

Maraviroc: a review of its use in HIV infection and beyond

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Abstract: The human immunodeficiency virus-1 (HIV-1) enters target cells by binding its envelope glycoprotein gp120 to the CD4 receptor and/or coreceptors such as C-C chemokine receptor type 5 (CCR5; R5) and C-X-C chemokine receptor type 4 (CXCR4; X4), and R5-tropic viruses predominate during the early stages of infection. CCR5 antagonists bind to CCR5 to prevent viral entry. Maraviroc (MVC) is the only CCR5 antagonist currently approved by the United States Food and Drug Administration, the European Commission, Health Canada, and several other countries for the treatment of patients infected with R5-tropic HIV-1. MVC has been shown to be effective at inhibiting HIV-1 entry into cells and is well tolerated. With expanding MVC use by HIV-1-infected humans, different clinical outcomes post-approval have been observed with MVC monotherapy or combination therapy with other antiretroviral drugs, with MVC use in humans infected with dual-R5- and X4-tropic HIV-1, infected with different HIV-1 genotype or infected with HIV-2. This review discusses the role of CCR5 in HIV-1 infection, the development of the CCR5 antagonist MVC, its pharmacokinetics, pharmacodynamics, drug-drug interactions, and the implications of these interactions on treatment outcomes, including viral mutations and drug resistance, and the mechanisms associated with the development of resistance to MVC. This review also discusses available studies investigating the use of MVC in the treatment of other diseases such as cancer, graft-versus-host disease, and inflammatory diseases.

Keywords: chemokine receptors, human immunodeficiency virus, CCR5 antagonists, pharmacokinetics, pharmacodynamics, drug interactions, mutations, resistance, AIDS

Introduction

The human immunodeficiency virus-1 (HIV-1) enters target cells by binding its envelope glycoprotein gp120 to the CD4 receptor and/or coreceptors such as the C-C chemokine receptor type 5 (CCR5; R5) and C-X-C chemokine receptor type 4 (CXCR4; X4).¹ R5-tropic and X4-tropic viral strains use CCR5 and CXCR4, respectively, as coreceptor to enter and infect target cells. Some HIV-1 strains are dual tropic and can use CCR5 and/or CXCR4.² CCR5 is expressed on several cell types, including T-cells, dendritic cells, and leukocytes.^{2,3} In HIV-infected humans, R5-tropic viruses predominate during the early stages of infection, whereas X4-tropic viruses usually emerge during the later stages.^{1,2} The importance of CCR5 in HIV/AIDS was demonstrated by studies showing that a 32-base-pair deletion in the CCR5 gene results in resistance to HIV-1 infection or slower progression to AIDS.^{4,5}

Given CCR5's importance in HIV-1 transmission, infection, and AIDS progression, drugs targeting CCR5 have been an important area of research. In a short-term trial with HIV-infected patients, aplaviroc, the first CCR5 antagonist to enter clinical trials, demonstrated significant antiretroviral activity.⁶ However, in subsequent Phase II trials, testing was discontinued due to increased cases of idiosyncratic hepatotoxicity.⁷

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Vicriviroc (VCV) significantly reduced viral loads (VL).⁸ Two subsequent Phase II trials confirmed VCV antiretroviral activity and safety.^{9,10} However, in a third Phase II and two Phase III trials, VCV showed higher rates of virological failure than other antiretroviral drugs,^{11,12} and its further development was terminated. Cenicriviroc, a CCR5 and CCR2 inhibitor, has completed Phase IIb trials and showed potent antiretroviral activity in vitro and in vivo.^{13,14} Maraviroc (MVC, Pfizer) is a small molecule, reversible CCR5 antagonist,¹⁵ currently approved for treatment of patients infected with R5-tropic HIV-1.¹⁵ This paper will review MVC discovery and development, its efficacy against HIV-1/AIDS, pharmacokinetics, pharmacodynamics and drug resistance, and its use in other diseases.

MVC discovery

MVC, originally called UK-427,857 (empirical formula: $C_{29}H_{41}F_2N_5O$), was developed by Pfizer during CCR5 ligand studies.¹⁶ High-throughput screening to identify small molecules that could inhibit the binding of macrophage inflammatory protein-1-beta to CCR5 stably expressed in HEK-293 cells lead to the discovery of imidazopyridine, UK-107,543.¹⁷ UK-107,543 displayed efficient and potent inhibition of macrophage inflammatory protein-1-beta binding to CCR5, with a half-maximal inhibitory concentration of 650 nM. However, UK-107,543 had no antiretroviral activity. MVC was the result of UK-107,543 optimization for binding potency against CCR5, antiretroviral activity, absorption, pharmacokinetics, and selectivity for the human ERG channel.¹⁶ This optimization is summarized in Figure 1. Modifications of UK-107,543 to UK-372,673 resulted in increased binding to CCR5 and antiretroviral activity, with 90% inhibitory concentration (IC_{90}) of 75 nM.¹⁸ Further modifications to make UK-382,055 increased its antiretroviral activity (IC_{90} : 3 nM), but blocked potassium channels.¹⁸ Modifications to make UK-396,794 further increased antiretroviral activity (IC_{90} : 0.6 nM) and increased absorption, but UK-396,794 was rapidly metabolized.¹⁸ In total, 956 analogues were screened before finally getting MVC, which displayed good antiretroviral activity (IC_{90} below 2 nM), did not block potassium channels, was not rapidly metabolized, and had good absorption.¹⁸

MVC clinical trials

In Phase I trial, MVC reached steady-state plasma concentrations after 7 days' treatment and was well tolerated at clinically relevant doses (<900 mg/kg).¹⁹ A phase II trial in asymptomatic HIV-1-infected humans receiving

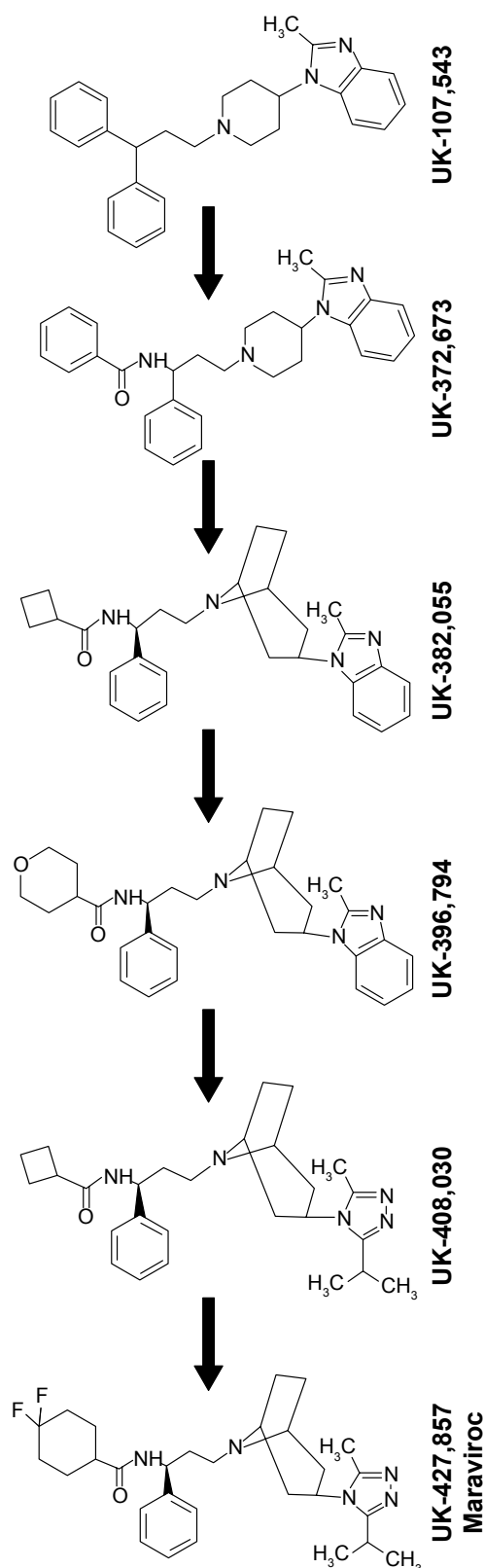


Figure 1 Development of maraviroc.

Notes: Panels show the sequential optimization from the initial compound UK-107,543 to UK-372,673; UK-382,055; UK-396,794; UK-408,030; and finally maraviroc. Reprinted from *Prog Med Chem*, 43. Wood A, Armour D. The discovery of the CCR5 receptor antagonist, UK-427,857, a new agent for the treatment of HIV infection and AIDS., 239–271, Copyright © 2015, with permission from Elsevier.¹⁸

MVC, 300 mg/kg twice daily showed that VL decreased by $1.6 \log_{10}$ copies/mL compared to $0.02 \log_{10}$ copies/mL in infected humans receiving placebo.²⁰ These results validated MVC as a non-viral target antiretroviral therapy (ART). The MOTIVATE trials were two Phase III trials to determine the efficacy and safety of MVC in patients infected with R5-tropic HIV-1.²¹ Patients received oral MVC or placebo once or twice daily, with doses adjusted based on other drugs in the patient's ART regimen. MVC decreased VL by $-1.84 \log_{10}$ copies/mL compared to $-0.79 \log_{10}$ copies/mL in placebo-treated patients.²¹ MVC showed efficacy throughout the 96 weeks of treatment; 86.7% and 81.4% of patients receiving MVC twice daily and once daily, respectively, who had VL below 50 copies/mL at week 48, maintained virological suppression up to week 96.²² From week 48 to week 96, the median CD4 count increased by 89 and 113 cells/mm³ in patients receiving MVC once daily and twice daily, respectively.²² The incidences of adverse events were similar for patients on ART regimens containing MVC twice daily, MVC once daily, or placebo, at week 96 and year 5.²³ Subgroup analyses of pooled data from week 48 of the MOTIVATE trials were performed based on parameters such as ethnicity, baseline VL, CD4 count, tropism, genetic polymorphisms, and ART regimens. Results showed that MVC was effective in multiple patients infected with R5-tropic HIV-1 who had previously been treated with other ART drugs, including patients with low baseline CD4 count or high VL.²⁴ Furthermore, more patients receiving MVC who failed treatment had X4-tropic HIV-1 at treatment failure compared to those receiving placebo, but MVC-treated patients showed no decrease in CD4 count.²⁴

