

## Case Report

# Deep Salvage Therapy with a Pegylated Interferon and Foscarnet Containing Regimen in an Advanced HIV -L Infected Patient

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## Keywords

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- Multidrug resistant HIV
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## Abstract

A multi-class drug resistant HIV-infected patient with very few antiretroviral drug options was presented. Full suppression of the viral load was achieved with an unusual salvage regimen including foscarnet, hydroxyurea and pegylated interferon. This case suggests that alternative strategies can be used in selected cases with few or no treatment options.

## ABBREVIATIONS

ART: Antiretroviral Therapy; cART: combination Antiretroviral Therapy; HIV: Human Immunodeficiency Virus; NRTIs: Nucleoside Reverse Transcriptase Inhibitors; NNRTIs: Non-Nucleoside Reverse Transcriptase Inhibitors; PIs: Protease Inhibitors; DHHS: Department of Health and Human Services; RNA: Ribonucleic Acid; 3TC: Lamivudine; AZT: Zidovudine; DRV: Darunavir; TDF: Tenofovir Disoproxil Fumarate; RAL: Raltegravir; /r: Boosted with Ritonavir.

## INTRODUCTION

The availability of combination antiretroviral treatment has decreased the HIV-related morbidity and mortality both in the short- and long-term [1,2]. Combination antiretroviral treatment has been shown to delay clinical progression and the development of opportunistic diseases even in patients with virologic failure defined as the inability to achieve or maintain suppression of viral replication to an HIV RNA level [3-6]. Currently, the antiretroviral armamentarium has expanded considerably with many more potent and more tolerable drugs with lower dosing frequencies compared to the past ensuring better patient compliance. However, multiple virologic failures due to adherence issues and mismanagement of the patient by the clinician may lead to the consumption of all effective antiretroviral drugs leaving few or no choices to establish a suppressive antiretroviral regimen. Guidelines in such settings suggest careful consideration of treatment options with regard to resistance test results and past

medication history to achieve the best results for the individual patient [6] (Table 1).

This case report describes a multi-drug resistant HIV-infected patient with very few antiretroviral drug options who ultimately was fully suppressed with an unusual salvage regimen including foscarnet and pegylated interferon.

Table 1: Medication history.

Antiretroviral treatment regimen	Duration	Result	Viral Load copies/mL
Lamivudine/Zidovudine + Nevirapine	2 mo	Pancytopenia	>10 <sup>5</sup>
Lamivudine/Zidovudine + Nevirapine	1 mo	Pancytopenia	>10 <sup>5</sup>
Stavudine + Lamivudine + Nevirapine	8 mo	Self-decision to stop	<50
Stavudine + Lamivudine + Nevirapine	2 mo	No response	>10 <sup>5</sup>
Lamivudine + Indinavir + Didanosine	1 yr	No response	>10 <sup>5</sup>
Lamivudine/Zidovudine + Efavirenz	7 mo	No response	>10 <sup>5</sup>
Tenofovirdf/emtricitabine + Lopinavir/r	1 yr	No response	83.000
Darunavir + Tenofovirdf/emtricitabine + Enfuvirtide	26 mo	Relapse	120.814

**Abbreviations:** [Mo: Months; Yr: Year] 3TC, Lamivudine; AZT: Zidovudine; DRV: Darunavir; TDF:

Tenofovir Disoproxil Fumarate; RAL: Raltegravir; /r, boosted with ritonavir.

