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Efficacy and safety of long-term maraviroc use in a heterogeneous group of HIV-infected patients: A retrospective cohort study

J.M. Weehuizen[a,*], A.M.J. Wensing[b], T. Mudrikova[a], F.W.N.M. Wit[c,d], A.I.M. Hoepelman[a]

[a] Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht, Utrecht, the Netherlands
[b] Virology, Department of Medical Microbiology, University Medical Centre Utrecht, Utrecht, the Netherlands
[c] HIV Monitoring Foundation, Amsterdam, the Netherlands
[d] Department of Global Health & Division of Infectious Diseases, Amsterdam University Medical Centres, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands

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ABSTRACT

Since the registration of maraviroc (MVC) as an antiretroviral agent in 2008, only studies with a follow-up time of <5 years have been published. Therefore, little is known about its long-term safety and efficacy in clinical practice. In this cohort study, data on long-term follow-up of MVC treatment in routine practice were analysed. A retrospective cohort study was conducted at University Medical Centre Utrecht with a follow-up period up to almost 10 years. The efficacy and tolerability of MVC-containing antiretroviral therapy (ART) was analysed in human immunodeficiency virus type 1 (HIV-1)-infected patients. The cohort consisted of 111 HIV patients who were treated for a median of 11.0 years (IQR 4.0–15.0 years) and with a median of 4 (IQR 2–6) previous ART regimens. The median time of MVC use was 49 months (IQR 21–82 months). Mean $CD4^+$ T-cell counts continued to increase up to 9 years following initiation of MVC. Patients with a detectable viral load (≥50 copies/mL HIV-RNA) at the start of MVC-containing ART reached high proportions of viral suppression. Only three patients (2.7%) experienced treatment failure despite optimal therapy. Nine patients (8.1%) discontinued MVC owing to intolerance of their ART regimen. Severe laboratory abnormalities were deemed to be unrelated to MVC use. During the 487 person-years of follow-up, 18 patients (16.2%) died. MVC use in this heavily pre-treated cohort was generally well tolerated during long-term follow-up. Furthermore, use of MVC resulted in a good immunological and virological response in clinical practice.

1. Introduction

Maraviroc (MVC; brand name Celsentri®, Selzentry®) was registered in 2008 as an antiretroviral drug for the treatment of human immunodeficiency virus type 1 (HIV-1) infection [1]. MVC is an HIV-1 entry inhibitor and works as an antagonist for the chemokine receptor 5 (CCR5 co-receptor) on the $CD4^+$ T-cell membrane [2,3]. The CCR5 co-receptor, together with the chemokine receptor 4 (CXCR4 co-receptor), is used by the HIV-1 virus to enter the $CD4^+$ T-cell, and the virus can use either co-receptor on the $CD4^+$ T-cell membrane. It is also possible that some (dual-tropic) HIV-1 strains use both receptors [4,5]. Typically, in the early stage of infection most of the viral strains are R5-tropic. A switch to X4 usage may occur in later stages of the disease and is associated with more rapid disease progression [6–8].

Approval of MVC for treatment-experienced adults with R5-tropic HIV-1 was based on the results of the Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) studies [1]. Moreover, the Maraviroc versus Efavirenz in Treatment-Naive Patients (MERIT) study and the maraviroc expanded access program showed promising results regarding the efficacy and safety of MVC during 48 weeks of follow-up [9,10]. However, due to the unique mechanism targeting the host cell instead of the viral protein, there were initially concerns about possible adverse effects [11]. In the early development of other CCR5 receptor antagonists (aplaviroc and vicriviroc), severe hepatotoxicity and an association with malignancies, especially Hodgkin's and non-Hodgkin's lymphoma, were observed.

These results contributed to concerns about MVC's potential for adverse events. However, the initial finding of an association of vicriviroc with malignancies was not confirmed in a larger study [12–14].

Apart from the 5-year follow-up of the MOTIVATE and MERIT studies, little is known about the long-term clinical use and safety

* Corresponding author. Tel.: +31 61 225 4457.
E-mail address: j.m.weehuizen@umcutrecht.nl (J.M. Weehuizen).

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Table 1
Baseline characteristics of patients included in this study[a].

Characteristic	Indication for MVC			
	Total population ($n=111$)	Virological failure ($n=47$)	Immunological intensification ($n=16$)	Intolerance or interaction of previous ART ($n=48$)
Age (years) (mean ± S.D.)	50.2 ± 10.9	46.2 ± 11.1	48.7 ± 9.6	54.7 ± 9.5
Male sex	87 (78.4)	32 (68.1)	15 (93.8)	40 (83.3)
Time since HIV-1 diagnosis (years)	13.0 (7.0–17.0)	13.0 (5.0–17.0)	8.5 (3.8–13.8)	14.0 (8.3–17.0)
Duration of ART (years)	11.0 (4.0–15.0)	11.0 (4.0–14.0)	7.5 (2.3–12.8)	12.5 (7.3–15.8)
$CD4^+$ T-cell nadir (cells/mm^2)	92 (27–219)	35 (16–158)	62 (23–124)	161 (67–257)
No. of previous ART regimens	4 (2–6)	4 (2–6)	4 (1–6)	4 (2–6)
Virological failure with earlier ART regimen	62 (55.9)	32 (68.1)	5 (31.3)	25 (52.1)
Prior AIDS-defining diagnosis	64 (57.7)	31 (66.0)	10 (62.5)	23 (47.9)
$CD4^+$ T-cells <200 cells/mm^2	30 (27.0)	23 (48.9)	5 (31.3)	2 (4.2)
$CD4^+$ T-cell count (cells/mm^2)	379 (195–580)	201 (46–459)	254 (196–294)	586 (389–772)
VL<50 copies/mL HIV-RNA	60 (54.1)	0	16 (100)	44 (91.7)
HIV-RNA ($\log_{10}$ copies/mL)	1.7 (1.7–3.5)	3.9 (2.7–5.1)	<1.7 (–)[b]	1.7 (1.7–1.7)
Use of PI	84 (75.7)	42 (89.4)	11 (68.8)	31 (64.6)
Newly introduced PI	24 (21.6)	20 (42.6)	0 (–)	4 (8.3)
Use of INI	46 (41.4)	25 (53.2)	4 (25.0)	17 (35.4)
Newly introduced INI	35 (31.5)	23 (48.9)	0 (–)	12 (25.0)
ALT (U/L)	25 (19–36)	23 (17–35)	30 (20–65)	26 (18–35)
SCr (μmol/L)	86 (73–102)	79 (67–94)	91 (79–101)	95 (76–122)