The MERIT study was a Phase IIb/III trial to determine the efficacy of MVC versus efavirenz (EFV) in treatment-naïve patients infected with R5-tropic HIV-1.²⁵ MVC treatment did not initially demonstrate noninferiority for patients with VL below 50 copies/mL, with 65.3% and 69.3% of patients receiving EFV and MVC, respectively, having VL below 50 copies/mL. However, in post hoc reanalysis after removal of patients with previously undetectable X4-tropic viruses, MVC was noninferior to EFV, with 68.3% and 68.5% of patients in the EFV and MVC groups, respectively, having VL below 50 copies/mL.²⁵ Analysis at 5 years showed that 50.8% and 45.9% of patients receiving MVC and EFV, respectively, had maintained VL below 50 copies/mL.²⁶ The mean increased in CD4 count was 293 cells/ μ L in MVC-treated patients compared to 271 cells/ μ L in EFV-treated patients;²⁶ compared to the EFV group, fewer MVC-treated patients discontinued treatment due to adverse events.²⁶

Following these studies, MVC was approved by United States Food and Drug Administration and the European Commission for treatment-experienced HIV-1-infected humans, and was subsequently also approved for treatment-naïve HIV-1-infected humans.¹⁵

MVC pharmacokinetics

Dosage, absorption, and bioavailability

Standard MVC dosage is 300 mg/kg twice daily;¹⁵ for patients receiving a cytochrome P450-3A4 (CYP3A4) inhibitor or inducer, dosage is adjusted to 150 or 600 mg/kg twice daily, respectively.¹⁵ In an effort to reduce possible toxicity associated with high drug concentrations, simplify drug regimens, and reduce costs, the clinical outcomes of 150 or 300 mg/kg MVC once daily have been examined. In the MOTIVATE trials, once daily MVC showed virological suppression (mean change in plasma HIV-1 RNA levels of $-1.68 \log_{10}$ copies/mL), although this was not as robust as the levels of virological suppression in subjects receiving MVC twice daily.²¹ The Maraviroc Once Daily with Darunavir Enhanced by Ritonavir in a New Regimen study, comparing the efficacy of 150 mg/kg MVC plus darunavir/ritonavir (DRV/RTV) once daily versus tenofovir (TDF) plus DRV/RTV once daily, was terminated due to inferiority of the MVC-containing regimen.²⁷ However, other studies have shown that 150 mg/kg MVC plus DRV/RTV once daily can effectively suppress HIV-1 infection.²⁸ Virological suppression was also demonstrated with nucleoside reverse-transcriptase inhibitor (NRTI)-sparing regimens of 150 mg/kg MVC once daily plus lopinavir (LPV)/RTV and atazanavir (ATV)/RTV.^{29,30} Another study examined the effect of MVC-containing regimens with TDF-containing regimens on bone loss; the authors used a dose of 150 mg/kg MVC once daily in combination with DRV/RTV and emtricitabine (FTC), and showed that, although bone mineral density decreased in both groups, the magnitude of decrease was less in patients receiving MVC.³¹ However, this latter study did not analyze the effects of treatment regimens on viremia.

MVC (molecular weight: 513.67 g/mol) is moderately lipophilic, with a distribution constant at pH 7.4 ($\log D_{7.4}$) of 2.1.³² Drug lipophilicity can increase its ability to penetrate lipid membranes such as the blood-brain barrier;³³ and the optimal $\log D_{7.4}$ for diffusion from plasma into cerebrospinal fluid (CSF) is 1–10.³⁴ MVC is a weak base with a pK_a of 7.3,³⁵ is highly soluble at pH 1–7.5,¹⁵ and 76% of MVC binds to plasma proteins.³⁵ At a single MVC dose of 300 mg/kg, time to maximum concentration (T_{max}) occurred by 2 hours post-treatment in humans;³² with higher MVC levels in plasma (median maximum concentration [C_{max} : 800 ng/g])

compared to whole blood (C_{max} : 489 ng/g).³² MVC exposure (area under the curve; AUC) was 4,497 ng h/L for plasma and 2,251 ng h/L for blood.³² MVC AUC decreased by 33%–37% after a high fat meal,^{15,36} but this did not affect MVC antiviral activity.¹⁵ At 100 and 300 mg/kg, the absolute MVC oral bioavailability is 23.1% and 33%, respectively.³²

Distribution

MVC is distributed throughout the body and can be detected in the seminal plasma (SP), vaginal tissues (VT), cervicovaginal fluids (CF), rectum, and CSF.^{15,37–47} Pharmacokinetic data are summarized in Table 1. MVC concentrations and AUC in the SP are lower than in the blood plasma (plasma).³⁷ However, the median protein binding in the SP is 9% compared to 76% in the plasma; more pharmacologically available MVC are found in the SP,³⁷ and most patients on MVC had undetectable VL in SP,³⁸ suggesting that MVC might reduce sexual HIV-1 transmission. MVC has higher concentrations in vaginal tissue and CF than in plasma, and also has lower protein binding (7.6%) in CF than in plasma.⁴⁰

Compared to plasma, MVC concentrations in rectal tissues are 7.5-fold higher after a single dose and 26-fold higher after multiple doses.³⁷ These results were corroborated by animal studies showing that MVC concentrations in macaques' rectal tissues were 23% higher than in plasma,³⁹ however, despite high concentrations in rectal tissues, MVC could not prevent simian-HIV (SHIV) rectal transmission.³⁹ MVC CSF concentrations are often low but vary; studies of asymptomatic HIV-1-infected humans^{42,43,45,46} showed lower concentrations than a study of HIV-1-infected patients with central nervous system (CNS) impairment.⁴⁴ These discrepancies could be due to differences in drug regimens or increased drug entry into the brain due to blood–brain barrier inflammation in patients with CNS impairment. Despite low CSF concentrations, MVC suppressed CSF VL.^{42,43} MVC is detectable in humans' saliva and correlates with its plasma concentrations;³⁷ thus, measuring MVC saliva concentrations could be a less invasive option of monitoring adherence. Quantification of MVC in humans' intestines has not been done, however, in MVC-treated humanized mice, the highest drug concentrations were in the intestine.⁴⁷ This is likely due to MVC excretion through feces.³⁵

Metabolism

Unmetabolized MVC constitutes 42% of circulating drug.³² The most abundant metabolite in the plasma is a secondary amine product of N-dealkylation (UK-408,027).³² MVC is metabolized by CYP3A4 and CYP3A5;^{35,48} CYP3A4

Table 1 Maraviroc tissue distribution

Tissue/sample	Host	Dose	C_{max} (range)	T_{max} (range)	AUC (range)
Plasma ³²	Human	300 mg/kg twice daily	800 ng/mL	2 hours	4,497 ng h/mL
Semen ³⁷	Human	300 mg/kg twice daily	190 ng/mL (90.2–664 ng/mL)	2.2 hours (2.4–6.3 hours)	1,123 ng h/mL (633–2,087 ng h/mL)
Semen ³⁸	Human	150–600 mg/kg twice daily	197 ng/mL (15.8–1,650 ng/mL)	N/A	N/A
Rectal tissue ³⁷	Human	300 mg/kg twice daily	7,119 ng/mL	1.3 hours	57,326 ng h/g
Rectal tissue ³⁹	Rhesus macaques	Single dose of 44 mg/kg	10,242 ng/g	N/A	131,164 ng h/mL
Vaginal tissue ⁴⁰	Human	300 mg/kg twice daily	848 ng/mL	4 hours	4,857 ng h/mL
Cervicovaginal fluid ⁴⁰	Human	300 mg/kg twice daily	1,230 ng/mL (409–1,810 ng/mL)	6 hours (0–12 hours)	750 ng h/mL (3,078–9,090 ng h/mL)
Cerebrospinal fluid ⁴²	Human	150–600 mg/kg twice daily	3.63 ng/mL (1.83–12.2 ng/mL)	N/A	N/A
Cerebrospinal fluid ⁴³	Human	150–600 mg/kg twice daily	2.58 ng/mL (>0.5–7.22 ng/mL)	N/A	N/A
Cerebrospinal fluid ⁴⁴	Human	150–600 mg/kg twice daily	102 ng/mL (35–173 ng/mL)	N/A	N/A
Cerebrospinal fluid ⁴⁵	Human	150 mg/kg twice daily	6.32 ng/mL (3.41–8.67 ng/mL)	N/A	N/A
Cerebrospinal fluid ⁴⁶	Human	150–300 mg/kg twice daily	2.4 ng/mL (1.5–4.0 ng/mL)	N/A	N/A
Saliva ³⁷	Human	300 mg/kg twice daily	186 ng/mL (58.6–325 ng/mL)	3.0 hours (1.0–6.1 hours)	827 ng h/mL (252–1,298 ng h/mL)
Intestines ⁴³	Humanized mice	62 mg/kg once daily	33,462 ng/g (31,958–36,819 ng/g)	4 hours	140,159 ng g/mL

Abbreviations: C_{max} , maximum concentration; T_{max} , time at C_{max} ; AUC, area under the curve; N/A, Not available.

is its major enzyme,³⁵ while CYP3A5 is involved in the formation of mono-oxygenated metabolites.^{48,49} In fact, ketoconazole, a potent CYP3A4 inhibitor, reduced MVC metabolism and UK-408,207 formation by over 80%,⁵⁰ while specific inhibitors of CYP1A2, CYP2C9, CYP2C19, and CYP2D6 had no significant effect.⁵⁰ MVC is a P-glycoprotein (Pgp) substrate; in MVC-treated Pgp-knockout-friend-leukemia-virus-B mice C_{max} and AUC increased by 108% and 183%, respectively, compared to MVC-treated wild-type mice.³⁵

