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(Article begins on next page)

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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-naïve 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, NNRTIs 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

patients were Italian and the median CD4 lymphocyte count was 348 cells/mm³. 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)

HIV transmission risk category, n. (%):

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