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(Letter to the Editor)

PREVALENCE OF TRANSMITTED DRUG RESISTANCE MUTATIONS AMONG NEWLY DIAGNOSED HIV-1-INFECTED PATIENTS IN A LARGE TEACHING HOSPITAL OF THE NORTHERN ITALY

Running head: HIV and transmitted drug resistance

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Abstract

The prevalence of transmitted drug resistance (TDR) was investigated among 178 patients with new diagnosis of HIV-1 infection (57% with B subtype) performed between 2017 and 2019. Overall, the global prevalence of TDR was 7.9% (NRTIs, 3.9%;

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NNRTIs, 3.4%; PIs, 2.8%, INSTIs, 0.9%). The most frequent mutations were T215S/I/D (3.4%) in the reverse transcriptase region and M46I/L (1.1%) in the protease region, while in the integrase region the E138K was present in one case (0.6%).

Keywords

Horizontal transmission, Epidemiology, Resistance, Infection, Chemotherapy, Disease control, Human immunodeficiency virus, Virus classification

To the Editors:

Transmission of drug-resistant HIV-1 strains is well documented and may compromise the efficacy of combination antiretroviral therapy (cART) started as initial treatment or as post-exposure/pre-exposure prophylaxis (PEP or PrEP). Approximately 10% to 17% of cART-naive HIV-positive patients have drug resistance mutations (DRMs) to at least one antiretroviral drug, and up to 8% show DRMs to at least two antiretroviral classes.[1,2]

In the last years, clinical data about trend of transmitted drug resistance (TDR) among newly diagnosed cART-naïve individuals have led to conflicting results. Some studies have shown increased or at least steady rates of TDR,[3,4] while other reports have demonstrated a trend for decreasing prevalence of DRMs.[5,6]

We performed a retrospective analysis of TDR on 178 newly diagnosed HIV-1 patients attending the Infectious Diseases Unit of S. Orsola Hospital (Bologna, Italy) between January 2017 and December 2019. The baseline data (age, sex, ethnicity and transmission routes) were collected. HIV-RNA load was detected on plasma samples by standard commercial viral assay (COBAS® AmpliPrep/COBAS®TaqMan® HIV-1 Test, v2.0, Roche Molecular Systems, Inc., Branchburg, NJ, USA) with analytical sensitivity of 20 HIV-RNA copies/mL. HIV-1 genotyping analysis was performed using a Sanger sequencing approach (Viroseq, Abbott Diagnostics, Abbott Park Road, IL, USA) according to manufacturer's instructions. The protease/reverse transcriptase and the integrase sequences obtained (nucleotide positions 2268–3287 and 3776-4639 of HXB2, GenBank accession number K03455) were examined using the Calibrated Population Resistance (CPR) tool in the Stanford University HIV Drug Resistance Database.[7] The tool includes a list of suggestive mutations, commonly causing or contributing to resistance. The surveillance DRMs were associated with the main classes of antiretroviral agents: nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs). The following codon sites are checked: 23, 24, 30, 32, 46, 47, 48, 50, 53, 54, 73, 76, 82, 83, 84, 85, 88, 90 in the protease region; 41, 65, 67, 69, 70, 74, 75, 77, 100, 101, 103, 106, 115, 116, 151, 179, 181, 184, 188, 190, 210, 215, 219, 225, 230 in the reverse transcriptase region; 66A, 92, 118, 121, 138, 140, 143, 147, 148, 155, 230, 263 in the

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integrase region. In order to identify the viral subtype, the MEGA v.5.0 was used to establish phylogenetic tree.

The study was approved by the Ethics Committee of the S.Orsola-Malpighi Hospital in Bologna and all the enrolled patients provided a signed written consent before participating in the study.

Overall, 162 out of 178 (91%) patients were men, 156 (88%) were Caucasian, 122 (69%) were Italian, the average age was 38.2 years and 101 (57%) harbored a B subtype. The epidemiological characteristics of the patients are summarized in Table 1.

In detail, 178 protease/reverse transcriptase and 117 integrase sequences were analyzed. A TDR to any class of antiretroviral agents was detected in 14 out of 178 sequences (7.9%). The prevalence of antiretroviral DRMs to the major classes of drugs was the following: 3.9% for NRTIs, 3.4% for NNRTIs, 2.8% for PIs, and 0.9% for INSTIs. The prevalence of sequences with any NRTIs plus any NNRTIs DRMs was 1.1%; no patients had sequence with mutations to more than two classes of antiretroviral drugs (Table 1).