Genetic polymorphisms

CYP3A5 is involved in the oxidative metabolism of MVC, and it has been suggested that CYP3A5 genetic polymorphisms may influence MVC pharmacokinetics.⁴⁹ The wild-type homozygous allele, CYP3A5*1, is associated with the highest CYP3A5 protein expression, whereas the CYP3A5*3, CYP3A5*6, and CYP3A5*7 alleles are associated with nonfunctional or dysfunctional CYP3A5 expression.^{49,51–54} CYP3A5 expression varies by ethnicity, 80%–90% of Caucasians are non-expressers due to a high prevalence of CYP3A5*3, while the majority of African-Americans are expressers, with 45% being homozygous for CYP3A5*1.^{51,55} Individuals with no CYP3A5*1 had similar MVC plasma concentrations as those with heterozygous CYP3A5*1.⁴⁹ However, compared to humans with no CYP3A5*1 and heterozygous subjects, individuals with homozygous CYP3A5*1 allele had lower MVC exposures and lower MVC plasma concentrations, with half of the individuals in the homozygous group having average MVC concentrations below 100 ng/mL, the threshold value below which there is increased risk of virological failure.⁴⁹ Compared to individuals with no CYP3A5*1 and heterozygous individuals, MVC C_{max} in homozygous individuals decreased by 33% and 22%, respectively; and MVC exposure also decreased in homozygous individuals by 41% and 30%.⁴⁹ Individuals with no CYP3A5*1 showed decreased exposure to the predominant MVC oxidative metabolite compared to the homozygous group.⁴⁹

MVC is a substrate for the organic anion transporter polypeptide-1B1, an influx transporter, also known as solute carrier organic anion transporter family member-1B1.⁵⁶ The solute carrier organic anion transporter family member-1B1 gene has two functional single nucleotide polymorphisms (SNPs), c.521 T>C and c.388 A>G.^{56–58} The c.521 T>C SNP contains two haplotypes, *5 (388A-521 C) and *15 (388G-521 C), that have been associated with reduced activity and increased plasma concentrations of several drugs.^{58–60}

HIV-1-infected patients who were heterozygous for the c.521 T>C SNP had a 55% increase in MVC concentrations compared to patients who were homozygous for the wild-type allele.⁵⁶

Excretion

MVC is primarily excreted through feces, with 76% excreted through this route, and 19%–20% excreted through urine at 36–96 hours post-dose.^{32,35} Unmetabolized MVC accounts for 33% of excreted drug,³⁵ major excreted metabolites include a product of hydroxylation of the methyl group of the triazole moiety, four products of mono-oxidation in the difluorocyclohexyl ring, and N-dealkylation adjacent to the tropane ring, resulting in a secondary amine.^{32,35}

MVC pharmacodynamics

In radioligand-binding assays, MVC inhibited the binding of chemokine (C-C motif) ligand (CCL)-3, CCL4, and CCL5 to CCR5 with a half-maximal inhibitory concentration of 3.3, 7.2, and 5.2 nM, respectively.³⁵ Furthermore, MVC potently inhibited downstream CCR5 signaling and did not induce CCR5 internalization, suggesting that MVC is a functional CCR5 antagonist.³⁵ MVC showed no significant affinity for other receptors, including CCR2, which has sequence similarity to CCR5 and is susceptible to other CCR5 antagonists.^{61,62} MVC inhibits HIV-1 binding to peripheral blood mononuclear cells (PBMC) (IC₅₀: 3.1 nM), and up to 10 μM MVC had no effect on cell proliferation.³⁵ MVC effectively inhibited infection of several R5-tropic HIV-1 strains, but not X4-tropic HIV-1.³⁵

MVC concentrations increase by 11%–32% in humans with mild-to-moderate hepatic impairment, but with proper monitoring, no dose adjustment is necessary.⁶³ In individuals with severe renal impairment, MVC renal clearance was fourfold lower than in patients with normal renal function (27 versus 110 mg/min, respectively).⁶⁴ In a patient with end-stage liver disease and renal impairment receiving 300 mg/kg MVC, raltegravir (RAL), and enfuvirtide (ENF) twice daily, MVC serum concentrations were 25-fold higher than expected, and remained high after doses were adjusted to every 48 hours.⁶⁵ No dose adjustment is necessary in patients with mild-to-moderate renal impairment, but in patients with severe renal impairment or end-stage renal disease, MVC should not be given if the patient is also taking CYP3A4 inducers or inhibitors.¹⁵ Compared to untreated patients, MVC treatment of humans infected with R5-tropic HIV-1 resulted in improved lipid profiles, increased CD4 count, and decreased levels of soluble endothelial protein-C receptor.^{66,67}

MVC and immune cell restoration

MVC improves T-cell counts, and higher baseline CD4 counts correlate with better response to MVC treatment.⁶⁸ In the MOTIVATE trials, patients receiving MVC had larger CD4⁺ T-cell increases than those receiving placebo, even after adjusting for the greater virological potency of MVC-containing regimens.⁶⁹ Short-term MVC treatment of patients with persistent virological failure resulted in increased CD4⁺ and CD8⁺ T-cells and positively correlated with improved antiviral activity.⁷⁰ Following virological failure, infected patients treated for 96 weeks with RAL, etravirine (ETR), and MVC showed a greater increase in CD4⁺ T-cells than patients receiving RAL, ETR, and DRV/RTV.⁷¹ Patients on MVC intensification showed increased CD4 count slope,⁷² maintained higher CD4 counts after MVC discontinuation,⁷³ and showed decreased VL in memory T-cells.⁷⁴ In vitro studies also showed that MVC blocks CCR5 and CCR2 internalization and inhibits T-cell chemotaxis,⁷⁴ increases CCR5 expression on activated T-cells, decreases the expression of CD25, CD38, and HLA-DR, and increases the expression of CD69 in CD4⁺ and CD8⁺ T-lymphocytes.⁷⁵

In patients with suppressed viremia, MVC treatment modestly increased CD4 and CD8 counts and reduced the percentages of regulatory T-cells (Tregs).⁷⁶ ART regimens containing MVC or MVC monotherapy decreased the frequency of Tregs in treatment-naïve HIV-1-infected patients from day 8 post-treatment initiation, and dose-dependently reduced Tregs frequency in PBMC.⁷⁷ Treatment of virologically suppressed patients with ART regimens containing MVC decreased the expression of natural killer cell activation markers, decreased the frequency of inflammatory monocytes, including CD16⁺ monocytes, and this was associated with improved neuropsychological performance.^{78,79} However, in some HIV-1-infected patients with low baseline T-cells counts, MVC intensification had limited-to-no effect on CD4 counts, compared to patients on ART regimens without MVC;^{80–82} although patients on MVC-containing ART regimens showed increased CD8 counts.⁸⁰

MVC and HIV-1 mother-to-child transmission

Mother-to-child transmission (MTCT) is the most common route of pediatric HIV-1 transmission and occurs in utero, intrapartum, or during breastfeeding.⁸³ The mother's plasma VL can predict the likelihood of HIV-1 transmission to the child; in developed countries where ART is readily available, MTCT is below 2%.⁸⁴ A study of MVC placental transfer in macaques showed that after a single MVC dose 2 hours pre-delivery, maximal plasma MVC concentrations in

infants occurred immediately after birth, C_{max}: 22 ng/mL.⁸⁵ Infants' C_{max} were 44-fold lower than mothers' C_{max}, and MVC was not detectable in infants 3.5 hours after birth.⁸⁵ This suggests that a single MVC dose may not protect babies during vaginal delivery. Previous World Health Organization (WHO) recommendation for reducing MTCT, when access to ART is insufficient for a complete antepartum, intrapartum, and postpartum regimen, was a single-dose nevirapine (NVP) during labor.⁸⁵ This single NVP dose reduced MTCT by approximately 50%,⁸⁶ but increased drug resistance.⁸⁷ The macaque study⁸⁵ sought to determine whether MVC could replace NVP as a single intrapartum dose option. However, while WHO guidelines have since been revised, many low-income countries continue to use single-dose NVP.⁸⁸ There have been no other major studies on MVC placental transfer after multiple doses. The low MVC placental transfer was confirmed using an ex vivo human perfused cotyledon model, which reproduces the third-trimester pregnancy conditions, and is considered the gold standard method for measuring fetal exposure risk during maternal treatment.⁸³ The MVC fetal transfer rate was 8% and its clearance index was 0.26;⁸³ low MVC transfer was associated with transporters-mediated drug efflux across placental membranes.⁸³ However, an ART regimen consisting of 600/100 mg DRV/RTV, 150 mg MVC, and 200 mg ETR twice daily, with TDF/FTC prevented HIV-1 MTCT.⁸⁹ In this case, MVC concentration in the umbilical cord blood was 69 ng/mL and the umbilical cord-to-plasma ratio was 0.37.⁸⁹ Studies are needed to determine MVC levels in breast milk, quantify MVC transfer after multiple/prolonged dosing, and determine the long-term efficacy of MVC in preventing HIV-1 MTCT.

