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Effectiveness, safety, durability and immune recovery in a retrospective, multicentre, observational cohort of ART-experienced, HIV-1-infected patients receiving maraviroc

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Abstract

The aim of this retrospective, multicentre, observational study was to assess the durability, safety, immune recovery and effectiveness on viral suppression of antiretroviral therapy (ART) in a maraviroc (MVC)-based cohort. We collected clinical, demographical, immunological and virological parameters of adult HIV patients who were infected by CCR5-tropic virus and started an ART regimen containing MVC from 2005 to 2012. We created a longitudinal mixed model to assess the change over time of data. We enrolled 126 drug-experienced patients; the median duration of MVC treatment was 25 months. The probability of stopping ART at one year was 13.3%, and at three years was 27.3%. Statistically significant changes were observed for CD4+ cell count increase ($p < 0.001$), HIV-RNA decrease ($p < 0.001$) and total cholesterol decrease ($p = 0.005$). Ninety-four patients (79.7%) had CD4 $\geq$ 200 cells/mm^3 at baseline while nine of them reached this threshold at nine months (7.6%), 17 (13%) after nine months and six (5%) remained below 200 cells/mm^3 at the end of the study. Overall, 114 patients (90.5%) achieved an HIV-RNA $\leq$ 50 cp/ml. A majority of patients maintained CD4 cell counts of $\geq$ 200 cells/mm^3 and achieved an undetectable HIV viral load within three months. MVC-containing regimens are safe and appear to be a feasible therapeutic option for ART.

Keywords

Maraviroc, antiretroviral therapy, clinical practice, safety, HIV, AIDS

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Introduction

Maraviroc (MVC) is the only CCR5 inhibitor currently used in clinical practice and it has been tested and approved in the treatment of both treatment-naïve and -experienced patients carrying the CCR5 tropism who are antiretroviral-naïve or have experienced therapeutic failure following traditional antiretroviral therapies.[1] In human immunodeficiency virus type 1 (HIV-1)-infected patients in the Motivate 1 and Motivate 2 phase 3 trials, MVC demonstrated superior 48 weeks' virologic efficacy compared to placebo,[2] and Gulick et al. also reported the pooled safety findings from these two studies over more than five years.[3] MVC is associated with low levels of toxicity in studies of the treatment of naïve[4] and experienced patients.[2] As a representative of a new class of anti-HIV drugs, MVC faces certain challenges unique to its use as well as some challenges it shares with other antiretroviral drugs.[5] Several data from Motivate 1 and 2 studies and the Merit study have showed that MVC is effective and well tolerated both in pre-treated and antiretroviral-naïve patients and significantly increases CD4+ T cell count even in cases where viral loads are not completely suppressed.[6] Some studies have demonstrated that the immunological recovery of antiretroviral regimens containing MVC increase the normalization ratio of CD4/CD8 T cells[7] and virological recovery.[8] Moreover, the tolerability profile of the drug makes MVC particularly appealing as a combination partner in antiretroviral therapy (ART).[9,10]

Apart from the Motivate study, however, there are no large observational experiences describing the long-term efficacy and safety of salvage regimens with MVC for HIV-1 infection. Furthermore, experience with regimens containing MVC and newer antiretroviral agents is limited.

The aim of this multicentre observational study, therefore, was to assess the durability, safety, immune recovery and effectiveness on viral suppression of MVC-based regimens.

Methods

This observational study presents three outcomes: the first outcome was durability (time) of the antiretroviral regimens containing MVC; the second outcome was the safety of the regimens containing MVC (evaluating the metabolic and hepatic profiles) and the third outcome was immune recovery and effectiveness on viral suppression of these patients.

HIV-1-infected, drug-experienced patients attending 10 Italian Infectious Diseases Centres were included in the study from September 2005 to September 2012. The inclusion criteria were adult patients infected by CCR5-tropic virus who were to start treatment with ART containing MVC. Follow-up for patients commenced at the initiation of MVC.

Clinical, demographic, immunological and virological parameters were collected at baseline and every three months in a database connected through a web-based interface. This web tool made it possible to collect pseudo-anonymous data from several contemporary clinical studies providing highly structured and standardized information.[11,12] To obtain the data for the first outcome, we analysed the probabilities of stopping ART containing MVC according to demographic and clinical characteristics. We also analysed if the HIV stage disease had an impact on this outcome. We used the Centers for Diseases Control (CDC) classification (revised in 1993) to assess the severity of HIV disease by CD4 cell count (categories 1, 2 and 3) and by the presence of specific HIV-related conditions (categories A, B and C).

