



ATTAINING VIRAL SUPPRESSION IN AN HIV TREATMENT-EXPERIENCED PATIENT WITH PERSISTENT VIROLOGICAL FAILURE – A CASE REPORT SIGNAL

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Abstract. Virological failure in treatment-experienced HIV patients is often due to the presence of resistance mutations acquired during therapy. With the discovery of new antiretroviral (ARV) drugs new options for the management of these patients emerged. **Case presentation.** We present the case of a 45-year-old treatment-experienced, female patient diagnosed with HIV infection in 1997. Throughout almost the entire duration of her follow-up, her HIV viral loads were consistently detectable. Her CD4 count was relatively stable and she did not experience any significant clinical events. Resistance tests performed predicted reduced response to all 3 major ARV classes. Adherence to therapy was reportedly inadequate during the first years. Only when novel treatment options became available, could our patient finally attain virological suppression and an increase in CD4 count was observed. The treatment regimen on which undetectability was reached comprised the integrase inhibitor, raltegravir, boosted darunavir and enfuvirtide. Additionally, an improvement in the patient's lipid profile was also noted after switching from the previous regimen which had included 2 boosted protease inhibitors. **Conclusions.** Novel agents can prove extremely useful for treatment-experienced patients, allowing them to attain virological suppression in the setting of multi-class resistance. Adherence to therapy is essential. Additionally, the beneficial effect on lipids of these agents vs. other ARVs is not to be neglected.

Keywords: HIV, treatment-experienced, resistance.

Background

Unsuppressed viremia in treatment-experienced HIV patients is due to the presence of resistance mutations acquired during therapy. In the past this situation left for few options. With the discovery of new ARV classes as well as novel agents belonging to older classes, new alternatives for these difficult situations emerged, which allowed patients to achieve viral suppression.

The case we are going to present is not uncommon, however it gives us the opportunity to address a number of important issues concerning the management of treatment-experienced HIV patients.

Case Presentation

We present the case of a 45-year-old treatment-experienced, female patient diagnosed with HIV infection in 1997, who received during the course of her 13-year follow-up no less than 9 ARV regimens. Her early regimens comprised, aside from a NRTI backbone, both protease inhibitors and NNRTIs. During the first 11 years of follow-up she consistently had detectable viremias despite treatment. Her CD4 count was relatively stable and she did not experience any significant clinical events. The ARV regimens of our patient during the course of her follow-up as well as the evolution of her viral loads and CD4 counts are shown in Figure 1.

Patient adherence to treatment was admittedly less than adequate during the first years. In 2004 following a major depressive episode the patient decided of her own accord to stop taking her ARV treatment (Jan. 2004 - Jan. 2005). When she returned for evaluation twelve months later, a rise

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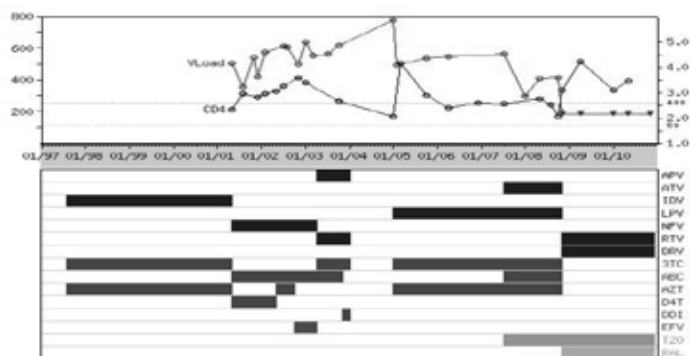


Figure 1. Antiretroviral regimens administered, viral loads and CD4 counts. (August 1997 – November 2010).

in the HIV viral load and a drop in CD4 count were observed, reaching levels of 749,000 copies/ml, and 172 cells/mm³, respectively.

A resistance test performed prior to restarting therapy in 2005 showed that resistance mutations to NNRTIs, NRTIs, and PIs were present (Table I). Treatment was then initiated with ARVs available at that time: lamivudine, zidovudine and boosted lopinavir. Nine months later, our patient had reached a viral load of 23,800 copies/ml and a CD4 count of 308 cells/mm³. Another resistance test, performed in 2006 showed a similar resistance pattern to the previous one. During the following three and a half years, these values remained relatively stable.

With enfuvirtide newly available, a regimen containing a combination of 3 NRTIs, double boosted protease inhibitors (DBPI), and enfuvirtide

was initiated. This led to a decrease in viral load to 760 copies/ml at 6 months and a CD4 level of 283 cells/mm³. On this regimen, while the viral loads remained for the following year detectable, but low, the CD4 count slowly decreased, reaching a level of 175 cells/mm³ at the end of 2008. At that time, with two new drug options for experienced patients available, the patient was started on the integrase inhibitor, raltegravir, boosted darunavir and enfuvirtide. At one month on the new regimen, the patient had reached virological suppression which she maintained to date, and an increase in CD4 count to 339 cells/mm³.

Additionally, an improvement of her lipid profile was observed following the discontinuation of her previous therapy which included DBPI (Figure 2).