MVC drug–drug interactions MVC interactions with protease inhibitors

Protease inhibitors (PIs) bind to HIV-1 protease, preventing its cleavage of Gag and GagPol precursors into their mature/infective forms.⁹⁰ PIs, including saquinavir (SQV), RTV, LPV, ATV, tipranavir (TPV), amprenavir (APV), and DRV, are common CYP3A4 inhibitors⁹¹ and would increase MVC concentrations. Co-administration of MVC with SQV, SQV/RTV, LPV/RTV, RTV, ATV, ATV/RTV, or DRV/RTV increased MVC plasma C_{max} by 332%, 423%, 161%, 128%, 209%, 267%, and 229%, respectively.^{92,93} However, TPV/RTV had no effect on MVC plasma concentrations.⁹² Fosamprenavir (FPV), an APV pro-drug, is used as a slow-release version of APV. In a treatment regimen including FPV, RTV, and MVC, MVC AUC and C_{max} increased by 249% and 152%, respectively;⁹⁴ APV AUC and C_{max}

decreased by 35% and 34%, respectively;⁹⁴ RTV AUC and Cmax decreased by 34% and 39%, respectively.⁹⁴ While FPV/RTV increasing MVC concentrations is not surprising, since both are CYP3A4 inhibitors, the mechanisms of MVC reducing RTV and FPV concentrations are not known. This may involve protein-binding displacement, which is associated with increase in unbound FPV and RTV ready to be metabolized. Overall, adjustments of MVC doses to 150 mg/kg twice daily are recommended when co-administered with PIs, except for TPV/RTV¹⁵ (Table 2).

MVC interactions with nucleoside/nucleotide analog reverse-transcriptase inhibitors

NRTIs and nucleotide analog reverse-transcriptase inhibitors (NtRTIs) are nucleoside or nucleotide analogs that block the reverse transcriptase activity by incorporating themselves into viral RNA. TDF, a NtRTI, does not affect MVC concentration;⁹⁵ MVC treatment had no effect on lamivudine/zidovudine (3TC/ZDV) concentrations, both NRTIs.⁹⁶ NRTIs are mostly cleared renally and are not metabolized by CYPs enzymes;⁹⁷ therefore, no dose adjustments are necessary when NRTIs are co-administered with MVC¹⁵ (Table 2).

MVC interactions with non-nucleoside reverse-transcriptase inhibitors

Non-nucleoside reverse-transcriptase inhibitors (NNRTIs) bind to the reverse transcriptase to prevent RNA conversion to cDNA. EFV, a CYP3A4 inducer, reduced MVC concentrations by over 50% in healthy subjects⁹⁸ and by 25%–40% in HIV-1-infected patients.⁹⁹ ETR, another CYP3A4 inducer^{100,101} decreased MVC Cmax by 60%, but co-administration of MVC with ETR/DRV/RTV increased MVC Cmax by 176%.⁹³ MVC dosage should be increased to 600 mg/kg twice daily when co-administered with EFV or ETR.¹⁵ Lersivirine is a weak CYP3A4 inducer, although its further development was stopped in 2013.¹⁰² In healthy subjects given 300 mg MVC and 500 mg Lersivirine twice daily, MVC Cmax and AUC increased by 3.4% and 6.2%, respectively, compared to subjects given MVC plus placebo.¹⁰² NVP increased MVC Cmax and AUC by 101% and 154%, respectively⁹⁹ (Table 2).

MVC interactions with integrase inhibitors

Integrase inhibitors are a newer class of ART drugs that inhibit integrase to prevent insertion of the HIV-1 genome into cellular DNA. Co-administration of RAL with

Table 2 Interaction of MVC with other drugs

Drugs	Net effect on CYP3A4	Effect on MVC concentrations	Recommended MVC dosage
Protease inhibitors			
Saquinavir ⁹²	Inhibits	Increase by 332%	150 mg/kg twice daily
Lopinavir/ritonavir ⁹²	Inhibits	Increase by 128%	150 mg/kg twice daily
Atazanavir ⁹²	Inhibits	Increase by 267%	150 mg/kg twice daily
Ritonavir ⁹²	Inhibits	Increase by 209%	150 mg/kg twice daily
Darunavir/ritonavir ⁹³	Inhibits	Increase by 229%	150 mg/kg twice daily
Tipranavir/ritonavir ⁹²	Inhibits	No effect	300 mg/kg twice daily
Fosamprenavir/ritonavir ⁹⁴	Inhibits	Increased by 152%	150 mg/kg twice daily
Nucleoside/nucleotide analog reverse-transcriptase inhibitors			
Lamivudine/zidovudine ⁹⁶	N/A	No effect	300 mg/kg twice daily
Tenofovir ⁹⁵	N/A	No effect	300 mg/kg twice daily
Non-nucleoside reverse-transcriptase inhibitors			
Efavirenz ^{98,99}	Induces	Decrease by 25%–40%	600 mg/kg twice daily
Etravirine ⁹³	Induces	Decrease by 60%	600 mg/kg twice daily
Lersivirine ¹⁰²	Induces	Increase by 3.4%	300 mg/kg twice daily
Nevirapine ⁹⁹	Induces	Increase by 101%	150 mg/kg twice daily
Integrase inhibitors			
Raltegravir ¹⁰³	Induces	Decrease by 20%	300 mg/kg twice daily
Elvitegravir/ritonavir ¹⁰⁵	Inhibits	Increase by 215%	150 mg/kg twice daily
Other (non-HIV) drugs			
Ethinylestradiol/levonorgestrel ⁹⁶	N/A	No effect	300 mg/kg twice daily
Ethanol ¹⁰⁷	N/A	No effect	300 mg/kg twice daily
Ketaconazole ⁹²	Inhibits	Increase by 338%	150 mg/kg twice daily
Cotrimoxazole ⁹⁵	Inhibits	No effect	300 mg/kg twice daily
Boceprevir ¹⁰⁸	Induces	Increase by 300%	150 mg/kg twice daily
Telaprevir ¹⁰⁸	Inhibits	Increase by 9%	300 mg/kg twice daily

Abbreviations: MVC, maraviroc; CYP3A4, cytochrome P450-3A4; N/A, not available.

MVC decreased RAL and MVC plasma concentrations, respectively, by 33% and 20%.¹⁰³ However, another study showed no MVC effects on RAL concentrations.¹⁰⁴ Elvitegravir (EVG) is often given in combination with RTV, and is metabolized by CYP3A4.^{105,106} Co-administration of EVG/RTV with MVC resulted in a 215% increase in MVC plasma concentration, while EVG and RTV concentrations remained unchanged.¹⁰⁵ No dose adjustments are necessary when integrase inhibitors are co-administered with MVC.¹⁵

MVC interactions with non-HIV-I drugs

MVC does not affect the pharmacokinetics of midazolam, a benzodiazepine metabolized by CYP3A4, and had no effect on oral contraceptives ethinylloestradiol and levonorgestrel.⁹⁶ When used with alcohol, MVC increased alcohol concentrations by 12%, but alcohol use did not affect MVC plasma concentrations.¹⁰⁷ Ketoconazole, an antifungal commonly used for the treatment of opportunistic infections in HIV-1/AIDS patients, and a CYP3A4 inhibitor, increased MVC plasma C_{max} by 338%; thus, MVC dosage should be decreased to 150 mg/kg twice daily when given with ketoconazole.⁹² Cotrimoxazole, an antibiotic commonly used to treat HIV-1-associated pneumocystis jiroveci infections, had no effect on MVC plasma concentrations or its clearance.⁹⁵ Boceprevir, an antiviral used for hepatitis-C treatment, increased MVC plasma concentrations by 300%, thus, MVC dosage should be decreased to 150 mg/kg twice daily when given with boceprevir.¹⁰⁸ Telaprevir is a hepatitis-C PI and inhibitor of CYP3A and Pgp.¹⁰⁸ Co-administration of telaprevir and MVC to healthy subjects increased MVC AUC and C_{max}, respectively, by ninefold and tenfold, compared to subjects treated only with MVC.¹⁰⁸ Data on MVC interactions with other drugs are summarized in Table 2.

MVC drug resistance

Resistance due to the outgrowth of X4-tropic HIV-I strains

Resistance to MVC often occurs when previously undetectable X4-tropic HIV-1 are selected under pressure from drug treatment.²⁵ This occurs when R5-tropic viruses, which previously constitute the majority of viral species, are sufficiently repressed. Viruses capable of using X4, which previously constituted a small minority, then multiply and become the dominant viral species.¹⁰⁹ In the MOTIVATE trials, patients who were unresponsive to MVC treatment often had detectable X4-tropic viruses at treatment failure;²⁴ 76 (57%) of MVC-treated subjects that failed treatment had

X4-tropic or dual-R5X4-tropic HIV-1 at the time of treatment failure, whereas only 6 (6%) of subjects receiving optimized background therapy plus placebo had detectable X4-tropic or dual-R5X4-tropic viral strains.²⁴ In deep-sequencing analysis of plasma samples from subjects who experienced treatment failure, subjects who had a tropism shift had multiple amino acid mutations in the gp120 third variable (V3) region; the most common mutations included substitutions of glycine (G) to arginine (R) at position 11 (G11R), proline (P) to R at position 13 (P13R), and alanine to lysine (K) at position 25 (A25K).¹¹⁰ Deep sequencing further showed that most of these patients had some non-R5-tropic viruses at the time of initial screening.¹¹⁰ In a study of 62 individuals infected with R5-tropic HIV-1 who had been receiving MVC for 10 days, only two showed emergence of dual-X4R5-tropic HIV-1 strains.^{20,109} Phenotype and genotype screening showed that one patient had dual-tropic strains at baseline, and HIV-1 variants using X4 were genetically distinct from variants using R5.¹⁰⁹ In one patient on MVC-containing regimen who had failed treatment, X4-tropic HIV-1 strains were rescued from previously stored PBMC samples, and became the main circulating strain under selective pressure from MVC.²⁰