As a cut-off for the statistical analysis, explained in the next section, and to assess the second and the third outcomes, we considered as abnormal a CD4+ T cell count < 200 cells/mm^3, HIVRNA (VL) > 50 copies (cp)/ml, total cholesterol > 200 mg/dl, HDL cholesterol < 40 mg/dl, triglycerides > 160 mg/dl, and transaminases > 40 mg/dl.

Statistical methods

Linear mixed models with random intercept were used to assess the global change over all follow-up of clinical characteristics as HIV-RNA, CD4 + T cells, cholesterol levels and triglycerides. Since the frequency distribution of HIV-RNA and triglycerides was highly skewed, a cubic root transformation was performed to be used as dependent variable in a linear mixed model. Further, using a Kaplan–Meier estimator, the probabilities of stopping treatment were calculated and plotted. Probability estimation with the associate standard error (SE) was reported at one, two and three years from start of treatment. A $p < 0.05$ was considered statistically significant. SAS (version 9.2) was used for computation.

Results

Description of the cohort

We enrolled 126 drug-experienced patients whose clinical and demographic characteristics are shown in Table 1. In 70 patients (55.5%), MVC was added to the antiretroviral regimen for 'salvage therapy', in 51 (40.5%) for therapeutic/immunological intensification and in five patients (4%) in the context of therapeutic simplification. The median time of MVC in the three drug regimens was 30 months (IQR 20-41).

Table 1. Baseline characteristics of the study population ($N = 126$ patients).

Characteristics	Number (%)
Gender, males	91 (72)
HCV and/or HBV co-infection	38 (30)
Drug users	31 (25)
Ethinicity, Caucasians	119 (94)
CDC category A, B, C	43 (34), 35 (28), 48 (38)
Concomitant ARVs with MVC	
Protease Inhibitor	76 (60)
Raltegravir	86 (68)
Etravirine	34 (27)
Dual therapy (as current regimen)	24 (19)
Raltegravir-based	7 (14)
Protease inhibitor-based	9 (37)
NNRTI-based	5 (21)
NRTI-based	3 (12)

	Median	Range	IQR
Age	49	18–77	45–53
Nadir CD4+ T cell count/mm^3	157	1–572	72–301
CD4+T cell count/mm^3	359	21–1133	234–499
HIV-RNA cp/ml	3393	20–3.6 10^6	227–45,000
Time on cART (years)	16	1–27	11–17
Number of ARV regimens	6	2–15	4–8
MVC therapy (months)	25	1–83	15–40

CDC: Centers for Disease Control, ARVs: antiretrovirals, MVC: maraviroc, NNRTI: non-nucleoside reverse transcriptase inhibitors, NRTI: nucleos(t)ide RTI, IQR: inter-quartile range 1st quartile–3rd quartile, cp: copies, cART: combination antiretroviral therapy.

Durability of the regimens containing MVC

In the total study population, the probability of stopping ART at one year was 13.3% (SE: 3.1%), at two years it was 21.8% (SE: 4%) and at three years it was 27.3% (SE: 4.6%) (Figure 1(a)). We did not find any significant difference between genders ($p = 0.27$) although men had a higher probability of stopping treatment compared to women. There were no significant differences between groups divided according to the CDC classification (log-rank test; $p = 0.095$) even if there was a trend for a higher probability in patients in category C of CDC. If category A and B are considered as a single group, the difference compared to C was significant (log-rank; $p = 0.047$) (Figure 1(b)). In A plus B categories at one year, the probability of stopping treatment was 9.4% (SE: 3.4%) while it was 20.4% (SE: 6.1%) in group C; at two years the probabilities were 15.9% (SE: 4.4%) and 33.2 (SE: 7.9%), respectively.

Overall, 31 patients discontinued MVC: 17 for failure, 5 for ART simplification, 3 for toxicity, 3 for poor adherence and 3 died. The causes of death were non-Hodgkin lymphoma, hepatic carcinoma and lung cancer. Only one patient shifted to X4 and two patients to dual mixed tropism.

Safety of MVC

A statistically significant longitudinal change for CD4 + T cells and HIV-RNA ($p < 0.001$) and for cholesterol ($p = 0.005$) except for HDL cholesterol ($p = 0.34$) and triglycerides ($p = 0.23$) was detected (Figures 2(a) to (e), respectively). We did not find any significant alterations or changes concerning the values of transaminases (data not shown).