MVC, maraviroc; ART, antiretroviral therapy; S.D., standard deviation; HIV-1, human immunodeficiency virus type 1; AIDS, acquired immune deficiency syndrome; VL, viral load; PI, protease inhibitor; INI, integrase inhibitor; ALT, alanine aminotransferase; SCr, serum creatinine.
[a] Data are expressed as the median (interquartile range) or number (%) of cases unless otherwise stated.
[b] All patients had an undetectable VL (<50 copies/mL HIV-RNA).

of MVC [3,11,15]. The aim of the current retrospective study was to analyse the efficacy and safety of long-term use of MVC in a heterogeneous clinical cohort of HIV-infected patients.

2. Patients and methods

Data were collected from the electronic patient filing system of the University Medical Centre Utrecht (UMCU, Utrecht, the Netherlands) and the ATHENA National HIV observation cohort. The UMCU is 1 of 30 HIV treatment centres in the Netherlands and has 1799 HIV patients in care.

2.1. Study population

A retrospective cohort study was conducted in UMCU. Included patients had a diagnosis of HIV-1 infection, were aged ≥18 years and had taken at least one dose of MVC. Patients who participated in the Maraviroc Immune Recovery Study (MIRS) or who participated in the Maraviroc Abacavir Study—effects on Endothelial Recovery (MASTER) [16,17] and only used MVC during these studies were excluded ($n=30$). Follow-up continued until November 2017, death or discontinuation of MVC.

2.2. Data collection

2.2.1. Baseline characteristics

Baseline information was collected at the start of MVC use (Table 1). The indication for switching to MVC-containing combination antiretroviral therapy (cART) was categorised into three groups: (i) virological failure; (ii) immunological intensification in patients with undetectable viraemia but unsatisfying immunological recovery on cART; and (iii) intolerance or drug–drug interaction of the current virologically suppressive regimen. The first group contained patients whose ART failed to decrease the HIV viral load (VL) below the detection range of <50 copies/mL HIV-RNA in plasma or failed to maintain this level of virological suppression with their previous ART regimen. In the second group, MVC was started due to a viro-immunological dissociation during their previous ART. Viro-immunological dissociation entails a persistent low $CD4^+$ T-cell count despite an undetectable VL. In the third group, MVC treatment was started due to adverse effects or pharmacokinetic interactions.

2.2.2. Tropism testing

Assessment of HIV co-receptor tropism was done with different phenotypic and genotypic tropism assays, namely the genotypic tropism test, the enhanced sensitivity Trofile® assay or the original Trofile® assay. The choice of tropism assay was determined according to European guidelines [18] and was influenced by logistics, clinical variability and new developments.

2.2.3. Immunological response

The $CD4^+$ T-cell count was recorded at baseline and at 12-month intervals with a window of 3 months before and after these time points. Moreover, immunological response was measured as the mean difference in $CD4^+$ T-cell count compared with baseline.

2.2.4. Virological response

In patients with a detectable VL at baseline (≥50 copies/mL HIV-RNA in plasma), virological response was assessed as time until an undetectable VL (<50 copies/mL HIV-RNA) was measured. This was noted as a percentage of patients undetectable at time points of 3, 6 and 12 months and continued with a 1-year interval from baseline. Furthermore, virological failure was noted as a VL ≥ 200 copies/mL HIV-RNA in two consecutive measurements. Two consecutive measurements of a VL between 50–200 copies/mL were considered as clinically irrelevant low-level viraemia.

Patients who failed to reach an undetectable VL (<50 copies/mL HIV-RNA) during their period of MVC use as well as patients who experienced virological failure with a VL ≥ 200 copies/mL were labelled as therapy failures. Regarding these patients, further research in the Electronic Patient Dossier (EPD) was conducted for a possible explanation of the virological failure. Furthermore, the cumulative genotypic sensitivity score (GSS) of the backbone regimen was calculated for these patients. The GSS was determined by uploading all of the previously observed mutations for a particular patient in the Genotypic Resistance Interpretation Algorithm of the Stanford University HIV Drug Resistance Database v.8.4. (https://hivdb.stanford.edu/hivdb/by-mutations). The different antiretroviral drugs were scored as 1 when the virus was 'susceptible' or

'potentially resistant', 0.5 when the drugs were 'low' or 'intermediate' resistant, and 0 in the case of 'high resistance'. The scores of the individual drugs are summed to obtain the GSS score of the total regimen used.

