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Letter to the Editor

Successful Rescue Therapy with Raltegravir (MK-0518) and Etravirine (TMC125) in an HIV-Infected Patient Failing All Four Classes of Antiretroviral Drugs

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Dear Editor:

It is mandatory to find antiretroviral therapies that offer increased efficacy in treatment-experienced patients with HIV-1 infection, a population whose extensive drug resistance restricts treatment options and has a severe effect on infection management.[1] The aim in salvage therapy in patients who were highly treatment-experienced and in whom multiple regimens had failed was so far limited to the new protease inhibitors (PI) and combination with enfuvirtide.[2,3]

The new antiretrovirals currently in expanded access programs, such as raltegravir and etravirine, show unprecedented level of virologic efficacy. Raltegravir, formerly MK-0518, the first integrase inhibitor under clinical development, showed high potency in multidrug-resistant HIV patients including those resistant to currently available antiretroviral drugs.[4] Etravirine, formerly TMC-125, a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) appears to be effective against a variety of HIV viruses that are resistant to efavirenz and nevirapine.[5]

Few data are available regarding the performance of these drugs combinations in heavily PI-experienced patients, including those for whom tipranavir, darunavir, and enfuvirtide have failed. Hereby, we describe the outcome of salvage therapy based on raltegravir and etravirine in a heavily antiretroviral-experienced patient. A 37-year-old Caucasian male, CDC status C3, had experienced multiple failures to all current classes of antiretroviral agents. Specifically, he had failed eight ritonavir-boosted PI combinations, including tenofovir-lamivudine-enfuvirtide-tipranavir/ritonavir, given in May 2004 with replacement of the latest with darunavir/ritonavir in December 2006.

Plasma HIV-RNA levels were measured at baseline and during therapy using a commercial assay, the Versant HIV-1 RNA 3.0 Assay (bDNA; Siemens Medical Solutions Diagnostics, Malvern, PA), with a dynamic range of 50–500,000 HIV-1 RNA copies per milliliter. CD4 cell count was determined by direct immunofluorescence in flow cytometry (Beckman Coulter, Fullerton, CA).

Genetic analysis of the pol gene including both HIV-1 reverse transcriptase (codons 4-99) and protease (codons 35-247) regions was performed using the Trugene HIV-1 Genotyping Kit (Siemens Medical Solutions Diagnostics).

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Genetic analysis of the env gene was performed amplifying and sequencing a gp41 fragment that included HR1 and HR2 regions using primers supplied by Siemens Medical Solutions Diagnostics. Drug resistance mutations within the pol and env genes were examined following the latest International AIDS Society—USA panel list published in 2007.[6] In April 2007 the patient's plasma HIV-RNA level was more than 5.7 $\log_{10}$ copies per milliliter and the CD4 cell count was 18 cells per microliter. The genotype revealed the presence of L10I, K20R, V32I, L33F, M36I, I47V, G48V, I50V, I54L/M, L63P, A71V, G73S, V82T, I84V mutations within protease; and M41L, D67N, V75T, T69D, A98G, K101A, V118C, Y181C, G190A, M184V, L210W, T215F mutations within transcriptase.

In summary there were multiple drug resistance mutations, which conferred high-level resistance to most currently available antiretroviral agents, included tipranavir and darunavir, and the mutation V38A to enfuvirtide in the HR1 region of the gp41.

Given the dramatic clinical and virological situation, a new regimen including emtricitabine/tenofovir fixed dose, darunavir/ritonavir, raltegravir 600 mg twice per day and etravirine 200 mg twice per day was started. The patient had a significant decline in plasma HIV RNA to 2.4 $\log_{10}$, and an increase in the CD4 cell count to 194 cells per microliter (8%), within 24 weeks of therapy (Fig. 1). Recent reports have highlighted the fact that mutations V32I, L33F, I47V, I50V I54L/M and G73S, are associated with lower susceptibility to darunavir and selected in patients failing this drug.[7]

In regard to entry inhibitors, it is known that gp41 single-point mutation between positions 36-45 reduces enfuvirtide susceptibility from 10- to 20-fold. Our patient exhibited only the V38A mutation in the HR1 region. This amino acid change is known to sustain an immunologic response.[8] Unfortunately, this finding was not present in our patient who presented CD4 cell count <50 cells per μL all along enfuvirtide treatment. And enfuvirtide was not included in the last regimen due to very painful injections, after a longer than 2-year treatment period.

