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Multiclass primary antiretroviral drug resistance in a patient presenting HIV-1/2 dual infection.

Running head: HIV-1/2 multi-resistant infection

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HIV-2 infection is mainly concentrated in West African countries with an estimate number of 1 to 2 million infections [1-2]. As a result of socio-economic links to West African countries and human migration, HIV-2 infection is also found in European countries. For instance, HIV-2 is responsible for 4.5% of AIDS cases in Portugal [3] and has been associated with 1.8% of new HIV infections documented in France between 2003 to 2006 [4].

HIV-2 is known for intrinsic resistance to NNRTI, therefore best treatment options for naïve patients rely on boosted-PI regimens [5-6]. Based on *in vitro* PI sensitivity data, two effective treatment combinations consist of tenofovir/emtricitabine + lopinavir/ritonavir or zidovudine/lamivudine + darunavir/ritonavir [7]. However, high frequency of K65R and Q151M mutations have been reported in patients receiving NRTIs as well as multiclass drug resistance emergence in a cohort from Senegal [8-9]. By contrast, emerging data from HIV-2 integrase sequences coming from naïve patients show no major mutations to integrase inhibitors, providing an opportunity of treatment for HIV-2 infected patients [10].

Key mutations sites conferring resistance to drug classes are not fully shared by HIV-1 and HIV-2 viruses due to genome differences. Therefore global spread of HIV-2 epidemic can lead to a greater frequency of HIV-1/2 dual infections with complex drug resistance challenges for antiretroviral treatment options.

Case report

The case of a 23-year-old heterosexual man, born in Côte d'Ivoire in good health until October 2010 when he complained of persistent diarrhoea, fatigue and weight loss. In March 2011 he decided to move to Switzerland for appropriate medical care. He denied previous HIV test, exposure to antiretroviral drugs, intravenous drug use or having had a blood transfusion.

Immunovirological assessment

The positive antibody result of a fourth generation HIV screening test (HIV Ag/Ab Combo Assay, COBAS ELECSYS HIV combi PT, Roche Diagnostics, Rotkreuz, Switzerland) was followed by an immunodot directed against HIV-1 and HIV-2 specific antigens revealing a strong positive antibody response (3+) in all bands (INNO-LIA HIV 1/2 Score - Innogenetics). Patient's CD4+ T-cell counts were 408 cell/mm^3 (25.4%) as determined by multiparameter flow cytometry.

HIV-1/2 reverse transcriptase activity was 4.351 nU/ml equivalent to 82.902 copies/ml total viraemia, measured by product-enhanced reverse transcriptase assay [11]. At the same timepoint, HIV-1 viral load was 21.000 copies/ml   (COBAS AmpliPrep/COBAS TaqMan version 1.0 Roche Diagnostics), demonstrating a major role of HIV-2 contribution to total viraemia.

Genotypic analysis

Results of both viruses' genotypic analyses are summarized in table 1. Briefly, HIV-1 analysis was performed with Virco algorithm (VirtualPhenotypeTM) as part of the routine HIV assessment from the Lausanne hospital. Related drug resistance mutations were assigned according to the IAS-USA 2011 consensus. HIV-2 genotypic analysis was done at the Virology laboratory from the University Hospital of Bordeaux using primers previously described for amplification of Reverse transcriptase and Protease regions [12]. The obtained fragments were sequenced on both strands using the ABI BDV3.1 on an automated Applied Biosystems 3500XL DX sequencer. The sequences were identified by alignment on reference HIV-2 sequences and ANRS algorithm V20 (French National Agency for AIDS Research, HIV-1 genotypic drug resistance interpretations algorithms, version 20, updated 12 July 2011, France) was used for interpretation of HIV-2 resistance mutations. The patient was confirmed to be infected with HIV-1 (CRF02_AG) and HIV-2 (clade A). The HIV-1 virus harbored

resistance mutation M184V to NRTIs and V90I, a secondary mutation implicated in the development of resistance to etravirine. Whereas HIV-2 virus carried also resistance to NRTIs with mutations K65R and D67N as well as a naturally expected resistance to NNRTI drugs. Different polymorphisms at related PI drug resistance positions were observed for both viruses.

Table 1

Primary drug resistance mutations and related polymorphisms present in a dual HIV-1/2 infected individual.

Viral clade	NRTI mutations	NNRTI mutations	PI mutations	Integrase mutations
HIV-1				
CRF02_AG	M184V	V90wt/I	V11I, K20I, M36I, 69K, 89I	NONE
HIV-2				
A	K65R, D67N	V106I, E138A, V179I, Y181V, Y188L, G190A	L10V, G16E, V32I, L33V, M36I, M46I, I47V, 69K, 89I	N/A

Note CRF: HIV-1 circulating recombinant form. NNRTI: nonnucleoside analogue reverse transcriptase inhibitors. NRTI: nucleoside and nucleotide analogue reverse transcriptase inhibitors. PI: protease inhibitors. N/A: not available.

Discussion

To the best of our knowledge this is the first report of multiclass primary drug resistance in the context of HIV-1/2 dual infection. This case underlines the pitfall of dual HIV infection with two different patterns of resistance to NRTIs as demonstrated in the genotypic resistance tests performed on both viruses. Surprisingly, mutation M184V is traced in this patient after several months of HIV infection onset according to epidemiological, clinical and immunological information. Based on the knowledge we have from HIV-1 infection, NRTI mutation M184V becomes quickly undetectable when transmitted as primary resistance in naïve patients. However, we ignore if a different kinetic applies for resistant viral populations in the context of HIV-1/2 co-infection. Furthermore, this report underscores the limitations of current treatment options in the context of circulating HIV-1/2 dual infections despite the irrefutable progress achieved in HIV-1 treatment. Also it highlights the pertinence of guiding HIV-1/2 dual infection treatment choice on genotypic analysis of both viruses. To end, it brings awareness on the need of new drugs to treat multiclass resistant HIV-1/2 infections.

Disclosure statement

The authors declare no competing interests.

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