Immune recovery and effectiveness on viral suppression

In patients with baseline VL ≤ 50 cp/ml, the delta CD4+T cell count was 52 cells/mm^3 at three months, 45 cells/mm^3 at six months and 16 cells/mm^3 at 12 months. In patients with baseline VL > 50, however,

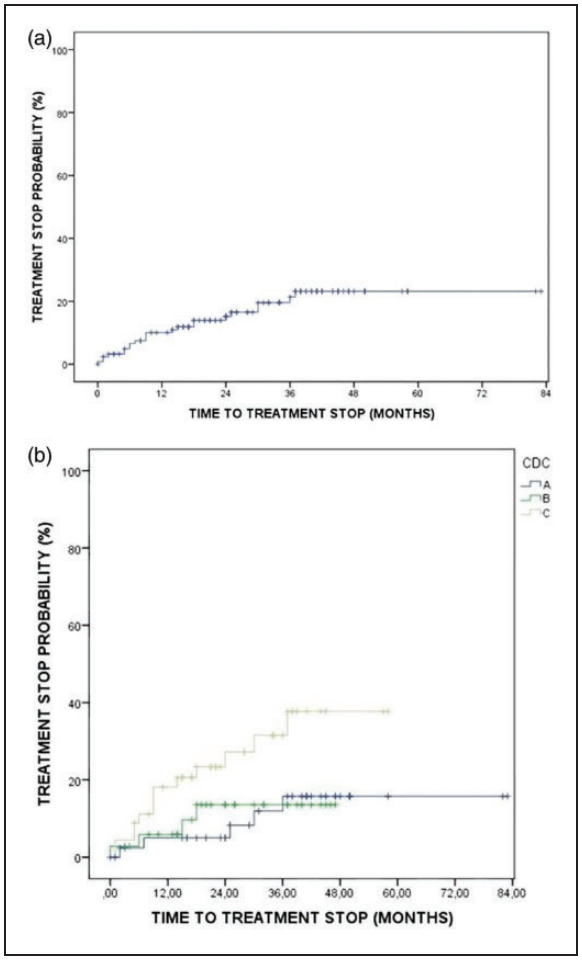

Figure 1. Using the Kaplan–Meier estimator, panel (a) shows that the probability of stopping antiretroviral therapy at one year was 13.3% [standard error (SE): 3.1%], at two years 21.8% (SE: 4%) and at three years: 27.3% (SE: 4.6%). In panel (b), gathering together both category A and B patients, the difference compared to patients in category C is significant (log-rank; $p = 0.047$). In A plus B categories at one year, the probability of stopping treatment was 9.4% (SE: 3.4%) while it was 20.4% (SE: 6.1%) in group C; at two years, the probabilities were 15.9% (SE: 4.4%) and 33.2 (SE: 7.9%), respectively.

we established at three months a median delta value of 80 CD4+ cells/mm^3, at six months 98 cells/mm^3 and at 12 months 120 cells/mm^3.

The study revealed that a total of 120/126 patients (95%) reached, at some point, a CD4 + T cell count higher than 200 cells/mm^3. A total of 94 patients (79.7%) had a CD4+ T cell count higher than 200 cells/mm^3 at baseline while nine patients reached this threshold at nine months (7.6%), 17 (13%) after nine months and six patients (5%) remained below 200 cells/mm^3 as at the end of the study. Of note, 19 patients reached the threshold of CD4 cell count ≥ 500 cells/mm^3 at three months of therapy and five patients at nine months.

Further, a total of 114 patients (90.5%) reached a value of VL ≤ 50 cp/ml. Among them, 19 (15%) had normal values at baseline while 28 (24.6%) and 25 (21.9%) reached this threshold at 1 and 3 months, respectively. Excluding those patients whose VL values was ≤ 50 cp/ml at baseline, 50% of patients reached the threshold in the first three months (median value) with a range between 1 and 21 months.

