


High Virologic Failure Rates with Maraviroc-Based Salvage Regimens Among Indian Patients: A Preliminary Analysis—Maraviroc Effectiveness in HIV-1 Subtype C

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Abstract

Background: There is no information on the clinical effectiveness of Maraviroc (MVC) amongst People Living with HIV (PLHIV) in India infected with HIV-1 Subtype C viruses. **Methods:** We conducted a retrospective chart review of adult PLHIV on MVC based Antiretroviral (ARV) regimens for at least 6 months. Maraviroc was initiated amongst PLHIV with documented R5 tropic viruses (determined by in-house population sequencing of the V3 loop in triplicate and interpreted using the Geno2Pheno algorithm) in combination with an Optimized Background regimen (designed using genotypic resistance testing and past ARV history). Plasma viral loads (PVL) are performed 6 months post-initiation and annually thereafter. Primary outcome d. Median duration on MVC treatment was 1.8 years (range 1-2.9 years) while median duration of ART prior to switching to MVC was 13 years. Maraviroc was combined with Darunavir/ritonavir (DRV/r) (n=10), Atazanavir/r (ATV/r) (n=2) and Lopinavir/r (LPV/r) (n=1). All PLHIV were infected with HIV-1 Subtype C. Only 23.3% PLHIV achieved virologic suppression at 6 months and sustained it for 2.3 years. Median CD4 count change from baseline was +117 (n=13), +228 (n=10), +253 (n=9), and +331 (n=4) at 6, 12, 18 and 24 months respectively. Repeat tropism among patients with virologic failure demonstrated R5 virus. **Conclusions:** High rates of virologic failure was seen when MVC was used amongst treatment experienced PLHIV infected with HIV-1 Subtype C in India. was the proportion of PLHIV with virologic success (PVL<50 copies/ml) at last follow up visit. **Results:** Data on 13 PLHIV were analyze

Keywords

maraviroc, virologic failure, subtype C, India

Introduction

Antiretroviral therapy (ART) has been responsible for achieving near normal life expectancy among people living with HIV (PLHIV) in high-income countries and low- and middle-income countries (LMIC).¹⁻³ A significant proportion of patients develop resistance to antiretroviral (ARV) medications necessitating switching to regimens typically combining ARV medications from newer classes namely boosted protease inhibitors (PI/r), integrase strand transfer inhibitors, and C-C chemokine receptor 5 (CCR5) antagonist. The proportion of PLHIV with triple class failure needing salvage regimens is still low in LMICs, although this is estimated to rise in the coming years.⁴

Maraviroc (MVC), an CCR5 antagonist when combined with an optimized background regimen (OBR) has been documented to achieve significant virologic success among PLHIV

needing salvage regimens.⁵ In India, generic MVC has been available for more than 3 years. We examined the effectiveness of MVC as salvage regimens among PLHIV in India.

Methods

Design

Retrospective chart review (2015-2017).

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Table 1. Characteristics of Pre-MVC ART Regimens.