Mutations associated with resistance to MVC

Mutations found in vitro

Variable mutations in the V3 loop of gp120 can occur but may not confer complete resistance to MVC,¹¹¹ and there has been no signature pattern of mutations described that can help predict resistance. Substitutions from alanine to threonine at position 316 (A316T), isoleucine to valine at position 323 (I323V), and alanine to serine at position 319 (A319S) were shown by genetic sequencing of clades-B and -G primary HIV-1 isolates following sequential passage.¹¹² Deletions of isoleucine and serine at position 315 and position 317, respectively, also occurred in some viral isolates.¹¹² Viral site-directed mutagenesis of the substitutions at position 316 and position 323 back to their original sequence, alanine to threonine and isoleucine to valine for position 316 and position 323, respectively, had full MVC response.¹¹² Site-directed mutagenesis of either substitution alone only partially restored MVC response.¹¹² That study also showed mutations outside the V3 loop: in the V1; V2; V4; and constant domains (C)-3, C4, and C5 regions of gp120, and in gp41.¹¹² The authors suggested that mutations outside the V3 loop could help accommodate the resistance mutations occurring inside the V3 loop. Mutations due to serial passage

of CC1/85 and Bal HIV-1 strains in vitro include valine to methionine (M) at position 169 (V169M) and asparagine (N) to K at position 192 (N192K) in the V2 region, leucine (L) to tryptophan (W) at position 317 (L317W) in the V3 region, I408A in the V4 region, aspartate (D) to N at position 462 (D462N), N463T, S464T, and N465aD in the V5 region, and L820I, I829V, and tyrosine (Y) to cysteine (C) at position 837 (Y837C) in gp41.¹¹³ Other mutations include T199K and T275M in the C2 region and I304V/F312W/T314A/glutamic acid (E) to D at position 317 (E317D)/I318V in the V3 loop.¹¹⁴ The T199K mutation has been shown to increase viral fitness;¹¹⁴ combination of F312W/T314A/E317D mutations with either I304V or I318V mutation was necessary for V3 loop binding to CCR5 in the presence of MVC.¹¹⁴ These mutations resulted in changes in the V3 loop configuration and secondary structure that enabled gp120 binding to drug-bound CCR5.¹¹⁴ In vitro selected mutations of a subtype-A HIV-1 showed mutations in the C4 but not the V3 region.¹¹⁵ Common mutations associated with resistance to MVC are summarized in Table 3.

Mutations found in clinical specimens

Mutations seen in patients enrolled in the MOTIVATE trials include G11S + I26V, S18G + A22T, A19S + I26V, I20F + A25D + I26V, and I20F + Y21I in the V3 region.¹¹⁰ In a patient resistant to MVC, the mutations present included P/T to histidine (H) at position 308 (P/T308H), T320H, and I322aV in the V3 loop; D407G and loss of a glycosylation site at residue-386 in the V4 region; and V489I in the C5 region.¹¹⁶ The P/T308H mutation seemed to be the most important, resulting in complete resistance to MVC treatment, while the H320T and V322aI mutations resulted in lesser resistance.¹¹⁶ Insertion of the resistant V3 loop into a MVC-sensitive ENV clone resulted in partial resistance to MVC, while addition of mutations from the V4 region showed complete resistance.¹¹⁶ However, when V4 mutations were added without V3 mutations, there was no resistance to MVC.¹¹⁶ Studies of MVC-naïve patients harboring commonly seen resistance mutations showed that 9.8% (93/951 subjects) had V3 mutations associated with MVC resistance.¹¹⁷ Common mutations included G11S/I26V

Table 3 Mutations associated with resistance to MVC

Mutations	HIV region	Specimens
Mutations found in clinical specimens		
G11R ¹¹⁰	V3 of gp120	Plasma
P13R ¹¹⁰	V3 of gp120	Plasma
A25K ¹¹⁰	V3 of gp120	Plasma
A316T ^{112,118}	V3 of gp120	Primary clinical isolates and plasma
P/T308H ¹¹⁶	V3 of gp120	Plasma
T320H ¹¹⁶	V3 of gp120	Plasma
I322aV ¹¹⁶	V3 of gp120	Plasma
D407G ¹¹⁶	V4 of gp120	Plasma
V489I ¹¹⁶	C5 of gp120	Plasma
I20F + Y21I ¹¹⁰	V3 of gp120	Plasma
Mutations found in vitro		
A319S ¹¹²	V3 of gp120	Primary clinical isolates
V169M ¹¹³	V2 of gp120	HIV strain CC1/85
N192K ¹¹³	V2 of gp120	HIV strain CC1/85
L317W ¹¹³	V3 of gp120	HIV strain CC1/85
I408A ¹¹³	V4 of gp120	HIV strain CC1/85
D462N ¹¹³	V5 of gp120	HIV strain CC1/85
N463T ¹¹³	V5 of gp120	HIV strain CC1/85
S464T ¹¹³	V5 of gp120	HIV strain CC1/85
N465aD ¹¹³	V5 of gp120	HIV strain CC1/85
L820I ¹¹³	gp41	HIV strain CC1/85
I829V ¹¹³	gp41	HIV strain CC1/85
Y837C ¹¹³	gp41	HIV strain CC1/85
T199K/T275M ¹¹⁴	C2 of gp120	HIV-IJR-FL-P17 and/or HIV-IV3Lib-P17
T275M ¹¹⁴	C2 of gp120	HIV-IJR-FL-P17 and/or HIV-IV3Lib-P17
I304V ¹¹⁴	V3 of gp120	HIV-IJR-FL-P17 and/or HIV-IV3Lib-P17
F312W ¹¹⁴	V3 of gp120	HIV-IJR-FL-P17 and/or HIV-IV3Lib-P17
T314A ¹¹⁴	V3 of gp120	HIV-IJR-FL-P17 and/or HIV-IV3Lib-P17
E317D ¹¹⁴	V3 of gp120	HIV-IJR-FL-P17 and/or HIV-IV3Lib-P17

Abbreviation: MVC, maraviroc.

(6.4%) and I20F/A25D/I26V (2.2%); 14 isolates with these mutation patterns were selected for MVC sensitivity tests, 13 were fully sensitive to MVC; the MVC-resistant isolate had I20F/Y21I mutations and reversing this mutation restored the sensitivity to MVC.¹¹⁷ However, when V3 MVC-resistant mutations from one isolate were cloned into other isolates, there was lesser or no resistance to MVC, suggesting that resistance due to V3 mutations may be dependent on which env sequence they occur in.¹¹⁷ Common mutations associated with resistance to MVC are summarized in Table 3.

Resistance-associated mutations and viral subtype

It has been suggested that naturally occurring mutations to MVC might be more common in subtype-C than subtype-B HIV-1. Analysis of 65 samples showed that 52.3% (75% of subtype-C and 18.2% of subtype-B) had at least one mutation associated with MVC resistance.¹¹⁸ A commonly seen mutation was A316T in the gp120 region, occurring in 67.8% of subtype-C samples and 18.2% of subtype-B samples.¹¹⁸ The I323V mutation in the gp120 region occurred in 7.14% of subtype-C and was not seen in subtype-B samples.¹¹⁸ This observation was further confirmed in treatment-naïve HIV-1 infected patients in Zambia, all with subtype-C HIV-1.¹¹⁹ In an analysis of patients' PBMC from three different study populations, the A316T mutation was found in 68%, 80.7%, and 64.5% of the 28, 32, and 90 samples analyzed, respectively.¹¹⁹ The I323V mutation in the gp120 was rare but was only present with the A316T mutation.¹¹⁹ A high prevalence of the A316T mutation, which results in partial resistance to MVC, was found in Zambian mother-infant pairs infected with HIV-1 subtype-C.¹²⁰ A study of 80 HIV-infected patients in Brazil who had failed treatment showed that 27.5% harbored the A316T, I323V, and/or S405A mutations in the gp120.¹²¹ However, in another study of 498 individuals infected with R5-tropic, subtype-B HIV-1, mutation patterns associated with MVC resistance were less than 5%.¹²² Single mutations were more commonly observed, but their significance on MVC resistance was not examined.¹²²

Mechanisms involved in resistance to MVC

Resistance to MVC is typically non-competitive, characterized by a decrease in maximal percentage inhibition (MPI), with most resistant viruses having 80%–95% MPI.^{111,123} The mechanisms through which resistance to MVC evolves have not been fully elucidated, but involve mutations that result in increased affinity of gp120 to MVC-bound CCR5, enabling gp120 binding to CCR5 despite conformational changes from

MVC binding.¹²⁴ Resistant viruses could interact with CCR5 in the presence of MVC through increased binding to the CCR5 N-terminal domain.¹¹¹ In fact, CCR5 antagonists work by binding to a hydrophobic pocket in the CCR5 transmembrane region;¹¹¹ this results in conformational change in the extracellular loop (ECL) region, but little-to-no conformational change in the N-terminal domain.¹¹¹ Therefore, mutations resulting in increased binding to the N-terminal domain would enable binding to MVC-bound CCR5. This could cause broad cross-resistance among several CCR5 antagonists, since most do not affect N-terminal conformation.¹¹¹ In fact, three HIV-1 isolates resistant to VCV also displayed resistance to MVC, as well as resistance to TAK-779, another small-molecule CCR5 inhibitor.¹²⁵ Another model for resistance to MVC is the requirement of both the N-terminal and ECL domains for viral binding; mutations in the V3 loop would thus allow its binding to the ECL in the presence of MVC, due to increased affinity for the binding site.¹²⁴ Conformational change to the ECL region differs among CCR5 antagonists, thus, mutations resulting in the V3 loop binding to MVC-bound CCR5 may not result in binding in the presence of other CCR5 antagonists.¹¹⁶ The I322a residue is in contact with D11, Y10, and Y14, three key amino acid residues of the CCR5 N-terminal domain that are predicted to interact with the V3 loop.¹²⁶ The hydrophobic side chain of I322a intercalates between all three residues, making hydrophobic contacts with the aromatic rings of both Y residues and the backbone of D11.¹²⁶ Replacement of I with V likely alters the hydrophobic packing of these interactions and thereby modulates how V3 interacts with the CCR5 N-terminal.¹²⁶