2.2.5. Tolerability

Laboratory data on liver biochemistry and renal function were collected. Furthermore, information on cardiovascular events, malignancies and adverse events noted by the clinician were recorded to evaluate the tolerability of MVC-containing ART. Moreover, the ATHENA cohort database was also checked for these data.

Laboratory abnormalities were evaluated according to the Division of AIDS (DAIDS) *Table for grading the severity of adult and paediatric adverse events, version 2.0* [19]. Alanine aminotransferase (ALT) values were noted at baseline and as the highest value above the upper limit of normal (ULN) while on MVC. The ULN for ALT was 35 U/L for women and 45 U/L for men. Toxicity was graded as follows: grade 1, 1.25 to $<2.5 \times$ ULN; grade 2, 2.5 to $<5.0 \times$ ULN; grade 3, 5.0 to $<10.0 \times$ ULN; and grade 4, $\geq 10.0 \times$ ULN. When the highest ALT during MVC use scored the same toxicity grade as the baseline ALT, no hepatotoxicity was noted. Nephrotoxicity was noted as an abnormal serum creatinine (SCr) during MVC use with a 40 μmol/L (baseline SCr < 300 μmol/L) or 80 μmol/L (baseline SCr > 300 μmol/L) increase from baseline creatinine [20]. The ULN for SCr was set at 90 μmol/L for women and 100 μmol/L for men. The cut-off values for grades 1 to 4 were, respectively, 1.1–1.3 ×, >1.3–1.8 ×, >1.8 to <3.5 ×, and $\geq 3.5 \times$ ULN [19].

In cases of MVC discontinuation, the date and reason of discontinuation were noted. Reasons for discontinuation were grouped as follows: intolerance of MVC; little or no effect on immunological parameters (for patients who started MVC as immunological intensification); virological failure; treatment simplification; death; or other reason. If a patient died during follow-up, the cause of death was recorded.

2.3. Statistical analysis

Statistical analyses were performed with IBM SPSS Statistics for Windows v.21.0 (IBM Corp., Armonk, NY). Student's *t*-test was used to compare continuous variables. The χ^2 and Fisher's exact test were used for comparison of categorical variables. A two-sided *P*-value of <0.05 was considered statistically significant. Furthermore, the 'last observation carried forward' method was used for handling missing $CD4^+$ T-cell and HIV-RNA values.

3. Results

3.1. Baseline characteristics

A total of 141 patients using MVC were identified, of whom 30 solely used MVC in the study context and were excluded from this cohort. Thus, 111 patients were included in this study. Their baseline characteristics are shown in Table 1. The HIV subtypes and results of the different tropism tests are displayed in Table 2. HIV-1 subtypes B and C were observed in 75 patients (67.6%) and 11 patients (9.9%), respectively. The mean ± standard deviation age of the included patients was 50.2 ± 10.9 years. The majority of patients were male (87/111; 78.4%) and had been diagnosed with HIV-1 infection for a median of 13.0 years [interquartile range (IQR) 7.0 – 17.0 years]. Furthermore, the patients had a long history of ART [median 11.0 years, IQR 4.0–15.0 years), with a median of 4 (IQR 2–6) previous regimens before starting MVC. There was a prior AIDS-defining diagnosis [21] in 64 patients (57.7%), and 62 patients (55.9%) had experienced virological failure with an earlier regimen (Table 1).

Of the 47 patients (42.3%) in the virological failure group, all 47 (100%) had a detectable VL with ≥50 copies/mL HIV-RNA. The median baseline VL in this group was 3.9 $\log_{10}$ copies/mL (IQR 2.7–5.1 $\log_{10}$ copies/mL). Of the 16 patients (14.4%) in the intensification group, all 16 (100%) had an undetectable VL (<50 copies/mL HIV-RNA). Their median $CD4^+$ T-cell nadir was 62 cells/mm^2 (IQR 23–124 cells/mm^2) and they had a median baseline $CD4^+$ T-cell count of 254 cells/mm^2 (IQR 196–294 cells/mm^2). Finally, 48 patients (43.2%) started MVC because of intolerance to their previous ART regimen or interaction of their previous ART with another treatment, of whom 44/48 (91.7%) had an undetectable VL (<50 copies/mL HIV-RNA) at baseline. Reasons to change previous ART were renal disease with tenofovir treatment in 15/48 patients (31.3%), cardiovascular risk with abacavir in 4/48 patients (8.3%), treatment of progressive Kaposi's sarcoma (HHV-8 positive) in 4/48 patients (8.3%) and interaction with chemotherapy of hepatitis C virus (HCV) in 3/48 patients (6.3%).

3.2. Immunological response

The aggregated follow-up time was 487 person-years. The median follow-up time was 49.0 months (IQR 21.0–82.0 months) with a maximum of 118 months. A significant increase in $CD4^+$ T-cell count was detected throughout the follow-up period (Fig. 1A).

Separating the cohort based in indication for MVC initiation, patients who started MVC owing to virological failure of the previous ART regimen ($n = 47$) showed a significant increase in $CD4^+$ T-cell count over the follow-up period. During the first year, a mean increase of 212 cells/mm^2 [95% confidence interval (CI) 158–266 cells/mm^2] was observed. The mean increase was 304 cells/mm^2 (95% CI 195–414 cells/mm^2) after 5 years in this group. The difference in $CD4^+$ T-cell count compared with the baseline result for patients who started MVC as immunological intensification ($n = 16$) showed a significant increase compared with baseline for the first 4 years. The $CD4^+$ count increased by 67 cells/mm^2 (95% CI 23–112 cells/mm^2) during the first year and by 122 cells/mm^2 (95% CI −54 to 298 cells/mm^2) after 5 years. However, 4/16 patients (25.0%) in this group discontinued MVC owing to lack of effect on the $CD4^+$ T-cell count. In patients with intolerance to the previous regimen or an interaction issue ($n = 48$), a small increase in $CD4^+$ T-cell count was seen over time. However, the increase was only significant in the first year (64 cells/mm^2, 95% CI 3–124 cells/mm^2). After 5 years, the mean increase in $CD4^+$ T-cell count was 100 cells/mm^2 (95% CI −10 to 209 cells/mm^2) (Table 3; Fig. 1B).