Immune recovery and effectiveness on viral suppression in patients treated with MVC-based dual therapy

Considering MVC-based dual therapy, in our cohort we had 24 (19%) patients: in seven patients MVC was combined with raltegravir; in nine patients with a protease inhibitor; in five patients with a non-nucleoside reverse transcriptase inhibitor (NNRTI); and in three patients with a nucleos(t)ide RTI (NRTI). In this population, we found only three virological failures (one in raltegravir-based and two in NRTI-based dual therapy). We did not observe any tropism switch. The median time on dual therapy was 20 months (IQR 15-25); the median value of baseline CD4+T cell count/mm^3 was 348 (IQR 251-503) and the median value of the last determination of CD4+ T cell count/mm^3 was 425 (IQR 303-575).

Discussion

In this observational, multicentre and retrospective cohort study, we describe in a real-life setting, the safety, the immunovirologic recovery and the durability of MVC as part of combined ART regimens in multi-experienced CCR5-tropic, HIV-1-positive patients with about a fifth of the patients treated with a novel two-drug combinations. The study, with a relatively small sample size of patients, is an observational study and presents all the limitations concerning this type of study. These limitations include problems of internal validity, impossibility to randomize individuals and some missing data. So as to remedy the presence of missing observations in clinical characteristics (CD4, HIV-RNA, etc.) during follow-up, a mixed model approach was used. This model allowed for the carrying out of analysis even for patients with missing observations and not just for patients who had complete data as may happen in other models for repeated measures (i.e. analysis of variance). As a consequence, the impact of lost data or observations during follow-up on results was minimized.

With respect to the Motivate study, in our setting median CD4+T cells at baseline was higher and VL was lower, and unlike Motivate the ART regimens considered in this study included recent antiretroviral agents

