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Transmitted drug resistance in patients with acute/recent HIV infection in Brazil

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ABSTRACT

Introduction: The widespread use of antiretroviral therapy increased the transmission of antiretroviral resistant HIV strains. Antiretroviral therapy initiation during acute/recent HIV infection limits HIV reservoirs and improves immune response in HIV infected individuals. Transmitted drug resistance may jeopardize the early goals of early antiretroviral treatment among acute/recent HIV infected patients.

Methods: Patients with acute/recent HIV infection who underwent resistance test before antiretroviral treatment initiation were included in this analysis. HIV-1 sequences were obtained using an in house protease/reverse transcriptase genotyping assay. Transmitted drug resistance was identified according to the Stanford HIV Database for Transmitted Drug Resistance Mutations, based on WHO 2009 surveillance list, and HIV-1 subtyping according to Rega HIV-1 subtyping tool. Comparison between patients with and without transmitted drug resistance was made using Kruskal–Wallis and Chi-square tests.

Results: Forty-three patients were included, 13 with acute HIV infection and 30 with recent HIV infection. The overall transmitted drug resistance prevalence was 16.3% (95% confidence interval [CI]: 8.1–30.0%). The highest prevalence of resistance (11.6%, 95% CI: 8.1–24.5) was against non-nucleoside reverse transcriptase inhibitors, and K103N was the most frequently identified mutation.

Conclusions: The high prevalence of nonnucleoside reverse transcriptase inhibitors resistance indicates that efavirenz-based regimen without prior resistance testing is not ideal for acutely/recently HIV-infected individuals in our setting. In this context, the recent proposal of including integrase inhibitors as a first line regimen in Brazil could be an advantage for the treatment of newly HIV infected individuals. However, it also poses a new challenge, since integrase resistance test is not routinely performed for antiretroviral naive individuals. Further studies on transmitted drug resistance among acutely/recently HIV-infected are needed to inform the predictors of transmitted resistance and the antiretroviral therapy outcomes among these population.

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Introduction

The widespread usage of antiretroviral therapy (ART) and the increased survival of individuals using it favor the transmission of resistant HIV strains. Transmitted drug resistance (TDR) may be higher among patients with acute infection than in patients with chronic HIV infection.[1,2] This may lead to a more rapid decline in CD4 cell counts prior to ART initiation and limit both the magnitude and duration of treatment response.[3–7] TDR testing during acute HIV infection (AHI) provides increased sensitivity for the detection of primary drug resistance even before the overgrowth of drug-sensitive viral quasi-species.[8]

Early ART initiation during acute and recent HIV infection have benefits in limiting HIV reservoirs and improving immune response[9,10] if a full active ART regimen is promptly initiated. TDR may affect the time for ART response (virologic clearance) and jeopardize the early treatment goals among acute/early HIV infected individuals.

Currently, TDR testing is not standardized in most resource-limited settings, including Brazil. However, TDR surveillance is needed to assess the emergence and spread of drug-resistant strains in order to inform HIV treatment guidelines.

The HIV epidemic in Brazil persists concentrated and unabated among men who have sex with men (MSM), with a high proportion of them remaining unaware of their HIV status.[11] Rio de Janeiro is one of the major epicenters of the HIV epidemic in Brazil, contributing with 79,078 AIDS cases from 2000 to July 2015, holding the second position in number of cases within the country.[12]

We hereby report the prevalence of TDR and drug mutations associated with resistance in a cohort of acutely/recently HIV-infected individuals in Rio de Janeiro, Brazil, majority of whom MSM, to assess the need for routine TDR surveillance in Brazil.

Methods

The Instituto Nacional de Infectologia Evandro Chagas – Fiocruz (INI) is the largest provider of primary, specialty, and tertiary care for individuals living with HIV/AIDS in Rio de Janeiro, Brazil. A clinical cohort has been maintained since 1986 and cohort procedures have been described elsewhere.[13] Since August 2013, we have been enrolling individuals with acute and recent HIV infection and offering them immediate ART, with the goal of reducing inflammation and HIV reservoirs.

