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CASE REPORTS

"BUILDING THE FUTURE ON PAST REMAINS" – CASE PRESENTATION OF HIV MULTIEXPERIENCED PATIENT

Daniela Ioana Munteanu[1], Raluca Mihailescu[1], Anca Streinu Cercel[2], Victoria Aramă[1,2]

[1.] *National Institute of infectious Diseases Prof. Dr. Matei Bals, Bucharest*
[2.] *University of Medicine and Pharmacy Carol Davila, Bucharest*

Abstract. Introduction – HAART history is a history of changes, each new antiretroviral combination represents a chance to obtain viral undetectability. Objective – case presentation of HIV multiexperienced patient with virological failure, which belongs to the Romanian cohort of children and adolescents parenterally infected before 1990. Case presentation – we report the case of a 27 year old female, HIV positive since 1998 (at the age of 15 years), F genotype. First, she was diagnosed in B2 CDC clinico-immunological stage with 380/mmc CD4 count and HIV viremia of 5120 c/ml. The antiretroviral therapy was initiated in 1998, according to that time guidelines, first IDV+AZT+DDC, then EFV+3TC+d4T, NFV+DDI+d4T, LPV/r+NFV+3TC, LPV/r+SQV+3TC. Since 2001 the viremia remained detectable all the time, despite her good compliance to multiple antiretroviral regimen. In 2006, the CD4 count declined below 200 cell/mm3 and therefore a salvage therapy was introduced TPV/r+3TC+T20, but the viral replication persisted (HIV-RNA 243.179c/ml). The resistance tests performed in this case showed multiple mutations with decreased susceptibility to all available drugs. In 2008, new drugs became available on Romanian pharmaceutical market and other combinations were built, first RAL+DRV/r+3TC+T20 and then RAL+DRV/r+3TC+MVC+ETR and consequently the viremia became undetectable (May 2010 HIV-RNA <150c/ml, CD4 cell count 366/mm3). Conclusions – the patient represents an HIV multiexperienced case, with virological failure, despite good adherence to therapy. This case was among the first in our country who received new molecules, such as RAL, MAR, ETR and obtained the undetectability after 11 years of persistant viral replication. The new antiretroviral drug classes represent a step forward to obtain a durable viral suppression in multiexperienced patients with several resistance mutations.
Keywords: HAART therapy, multiexperienced patient

Introduction

Highly Active Anti-Retroviral Therapy (HAART) history begins in 1996 and it is a history of continuous changes. Each new drug combination brings a refinement and a simplification in the way of treating HIV infection. HAART represents for the clinicians a challenge to learn to build more effective drug combinations, the main objective being a persistent suppression of viral replication. In the same time, clinicians must take into account the financial limitations and the accessibility to the antiretroviral drugs at a certain point in time [1].

Victoria Aramă
1, D. Calistrat Grozovici Str., Sector 1, Bucharest
E-mail: dr.arama@mateibals.ro

Objective

To illustrate the HAART evolution in Romania, we present a case of an HIV multiexperienced patient with virological failure, which belongs to the Romanian cohort of children and adolescents parenterally infected before 1990.

Case presentation

We report the case of a 27 year old female, HIV positive since 1998 (at the age of 15 years), F genotype. At the time the infection was first discovered, the patient was in the CDC clinico-

immunologic stage B2 (history of herpes zoster and CD4 cell count of 380/mmc) and had an HIV viremia of 5120 c/ml. The antiretroviral therapy was initiated, according with the therapeutic guidelines of 1998 [2]: IDV+AZT+DDC. The viremia became undetectable, the lower limit of detection being at that time 400 c/ml. The viral suppression was not persistent (figure 1) and the therapy was changed, using a combination of two NRTIs plus an NNRTI (EFV+3TC+D4T). The patient obtained viral suppression with this regimen, but not for a long time, despite her good adherence to therapy (figure 1).

In 2003, it was performed the first resistance test. It showed good susceptibility only for the PIs and resistance to NRTIs and NNRTIs (table I) [3]. Current concepts would not sustain this combination because it had only one fully active drug, instead of two or better three. An other disadvantage of this regimen was the high risk of peripheral neuropathy, and a weak antiviral effect of DDI+D4T combination [3,4].

In 2004, another resistance test was performed, that showed the presence of PI resistance mutations, with low-level or intermediate resistance to all PI available at that time (table II) [3] A combination of 2 PIs and 1 NRTI was selected: LPV/r+NFV+3TC.

In that period, Miller showed that maintaining 3TC in patients with the M184V mutation impaired viral fitness, reducing the viral replication, especially when the other prescribed drugs were not fully active [5].

