. ABOF: Writing – review & editing. LFAM: Conceptualization, Project administration.

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Conflict of interests

The authors declare no conflict of interests.

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