The most common DRMs identified were: revertant T215S/I/D (n=6; 3.4%), M41L (n=3; 1.7%), D67N/G (n=3; 1.7%), L210W (n=3; 1.7%), K219Q (n=3; 1.7%), and T69D (n=1; 0.6%) for NRTIs; K103N (n=3; 1.7%), G190A (n=1; 0.6%) and Y188L (n=1; 0.6%) for NNRTIs; F53Y (n=3; 1.7%) and M46I/L (n=2; 1.1%) for PIs. The only DRM identified in the integrase region was the E138K, detected in one patient (0.8%) infected with a CRF01_AE subtype. DRMs were also more frequent among patients infected with B subtype (10 out of 101 patients; 9.9%) compared with those infected with non-B subtypes (4 out of 77 patients; 5.2%). Moreover, the prevalence of DRMs was higher among non-Italian patients (8 out of 56 subjects; 14.3%) than among Italian ones (6 out of 122; 4.9%).

Prevalence of TDR was stable at 11% between 2013 and 2016 among 1885 cART-naïve German patients,[4] while it declined from 8.1% in 2010 to 6.6% in 2013 in a surveillance study including 16425 treatment-naïve individuals in the United Kingdom.[5]

The SPREAD program collects data from 4140 cART-naïve patients from 26 European countries who were newly diagnosed between 2008 and 2010. The overall prevalence of TDR was 8.3% and did not change significantly during the observation period. Prevalence of DRMs to NRTIs, NNRTI s and PIs was 4.5%, 2.9%, and 2%, respectively.[8]

Prevalence of TDR was assessed among 3573 cART-naïve patients in the Italian Antiviral Response Cohort Analysis (ARCA) Collaborative Group from 2006 to 2016. In this cohort 68% of

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patients were Italian and the median CD4 lymphocyte count was 348 cells/mm^3. TDR was detected in 10.3% of patients: 6% had mutations to NRTIs, 4.4% to NNRTIs, 2.3% to PIs, 0.2% to INSTIs, and 2.1% to at least two drug classes. The multivariate analysis showed as predictors of TDR subtype B, lower viral load, site in Northern Italy, and earlier calendar year.[9]

In another Italian cohort study including 668 cART-naïve patients, the overall prevalence of TDR was 9.4%, and prevalence of DRMs to specific antiretroviral classes was 4.2% for NRTIs, 5.8% for NNRTIs, 1% for PIs, and 0.3% for INSTIs. In this study, prevalence of non-B subtypes was significant (33%), and a major INSTI mutation (Q148H) was detected in two naïve patients.[10]

In our study, the prevalence of TDR in newly diagnosed HIV-1-infected patients was comparable or lower than that observed in other Italian or European cohort studies. However, changes in epidemiology of HIV infection with increasing prevalence of non-B subtypes and increasing use of INSTIs underline the importance of a continuous monitoring of DRMs, in order to optimize the cART management.

CONFLICTS OF INTEREST

Nothing to declare.

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Table

Table 1. Patient characteristics and prevalence of drug resistance mutations.

Patients, n.	178
Sequences analyzed for reverse transcriptase and protease regions, n. (%)	178 (100)
Sequences analyzed for integrase region, n. (%)	117 (66)
Men, n. (%)	162 (91)
Caucasian, n. (%)	156 (88)
Italian, n. (%)	122 (69%)
Age (years), mean (95% CI)	38.2 (26.5; 50.7)

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HIV transmission risk category, n. (%):	
IDU	7 (3.9)
MSM	102 (57.3)
heterosexual	69 (38.8)
CD4+ lymphocyte count (cells/mm^3), mean (95% CI)	437 (202; 634)
HIV RNA (log_{10} copies/mL), mean (95% CI)	4.6 (3.1; 5.7)
Patients with AIDS diagnosis, n. (%)	34 (19.1)
Patients with CD4+ lymphocyte count <350 cells/mm^3, n. (%)	84 (47.2)
Sequences with any DRM, n. (%)	14 (7.9)
Sequences with DRMs for NRTIs, n. (%)	7 (3.9)
Sequences with DRMs for NNRTIs, n. (%)	6 (3.4)
Sequences with DRMs for PIs, n. (%)	5 (2.8)
Sequences with DRMs for INSTIs, n. (%)	1 (0.9)
Sequences with multidrug resistance mutations, n. (%)	2 (1.1)

CI, confidence intervals; IDU, injection drug users; MSM, men who have sex with men; DRMs, drug resistance mutations; NRTIs, nucleoside reverse transcriptase inhibitors; NNRTIs, non-nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors; INSTIs, integrase strand transfer inhibitors.

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