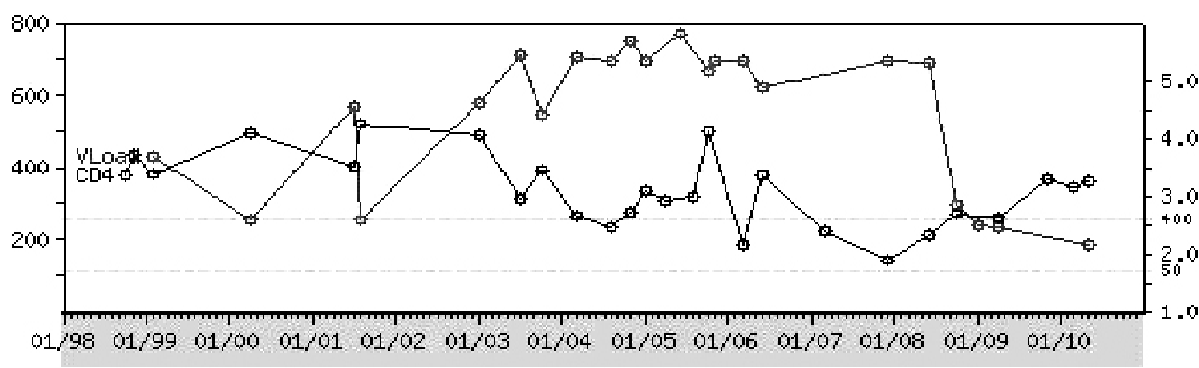

Figure 1. The dynamic of CD4 cell count and HIV-RNA [3]

	PIs	NRTIs	NNRTIs
Major resistance mutation	**none**	**D67N, M184V, T215Y**	**L100I, K103N**
High-level resistance	-	3TC *FTC (not available)*	EFV NVP
Intermediate resistance	-	ABC AZT D4T DDI	-
Susceptible	*ATV/r (not available)* *DRV/r (not available)* FPV/r IDV/r LPV/r NFV SQV/r *TPV/r (not available)*	*TDF (not available)*	*ETR (not available)*

Tabel I. 2003 resistance test[3]

In case of virological failure secondary to resistant mutations, EACS 2009 guidelines recommended prescription of 2 or better 3 active drugs in the new regimen, including at least 1 fully active PI and 1 drug from a class of antiretroviral that was not previously used [4].

In 2003, the chosen regimen was NFV+DDI+D4T, according to the results of the resistance test and the drugs availability in Romania.

According to this new data, 3TC was kept in the regimen, but the antiviral effect of this combination was very weak; this would be explained by the intermediate resistance to 2 PIs. For that reason, six months later NFV was changed to SQV, that had a low-level of resistance.

At that time, the double PI regimen was considered a salvage therapy in multi-experienced patients with major resistance mutations to NRTIs. This

	PIs	NRTIs	NNRTIs
Major resistance mutation	**I54V, V82A**	**D67N, M184V, T215Y, M41L, L74V**	**L100I, K103N**
High-level resistance	-	3TC *FTC (not available)* ABC AZT DDI	EFV NVP
Intermediate resistance	IDV/r LPV/r NFV	D4T *TDF (not available)*	-
Low-level resistance	*ATV/r (not available)* FPV/r SQV/r *TPV/r (not available)*	-	-
Susceptible	*DRV/r (not available)*	-	*ETR (not available)*

Tabel II. 2004 resistance test [3]

practice was based on several studies (Molla 2002 and Hellinger 2005) showing a synergistic effect for the combination LPV/r+SQV, good tolerability and no addition of side effects [6,7]. However, later studies (Staszewski 2006 and von Hentig 2007) showed that the viral response to this regimen, in patients with multiple PI resistance mutation, was a poor one [8,9].

In 2006, the CD4 cell count decreased below 200/mmc (figure 1), revealing the AIDS stage. A new salvage regimen was possible to select at that time, because 2 new drugs were available: TPV/r – a second generation PI and T20 – a drug with a new mechanism of action. So, a new combination was administered: TPV/r+3TC+T20, followed only by a good immunological response. In spite of experiencing painful skin nodules at the injection sites, the patient had a good adherence to the new regimen. We consider that the persistent viral replication was rather caused by a weak antiviral activity. This regimen was maintained one year, because not other options were available at that point in time [1].

In 2008, the development of integrase inhibitors (RAL) and of a new PI (DRV/r), with a high genetic barrier, made possible another salvage regimen: RAL+DRV/r+3TC+T20, with at least two fully active drugs. Also, the registration of other two drugs, ETR and MVC, allowed the replacement of T20. The final regimen was RAL+DRV/r+3TC+ MVC+ ETR and it was the only combination that suppressed the viral replication (may 2010 HIV-RNA <150c/ml and CD4 count 366/mmc).

Conclusions

The reported case is one of an HIV multiexperienced patient with virological failure, despite good adherence to therapy. The multiple therapeutic regimens used in this case were chosen according to the drugs available at that time, in Romania and with the international trends in therapy. The suppression of viral replication was obtained after 11 years of therapy, with a regimen having drugs with the newest mechanisms of action. This patient was among the first who received new molecules, such as RAL, MAR, ETR in our country.

The new antiretroviral drug classes represent a step forward to obtain a durable viral suppression in multiexperienced patients with several resistance mutations.

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