Use of MVC in HIV-1 infection

Routine treatment

Several studies have examined MVC use for treatment of HIV-1 infected humans. In a study of 32 patients, the most common reasons for MVC initiation were treatment failure, intolerance to previous ART regimens, and treatment intensification.¹²⁷ After 3 and 6 months MVC treatment, 75% and 78% of patients, respectively, had fully suppressed viremia;¹²⁷ the median increase in CD4⁺ count was 141 and 124 cells/ μ L at 3 and 6 months, respectively.¹²⁷ In a study of 27 patients (20 with R5-tropic HIV-1, 1 with dual-R5X4-tropic HIV-1, and 6 with undetermined viral tropism) receiving MVC-containing ART regimens, 59% (10/17) of patients with detectable viremia before MVC initiation achieved viral suppression; HIV-1 remained undetectable in 60% (6/10) of patients who had undetectable virus before MVC initiation.¹²⁸

CD4 count increased in 78%, remained unchanged in 11%, and decreased in 11% of patients.¹²⁸ Another study of 25 patients infected with R5-tropic HIV-1 who had failed treatment showed that 12 months' MVC intensification resulted in increased CD4 count and undetectable VL in 21 patients, and two patients without suppressed viremia showed a switch to X4-using HIV-1 by 24 months.¹²⁹ Another study of 27 patients receiving MVC who had experienced treatment failure showed that at the time of treatment failure, 12 patients had X4-using viruses and 15 had R5-using viruses.¹³⁰ Of the 12 patients with X4-tropic HIV-1 at treatment failure, four were infected with X4-tropic and dual-R5X4-tropic HIV-1 before MVC initiation.¹³⁰ Resistance profiles of four patients with R5-using viruses at treatment failure showed that two patients had MVC-resistant HIV-1.¹³⁰

Drug monitoring

The United States Department of Health and Human Services guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents suggest a minimum MVC plasma concentrations of 50 ng/mL.¹³¹ Intent-to-treat analysis of the MERIT study found that the probability of virological suppression decreased when average plasma concentrations were below 75 ng/mL.¹³² Additional studies are needed to determine which concentrations are optimal for accurate drug monitoring.

Since several drugs, including other ART drugs, can affect MVC concentrations, monitoring is important to ensure that patients maintain sufficient plasma drug concentrations.^{92,95,96,98} Several groups have developed high-performance liquid chromatography (HPLC) with ultra violet (UV) detection or with tandem mass spectrometry (MS/MS) for drug quantification.^{133–139} There are several drawbacks with many of these methods, including not being able to quantify low amounts of drug, the high cost of tests and equipment, and complicated procedures that may not be suitable for routine clinical practice, especially clinical practices in resource-limited settings. In the past few years, newer methods have been developed to address some of these concerns.¹⁴⁰ Simiele et al developed a method that used less sample volume (could quantify MVC in 100 μ L, compared to 500 μ L of sample required with similar HPLC methods), could be completed in a shorter time (20 minutes), and used a less expensive HPLC-MS instrument that had a UV detector instead of a more costly HPLC-MS/MS instrument.¹⁴⁰ This method had a similar lower limit of MVC quantification as other methods (4.9 ng/mL) and did not show any significant interference with other drugs likely to be used concomitantly

with MVC.¹⁴⁰ Emory et al developed a LC-MS/MS method that could quantify MVC levels from 0.5 ng/mL.¹³⁸ This method can be performed using a 96-well plate, making it suitable for high-throughput screening.¹³⁸ Overall, progress is being made in developing methods that will make drug monitoring easier in the future.

Pre-exposure and post-exposure prophylaxis

Pre-exposure prophylaxis (PrEP) can reduce the risk of HIV-1 infection by over 90% when taken consistently.¹⁴¹ The only drug currently approved for use as HIV-1 PrEP is tenofovir/emtricitabine (Truvada).¹⁴² Investigation of MVC for PrEP has been mostly limited to animal studies. MVC treatment, 62 mg/kg by oral gavage, protected humanized Rag22/2cc2/2(RAG-hu) mice against vaginal HIV-1 challenge;¹⁴³ MVC-treated mice had undetectable HIV-1 RNA and DNA, while all placebo-treated mice became infected.¹⁴³ MVC protective effects were further confirmed by 10 weeks monitoring data showing stable CD4⁺ T-cells in MVC-treated mice while placebo-treated mice had decreased CD4⁺ T-cells.^{39,143} However, MVC treatment, 44 mg/kg by oral gavage, did not protect macaques against rectal SHIV transmission, despite high MVC concentrations in rectal tissues.³⁹ This could be due to the high density of CCR5⁺ cells and activated memory CD4⁺ T-cells in macaques' gastrointestinal mucosa, which would suggest that higher MVC concentrations are needed to prevent rectal SHIV transmission.³⁹ These macaques received one dose 24 hours pre- and post-SHIV rectal challenge,³⁹ and accumulation of MVC in tissues from daily or twice daily use may be more effective at preventing rectal viral transmission.

ART drugs can also be used as microbicides in PrEP, often as gels or time-released rings applied vaginally or rectally. A MVC gel protected against SHIV and HIV-1 infection in macaques and RAG-hu mice, respectively.^{144,145} In macaques, vaginal application of MVC gel prevented SHIV infection in a time-dependent and dose-dependent manner, with half-maximal protection at 4 hours and 0.5 mM.¹⁴⁴ MVC gels were also able to prevent HIV-1 via rectal transmission in macaques.¹⁴⁶ Vaginal application of MVC gel to RAG-hu mice (5 mM 1 hours before HIV-1 vaginal challenge) protected all mice against infection.¹⁴⁵

An ex vivo model sought to determine whether MVC oral administration could block HIV-1 infection in Langerhans cells (LCs) and viral transmission to CD4⁺ T-cells.¹⁴⁷ Twenty healthy volunteers were given 300 mg/kg MVC twice daily for 1, 2, 3, and 14 days and epithelial tissue explants infected

with HIV-1.¹⁴⁷ One or 2 days MVC pretreatment partially inhibited infection of LCs within epithelial tissues and 3 or 14 days pretreatment completely inhibited LCs infection.¹⁴⁷ MVC treatment also prevented HIV-1 transmission from LCs to co-cultured CD4⁺ T-cells.¹⁴⁷

A Phase I clinical trial (MTN-013/IPM 026) evaluated the pharmacokinetics and pharmacodynamics of vaginal rings containing MVC.¹⁴⁸ The trial enrolled 48 HIV-1 negative individuals using vaginal rings containing 100 mg MVC and 25 mg dapivirine (DPV) or 100 mg MVC for 28 days. MVC concentrations in the CF peaked at day 2 of ring use (C_{max}: 22×10⁶ pg/mL and AUC: 3.7×10⁹ pg h/mL with the MVC-only ring).¹⁴⁸ With the MVC/DPV ring, MVC concentrations in the CF peaked at day 1 of ring use and were higher than in subjects with MVC ring alone (C_{max}: 97×10⁶ pg/mL and AUC: 6.2×10⁹ pg h/mL).¹⁴⁸ MVC was only detectable in the cervical tissues (CT) in 4 out of 12 individuals with the MVC-only ring and undetectable in all individuals with the MVC/DPV ring.¹⁴⁸ MVC plasma concentrations were below the limit of detection in both MVC and MVC/DPV rings subject groups.¹⁴⁸ Ex vivo HIV-1 challenge of CT from MVC ring users did not show any drug-associated viral inhibition.¹⁴⁸ Overall, although data are limited to animal and ex vivo models, MVC (oral or microbicides) could be useful in HIV-1 PrEP.

The only reported case of MVC use in post-exposure prophylaxis was a student exposed to multidrug-resistant HIV-1 using a needlestick.¹⁴⁹ The student received LPV/RTV, FPV, TDF, and 3TC 15 minutes after injury, and 3 days later LPV/RTV was replaced with MVC.¹⁴⁹ The student remained HIV-1-negative after a 6-month follow-up and the drug regimen was well tolerated.¹⁴⁹

Dual therapy

The MVC + DRV/RTV (MIDAS) study assessed the efficacy of MVC (150 mg) + DRV/RTV (800/100 mg) once daily, in 24 ART-naïve R5-tropic HIV-1-infected subjects.¹⁵⁰ At week 48, 92% had VL below 50 copies/mL; their median CD4 count increased by 216 cells/mm³ at week 96.¹⁵⁰ A retrospective cohort study of 60 treatment-experienced R5-tropic HIV-1-infected patients²⁸ corroborated these findings; in this second study patients received MVC (150 mg) + DRV/RTV (800/100 mg) once daily. At week 48, 78% of patients had VL below 50 copies/mL and median CD4 count increased by 70 cells/μL.²⁸ This suggests that MVC + DRV/RTV may be a viable NRTI-sparing regimen,²⁸ however, additional studies with larger sample sizes and appropriate controls are needed to confirm this hypothesis.