Patient	Initial Regimen (Duration Years)	Second Regimen (Duration Years)	Third Regimen (Duration Years)	Resistance Testing (Pre-MVC)
1	d4T/3TC/NVP (1.8)	TDF/3TC/ATV/r (4.8)	NA	K70E, M184V, T215I, Y181C, M46I, N88T
2	d4T/3TC/NVP (2)	ZDV/ddI/ATV/r and LPV (2.8)	RAL/LPV/r (1.6)	M46I, I54V, V82A
3	TDF/3TC/RTV (2.7)	TDF/FTC/DRV/r (2.2)	RAL/DRV/r (1.9)	Y143R, L74M, T97A, G163 R
4	d4T/3TC (3)	ZDV/TDF/FTC/ATV/r and DRV/r (10)	RAL/LPV/r (2)	M46I, V82A, NRTI: M41L, T215F, V106M, E138G, F227L, M230L, ISTI: N155H
5	d4T/3TC/NVP (12)	TDF/3TC/ATV/r (1)	RAL/ATV/r (0.9)	K101E, G190A, N155H
6	d4T/3TC/EFV (14)	TDF/3TC/ATV/r (0.9)	NA	M41L, V75M, M184V, T215F, K219R, K103N, P225H
7	ZDV/3TC/NVP (5.4)	ZDV/3TC/TDF/ATV/r (3.9)	RAL/DRV/r (2.6)	K103N, P236L
8	ZDV/3TC/NVP (2.8)	TDF/FTC/ATV/r and DRV/r/LPV/r (3)	RAL/DRV/r (2.9)	D67DN, T69DN, K70KR, V75IMV, M184MV, K103KNRS, V106MV
9	d4T/3TC/NVP (6.8)	TDF/3TC/ATV/r (4.3)	RAL/ATV/r (1.4)	Y134R, L74V, K219Q, K101E, Y1
10	d4T/3TC/NVP and TDF (3.5)	ZDV/TDF/FTC/LPV/r (1.9)	RAL/LPV/r (4.6)	ND
11	d4T/ddI/EFV (2)	ZDV/TDF/3TC/LPV/r (2.4)	3TC/RAL/DRV/r (4.6)	ND
12	ZDV/3TC/NVP (1.1)	TDF/ZDV/3TC/LPV/r (2.5)	RAL/DRV/r (2)	A98G, K101E, Y181C, G190A
13	Not known	LPV/IDV/r (5.3)	3TC/RAL/DRV/r (3)	E92Q, N155H

Abbreviations: 3TC, lamivudine; ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; d4T, stavudine; ddI, didanosine; DRV/r, darunavir/ritonavir; EFV, efavirenz; IDV, indinavir; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NVP, nevirapine; NRTI, nucleoside reverse transcriptase inhibitor; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir; ZDV, zidovudine; NA, not applicable; ND, not done; INSTI, Integrase Strand transfer Inhibitors.

Setting

Tertiary-level private HIV clinic in Western India.

Ethics Statement

All registered patients provide an independent ethics committee-approved informed consent for using routinely collected clinical and laboratory data for research analysis.

Patients

Adult HIV-1-infected patients on MVC-based ARV medication regimens for at least 6 months were included in the analysis. Information on demographics, clinical status, HIV- and ART-related information, and laboratory results especially CD4 counts and viral loads (VLs) were abstracted from the electronic database. Maraviroc was initiated among PLHIV with documented R5 tropic viruses and an OBR was constructed with the help of resistance testing and past ART history. At least 1 fully active ARV medication was included in the OBR. Darunavir/ritonavir (DRV/r) was used if there were <3 DRV-associated mutations. Readiness especially financial was assessed prior to initiating treatment. Adherence were assessed by self-report using a visual analog scale.

Measurements

Plasma viral loads (PVL) and CD4 counts were determined by Cobas TaqMan (Roche, CA, USA) and FACS Count (Becton Dickinson, New Jersey, USA), respectively. After initiating MVC-based regimen, CD4 counts were determined at 6 months

while VL were determined at 6 months and then annually. A VL >50 copies/mL at least on 2 follow-up visits was defined as virologic failure. Loss to follow-up was defined as not seen in the clinic for more than a year.

Resistance testing, subtype, and tropism were determined by sequencing (in-house protocol). HIV-1 tropism was determined by population sequencing of the V3 loop in triplicate and interpreted using the Geno2Pheno algorithm. A false-positive rate cutoff of 15% was used. Subtype was determined by sequencing the Protease codons (1-99), Reverse Transcriptase codons (1-267), and V3 loop.

The primary outcome of the analysis was to determine the proportion of PLHIV with virologic success at last follow-up visit. Repeat tropism testing were performed at failure and patients continued with the same regimen if R5 virus were documented.

