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Transmitted Drug Resistance in Hiv-1 Non-B Subtypes Newly Diagnosed Patient: Case Report

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Abstract

Antiretroviral therapy has a very high efficacy and has substantially changed patients' quality of life, although it does need an equally-high adherence. The widespread use of antiretroviral therapy has significantly reduced the risk of HIV. However, at the same time it has resulted in an increase in HIV-drug resistance, which can be transmitted to newly-infected individuals, thus compromising the efficacy of combination regimens and potentially leading to the their failure. In Europe the overall prevalence of transmitted HIV-drug resistance was 8.3% in 2008-2010 and it is considered rather uncommon in non-B subtypes. In this study we report a case of drug-resistance transmission in a patient with HIV inter recombinant form infection. The transmission occurred heterosexually in a couple of immigrants without stay permit. Phylogenetic analysis was performed. Our report underlines how, even if not very high, the prevalence of HIV primary drug resistance is essential to perform the resistance test, at least of the pol gene in all new HIV diagnoses. Even in countries with high income and almost total-free diagnosis and treatment, some patient settings are at risk of developing drug-resistant strains. More studies are needed for the proper evaluation of transmitted HIVDR in non-B subtypes of HIV.

Keywords: HIV drug resistance transmission; Transmitted HIVDR; CRFs

Introduction

Antiretroviral therapy (ART) has a very high efficacy and has substantially changed the quality of life of patients but needs an equally-high adherence [1]. The widespread use and increased coverage of ART has significantly reduced the risk of HIV transmission and decreased HIV-related morbidity and mortality [2]. At the same time, however, the greater availability of ART globally has determined and continues to determine the increase in resistant strains even in treatment-naive patients. The transmission of HIV drug-resistant strains has gradually become a concern because it has the potential to compromise the efficacy of combination ART regimens and may lead to the failure in first-line ART [3]. Patients who acquire or are primarily infected with HIV-1 drug-resistant viruses have fewer treatment options and are at increased risk of morbidity and mortality, particularly in developing countries where choices for ART are limited [4,5]. For this reason, the international organizations and guidelines of many countries recommend performing the pol gene-resistance test in all newly-diagnosed cases of HIV infection, despite being an expensive test and not available in the Pediatric centers [6-8].

Poor adherence is the main cause of drug resistance [9]. In high-income countries and ones in which the health system guarantees all expenses related to the diagnosis and treatment of HIV infection (such as Italy), adherence is lower in some categories of patients: immigrants (especially those without a regular residence permit), adolescents, patients with mental illness or addictions, patients with a lower cultural level [10,11]. The prevalence of transmitted HIV drug resistance (HIVDR) is highest in developed countries, estimated between 8.4% and 22.7% [12-18]. In a most recent European publication, where Italian data were included, a prevalence of TDR was of around 8% was estimated [19] and in any case until 2012 this was closely associated with HIV-1 subtype B infection [20,21]. The most frequent indicators of TDR were nucleoside reverse-transcriptase inhibitors (NRTIs) mutations (4.5%), followed by non-nucleoside reverse transcriptase inhibitors (NNRTIs) mutations (2.9%) and protease inhibitors (PIs) mutations (2.0%). Although TDR was highest for NRTIs, the impact of baseline drug-resistance patterns on susceptibility was largest for NNRTIs [20].

In this report we describe a case of primary transmission of drug resistance, occurred in a heterosexual couple of immigrants, lived in our country without a regular stay permit. The circulating recombinant form 02_AG (CRF02_AG) was involved. More precisely the strain was identified as an A1, G, CRF02_AG inter recombinant form, that grouped into CRF02_AG (when phylogenetic analysis was performed). According to the data present in the literature, non-B clades are less efficient in HIVDR and CRF02_AG is the least implicated subtype [20].

