# Long-term Maraviroc Therapy and Limited Side Effects in an HIV-1 Experienced Patient: Six Years of Antiretroviral Observation

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## INTRODUCTION

Maraviroc, originally designated UK-427857, is a small molecule and the first oral antiretroviral drug in the CCR5 receptor antagonist class used in the treatment of HIV infection. This drug, classed as an entry inhibitor, was developed by the drug company Pfizer in its United Kingdom laboratory located in Sandwich.

On April 24, 2007, the US Food and Drug Administration (FDA) advisory panel reviewing maraviroc's new drug application, unanimously recommended approval for the new drug (1), and the drug received full FDA approval on August 6, 2007, for use in treatment experienced patients.

Maraviroc is extensively metabolized by CYP3A4, with renal clearance accounting for approximately 23% of total clearance and it has been shown to achieve an undetectable HIV-1 RNA level in clinically advanced, class three antiretroviral treatment-experienced adults with evidence of CCR5-tropic HIV-1 replication despite ongoing antiretroviral therapy. It is well tolerated and its development is responding to a desperate need for new classes of antiretroviral agents that can target novel steps of the HIV lifecycle and not share cross-resistance with currently available therapy (2).

Our case report aims to explain the impact of maraviroc co-administered with agents from all classes of antiretroviral therapy in an HIV-1 experienced patient with six years of antiretroviral experience.

## CASE REPORT

In January 2008, a heterosexual 46-year old Italian female diagnosed with HIV-1 infection (September 1989) presented to the Hospital of Ancona without co-infections, a CD4 count of 116 cells/µL, and HIV-RNA 2604 cp/mL (detection limit 50 copies/mL). In January 2008, she started maraviroc, zidovudine (AZT), lamivudine (3TC), darunavir (DRV), ritonavir (RTV), attended clinic regularly and reported good treatment adherence. Her multidrug-resistance profile at baseline (test TRUGENE HIV-1) was: reverse transcriptase mutations M41L, K65R, K70R, V75I, F77L, Q151M;

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protease inhibitor mutations L10V, K20R, L33F, M36I, M46I, G48V, I54T, L63P, A71V, V77I, V82I, I84V.

At time of admission to our Department of Infectious Diseases, laboratory analysis revealed: aspartate transaminase (AST) 19 IU/mL (reference range, 1–36 IU/L), alanine transaminase (ALT) 23 IU/mL (reference range, 1–36 IU/L), total bilirubin 0.4 mg/dL, triglycerides 152 mg/dL, total cholesterol 269 mg/dL, high-density lipoprotein (HDL) cholesterol 59 mg/dL, creatinine 0.70 mg/dL, glycaemia 82 mg/dL, without history of insulin resistance, hypocomplementaemia, glomerulonephritis and autoimmune disorders and lipodystrophy. After two months of therapy, the patient revealed (at objective examination) a mixed lipodystrophy.

In April 2008, she switched to AZT/3TC, which was changed to tenofovir (TFV) and emtricitabine (FTC) for drug intolerance. During subsequent follow-ups, the patient maintained a good clinical condition. She was adherent to the highly active antiretroviral therapy (HAART) regimen with little side effects. In May 2010, biochemical, haematological and viro-immunological parameters demonstrated a good response to maraviroc without intolerance, drug resistance and side effects; CD4 T-cell count of 442 cell/mm³ and undetectable plasma HIV RNA concentration (detection limit 50 copies/mL), total bilirubin 0.50 mg/dL, triglycerides 153 mg/dL, total cholesterol 271 mg/dL, HDL cholesterol 52 mg/dL, creatinine 0.80 mg, glycaemia 73 mg/dL, ALT concentration 13 IU/L and AST 20 IU/L, and objective signs of lipodystrophy had decreased.

Currently, after five years of therapy with maraviroc, tenofovir, emtricitabine, ritonavir and darunavir, laboratory examination and objective examination revealed significant reduction in signs of mixed lipodystrophy without any interruption of antiretroviral therapy containing protease inhibitors as backbone [Figs. 1, 2].

In February 2014, CD4 T-cell count was 580 cell/mm³, plasma HIV RNA concentration was undetectable, AST 30 IU/mL, ALT 23 IU/mL, total bilirubin 0.5 mg/dL, triglycerides 170 mg/dL, total cholesterol 200 mg/dL, HDL cholesterol 50 mg/dL, creatinine 1.0 mg, glycaemia 78 mg/dL and bilirubin 0.8 mg/dL. Surgery (excision or liposuction) has not been performed on the patient because severe fat accumulation was reduced without the interruption of protease inhibitors.