3.3. Virological response

Failure of MVC-containing therapy was seen in 14 patients (12.6%). In the group who started MVC with a detectable VL, 5/51 (9.8%) patients never reached an undetectable level during the follow-up period. Virological failure was seen in 9 patients (8.1%), and an additional 14 patients (12.6%) experienced a period of low-level viral rebound between 50–200 copies/mL with subsequent suppression. Moreover, 83 patients (74.8%) reached/maintained an undetectable VL and/or never experienced two consecutive measurements of a detectable VL.

The time until patients reached an undetectable VL was noted for patients with a detectable baseline VL ($n = 51$). The median VL in this group was 3.8 $\log_{10}$ copies/mL HIV-RNA (IQR 2.4–5.1 $\log_{10}$ copies/mL HIV-RNA). Six months after switch to MVC, the VL was undetectable in 35/51 patients (68.6%). Eventually, 80.4% and 90.2% of these 51 patients reached an undetectable VL in 1 year and 5 years, respectively, while still using MVC (Fig. 2).

The baseline GSS of the backbone regimen was calculated in the 14 patients (12.6%) who were labelled as therapy failures. Ten patients had an MVC-containing regimen with GSS of ≥3 and one

Table 2
Human immunodeficiency virus type 1 (HIV-1) subtypes, plasma HIV-RNA and results of tropism assays.

Patient	HIV-1 subtype	Trofile®				GTT				
		Type	pVL	Result	Date	pVL	FPR	V3-seq	Result	Date
1	C					1.7	52.8	DNA	R5	23-1-2013
2	B	ESTA	4.6	R5	18-4-2007	3.2	23.6	RNA	R5	4-5-2012
3	B					1.7	49.0	DNA	R5	1-12-2010
4	B									
5	C					1.9	34.9	DNA	R5	12-8-2015
6	B					1.7	10.2	DNA	R5	18-1-2016
7	B					6.3	90.9	RNA	R5	3-8-2009
8	B	OTA	3.7	R5	27-2-2008	4.7	20.8	RNA	R5	Before start MVC
9	B					2.3	24.6	DNA	R5	3-11-2014
10	C	ESTA	6.5	R5	1-7-2010	6.5	87.2	RNA	R5	Before start MVC
11	B					1.7	54.2	DNA	R5	28-9-2011
12	B					1.7	23.6	DNA	R5	16-6-2014
13	B	ESTA	5.5	DM	11-2-2008	5.6	41.4	RNA	R5	Before start MVC
14	Unknown					1.7	1.7	DNA	X4	Before start MVC
15	B	ESTA	5.1	R5	5-3-2010					
16	B									
17	C	OTA	2.2	R5	12-6-2008	3.4	42.3	RNA	R5	25-7-2012
18	A1					1.7	74.0	DNA	R5	27-10-2010
19	B					2.7	89.3	RNA	R5	20-9-2006
20	B					1.7	51.8	DNA	R5	28-6-2010
21	B					1.7	67.0	DNA	R5	7-4-2014
22	B					1.7	44.9	DNA	R5	10-1-2011
23	B	OTA	5.7	R5	9-4-2008	5.7	58.6	RNA	R5	19-1-2011
24	B					5.7	22.0	RNA	R5	17-5-2011
25	D					4.5	95.5	RNA	R5	5-9-2005
26	Unknown					1.7	ND	DNA	ND	31-7-2013
27	J	ESTA	4.7	R5	18-10-2007	4.7	82.3	RNA	R5	29-6-2015
28	B	ESTA	6.5	R5	6-5-2009	1.7	53.5	DNA	R5	26-10-2015
29	B					1.7	50.9	DNA	R5	16-10-2013
30	A					4.9	22.8	RNA	R5	10-6-2016
31	A1					1.7	98.6	DNA	R5	25-2-2013
32	B					4.0	9.0	RNA	X4	4-7-2011
33	B									
34	B	ESTA	5.0	DM	4-1-2010					
35	B					1.7	1.7	DNA	X4	23-11-2015
36	B					1.7	31.1	DNA	R5	12-7-2012
37	Unknown									
38	Unknown									
39	B					4.6	30.7	RNA	R5	3-5-2013
40	B	OTA	5.6	R5	23-6-2008	5.6	41.6	RNA	R5	Before start MVC
41	B	ESTA	4.7	DM	22-10-2008	4.7	79.5	RNA	R5	Before start MVC
42	B					5.0	39.3	RNA	R5	7-4-2011
43	A/CRF02_AG					1.7	83.3	DNA	R5	5-10-2011
44	B					4.1	38.0	RNA	R5	29-7-2009
45	D	ESTA	5.0	DM	11-12-2009	5.0	2.3	RNA	X4	5-6-2015
46	B					2.0	44.8	DNA	R5	8-8-2012
47	CRF02_AG					5.8	69.1	DNA	R5	16-6-2010
48	CRF04_CPX	ESTA	2.5	R5	15-6-2009	2.5	46.8	RNA	R5	Before start MVC
49	B	ESTA	4.9	R5	26-7-2005	4.9	97.0	RNA	R5	Before start MVC
50	Unknown	OTA	4.9	R5	27-12-2005	4.9	6.9	RNA	X4	Before start MVC
51	CRF02_AG	OTA	5.3	R5	15-4-2008	5.3	58.6	RNA	R5	15-4-2008
52	B	OTA	3.6	R5	4-2-1999	3.2	9.7	RNA	X4	Before start MVC
53	B	ESTA	2.9	R5	11-2-2009					
54	A1	OTA	5.7	R5	28-5-2008	5.7	96.5	RNA	R5	Before start MVC
55	B	ESTA	5.3	R5	11-8-2008	5.3	28.8	RNA	R5	Before start MVC
56	B	ESTA	3.7	R5	12-1-2014	3.7	17.4	RNA	R5	Before start MVC
57	Unknown					1.7	1.3	DNA	X4	Before start MVC
58	C					1.7	65.9	DNA	R5	8-1-2014
59	B					1.7	1.7	DNA	X4	5-1-2011
60	G					5.5	ND	RNA	ND	24-10-2014
61	B					1.7	8.6	DNA	X4	10-4-2013
62	B					1.7	59.0	DNA	R5	11-9-2013
63	B					1.7	0.2	DNA	X4	19-10-2012
64	B	ESTA	2.9	DM	6-12-2004	2.7	17.0	RNA	R5	Before start MVC
65	B					2.9	74.6	RNA	R5	1-10-2012
66	CRF03_AB					1.7	68.3	RNA	R5	20-6-2012
67	B	OTA	5.0	DM	19-3-2008	4.7	10.5	RNA	R5	Before start MVC
68	B	OTA	5.8	R5	24-1-2007	5.8	13.2	RNA	R5	Before start MVC
69	B	OTA	5.1	R5	18-10-2007	5.1	73.3	RNA	R5	Before start MVC
70	B	ESTA	5.3	R5	28-1-2009					
71	C					1.7	74.4	DNA	R5	25-8-2010
72	B									
73	B	OTA	3.7	R5	22-2-2006	1.9	21.2	DNA	R5	30-6-2010