Few data are available on raltegravir: a recent study shows a rapid, and sustained anti-

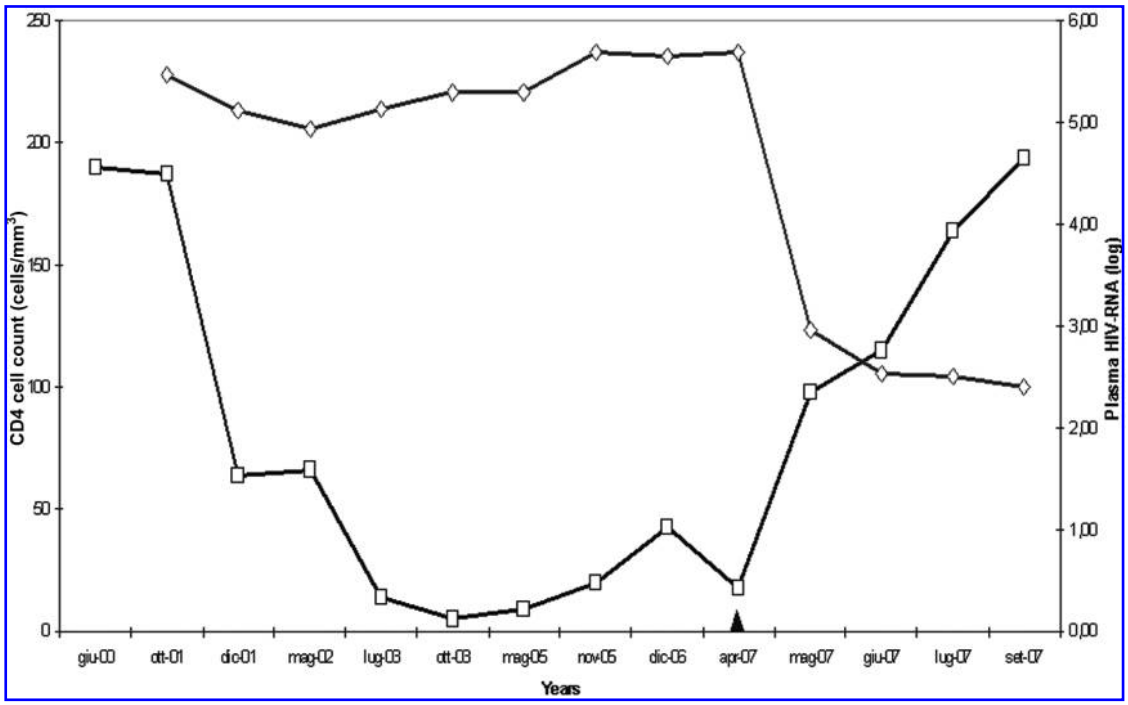

FIG. 1. Virologic and immunologic outcome: from April 2007 the patient started new regimen including emtricitabine/tenofovir fixed dose, darunavir/ritonavir, raltegravir and etravirine. ▲, start of the new regimen; □, CD4 cell count (cells/mm^3); ◇, viral load [plasma HIV-RNA (log)].

retroviral effect in patients who had triple class resistant virus, and a limited number of active antiretrovirals in their background regimen.[4]

Etravirine has antiviral activity in patients with NNRTI resistance, but three or more mutations were associated with decreased virologic response.[5] In our patient, the presence of three mutations (A98G, Y181C, and G190A), had not compromised the efficacy.

The tolerability was good and no serious adverse events were recorded. No signs of clinical progression were seen during the first 24 weeks of therapy. These results highlight the strong antiviral activity and good safety of raltegravir and etravirine in deep salvage in heavily antiretroviral-experienced patients, including individuals who had failed tipranavir, darunavir, and enfuvirtide.

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