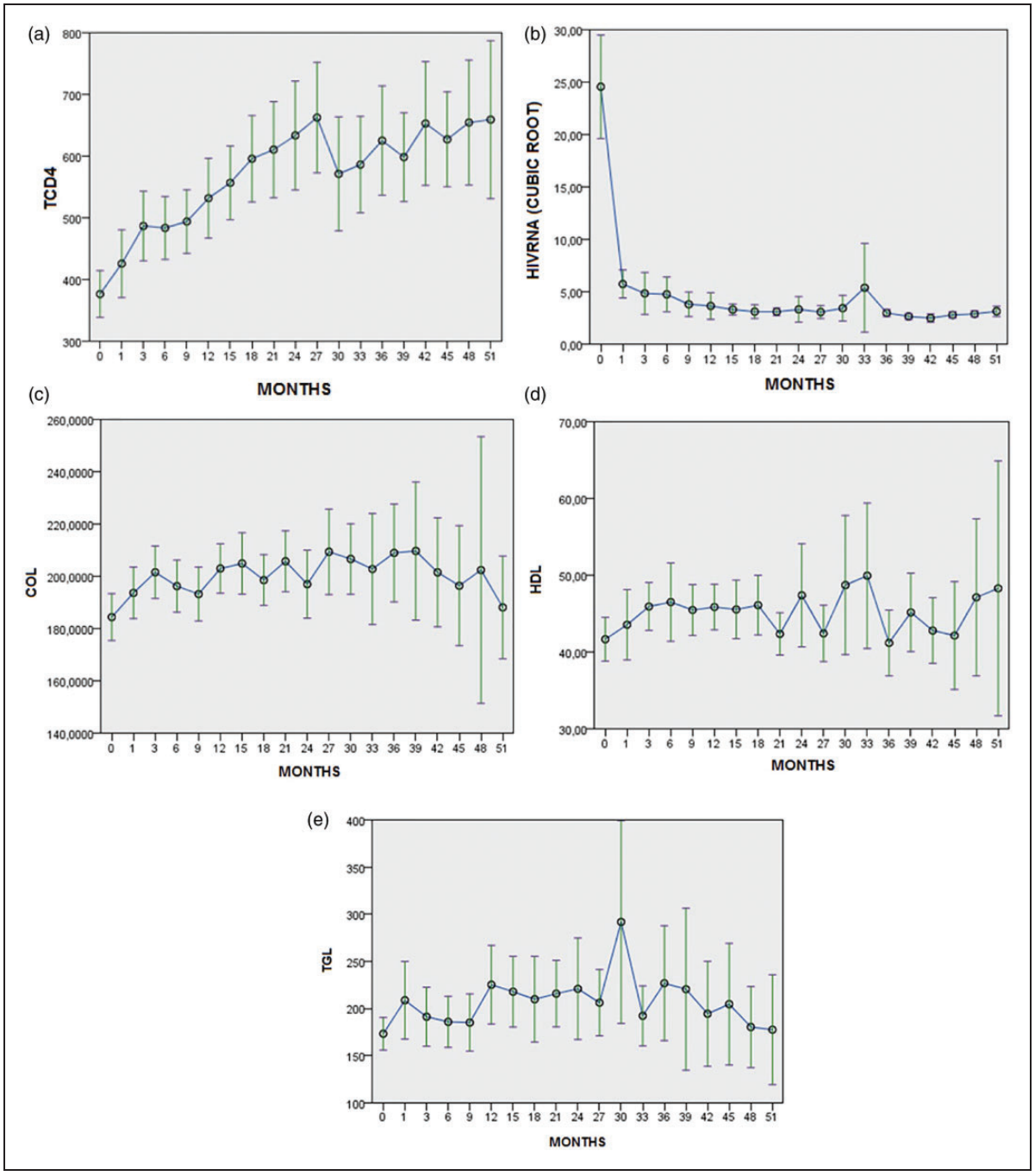

Figure 2. Data representing the changes over time (longitudinal mean values) of immune-virological and biochemical parameters. (a) CD4+T cell count/mm^3, (b) HIV-RNA copies/ml, (c) total cholesterol (COL), (d) HDL-cholesterol and (e) triglycerides (TGL). In all graphs, the circles indicate the mean values and the error bars indicate the confidential interval (CI) 95%.

such as darunavir, raltegravir and etravirine (42%, 68% and 27% of patients, respectively).

In our study, we observed that MVC has a favourable toxicity profile, with only 3 out of 31 patients discontinued from MVC due to toxicity: one for dyspepsia and two for persistent myalgia. In addition, no relevant changes in laboratory assessments were observed, apart from a significant beneficial decrease in total cholesterol levels. Furthermore, although the labelling information for MVC contains a boxed warning for hepatotoxicity, in our cohort in which 30% of patients were HBV or HCV co-infected, we did not find any significant alterations or changes in liver function. Finally, in our setting, cART containing MVC resulted in a significant

reduction of VL within three months. At the end of our data collection, 90.5% of patients reached an undetectable VL ($\leq$ 50 cp/mL). We also observed a significant increase of CD4+ T cell count that was sustained throughout the study in all patients, as demonstrated in other studies.[13,14]

Virological failure was, in multi-experienced patients, the most frequent reason for MVC discontinuation (17/31 patients, 54.8%), but only one patient shifted to X4 and 2 to mixed tropism. An increased number of trials have been conducted among specific patient groups, in order to better define the extent of MVC indications.[15,16]

There are, nonetheless, few conflicting data available on dual therapy with MVC: in naive patients, maraviroc administered once daily with darunavir boosted by ritonavir in a new regimen trial (MODERN) of ritonavir-boosted darunavir 800/100 mg and MVC 150 mg daily was prematurely terminated due to inferior efficacy. In experienced patients, the virological activity and immunological benefit of a once daily administered MVC with atazanavir/ritonavir (ATV/r) were demonstrated in a phase 2b, randomized study.[15] Efficacy and safety of the once-daily administered MVC with ritonavir-boosted darunavir in pre-treated HIV-infected patients was shown in 60 patients in a retrospective cohort study,[17] whereas a viral rebound after a switch to MVC/raltegravir dual therapy in highly experienced and virologically suppressed patients with HIV-1 infection was revealed.[18]

Considering overall data, in our observational study we established that MVC has a favourable toxicity profile regarding in particular HDL cholesterol and triglycerides values and we did not find any changes concerning transaminases, as reported in other studies.[19,20]

In our cohort, we observed excellent immunological recovery in 95% of patients who reached a CD4+ T cell count higher than 200 cells/mm^3 and 90% of patients with VL $\leq$ 50 cp/ml. In the subgroup of 24 patients treated with MVC dual therapy, we described few virological failures and in patients who failed, no change in viral tropism, suggesting that this strategy can also be used in selected multi-experienced patients.

Authors' contribution

CD, KS, DF, ADB designed the study, drafted the manuscript, selected and enrolled patients and collected data. AS performed the statistical analysis. GC, MG, PDL, VB, EM, GO selected and enrolled patients and collected data. MG created the database managed through a web-based interface. BB did the virological analysis.

MARHIV study group

The other members and collaborators of the MARHIV study group are: G Ferrea, D Fenoglio, P Fraccaro, G Filaci, A Parodi, F Kalli, A De Maria, F Bozzano, F Marras, M Zoppi, G Cassola, and C Viscoli.