(*continued on next page*)

Table 2 (*continued*)

Patient	HIV-1 subtype	Trofile®				GTT				
		Type	pVL	Result	Date	pVL	FPR	V3-seq	Result	Date
74	B	ESTA	6.0	R5	18-6-2010	2.5	13.2	RNA	R5	22-4-2013
75	B					1.7	82.4	DNA	R5	17-9-2014
76	B					1.7	47.8	DNA	R5	2-7-2014
77	B					1.8	22.1	DNA	R5	20-1-2013
78	B					1.7	71.7	DNA	R5	22-11-2010
79	B	OTA	3.6	R5	24-1-2008	3.6	59.0	RNA	R5	Before start MVC
80	A1									
81	B					1.7	31.0	DNA	R5	27-7-2011
82	Unknown									
83	B	ESTA	5.9	R5	12-1-2004					
84	B	ESTA	5.9	R5	13-5-2009	4.5	36.5	RNA	R5	20-7-2010
85	B	OTA	5.3	R5	25-10-2007	5.3	42.5	RNA	R5	16-3-2016
86	B	OTA	4.3	DM	10-4-2008					
87	B					5.2	91.6	RNA	R5	2-4-2012
88	B	ESTA	4.7	R5	3-5-2010					
89	B	ESTA	3.9	R5	9-4-2003	3.9	48.9	RNA	R5	Before start MVC
90	C	ESTA	6.0	R5	9-12-2009					
91	B					1.7	33.9	DNA	R5	2-2-2010
92	Unknown					1.7	9.9	DNA	R5	10-9-2014
93	C					1.7	82.4	DNA	R5	7-9-2015
94	B					2.0	24.6	DNA	R5	2-6-2014
95	B	OTA	3.0	DM	18-4-2008	3.0	1.1	RNA	X4	Before start MVC
96	B	OTA	3.7	R5	19-5-2008	3.7	27.2	RNA	R5	Before start MVC
97	B	OTA	4.1	R5	15-10-2008	5.0	73.6	RNA	R5	Before start MVC
98	Unknown									
99	B					1.7	96.2	DNA	R5	26-5-2010
100	B	ESTA	3.0	R5	6-9-2010	3.0	87.8	RNA	R5	6-9-2010
101	CRF03_AB					1.7	23.6	DNA	R5	6-12-2010
102	C	OTA	5.9	R5	20-12-2007	5.9	78.8	RNA	R5	20-12-2007
103	B	ESTA	5.8	N/R	10-5-2010	1.7	6.8	DNA	X4	31-8-2015
104	CRF02_AG					5.0	93.9	RNA	R5	10-4-2013
105	B	ESTA	4.1	DM	19-9-2008	4.1	4.8	RNA	X4	Before start MVC
106	B					1.7	34.9	DNA	R5	17-6-2013
107	C					1.7	38.8	DNA	R5	23-8-2010
108	B					1.7		DNA	R5	30-11-2015
109	B	ESTA	3.3	R5	14-7-2010	5.0	84.7	RNA	R5	Before start MVC
110	C					4.9	96.2	RNA	R5	22-4-2009
111	B	OTA	6.5	R5	Before start MVC	5.4	47.0	RNA	R5	Before start MVC

D/M, dual/mixed-tropic; ESTA, enhanced sensitivity Trofile® assay; FPR, false-positive rate; GTT, genotypic tropism test; MVC, maraviroc; ND, not determined; N/R, no result; OTA, original Trofile® assay; pVL, plasma viral load (log_{10} HIV-RNA copies/mL) of the sample on which the tropism assay was performed; R5, CCR5-tropic; V3-seq, third hypervariable loop (V3) sequence; X4, CXCR4-tropic.