Methods

Genotyping of the predominant HIV population was performed with the Viroseq HIV Genotyping Kit (Applied Biosystems, Foster City, CA), and the HIV Genotyping System SoftwareTM was used for data analysis. Nucleotide sequences of the pol gene were submitted to the Sequence Analysis Program of the Stanford HIV RT and Protease Sequence Database [21] which furnishes a computer assisted interpretation of mutational profiles. The sequences were then analyzed for phylogenetic relationships. BioEdit [22] was used to align query sequences (D.A. and G.N.) with pure subtype and circulating recombinant form (CRF) reference sequences obtained from the Los Alamos database [23]. The subtype assignment of the non-clade B strains was confirmed by a bootstrapped phylogenetic analysis using SEQBOOT with 1,000 replicates, followed by the DNAdist (with Kimura 2-parameter method and a transition/transversion ratio of 2.0), Neighbor and Consense programs contained in PHYLIP (PHYLogeny Inference package) [24,25]. The strains were subsequently analyzed by Simplot software (version 2.5) [26] by boot scanning application to identify the subtypes involved in the recombination and their breakpoints. The phyogenetic relationships were visualized by application called Tree View [27].

Case Report

The case of a 32-year-old man coming from Guinea (D.A.). In October 2013 the patient had a HIV-1 infection diagnosis at a different Hospital in Apulia. He manifested generalized tonic-clonic seizures followed by an altered state of consciousness. The MRI brain scan was consistent with *Toxoplasma gondii* brain abscesses and a treatment with pyrimethamine and sulfadiazine was started. Also, daily efavirenz, emtricitabine and tenofovir therapy was begun, but the patient in the same data self-resigned and was lost to follow-up. The genotypic analyses of viral sequence had not been made. In January 2014 the patient manifested an altered state of consciousness and a left-side hemiparesis and he was admitted to the Bari Infectious Diseases Clinic in. The brain MRI confirmed multiple brain abscesses surrounded by a perilesional edema. The CD4+ count was 49 cells/mm^3 and the HIV-1 plasma viral load was 1,950,000 copies/ml (RT-PCR). An anti-toxoplasma therapy was resumed.

