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Extensive variation in drug-resistance mutational profile of Brazilian patients failing antiretroviral therapy in five large Brazilian cities

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ABSTRACT

Background: Development of drug-resistance mutations is the main cause of failure in antiretroviral therapy. In Brazil, there is scarce information on resistance pattern for patients failing antiretroviral therapy.
Objectives: To define the HIV mutational profile associated with drug resistance in Brazilian patients from 5 large cities, after first, second or further failures to antiretroviral therapy.
Methods: We reviewed genotyping results of 1520 patients failing therapy in five Brazilian cities. Frequency of mutations, mean number of active drugs, viral susceptibility to each antiretrovirals drug, and regional differences were assessed.
Results: Mean time of antiretrovirals use was 22.7 ± 41.1 months. Mean pre-genotyping viral load was 4.2 ± 0.8 log (2.1 ± 2.0 after switching antiretrovirals). Mean number of remaining active drugs was 9.4, 9.0, and 7.9 after 1st, 2nd, and 3rd failure, respectively. We detected regional variations in drug susceptibility: while BA and RS showed the highest (~40%) resistance level to ATV/r, FPV/r and LPV/r, in the remaining cities it was around half of this rate. We detected 90% efavirenz/nevirapine resistance in SP, only 45% in RS, and levels between 25% and 30% in the other cities. Regarding NRTI, we found a similar pattern, with RJ presenting the highest, and CE the lowest susceptibility rates for all NRTI. Zidovudine resistance was detected in only 3% of patients in RJ, against 45–65% in the other cities. RJ and RS showed 3% resistance to tenofovir, while in CE it reached 55%. DRV/r (89–97%) and etravirine (61–85%) were the most active drugs, but again, with a wide variation across cities.

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Conclusions: The resistance mutational profile of Brazilian patients failing antiretroviral therapy is quite variable, depending on the city where patients were tested. This variation likely reflects distinctive choice of antiretrovirals drugs to initiate therapy, adherence to specific drugs, or circulating HIV-1 strains. Overall, etravirine and DRV/r remain as the most active drugs.

Introduction

Resistance to antiretrovirals (ARV) is a usual finding in HIV-infected patients failing antiretroviral therapy (ART). The mutational pattern after initial failure is quite predictable, but in subsequent ARV regimens it may become very complex, and frequently limit the available treatment options.[1] In addition, the use of different algorithms for interpretation of mutational profiles obtained by genotypic tests might provide divergent results regarding sensitivity of HIV to ARV drugs to be used in salvage therapy regimens.

The Brazilian Ministry of Health (BMOH) provides free universal access to ARV drugs since the beginning of the epidemic. The current official recommendation for patients failing therapy is to choose salvage regimens according to HIV-1 antiretroviral drug sensitivity, assessed by genotypic resistance tests.[2] However, although resistance tests are supposed to be readily available, many logistical problems have impaired this strategy, due to long turnaround time of results in some areas of the country, and to the fact that many physicians decide to switch therapy without a previous resistance test.

In addition, the genotypic characteristics of HIV in patients failing ART is still unclear, since the available information is restricted to small, specific groups of patients, from different sites. In Brazil, circulation of different viral subtypes has been reported, with variable prevalence according to different regions.[3–6] There is scarce information on regional differences regarding mutational profile, availability of remaining active drugs, and the variability of susceptibility rates for different ARV drugs, according to the use of different algorithms.

In the last years, the routine tool for genotypic interpretation was a locally developed algorithm (RENAGENO), in which interpretation of results are released along with that provided by TruGene platform (Siemens Healthcare Diagnostics, Inc, USA).[7] In last decade BMOH trained around 400 doctors for interpreting genotypic reports, and to provide suggestions for the next ARV regimen to be used by physicians. This strategy made easier the selection of appropriate ARV drugs in salvage therapy regimens.

In the present work we evaluated a large number of resistance tests, in five large Brazilian cities. This allowed us to define the frequency of mutations after first or subsequent failures, as well as the differences between drug susceptibility rates across these locations, and mean number of remaining active drugs for patients at each site.

Methods

We reviewed reports of resistance tests performed from 2010 to 2013 in five large Brazilian cities, from different regions. All available reports from patients tested in reference centers for HIV care in Porto Alegre (RS, South region), Campinas (SP, Southeast region), Rio de Janeiro (RJ, Southeast region), Vitoria (ES, Southeast region), Salvador (BA, Northeast region), and Fortaleza (CE, Northeast region) were reviewed.

Frequency of detected drug-resistance mutations (DRM), previous use of antiretroviral drugs, and patients' characteristics were evaluated, and the mean number of fully active drugs was calculated for each city and for the overall study population. Fully active drugs were attributed a weight equal to one. Drugs partially active ("intermediate resistance") were given a 0.5 weight, while for complete resistance the attributed weight was zero. The susceptibility for each drug was compared by using the Brazilian algorithm of interpretation (RENAGENO), according to patient's origin.[7]

Statistical analyses

We used SPSS (Statistical Package for Social Sciences) version 17.0 to perform all statistical calculations. Descriptive analyses (frequencies, mean, standard deviations) were performed, and comparisons of frequencies between groups were assessed by chi-square test.

Results

A total of 1512 genotypic tests was reviewed in the study period, but only 1481 had enough information to be included in the analysis. Most tests were performed in patients from Salvador (552), followed by Vitória (246), Fortaleza (219), Rio de Janeiro (152), Porto Alegre (112), and Campinas (102 tests). Table 1 shows the main characteristics of patients submitted to HIV-1 genotyping.

Most patients (675 subjects – 43.1%) were failing their second ARV regimen, 431 (37.8%) were failing their first ARV treatment, and the remaining 375 (15%) had already failed three or more regimens. The most frequently detected DRM (>10%) are shown in Tables 2 and 3. The susceptibility rates of HIV-1 strains to each ARV drug in the five different locations are shown in Figure 1a–c. It should be pointed out the clear difference between the susceptibility rates to reverse