Table 3
(a) Immunological response[a]. (b) Immunological response in patients who used MVC for ≥5 years[a].

ΔCD4+ T-cells (cells/mm²)	Indication for MVC								
	Virological failure ($n=47$)			Immunological intensification ($n=16$)			Intolerance/interaction ($n=48$)		
+1 year	212 (158–266)	$n=38$	$P=0.000$	67 (23–112)	$n=14$	$P=0.006$	64 (3–124)	$n=45$	$P=0.039$
+2 years	246 (181–312)	$n=35$	$P=0.000$	93 (37–149)	$n=10$	$P=0.004$	47 (–12 to 106)	$n=34$	$P=0.117$
+3 years	249 (173–327)	$n=33$	$P=0.000$	94 (35–153)	$n=9$	$P=0.006$	93 (10–176)	$n=30$	$P=0.029$
+4 years	241 (150–333)	$n=30$	$P=0.000$	115 (5–225)	$n=7$	$P=0.043$	81 (–21 to 183)	$n=22$	$P=0.115$
+5 years	304 (195–414)	$n=27$	$P=0.000$	122 (–54 to 298)	$n=7$	$P=0.140$	100 (–10 to 209)	$n=14$	$P=0.072$
+6 years	339 (205–475)	$n=22$	$P=0.000$	191 (–10 to 391)	$n=5$	$P=0.057$	45 (–85 to 176)	$n=9$	$P=0.447$
+7 years	430 (272–589)	$n=18$	$P=0.000$	199 (–3 to 400)	$n=4$	$P=0.052$	18 (–223 to 259)	$n=5$	$P=0.848$
+8 years	436 (184–687)	$n=12$	$P=0.003$	210 (–864 to 1283)	$n=2$	$P=0.244$		$n=1$	
+9 years	492 (213–772)	$n=10$	$P=0.003$		$n=1$			$n=0$	

ΔCD4+ T-cells (cells/mm²)	Indication for MVC					
	Virological failure ($n=27$)		Immunological intensification ($n=7$)		Intolerance/interaction ($n=14$)	
+1 year	220 (150–289)	$P=0.000$	83 (5–160)	$P=0.040$	123 (–20 to 265)	$P=0.086$
+2 years	257 (176–338)	$P=0.000$	101 (16–188)	$P=0.028$	100 (–16 to 217)	$P=0.085$
+3 years	288 (204–372)	$P=0.000$	109 (35–182)	$P=0.011$	152 (14–291)	$P=0.034$
+4 years	262 (170–354)	$P=0.000$	114 (5–225)	$P=0.044$	137 (4–271)	$P=0.045$
+5 years	304 (195–414)	$P=0.000$	122 (–54 to 298)	$P=0.140$	100 (–10 to 209)	$P=0.072$

[a] Mean difference (95% confidence interval).

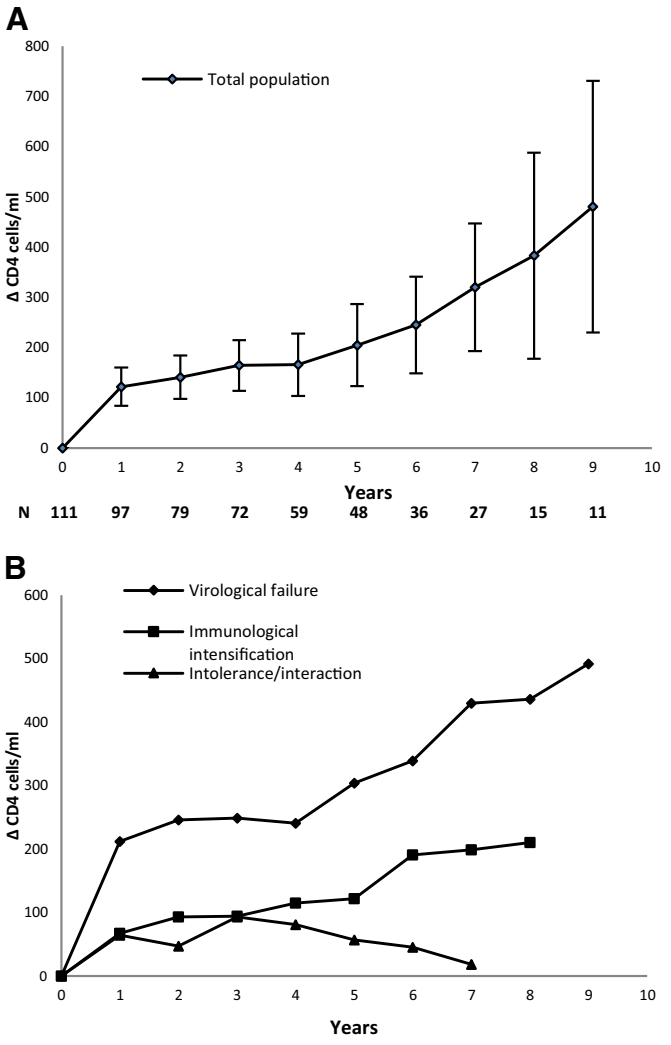

Fig. 1. Immunological response of patients receiving a maraviroc (MVC)-containing regimen: mean $CD4^+$ T-cell change (95% CI) (A) for the total population and (B) for the different indications for MVC. Number of patients (and 95% CI) are shown in Table 3. CI, confidence interval.