Combination of MVC (600 mg), RAL (400 mg), and ETR (200 mg) twice daily is effective in treatment-experienced R5-tropic HIV-1-infected patients.¹⁵¹ At week 48, all 28 patients had VL below 400 copies/mL; 93% had VL below 50 copies/mL and the median CD4 count increased by 267 cells/μL.¹⁵¹ The long-term efficacy of this regimen was confirmed at week 204, where 96% of patients had VL below 50 copies/mL and median CD4 count increased by 267 cells/mm³.¹⁵² In both studies, the treatment regimen was well tolerated.^{151,152} A 24-week study of 26 treatment-experienced patients given RAL (400 mg) + MVC (300 mg) twice daily showed higher than expected levels of viral rebound.¹⁵³ In the ROCnRAL study, RAL + MVC treatment of HIV-1-infected patients with lipodystrophy did not suppress viremia, despite improvements in lipid profile and bone density.¹⁵⁴ Another study assessed the efficacy of LPV/RTV + MVC (150 mg, once daily) or TDF/FTC, in HIV-1-infected patients with VL > 1,000 copies/mL.¹⁵⁵ At week 48, VL was below 50 copies/mL in all patients receiving MVC + LPV/RTV, and in 96% of patients receiving TDF/FTC + LPV/RTV.¹⁵⁵ Furthermore, patients receiving MVC + LPV/RTV showed a larger median increase in CD4 counts (MVC group: 286 cells/μL versus TDF/FTC group: 199 cells/μL).¹⁵⁵ MVC (150 mg) + ATV/RTV (300/100 mg) once daily had beneficial antiviral activity comparable to TDF/FTC (300/200 mg) + ATV/RTV; at week 48 74.6% (44/60) of patients had VL below 50 copies/mL, median CD4 count increased by 173 cells/mm³ in the MVC-treated group and 187 cells/mm³ in the TDF/FTC-treated group.¹⁵⁶

NRTIs are associated with endothelial dysfunction and increased inflammation.¹⁵⁷ Previously treated R5-HIV-1-infected patients with undetectable VL receiving a NRTI-sparing dual regimen (MVC (150 mg once daily) + RTV-boosted PI) showed improved endothelial function.¹⁵⁷ Treatment of human PBMC and polymorphonuclear neutrophils with MVC and DRV decreased cell apoptosis and migration.¹⁵⁸ The OPTIPRIM study¹⁵⁹ compared the standard three-drug regimen versus a five-drug regimen in reducing viral DNA load in HIV-1-infected patients. Patients in the five drugs group were given RAL (400 mg) + MVC (150 mg) twice daily with a fixed-dose combination of TDF (300 g) + FTC (200 g) + DRV (800 g) + RTV (100 g) once daily; patients in the three drugs group were given TDF (300 g) + FTC (200 g) + DRV (800 g) + RTV (100 g) once daily.¹⁵⁹ After 24 weeks treatment, there was no significant difference in HIV-1 DNA loads of patients in the three or five drugs regimen (2.25 log₁₀ per 10⁶ PBMC versus 2.35 log₁₀ per 10⁶ PBMC), suggesting that there was no virological benefit to the intensive five-drug regimen.¹⁵⁹

MVC and dual-tropic HIV-1 infection

MVC efficacy in dual/mixed-R5X4-tropic HIV-1 infection was examined in a randomized, placebo-controlled, double-blind, Phase II study of treatment-experienced patients (A4001029 study).¹⁶⁰ Patients received MVC (150 or 300 mg) or placebo plus optimized background therapy once or twice daily.¹⁶⁰ By week 24, 61% (38/62), 60% (38/63), and 52% (32/61) in the placebo, MVC once daily, and MVC twice daily groups, respectively, had discontinued treatment because of inefficacy.¹⁶⁰ The mean decrease in VL was $0.97 \log_{10}$, $0.91 \log_{10}$, and $1.2 \log_{10}$ copies/mL in patients receiving placebo, once daily MVC, and twice daily MVC, respectively;¹⁶⁰ the mean CD4 count increased by 36, 60, and 62 cells/ μ L in patients receiving placebo, once daily MVC, and twice daily MVC, respectively.¹⁶⁰ At treatment failure more patients receiving MVC had X4-tropic HIV-1 compared to patients receiving placebo.¹⁶⁰ These results showed that MVC treatment of humans infected with dual/mixed-R5X4-tropic HIV-1 have little-to-no virological benefit. Deep sequencing showed that patients receiving MVC twice daily had greater virological response when X4-using virus constituted less than 10% of the total viral population compared to patients with higher percentages of X4-using virus.¹⁶¹

In vitro studies showed that dual-R5X4-tropic HIV-1 strains that preferably use R5 are genetically and phenotypically similar to R5-tropic strains and can be inhibited by MVC.^{162,163} Human studies correlating HIV-1 tropism to virological response to short-term MVC exposure (8 days treatment, 300 mg/kg twice daily) showed that patients in the control group and patients with dual/mixed-tropic HIV-1 had no significant change in VL, but in patients with R5-tropic HIV-1, VL decreased by $1.41 \log_{10}$ copies/mL.¹⁶⁴ There was 93.5% concordance between virological response to MVC and viral tropism, with positive virological response in 95% (19/20) of patients with R5-tropic HIV-1 and negative virological response in 90.9% (10/11) of patients with dual/mixed virus.¹⁶⁴ These results suggested that short-term MVC exposure could help determine/confirm the genotypic or phenotypic HIV-1 tropism, particularly in patients with non-reportable results by a Trofile assay.¹⁶⁴ However, subsequent studies found no concordance between standard V3-based genotypic tropism assays and virological response to MVC monotherapy,¹⁶⁵ and determined that short-term MVC treatment of HIV-1-infected, treatment-naïve patients could not predict viral tropism.¹⁶⁶ In this later study, following 10 days MVC treatment (300 mg/kg twice daily) of 30 patients infected with R5-tropic and 10 patients infected with dual/mixed-tropic HIV-1, VL decreased by $1.52 \log_{10}$ and $1.62 \log_{10}$

copies/mL in patients with R5-tropic and dual/mixed-tropic virus, respectively;¹⁶⁶ thus, short-term MVC exposure cannot predict viral tropism in treatment-naïve patients. The discrepancies between findings in these different studies could be due to differences in the study population.^{166,164} It is also possible that short-term MVC treatment could help predict viral tropism in treatment-experienced patients, but not in treatment-naïve patients.

MVC and HIV-1/hepatitis-C co-infection

After 6-months MVC treatment of HIV-1/hepatitis-C virus (HCV) co-infected patients, there was no significant increase in serum mediators of fibrogenesis and fibrosis, such as transforming growth factor beta-1, tissue inhibitors of metalloproteinases-1, and matrix metalloproteinase-2.¹⁶⁷ The GUSTA study examined the effect of MVC/DRV/RTV dual therapy on hepatic injury in HIV-1/HCV co-infected patients;¹⁶⁸ patients on dual therapy did not show any increases in the incidence of adverse events or severe liver abnormalities.¹⁶⁸ MVC also reduced the progression of hepatic fibrosis in HIV-1/HCV co-infected patients.¹⁶⁹

MVC and immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS) occurs when a suppressed immune system begins to recover, and produces a massive inflammatory response to previously acquired pathogens. ART initiation in a treatment-naïve HIV-1 and polyomavirus-JC (JCV) co-infected patient with high VL and low CD4 count resulted in IRIS and decreased cognitive impairment, and this was markedly improved after ENF/MVC treatment.¹⁷⁰ MVC treatment of HIV-1/JCV co-infected patients with IRIS, cognitive impairments, and progressive multifocal leukoencephalopathy (PML) resulted in decreased levels of CCR5⁺ immune cells in the CSF and improved patients' conditions;¹⁷¹ this was reversed by treatment interruption, and restarting MVC treatment again improved the patients' conditions.¹⁷¹ However, another HIV-1/JCV + patient with virological failure, low CD4 count and PML-associated IRIS, treated with MVC displayed rapid clinical deterioration and died 21 days after MVC initiation.¹⁷² This difference in MVC treatment outcomes could be due to advanced AIDS and PML in this latter patient.

Synergistic antiviral effects of MVC and antibodies or peptides

Antibodies directed against the second CCR5 ECL such as HGS004 and HGS101 had greater antiviral activity against

MVC-bound than MVC-free CCR5, and inhibited infection by MVC-resistant HIV-1 more potently with MVC-bound than with free CCR5.^{173,174} HGS004 and MVC have potent antiviral synergy against R5-tropic HIV-1,¹⁷³ and the IgG-CD4-gp120(Bal) fusion protein synergizes with MVC.¹⁷⁵ The CCL5-derived R4.0 peptide, CCL5, and MVC exhibited concomitant interactions with CCR5 and promoted synergic inhibition of HIV-1 in acute-infection assays.¹⁷⁶ Another CCR5 antibody, PRO-140, also showed a synergistic antiviral effect with MVC.¹⁷⁷

MVC and HIV-2 infection

Of the 34 million HIV-infected individuals worldwide, one-to-two million (mostly in West Africa) are infected with HIV-2.¹⁷⁸ Although HIV-2 can progress to AIDS, VL are often lower and disease progression is slower compared to HIV-1 infection.¹⁷⁹ Treatment is complex due to limited clinical trials with HIV-2-infected patients; in fact, studies on current ART drugs were done using mostly HIV-1 isolates and HIV-1-infected patients. HIV-2 is resistant to NNRTIs and has reduced sensitivity to PIs.¹⁸⁰ Like HIV-1, the major HIV-2 coreceptors are CCR5 and CXCR4.^{181,182} In vitro studies showed that similar concentrations of MVC and other CCR5 antagonists that inhibit HIV-1 could also inhibit infection by primary CCR5-tropic HIV-2, with comparable MPI.^{183,184}

Treatment of an HIV-2-infected AIDS patient with cognitive impairment and resistant to NRTIs, NNRTIs, and PIs, with a salvage therapy consisting of TDF + FTC + TPV/RTV + RAL + MVC, decreased blood VL to undetectable levels, but CSF VL remained high, neurological impairments continued, and blood VL later increased.¹⁸⁵ Genotyping analyses suggested that treatment failure was not due to viral escape, but to poor CNS penetration of ART drugs.¹⁸⁵ However, salvage therapy containing MVC successfully repressed blood VL in other HIV-2-infected patients resistant to other ART drugs.^{186,187} The presence of neurocognitive impairment and high CSF VL before initiation of MVC salvage therapy may have contributed to treatment failure in the first study,¹⁸⁵ likely because of a large CNS/CSF viral reservoir, but it is not known whether this factor alone could explain the failure of MVC salvage therapy in that patient. The latter two studies^{186,187} did not indicate the patients' CSF VL or their neurocognitive status. Furthermore, none of these studies tested the tropism of HIV-2 strains circulating in the patients, therefore, it is possible that the patient who failed MVC salvage therapy¹⁸⁵ had mixed-/dual-R5X4-tropic HIV-2 strains, or HIV-2 strains using coreceptors other than CCR5. In fact, in addition to CCR5 and CXCR4, HIV-2

can use CCR3, G-protein-coupled receptor-15, or CXCR6 to enter and infect target cells.^{181,182} Overall, in vitro and in vivo evidence suggests that MVC can be effective against R5-tropic HIV-2.