This case demonstrates that maraviroc in combination with tenofovir and emtricitabine after six years was effective in suppressing the viral load of a highly treatment experienced patient with HIV-1. In treatment experienced and multidrug resistance patients with HIV-1 infection,
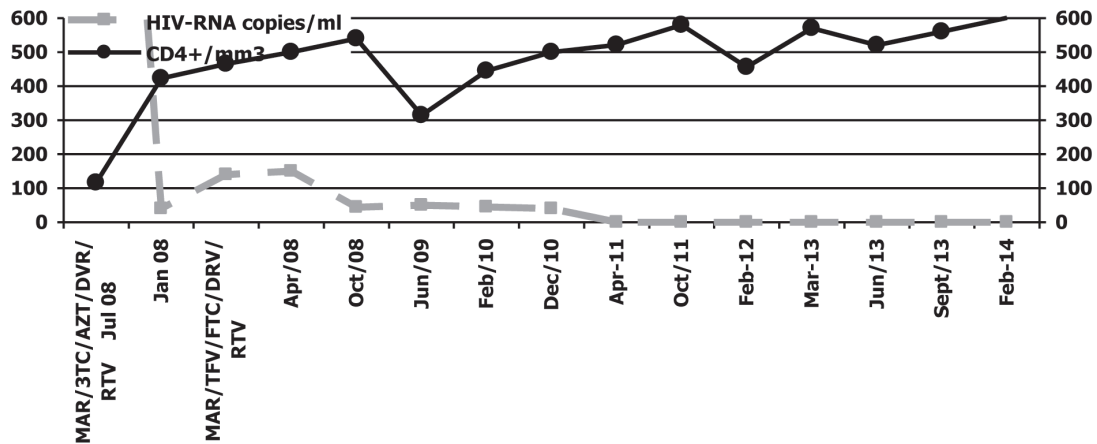
Fig. 1:    HIV-RNA viral load, CD4+ cell count and antiretroviral treatment.
MAR: maraviroc; 3TC: lamivudine; AZT: zidovudine; DVR: darunavir; RTV: ritonavir ; TFV: tenofovir; FTC: emtricitabine
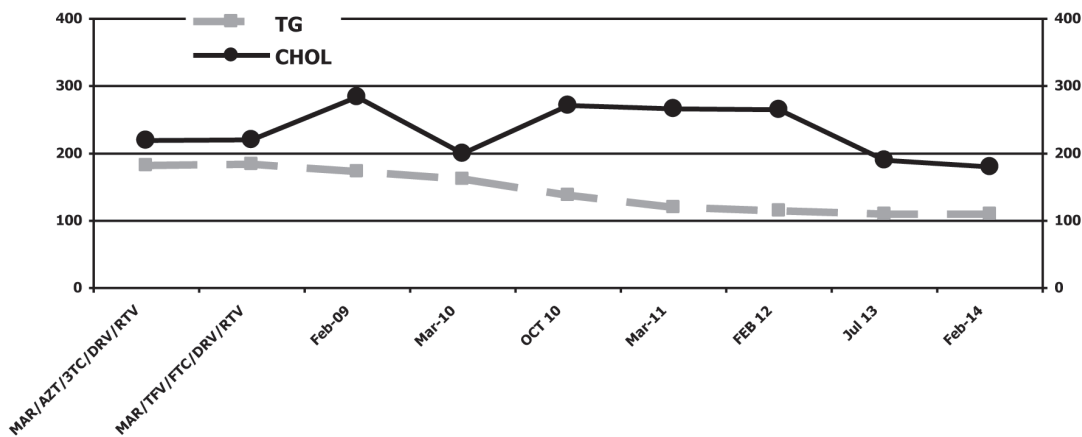


Fig. 2:    Serum triglycerides and cholesterol levels.
TG: triglycerides; CHOL: cholesterol; MAR: maraviroc; AZT: zidovudine; 3TC: lamivudine; DRV: darunavir; RTV: ritonavir;
TFV: tenofovir; FTC: emtricitabine

maraviroc has been shown to have maximum benefit when introduced with at least one other active agent.

**DISCUSSION**

Eradication of HIV infection cannot be achieved with existing regimens.  The goals of therapy are the prolonged suppression of viral levels to less than detection limits (< 50 copies/mL for Amplicor assay, < 75 copies/ mL for VERSANT assay and < 80 copies/mL for NucliSens assay), with the aim to restore and preserve immunologic function, improve quality of life and avoid HIV-associated morbidity and mortality. Treatment success needs strict lifelong drug adherence and maraviroc monotherapy has a high potency and long half-life, allowing single-pill dosing.

Maraviroc is only effective against CCR5-tropic virus, which predominates throughout infection but is more com-

mon in patients at the early asymptomatic stage of infection. It is not known how quickly resistance may develop to maraviroc in clinical practice.  Current evidence supports the continued development of maraviroc as a potentially useful, alternative treatment for the management of HIV infection. Our patient, experienced and multidrug resistant, has never stopped maraviroc during six years of antiretroviral therapy and therefore has not developed any resistance.

Preliminary evidence indicates that maraviroc is likely to provide an alternative therapy for treatment-experienced patients, and for treatment-naïve patients who are newly infected with drug-resistant virus.  However, improvements in efficacy or short- and long-term side effects for maraviroc compared with currently available regimens in treatment-naïve patients could positively impact on its use in this patient population, provided that its use does not promote the

selection of X4 HIV and more rapid disease progression. Approximately 50–60% of treatment-experienced patients and 80–85% of treatment-naïve patients are infected with the CCR5-tropic virus only. A viral tropism test (Monogram Biosciences, San Francisco, CA, USA) is available to determine the probability of successful treatment, but the cost and turnaround time is three to five weeks.

In summary, long-term maraviroc therapy meets an unmet need for a well-tolerated drug that reduces viral load with limited adverse events in an HIV-1 experienced patient with pre-existing class resistance. Current evidence supports the continued development of maraviroc as a potentially useful, alternative treatment for the management of HIV infection.

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