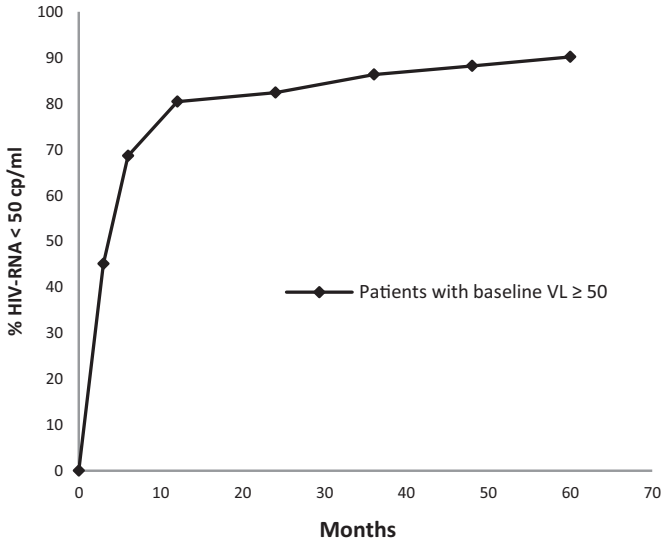

Fig. 2. Virological response in patients with detectable baseline viral load (VL) (≥50 copies/mL HIV-RNA) on a maraviroc (MVC)-containing regimen, showing the percentage of patients in whom the VL dropped to an undetectable range (<50 copies/mL HIV-RNA).

Table 4
Laboratory abnormalities in patients receiving maraviroc-containing antiretroviral therapy.

Grading	Patients with renal function impairment [*n* (%)]	Patients with elevated liver enzymes [*n* (%)]
None	97 (87.4)	86 (77.5)
Grade 1	3 (2.7)	19 (17.1)
Grade 2	4 (3.6)	3 (2.7)
Grade 3	4 (3.6)	1 (0.9)
Grade 4	3 (2.7)	2 (1.8)

patient had a GSS of 0.5. Owing to lack of information on genotype, no GSS was calculated in three patients.

Regarding these 14 patients with therapy failure, the clinician reported therapy adherence problems in 6 patients (42.9%). Three patients (21.4%) developed resistance to one or more drugs in their background regimen or started MVC with a low GSS. Two patients (14.3%) stopped MVC after reaching a VL < 200 copies/mL but before reaching an undetectable VL; the first patient stopped after 3 months owing to treatment simplification and the other patient died after 9 months.

Overall, three patients (2.7%) experienced treatment failure despite an optimal background therapy with a good GSS and without obvious adherence issues. In one of these three patients, a switch to CXCR4 tropism was detected.

3.4. Tolerability

Overall, MVC was well tolerated. Nine patients (8.1%) discontinued MVC owing to intolerance to the regimen. The median duration before discontinuation was 22 months (IQR 1–62 months). The reason for discontinuation was clinical adverse events for eight patients (7.2%). In only one patient (0.9%), the physician stopped MVC because of mild renal function impairment, possibly due to MVC.

The most frequently occurring clinical adverse events were gastrointestinal complaints (nausea, diarrhoea) (5.4%), fatigue (4.5%), dizziness (3.6%), muscle strain (2.7%) and sleeping disturbance (2.7%).

Three patients (2.7%) developed a 'grade 3' or 'grade 4' laboratory abnormality due to ALT increase (Table 4). However, two of the three patients had an acute HCV infection and in the other patient the ALT was promptly normalised without discontinuation of MVC. Of the 25 patients with an ALT increase, 16 (64.0%) used ritonavir in their backbone regimen. Furthermore, raltegravir, tenofovir and darunavir were used by 10/25 (40.0%), 10/25 (40.0%) and 9/25 (36.0%) patients, respectively, as their backbone regimen.

Clinically relevant SCr increases were seen in 14 patients (12.6%) with a MVC-containing regimen. None the less, in almost all patients with a substantial SCr increase during MVC use, other possible causes were found for the renal impairment (hypotension, nephrotoxic co-medication, etc.). No other reason was identified for the increase in SCr in only one patient (0.9%) with a grade 1 impairment. The backbone regimen of the 14 patients with a clinically relevant SCr increase contained ritonavir in 10 patients (71.4%), darunavir in 8 patients (57.1%), raltegravir in 7 patients (50.0%) and tenofovir in 4 patients (28.6%).

During the 487 person-years of follow-up, six patients (5.4%) developed a myocardial infarction (MI) or stroke. Furthermore, eight patients (7.2%) were diagnosed with a non-AIDS malignancy during follow-up. This corresponds to an unadjusted rate (event/100 patient-years) of 1.2 for MI/stroke and 1.6 for malignancies.

Eighteen patients (16.2%) died during follow-up, giving an unadjusted death rate of 3.7. An AIDS-related cause of death was observed in five patients (4.5%) (1.0/100 patient-years). Three months

after starting MVC, three patients (2.7%) died due to a pre-existing lymphoma, complications during stem cell therapy for myelodysplastic syndrome and complication due to a larynx carcinoma. No causal relationship was found between the cause of death and a MVC-containing regimen.

4. Discussion

A heavily pre-treated cohort of HIV-1 patients who started MVC for different reasons was followed over a period of 10 years. The median time of MVC use was 39 months (IQR 21–82 months). Mean $CD4^+$ T-cell counts continued to increase up to 9 years following initiation of MVC.