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Declaration of conflicting interests

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References

1. Wasmuth JC, Rockstroh JK and Hardy WD. Drug safety evaluation of maraviroc for the treatment of HIV infection. *Expert Opin Drug Safe* 2012; 11: 161–174.
2. Gulick RM, Lalezari J, Goodrich J, et al. Maraviroc for previously treated patients with R5 HIV-1 infection. *N Engl J Med* 2008; 359: 1429–1441.
3. Gulick RM, Fatkenheuer G, Burnside R, et al. Five-year safety evaluation of maraviroc in HIV-1-infected treatment-experienced patients. *J Acquir Immune Defic Syndr* 2014; 65: 78–81.
4. Sierra-Madero J, Di Perri G, Wood R, et al. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. *HIV Clin Trials* 2010; 11: 125–132.
5. Dolin R. A new class of anti-HIV therapy and new challenges. *N Engl J Med* 2008; 359: 1509–1511.
6. Reuter S, Braken P, Jensen B, et al. Maraviroc in treatment-experienced patients with HIV-1 infection - experience from routine clinical practice. *Eur J Med Res* 2010; 15: 231–237.
7. Chan ES, Landay AL, Brown TT, et al. Differential CD4+ cell count increase and CD4+: CD8+ ratio normalization with maraviroc compared with tenofovir. *AIDS* 2016; 30: 2091–2097.
8. Bocket L, Peytavin G, Alidjinou EK, et al. Factors associated with virological response to a switch regimen containing maraviroc for antiretroviral-experienced HIV-1-infected patients. *J Antimicrob Chemother* 2016; 71: 2651–2653.
9. Emmelkamp JM and Rockstroh JK. Maraviroc, risks and benefits: a review of the clinical literature. *Expert Opin Drug Safe* 2008; 7: 559–569.
10. Potard V, Reynes J, Ferry T, et al. Durability and effectiveness of Maraviroc-containing regimens in HIV-1-infected individuals with virological failure in routine clinical practice. *PLoS One* 2015; 10: e0144746.

11. Fraccaro P and Giacomini M. A web-based tool for patients cohorts and clinical trials management. *Stud Health Technol Inform* 2012; 180: 554–555.
12. Fraccaro P, Dentone C, Fenoglio D, et al. Multicentre clinical trials' data management: a hybrid solution to exploit the strengths of electronic data capture and electronic health records systems. *Inform Health Soc Care* 2013; 38: 313–329.
13. Cooper DA1, Heera J, Ive P, et al. Efficacy and safety of maraviroc vs. efavirenz in treatment-naive patients with HIV-1: 5-year findings. *AIDS* 2014; 28: 717–725.
14. Rossetti B, Bianco C, Bellazzi LI, et al. Virological and immunological response to antiretroviral regimens containing maraviroc in HIV type 1- infected patients in clinical practice: role of different tropism testing results and of concomitant treatments. *AIDS Res Hum Retroviruses* 2014; 30: 17–24.
15. Mills A, Mildvan D, Podzamczer D, et al. Maraviroc once-daily nucleoside analog-sparing regimen in treatment-naive patients: randomized, open-label pilot study. *J Acquir Immune Defic Syndr* 2013; 62: 164–170.
16. Panos G and Watson DC. Effect of HIV-1 subtype and tropism on treatment with chemokine coreceptor entry inhibitors; overview of viral entry inhibition. *Crit Rev Microbiol* 2015; 41: 473–487.
17. Macías J, Recio E, Márquez M, et al. Efficacy and safety of once-daily maraviroc plus ritonavir-boosted darunavir in pretreated HIV-infected patients in a real-life setting. *HIV Med* 2014; 15: 417–424.
18. Nozza S, Bigoloni A, Calcagno A, et al. Viral rebound after switch to maraviroc/raltegravir dual therapy in highly experienced and virologically suppressed patients with HIV-1 infection. *J Antimicrob Chemother* 2014; 69: 1436–1439.
19. Bonjoch A, Pou C, Pérez-Álvarez N, et al. Switching the third drug of antiretroviral therapy to maraviroc in aviraemic subjects: a pilot, prospective, randomized clinical trial. *J Antimicrob Chemother* 2013; 68: 1382–1387.
20. Soriano V, Geretti AM, Perno CF, et al. Optimal use of maraviroc in clinical practice. *AIDS* 2008; 22: 2231–2240.