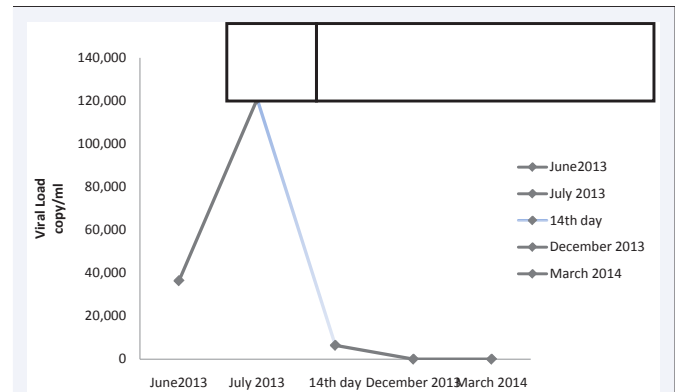
## CASE PRESENTATION

A 55-year-old male diagnosed with HIV-1 virus infection in 2009 presented to our clinic after 4 years of follow-up in another center. He had received five sequential lines of combination antiretroviral therapy (cART) regimens between 2005 and 2009. The switch or interruption reasons were intolerance, self-decision or virologic failure due to poor compliance. He had been exposed to almost all nucleoside reverse transcriptase inhibitors (NRTIs) (lamivudine, zidovudine, stavudine, didanosine, tenofovir, emtricitabine), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, efavirenz), and protease inhibitors (PIs) (indinavir and lopinavir/r) available in the country. He had presented to our clinic while he was using tenofovir/ emtricitabine + lopinavir/ ritonavir with a viral load 83,000 copies/mL and CD4 T lymphocyte count 18% (absolute number not available).

The patient was put on lamivudine holding treatment whilst waiting for resistance test results. The resistance test results revealed five NRTI (M41I, A62V, V75I, M184V, T215Y), five NNRTI (V90I, K103N, V179F, Y181C, H221Y) and six PI mutations (M46I, I54V, V82F, L90M L10I, A71T). The new regimen was designed to include two fully active drugs- darunavir/ ritonavir and enfuvirtide and one partially active drug tenofovir combined with emtricitabine to maintain the M184V mutation. The viral load decreased to <200 copies/mL at 15 months of treatment and was maintained at that level for another 16 months. However, a viral breakthrough developed in the second year of treatment due to the poor compliance of the patient. Enfuvirtide was stopped immediately due to predicted resistance. The second resistance test run in November 2012 revealed seven NRTI-resistance mutations (M41L, A62V, T69N, V75I, M184V, T215S, T215Y), three NNRT-resistance mutations (K103N, V179F, Y181C), and nine PI-resistance mutations (L10I, L33F, M46I, I54V, A71T, V82F, V82L, I84V, L90M). A second resistance test for integrase inhibitors and tropism assay were run in Dr. Yazdan Yazdanpanah's laboratory in France because of the unavailability of those assays in Turkey at that time point. No resistance mutations were detected for integrase inhibitors and the tropism test showed he had X4 tropic virus. Considering that he had resistance to almost all drug groups, a deep salvage regimen was designed including unconventional antiretroviral drugs such as foscarnet, pegylated interferon- $\alpha$ 2a and hydroxyurea upon advice from Dr. Mike Youle.

Following an induction therapy with foscarnet (90 mg/kg bid) for 14 days to reduce the viral load, cART with tenofovir, lamivudine, zidovudine, darunavir/r, raltegravir, pegylated interferon- $\alpha$ 2a 180 mg/wk and hydroxyurea was initiated in July 2013. Baseline CD4 cell count and HIV-1 RNA level were 16 cells/mm<sup>3</sup> (5%) and 120,814 copies/mL, respectively. The viral load on day 14 following the induction therapy with foscarnet decreased to 6430 copies/mL and it was undetectable at the end of the first month (Figure 1). The patient developed severe pancytopenia and received a number of blood transfusions and colony stimulating factor injections. Hydroxyurea was discontinued after five months and pegylated interferon after 10 months of therapy due to persisting severe pancytopenia.

The patient developed progressive multifocal



**Figure 1** Change in plasma HIV-1 RNA levels during salvage therapy.

leucoencephalopathy and related left hemiparesis in April 2014. Viral load remained undetectable up to date and the CD4+ T cell count increased to 77 cells/mm<sup>3</sup> (16%). The clinical condition and the pancytopenia improved considerably after hydroxyurea and pegylated interferon were discontinued and the left hemiparesis improved slightly with physical therapy. The clinical and virologic profile is stable currently.

## DISCUSSION

Current research suggests that multi-class drug resistant HIV infections are decreasing throughout Europe despite increasing drug exposure [7]. However, there still exists a group of highly treatment-experienced patients with resistance to almost all classes of drugs leaving them with few or no options for a fully suppressive regimen. Development of resistance may be due to various factors such as prior mono- or dual-therapy with antiretrovirals, poor compliance of the patient to the treatment regimen, frequent treatment interruptions with regimens with a low genetic barrier, and selection of suboptimal regimens by the clinician [8-10].