For this analysis, we included 46 patients who were diagnosed with acute/recent HIV infection, between August/2013 and March/2016. Inclusion criteria were age over 18 years, documented seroconversion within the previous six months and no prior ART. HIV drug resistance testing was performed using an in-house protease/reverse transcriptase genotyping assay developed by FIOCRUZ,[14] which is certified by the National Institute of Allergy and Infectious Diseases virology quality assessment (NIAID-VQA). Drug resistance mutations (DRMs) were identified through the Stanford HIV Database for Transmitted DRM (TDRM/CPR Tool) Code Version 6.0[15] on the 2009 World Health Organization surveillance of transmitted DRMs list.[16] HIV-1 subtyping was obtained by using REGA HIV-1 & 2 Automated Subtyping Tool (Version 2.0).[17] Acute HIV infection (AHI) was defined as a negative result for a third generation HIV rapid test followed by a reactive result for the HIV antigen/antibody combination assay, or a detectable HIV RNA testing on pooled and subsequently confirmed with an individual HIV RNA test. Recent HIV infection (RHI) was defined as a reactive HIV serology and a documented HIV negative serology within the prior six months or a reactive Western Blot lacking p31 (pol) reactivity. Between-groups comparisons were made using Kruskal–Wallis test and Chi-square tests for continuous and categorical variables, respectively.

Results

Out of the 46 included patients, 43 had a satisfactory protease/reverse transcriptase HIV-1 genotyping obtained prior to ART initiation and, of them 13 (30.2%) were defined as AHI and 30 (69.8%) as RHI (Fig. 1). The median time between the genotypic resistance test and HIV diagnosis was seven days (interquartile range [IQR]: 2–21 days). All patients were male at birth (one transgender woman), 95% reported having sex with men (Table 1). Median age at HIV diagnosis was 28 years old (IQR: 26–33 years), median CD4 and HIV RNA were 593 cells/mm^3 (IQR: 418–689 cells/mm^3) and 4.8 log (IQR: 4.0–5.6 log), respectively. The most frequent HIV subtype was B (60.5%), followed by subtypes C (23.3%) and F (7%). No significant differences in socio-demographic and clinical variables were observed between patients with and without DRM (Table 1).

The overall TDR prevalence was 16.3% (95% confidence interval [CI]: 8.1–30.0%), being 23.1% (95% CI: 8.2–50.3%) among those diagnosed with AHI and 13.3% (95% CI: 5.3–29.7%) among those with RHI. Overall, five patients presented non-nucleoside reverse transcriptase inhibitors (NNRTI) DRMs, yielding a prevalence 11.6% (95% CI: 5.1–24.5%), and K103N was the most frequently identified resistance mutation (three patients). The other NNRTI DRMs were K101E and G190A (one patient each). Two patients presented protease inhibitors (PI) DRMs (prevalence of 4.7%, 95% CI: 1.3–15.5%) (I47A, I85V), whereas only one presented nucleoside reverse transcriptase inhibitors (NRTI) DRMs (prevalence of 2.3%, 95% CI: 0.4–12.1%, all thymidine analog mutations [TAMs], including M41L, D67N, T215S/C, K219Q/E). No triple-class TDR was identified.

Of note, two individuals were exposed to pre-exposure prophylaxis (PrEP, oral daily tenofovir plus emtricitabine) before HIV diagnosis. One of them, defined as AHI, started PrEP 175 days before seroconversion and the genotypic test revealed only a PI DRM (I47A). The other patient, with RHI, had interrupted PrEP use 140 days before seroconversion (after almost one year on PrEP), and at baseline presented DRMs for both NRTI (TAMS: M41L, D67N, T215S/C, K219Q) and NNRTI (G190A). Neither of them presented emtricitabine or tenofovir DRM.

Seven patients used post-exposure prophylaxis (PEP) prior to HIV diagnosis and only one of them presented with a DRM (K103N), which was not related to the ARV used as PEP (PI