Results

Data on 13 patients with minimum 6 months of follow-up were included in the final analysis. Median age was 45 years (interquartile range [IQR] 40-49 years) and 80% were males. Median duration since HIV diagnosis was 14 years (IQR 9.5-20 years), while median duration of ART prior to switching to MVC was 13 years (IQR 9-14 years). The median (IQR) pre-MVC CD4 and log PVL were 324/mm³ (148-500) and 4.3 copies/mL (3.8-5.1), respectively. Median duration on MVC treatment was 1.8 years (range 1-2.9 years). The pre-MVC ART regimen consisted of raltegravir (RAL) + PI/r (n = 11, 81.2%, DRV/r = 6, lopinavir/ritonavir [LPV/r] = 3, atazanavir/ritonavir [ATV/r] = 2) and tenofovir [TDF]/Emtricitabine (FTC)/PI/r (n = 2). All patients had failed previous non-nucleoside reverse transcriptase inhibitor-based regimens (Table 1).

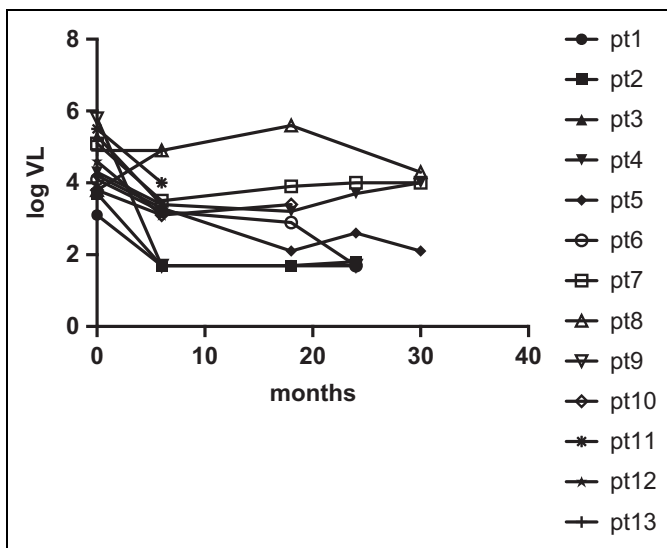


Figure 1. Log viral load response amongst all PLHIV receiving Maraviroc.

Maraviroc (dosed at 150 mg twice a day) was combined with DRV/r (n = 10), ATV/r (n = 2), and LPV/r (n = 1). All patients were infected with HIV-1 subtype C. Reported adherence was 95%. Three patients were lost to follow-up after 6 months. None of these patients had achieved virologic suppression at 6 months.

Only 23.3% (n = 3) patients achieved virologic suppression at 6 months and sustained it for 2.9 years. Figure 1 shows the log VL response among all patients on MVC-based salvage regimen. Median CD4 change from baseline was +117 (n = 13), +228 (n = 10), +253 (n = 9), and +331 (n = 4) at 6, 12, 18, and 24 months, respectively. There were no serious adverse events reported during the study period. Repeat tropism among patients with virologic failure demonstrated R5 virus.

Discussion

This is the first report on effectiveness of MVC-based ART among highly treatment-experienced patients in India. High rates of virologic failure was documented. It is worth noting that patients failing treatment never achieved VL <50 copies/mL. In a 2-year follow-up of Maraviroc versus Optimized Therapy in Viremic Antiretroviral Treatment-Experienced Patients (MOTIVATE) 1 and 2 trials, 39% and 41% patients had VL <50 copies/mL at 96 weeks with once and twice daily MVC, respectively.⁶ However, in these patients, use of concomitant DRV/r was precluded. In a recently reported retrospective, observational study from Italy, 90.5% patients achieved a VL <50 copies/mL with MVC regimens.⁷ Few other studies have also reported high rates of virologic success with MVC-based regimens in real world.^{8,9}

We propose few hypotheses for explaining the low effectiveness of MVC in our study. First adherence may have been overestimated as it was assessed by self-report. High cost of treatment may impact adherence. Second, population-based sequencing for determining tropism may not have detected low levels of X4 viruses, limiting the effectiveness of MVC.