Summary of MVC use in HIV-1 therapy

MVC is a small-molecule CCR5 antagonist used for the treatment of R5-tropic HIV-1 infection in both treatment-naïve and treatment-experienced patients.¹⁵ MVC has favorable safety, pharmacokinetic and pharmacodynamic profiles. MVC is a substrate for CYP3A4, CYP3A5, Pgp, and organic anion transporter polypeptide-1B1, but is primarily metabolized by CYP3A4.^{35,48,56} As a substrate for CYP3A4, MVC's pharmacokinetics is affected by the concurrent use of CYP3A4 inhibitors and inducers.⁴⁹ Typical dosage is 300 mg/kg twice daily.¹⁵ However, when combined with a CYP3A4 inducer the dosage is increased to 600 mg/kg twice daily; and when combined with a CYP3A4 inhibitor the dosage is decreased to 150 mg/kg twice daily.¹⁵ MVC has been used successfully for routine treatment of HIV-1-infected patients, with both decreases in VL and increases in CD4⁺ cell levels observed in treated individuals.^{127,128} MVC has shown promise in pre- and post-exposure prophylaxis, although current data are conflicting. Microbicide gels containing MVC reduced vaginal and rectal SHIV transmission in macaques,^{144,146} but women using vaginal rings containing MVC had low drug concentrations in their CF, and their CT was not resistant to ex vivo HIV-1 infection.¹⁴⁸ NRTIs are often associated with harsh side effects and because MVC has a favorable safety profile, MVC has been used in NRTI- and PI-sparing dual regimens.^{28,150,156} MVC could reduce hepatic fibrosis in HIV-1/HCV co-infected patients, reduce the severity of IRIS, and suppress VL in HIV-2-infected humans.^{169–171,186,187} In addition to its virological benefits, MVC has been shown to increase the levels of immune cells, including CD4⁺ and CD8⁺ cells, suggesting an additional immunological benefit.^{70,76} Resistance to MVC is often associated with the outgrowth of previously undetectable X4-tropic viral strains.¹⁰⁹ Overall, current studies showed that MVC is safe and efficacious against infection with R5-tropic virus in vivo, ex vivo, and in vitro.

Use of MVC in other diseases

CCR5 has been implicated in other diseases besides HIV-1/AIDS, including cancer, inflammatory and graft-versus-host diseases (GVHDs).^{188–206} Therefore, it was proposed that blocking CCR5 can attenuate the severity or progression of these diseases.

Cancer

CCL5 and CCR5 expression are increased in breast cancer cells, correlate with poor prognosis,¹⁸⁸ and breast cancer patients with CCR5-delta32 have longer metastasis-free survival.²⁰⁷ MVC blocked CCR5 on breast cancer cells and this was associated with decreased CCL5-induced calcium signaling and cell invasion.¹⁸⁸ In vivo studies also showed that MVC significantly reduces the number and size of breast cancer metastasis in mice,¹⁸⁸ increases survival, reduces weight loss, attenuates liver damage, and reduces the number and size of hepatic tumors in a mouse model of hepatocellular carcinoma.¹⁸⁹ CCR5 expression negatively correlates with gastric cancer progression, and MVC reduced the number of peritoneal and mesenteric nodules, and decreased tumor burden in mice.¹⁹⁰ CCR5 is also involved in prostate cancer metastasis; the proto-oncogene tyrosine-protein kinase induces CCR5 signaling in prostate epithelial cells and there is increased CCR5 expression in humans with prostate cancer, with higher CCR5 expression in metastases, compared to primary tumors.¹⁹¹ MVC treatment of mice injected with a prostate cancer cell line reduced the bone and brain metastasis burden by 80% and 60%, respectively.¹⁹¹ Perineural invasion in salivary adenoid cystic carcinoma (SACC) is also associated with increased CCR5 and CCL5 expression,¹⁹² and MVC blocked CCL5-induced increase in migration and perineural invasion of salivary adenoid cystic carcinoma.¹⁹²

Graft-versus-host disease

GVHD often occurs following an allogeneic transplant, and its incidence is 30%–70% among transplant patients.¹⁹³ During GVHD activated donor leukocytes recognize the recipient's antigens as foreign, resulting in tissue damage. CCR5 is involved in GVHD pathology as it binds CCL5 and recruits leukocytes to tissue sites;^{193,194} humans without genetically functional CCR5 have longer survival rates after renal transplantation.¹⁹³ MVC blocks T-lymphocyte chemotaxis in vitro, and adding MVC to the standard therapy of patients undergoing hematopoietic stem-cell transplantation resulted in lower GVHD incidence.¹⁹⁴ The use of MVC for GVHD prevention is currently in Phase II trials.¹⁹³

Heart and lung diseases

Pulmonary arterial hypertension (PH) is partly caused by chronic lung inflammation, and chemokines, including CCL5, play a major role in pulmonary vascular remodeling, a PH hallmark pathological feature.^{195,196} CCR5 expression in the lungs of humans with PH is increased compared to healthy donors.¹⁹⁷ MVC treatment decreased PH development, or

reversed PH in CCR5-knockout mice that had murine CCR5 replaced by human CCR5, and in animals subjected to PH-inducing conditions.¹⁹⁷ Cardiac dysfunction is prevalent among HIV-1-infected patients,¹⁹⁸ resulting from damage to cardiomyocytes by proinflammatory mediators and viral proteins.¹⁹⁹ In MVC-treated Simian Immunodeficiency Virus (SIV)-infected macaques, diastolic function was similar to uninfected animals, whereas untreated and infected animals displayed diastolic dysfunction.¹⁹⁹ Diastolic dysfunction was associated with myocardial macrophages activation and MVC decreased the expression of the macrophage marker CD163 compared to untreated animals, but CD68 expression remained unchanged.¹⁹⁹ CCR5 antagonists also reduced the atherosclerotic burden and secretion of proinflammatory Th1-cytokines in dyslipidemia mouse models.^{208,209} RTV induces inflammation in adipose tissues, and this is associated with increased expression of proinflammatory cytokines and accelerated formation of atherosclerotic aortic plaques.²¹⁰ C57BL6/J ApoE^{-/-} mice treated with RTV + MVC were protected against aortic plaque progression; and showed less macrophage infiltration into the aortic wall, decreased levels of intercellular adhesion molecule-1, vascular cell-adhesion protein-1, CCL2, interleukin-17A, CCL5, and tumor necrosis factor-alpha, compared to mice treated with RTV alone.²¹¹ These data suggest that MVC has protective and anti-inflammatory properties on the vasculature.

Hemorrhage

Trauma-induced hemorrhage often results in increased inflammation and liver damage.²⁰² This likely involves CCR5, as MVC treatment attenuates liver injury in rats subjected to trauma-induced hemorrhage by increasing peroxisome proliferator-activated receptor-gamma activity and decreasing proinflammatory factors.²⁰² Peroxisome proliferator-activated receptor-gamma activation also improved liver function during trauma-induced hemorrhage,²⁰¹ and CCR5-deficient mice have lower inflammatory pain under chemical or inflammatory stimuli.²¹²

Rheumatoid arthritis

CCR5 ligands and other chemokines are increased in synovial fluids during rheumatoid arthritis (RA), resulting in tissue and joint damage.^{204,205} Therefore, blocking CCR5 could reduce inflammation at synovial joints and reduce RA symptoms. In support of this hypothesis, previous work demonstrated that CCR5-delta32 mutation had protective effects in patients with RA.²⁰⁶ However, in a Phase IIa study, MVC showed no efficacy in the treatment of RA.²⁰³

Liver disease

CCL5 has been implicated in the pathogenesis of different hepatic disorders: HCV-infected patients with advanced stage liver injury have high levels of CCL5 mRNA,²¹³ and hepatic CCL5 expression is increased in a mouse model of hepatic steatosis.²¹⁴ Furthermore, CCL5 promotes hepatic inflammation and fibrosis in experimental fibrogenesis models.²¹⁵ Mice on high fat diet treated with MVC showed less weight gain or liver damage compared to untreated mice on a similar diet.²¹⁵ Furthermore, MVC-treated mice had lower hepatic triglycerides, lower degrees of steatosis, and decreased CCL5 expression compared to untreated mice on high fat diet.²¹⁶

Summary

MVC, a CCR5 antagonist, is effective against infection with R5-tropic HIV-1 in vivo and in vitro;^{15,20,25} it is well tolerated and safe for most individuals. MVC has a good pharmacokinetic profile, with relatively low protein binding and high bioavailability.³² It also has a wide distribution throughout the body, with high concentrations found in the vaginal and rectal tissues.^{15,37–41,43–47,143,145} MVC appears to be safe in patients with mild-to-moderate hepatic and renal disorders.^{39,63} Limited studies have examined MVC effects on HIV-1 MTCT; however, MVC placental MVC is low.^{83,85} MVC is metabolized by CYP3A4, and dosing must be adjusted when given with CYP3A4 inducers or inhibitors.¹⁵ True resistance to MVC is rare, as most cases of virological failure seen are associated with outgrowth of previously undetectable X4-tropic HIV-1 strains.^{25,109} Current evidence suggests that MVC is not effective against dual-/mixed-R5X4-tropic HIV-1 infections. Although there have been mutations associated with resistance to MVC, mutation patterns observed vary with HIV-1 strains and no specific mutation patterns identified can predict resistance to MVC. In addition to its role against HIV-1 infection, clinical trial data and animal studies suggest that MVC may help in the treatment of other diseases, including cancer, GVHD, and inflammatory diseases.^{188–206} Additional studies are needed to further our knowledge about the safety of long-term MVC use, its effectiveness against HIV-1 MTCT, its antiviral efficacy in HIV-1 reservoirs such as the CNS and lymphoid tissues, and its potential role in post-exposure prophylaxis.

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Disclosure

The authors report no conflicts of interest in this work.

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