The DHHS Adult and Adolescent HIV Treatment Guidelines define the goal in a treatment-experienced patient with a viral load >1000 copies/mL and with defined resistance as maximal suppression of HIV RNA levels to prevent further selection of resistance mutations and suggests the use of at least two fully active new antiretrovirals in the regimen to be selected [6]. The patient presenting to the Ege University Infectious Diseases clinic described in the case report had used five sequential regimens from 2005 to 2009 with a history of poor compliance and long times on failing regimens. The resistance test result had revealed no resistance to darunavir only and as a second fully active drug, T20 was selected upon expert advice from Anna Maria Geretti from UK to be added to the TDF/FTC combination where TDF had intermediate activity and FTC no activity. Integrase inhibitors, resistance tests for integrase inhibitors and the tropism assay were not available in Turkey at that time.

Although the patient seemed to achieve a complete virologic response with this regimen as expected with a gradual but consistent fall of the viral load to <200 copies/mL as suggested by the DHHS Guidelines [6], the HIV RNA level displayed a sharp increase at 21 months of treatment. A second resistance test revealed resistance to the three major classes of drugs and no

resistance to raltegravir and elvitegravir. Viral tropism test for R5 was negative. Although resistance testing for T20 was not available, considering the low genetic barrier of the drug it was stopped for predicted resistance.

Continuing with a failing antiretroviral regimen is not recommended due to the accumulation of resistance mutations limiting further treatment options [11]. On the other hand, even partial virologic suppression of HIV RNA without any increase in CD4 count or maintaining the RNA at low levels was shown to be associated with clinical benefits and to reduce the risk of progression [12-16]. Thus, the patient was kept on TDF/FTC + DRV/r until all the resistance test results were available, which took a few months.

Considering the resistance test results, the only fully effective antiretroviral drug seemed to be integrase inhibitors, where raltegravir was the only available drug in Turkey. However, adding a single fully active drug to the ART regimen is not recommended due to the rapid development of resistance to the new drug [6]. There are anecdotal reports regarding the use of experimental drugs with antiretroviral activity such as pegylated interferon, foscarnet and hydroxyurea.

In very early reports, foscarnet has been shown to be effective on HIV-1 replication *in vitro* [17,18] followed by small-scale non-randomized case series also suggesting an *in-vivo* antiretroviral effect [19-22]. However, it has not been studied extensively in large-scale randomized studies for antiretroviral efficacy and safety.

Interferon alpha is another experimental drug in antiretroviral treatment studied in a few small-scale randomized and non-randomized clinical trials where both interferon and pegylated interferon were proved effective in reducing HIV viral load significantly in antiretroviral-naïve and -experienced patients and were found safe and tolerable [23-27].

Hydroxyurea-an immunomodulator-combined with didanosine was shown to synergize to control HIV viral replication where the major effect of hydroxyurea was defined as inhibiting the virus by reducing cellular proliferation [28]. Although this synergistic effect was confirmed in small-scale non-randomized [29] and randomized [30] clinical trials, another phase-IV study in HIV-infected patients using abacavir, efavirenz and didanosine suggested that adding hydroxyurea had no beneficial effect [31]. The controversy over its antiviral activity and severe adverse events associated with its use has limited extensive research over the safety and efficacy of this drug as an adjunct to antiretroviral therapy.

Reports suggest that the use of alternative strategies such as higher doses of drugs, combination of antiretrovirals with low or intermediate activity and use of alternative compounds have proved effective in selected cases with no treatment options left [32].

Considering that the patient had no choice to be included in ongoing research and to use investigational new drugs as suggested in the DHHS guidelines [6], the treatment regimen was designed to include experimental drugs with proof of antiviral

activity although slight. The patient responded very well to the tailored regimen with a significant fall in viral load achieving undetectable levels but at the expense of severe adverse events. Despite a significant increase in the CD4 count, the absolute number remained low due to persistent leucopenia, which ultimately led to the development of progressive multifocal leukoencephalopathy.

## CONCLUSION

Management of highly treatment-experienced patients with high levels of multiclass drug resistance is complex and challenging and may require difficult decisions regarding the selection of alternative strategies that the patient would most benefit from. Experience is the key factor in making such decisions and consultation with an expert for advice is strongly suggested.

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