However, patients at virologic failure did not show tropism switch. Additionally, genotypic tropism determination using the Geno2Pheno algorithm (used in our study) has been demonstrated to be noninferior to the Trofile assay.¹⁰

Third, the pharmacokinetics of MVC has not been studied among Indians. We used the recommended 150 mg twice-a-day dose when combined with PI/r. In fact, MVC when used as 150 mg once a day with LPV/r and ATV/r among naïve patients achieved VL <50 copies/mL in 96% and 87.5% patients, respectively, and 68.2% among ARV medication-experienced patients.^{11,12} Additionally, in our study the pretherapy VL was <100 000 copies/mL which has actually been associated with better virologic success in the real-world settings.¹³

Finally, the most plausible explanation may be the lower inhibition of subtype C HIV by MVC. In R5 Envelops (ENVs) cloned from ART-naïve patients with progressive subtype C infection, 40% harbored viruses that displayed incomplete inhibition by MVC.¹⁴ The ENVs exhibiting reduced inhibition by MVC used MVC bound CCR5 less efficiently than MVC-free CCR5 that is similar to the mechanism of resistance among patients failing MVC-based treatment. Furthermore, mutations in the gp120 V3 loop associated with reduced inhibition by MVC was documented in this study. Among MVC naïve Indian HIV-1 subtype C V3 loop sequences, 19 S/T substitution (associated with partial MVC resistance) was documented in approximately 90% strains.¹⁵ High prevalence of 19 S/T polymorphism has also been reported among African subtype C strains.¹⁶ The clinical relevance of these in vitro findings is unclear with a suggestion of limited efficacy of MVC among HIV-1 subtype C viruses.

There is limited information on the clinical effectiveness of MVC stratified according to subtypes. In France among patients switched to MVC as maintenance therapy, the only factor associated with virologic success was subtype B.¹⁷

In spite of limited virologic success, patients demonstrated a significant gain in CD4 counts. Studies have documented enhanced CD4 response independent of virologic suppression on MVC-based regimens including in primary HIV infection.^{12,18} However, the use of MVC among patients with immunologic disconnect has been disappointing.^{19,20} The mechanism of enhanced CD4 improvement with MVC is unclear, although decrease in messenger RNA level of interferon- γ in CD4 cells may contribute to the same.²¹ Interestingly, MVC has been associated with less improvement in CD4:CD8 ratio due to slower decline in CD8 counts.²²

The low effectiveness of MVC in our study in subtype C may potentially impact its use in oral/vaginal ring-based pre-exposure prophylaxis, possible neurocognitive benefit, and primary HIV infection.^{18,23-25}

There are few limitations of our study. Our sample size is small, since MVC-based regimens are expensive and small proportion of patients with multiclass failure (including integrase inhibitors) were eligible. Adherence was not assessed by other means like pharmacy refills as patients often buy medications locally. We were unable to measure MVC levels in plasma and also unable to carry out in vitro studies to assess

MVC inhibition in the viruses isolated from our patients. We could not add dolutegravir/etravirine to reinforce the regimen or switch after failure as it was not available in India. Finally, we did not perform resistance testing at failure to document occurrence/evolution of DRV resistance or for MVC resistance. Few other patients using RAL + DRV/r achieved good virologic success in our practice (data not shown).

In conclusion, this preliminary analysis documents high rate of virologic failure with MVC among treatment-experienced HIV-1-infected patients in India. The most likely reason is incomplete inhibition of subtype C viruses by MVC partially mediated through high prevalence of naturally occurring MVC-resistant mutations in these viruses. Larger studies are urgently needed to confirm this finding as subtype C is the major HIV-1 subtype in Africa and some parts of Asia, and MVC is being explored for potential role as a prophylactic agent apart from treatment of multiclass-failure patients.

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Declaration of Conflicting Interests

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