The increase in $CD4^+$ T-cell count from baseline was 122 cells/mm^2 after 1 year, 141 cells/mm^2 after 2 years, 205 cells/mm^2 after 5 years and 481 cells/mm^2 after 9 years of follow-up, which is in line with other published studies. However, none of these studies had a follow-up of more than 5 years. In the MERIT study, the median $CD4^+$ T-cell count increased by 158, 188 and 245 cells/mm^2 after 48 weeks ($n = 235$), 96 weeks ($n = 209$) and 240 weeks ($n = 166$), respectively. However, the included patients in that study were all cART-naïve [15]. In 26 patients starting MVC, raltegravir and etravirine because of treatment failure, the median $CD4^+$ T-cell count increase was 244 cells/mm^2 after 204 weeks [22]. A Brazilian cohort ($n = 109$) demonstrated a median $CD4^+$ T-cell count increase of 174 cells/mm^2 after 96 weeks [23]. In a retrospective Dutch cohort, the median $CD4^+$ T-cell count for 12 months ($n = 28$), 24 months ($n = 20$) and 36 months ($n = 16$) was 199, 291 and 235 cells/mm^2, respectively [7].

In patients who started MVC as immunological intensification treatment, a significant increase in $CD4^+$ T-cell count was only seen in the first 4 years. However, the lack of significant increase after 4 years can partially be explained by the small number of patients in this subgroup.

Treatment intensification with MVC in patients with a suboptimal immunological response was described in three articles with a 1-year follow-up. The mean increase in $CD4^+$ T-cell count was in the same range as the current study. These publications showed a median $CD4^+$ T-cell count increase of 145 cells/mm^2 ($n = 12$), 22 cells/mm^2 ($n = 41$) and 34 cells/mm^2 ($n = 45$) [7,16,24]. However, no significant increase was found compared with the control group in these studies.

The majority of patients who started MVC with a detectable VL ($\geq$50 copies/mL HIV-RNA) suppressed their VL to an undetectable range. Only a limited number of patients experienced virological failure or never reached an undetectable VL. Several reasons for these treatment failures were found, including treatment adherence issues and the use of suboptimal background therapy owing to extensive resistance. Only three patients (2.7%) experienced treatment failure despite an optimal background therapy with a good GSS and without obvious adherence issues.

The virological response in studies involving patients with a MVC-containing regimen in clinical practice is in line with the current study. The Virological Efficacy of Maraviroc in Antiretroviral Naïve patients (VEMAN) study showed a 100% VL suppression to an undetectable range (<50 copies/mL HIV-RNA) within 1 year ($n = 26$) [25]. In another retrospective cohort study, the percentage of virological suppression was 82% ($n = 28$), 85% ($n = 20$) and 68% ($n = 16$) after 12, 24 and 36 months, respectively. However, it must be noted that these are the percentages of patients with an undetectable VL at a certain time point rather than time until the first undetectable VL [7]. Of 66 patients in an Italian cohort, 94% reached an undetectable VL after 16 weeks [26]. Another study demonstrated that 93% ($n = 26$) of patients starting MVC, raltegravir and etravirine had an undetectable VL after 1 year [22]. Lastly, a German cohort and a Spanish cohort showed viral suppression in 78% ($n = 44$) in 6 months and 96% ($n = 46$) in 1 year [27,28].

Academic research published on virological failure of MVC-containing ART in long-term follow-up is currently insufficient. Only one study has been published which demonstrated that 4% of patients ($n = 26$) experienced virological failure (two consecutive measurements of VL >50 copies/mL HIV-RNA) in 205 weeks of follow-up [11].

MVC treatment was well tolerated in the current study. Only 9 patients (8.1%) discontinued MVC owing to intolerance of the regimen. The observed severe renal and liver function impairments as well as the causes of death appeared not to be directly related to treatment with MVC. The HIV Monitoring Report from the Dutch HIV Monitoring Foundation published data on the national incidence of cardiovascular diseases and malignancies in HIV patients [29]. Corrected for the percentage of men in this cohort, the adjusted rate (event/100 patient-years) for cardiovascular events was 0.95. The adjusted rate for non-AIDS-defining malignancies was 0.58. The incidence of cardiovascular events and malignancies in the current study population is higher compared with the national report. However, this may be due to the fact that this is a heavily pre-treated cohort of HIV patients.

The MERIT [15] and MOTIVATE [11] studies followed patients for 5 years and showed similar findings regarding tolerability. However, the population was ART-naïve, thus the comparison with these studies is not ideal.

The fact that this study contains a heterogeneous, heavily pre-treated group of patients should be considered as a strength as it makes the results more relevant to clinical practice. Second, this study involves a long follow-up compared with previous clinical cohort studies and has a relatively large sample size. Thus, concerns regarding long-term safety can be answered with more certainty.

However, the study does have some limitations. As a result of the retrospective design of this study, there could be unmeasured confounders. Furthermore, for more precise determination of the efficacy, a control group should be included. Moreover, due to the heavily pre-treated study population, the efficacy of MVC in this study may be underestimated. Lastly, a larger sample size would result in more statistical power, especially with regard to the different indications for MVC.

In summary, this study shows that MVC use in heterogeneous, heavily pre-treated patients with HIV infection was generally well tolerated, even in the patient who used MVC for 10 years. In addition, the MVC-containing regimen resulted in an acceptable virological response and significant immunological recovery.

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Competing interests

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Ethical approval

Not required.

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