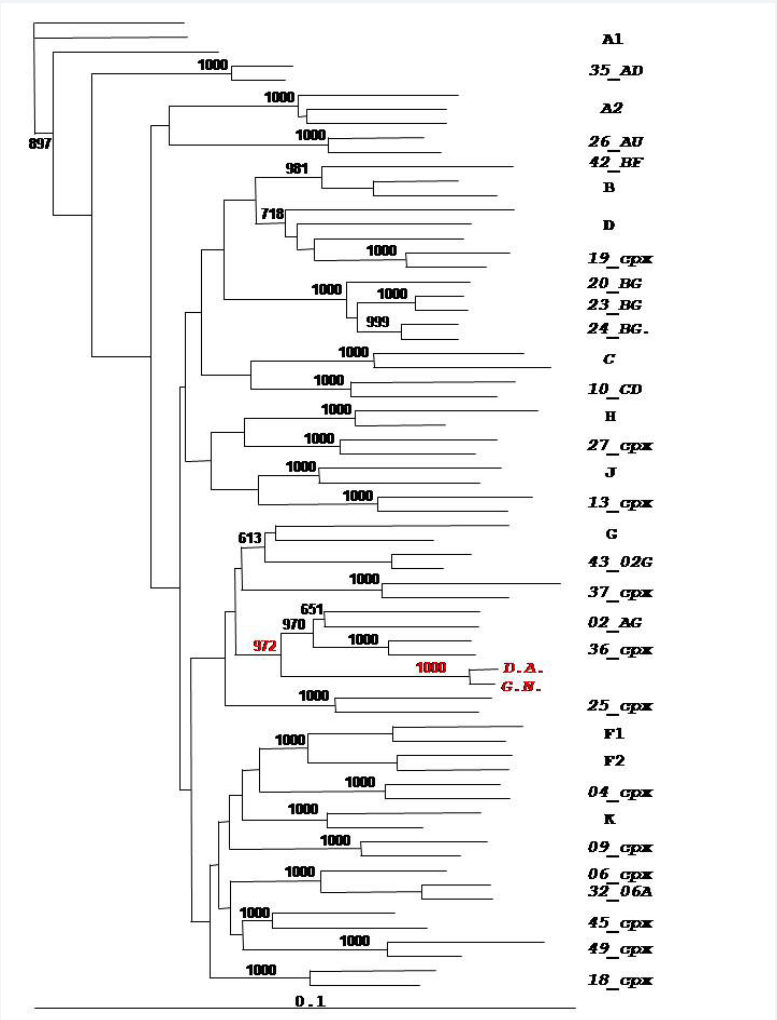

Figure 1: Phylogenetic neighbor-joining tree of pol gene (protease and reverse transcriptase domains) (nt. 2253-3221) sequences from our patients. Bootstrap values (1000 replicates) are indicated on the branch leading to the subtype.

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Genotypic-resistance testing on plasma and phylogenetic analysis by neighbour-joining (NJ) trees and boot-scanning software was performed. Phylogenetic analyses showed that the patients were infected with a complex recombinant form that involved clade A1, G and CRF02_AG. The breakpoints however were different respect on the and the other known A/G inter-recombinant forms (Figures 1 & 2). Primary-resistance mutations associated with NRTIs and NNRTIs were reported (Figure 3a). PIs primary resistance were absent. A new ART regimen was started with boosted lopinavir/emtricitabine/tenofovir and one month later CD4+ cells were 105/mm^3 and HIV-1 plasma viral load was 3195 copies/ml. A follow-up MRI brain scan at the end of 6 weeks of treatment confirmed complete edema resolution. An improvement of patient's clinical condition was reported too. Moreover, the patient's partner from Georgia was tested and she was diagnosed with HIV-1 infection too. She was a naïve advanced subject; her CD4 count was 120 cells/mm^3 and HIV-1 plasma viral load was 98,000 copies/ml. The resistance profile showed the presence of three mutations responsible for drug-resistance to NNRTIs (also present in the partner): V90I, A98G, Y181C. The M184V mutation responsible for resistance to NRTIs was not transmitted (Figure 3b). Phylogenetic analyses revealed that the patient's partner was infected with the same recombinant form (Figure 3) never described in Georgian patients.