Resistance mutations			
NRTIs: 41L, 67N, 70R, 215F/I/S, 219Q, 75I, 69N, 62V			
NNRTIs: 98G, 103N, 188F/L			
PIs: 10V, 20R, 33E, 36I, 54V, 82E, 89M			
Predicted response according to the ANRS algorithm			
Resistance level	NRTIs	NRTIs	PIs
Susceptible	3TC, ABC, FTC	-	ATV, DRV
Possible resistance	TDF	ETV	LPV, NFV, SQV, TPV
Resistance	D4T, DDI, AZT	EFV, NVP	FPV, IDV

Table I. Resistance mutations and predicted response to various ARVs according to the ANRS (National Agency for AIDS Research) algorithm[1]

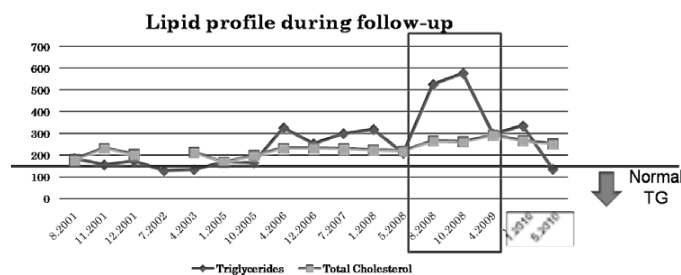


Figure 2. Lipid profile: the dynamics of triglyceride and cholesterol levels during treatment.

Discussions

Constant treatment adherence plays a crucial role in the success of any treatment regimen, therefore we believe that our patient's inadequate adherence during the first years of therapy led to the accumulation of resistance mutations and subsequent virological failure.

Resistance can result in reduced response to a particular drug or even complete loss of drug activity. The presence of mutations can cause cross-resistance to drugs from the same class. Genotypic resistance tests identify the mutations present and can predict susceptibility to different antiretrovirals[1] and thus guide the choice of a particular drug in the subsequent regimens. These, while essential in every patient with treatment failure, need careful consideration. Certain circumstances, like the lack of financial resources, unavailability of drugs and overlooking results may impede on the choice of the ideal treatment regimen when faced with the presence of multiple resistance mutations.

Therefore, when confronted with resistance, the choice of drugs that belong to new classes or that have high genetic barriers, and which would be expected to be efficient in these situations, is warranted.

In the past, these cases of patients with numerous resistance mutations left for few therapeutic options. Enfuvirtide was the first drug from a completely novel drug-class, for patients with resistance mutations to multiple ARV classes. This drug has proven to be more efficient, administered with an optimal background regimen vs. the optimal background regimen alone, leading to more important drop in viral load and an increase in the CD4 count[2]. In our patient, the decision was made to include in the treatment regimen, in addition to enfuvirtide, a combination of 3 NRTIs – lamivudine, abacavir, and zidovudine – as well as the DBPI atazanavir and lopinavir/ritonavir. Since NRTIs are considered to retain a degree of activity despite the presence of resistance mutations[3], and lamivudine and abacavir were still effective according to the resistance prediction algorithm employed, the use of NRTIs in this regimen was considered appropriate. The rationale for the past use of double boosted protease inhibitor therapy was thought to be the following: (1) in order to obtain a synergistic or additive effect on HIV replication; (2) to attain higher plasmatic concentrations of the two PIs using a single booster; as well as (3) raising the genetic barrier[4]. Gillian et al. have shown that the co-administration of atazanavir, and boosted-lopinavir, plus a NRTI backbone can prove to be efficient in patients with multi-class resistance, 91% of patients included in their study attained viral suppression on DBPI treatment[5]. In another study conducted

in Switzerland on a relatively large number of patients who were given DBPI, more than half of them reached and maintained viral suppression; the authors concluded that DBPI might play a role, particularly in situations where alternate options are lacking[6]. However, this was not the case for our patient who continued to have detectable viral loads while on that particular treatment regimen.

When new treatment options became available, viral suppression could be reached. The previous regimen was replaced with a new one containing the integrase inhibitor, raltegravir, a novel boosted PI – darunavir/r; it was decided to continue therapy with enfuvirtide even though resistance to this drug may have already developed. Raltegravir has been proven to be effective in treatment-experienced patients in the BENCHMRK 1 and 2 studies which demonstrated a better virological response and an increase in CD4 count in patients receiving raltegravir, in the absence of significant adverse effects[7,8].

Darunavir is a new protease inhibitor with a high genetic barrier. The POWER 1 and 2 studies showed that patients on darunavir/r had a better virological response, and this was also linked to the number of mutations associated with a reduced response to darunavir present[9]. In our case only one such mutation was detected (33F)[10]. The simplification of the treatment regimen compared to the preceding one represented another advantage leading to a decrease in the risk for adverse events, and a consequent increase in treatment adherence.

A treatment regimen that would also comprise, aside from raltegravir and darunavir/r, maraviroc and/or etravirine would certainly have been a better option for this patient, than the one containing enfuvirtide because of a greater number of fully active drugs. However, when maraviroc became accessible, her viremia was already undetectable and the CCR5 tropism test could not be performed with the equipment at hand, and etravirine has not been available until recently.

Another advantage of the new regimen was the effect on the patient's lipid profile. It is known that dyslipidemia can be associated with PI treatment, the impact on the lipid profile being also related to the specific PI used. An increase in triglycerides is more frequent in patients on DBPI[11]. On the other hand, DRV has a minor effect on the lipid profile[12], and raltegravir, as shown in the SWITHCHMRK study can have a favorable effect on lipids[13].

Conclusions

Novel ARV agents have proven to be extremely useful for the management of treatment-experienced patients, allowing them to attain virological suppression even in the presence of multi-class re-

sistance mutations, however, treatment adherence also plays an important role in the success of any treatment regimen and is vital in patients with multiple resistance mutations and few therapeutic options. The beneficial effect of these new drugs on the lipid profile vs. other ARVs represents an additional advantage which cannot be overlooked.

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