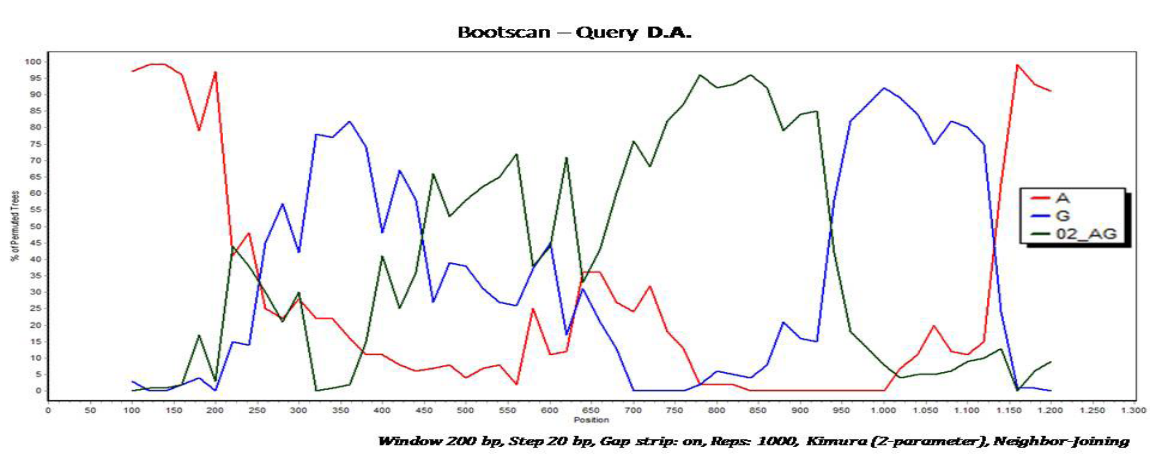

Figure 2: Bootscan analysis of D.A pol gene sequence. Boot scanning plot is performed with the Simplot program using 200 bp window and step size of 20 bp. Breakpoint locations are based on the HXB2 numbering engine. Recombinants segments are indicated above the plot.

Patient D.A.

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	M184I
NNRTI Resistance Mutations:	V90I, A98G, Y181C, G190A, P225H
Other Mutations:	K20R, V35T, E36A, T39K, K43E, K122E, D123N, S162A, T165I, K173T, Q174K, D177E, T200A, Q207E, D237N, V245Q, E248N, D250E, E291D, V292I, I293V, P294T, I326V

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	High-level resistance	efavirenz (EFV)	High-level resistance
abacavir (ABC)	Low-level resistance	etravirine (ETR)	High-level resistance
zidovudine (AZT)	Susceptible	nevirapine (NVP)	High-level resistance
stavudine (D4T)	Susceptible	rilpivirine (RPV)	High-level resistance
didanosine (DDI)	Potential low-level resistance		
emtricitabine (FTC)	High-level resistance		
tenofovir (TDF)	Susceptible		

3a

Patient G.N.

Drug Resistance Interpretation: RT

NRTI Resistance Mutations:	None
NNRTI Resistance Mutations:	V90I, A98G, Y181C
Other Mutations:	V35T, E36A, T39K, K43E, K122E, D123N, S162A, T165I, K173T, Q174K, D177E, I178M, G196R, T200A, Q207E, R211KR, F214FL, V245Q, E248N, D250E, E291D, V292I, I293V, P294T, I326V

Nucleoside RTI		Non-Nucleoside RTI	
lamivudine (3TC)	Susceptible	efavirenz (EFV)	Intermediate resistance
abacavir (ABC)	Susceptible	etravirine (ETR)	Intermediate resistance
zidovudine (AZT)	Susceptible	nevirapine (NVP)	High-level resistance
stavudine (D4T)	Susceptible	rilpivirine (RPV)	Intermediate resistance
didanosine (DDI)	Susceptible		
emtricitabine (FTC)	Susceptible		
tenofovir (TDF)	Susceptible		

3b

Figure 3: Drug Resistance interpretation of retrotrascriptase of the two patients.

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Discussion

Our case report leads us to make different considerations. First of all, the primary transmission of resistance, although not common in high-income countries, can be a dangerous event, especially in those patients who have less access to the health system. Even in countries like Italy, where access to the diagnosis and treatment of infectious diseases, chronic diseases and maternal and child health is free and universally- guaranteed by law (even to those who do not have a regular permit to stay) there are particular settings of patients who can, for various reasons, have difficulty using health services. That is to say, indigent, elderly people with addictions, along with immigrants are our most vulnerable categories of people in our society. As far as HIV infection is concerned, we would above all like to point out repeatedly that among migrants there is a greater number of diagnoses in late stages of the disease, a faster progression of the disease, a lower percentage of retention in care, but also a lower perception of being taken care of by the health system. Moreover, our cases are original because they occurred in a clade considered not to be very involved in the transmission of drug resistance. Larger-scale studies should be conducted on the implications of the subtype on drug resistance transduction. It is possible that this varies from clade to clade and therefore it is important to study each one individually. It is more than probable that with the increase in non-B subtypes and CFRs in high-income countries that have been reported for years in all of Europe, even cases of resistance transmitted in non-B subtypes will increase. Lastly, it is further confirmed that the genotypic test is fundamental before starting ART therapy.

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Conflicts of Interest

None.

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