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CCR5 Antagonism in HIV Infection: Current Concepts and Future Opportunities

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Abstract

CCR5 antagonists inhibit HIV-1 entry by blocking the interaction of HIV-1 with the CCR5 cellular receptor. In patients with established HIV-1 infection, some viral strains use an alternative coreceptor for HIV-1 entry, CXCR4; CCR5 antagonists are not effective in patients harboring these viral strains. Coreceptor tropism testing of viral strains in an individual patient is necessary prior to treating with a CCR5 antagonist. There is one CCR5 antagonist, maraviroc, that is FDA-approved for treatment of HIV-1 infection. This drug is used most commonly for the treatment of HIV-1 infection in patients who have failed other antiretroviral regimens. In addition to virologic effects, CCR5 antagonists are under investigation for immune-modulating effects and for HIV-1 prevention. Ongoing research will further elucidate the role of CCR5 antagonists in combating HIV disease.

Keywords

coreceptor tropism; CXCR4; CD4; maraviroc; vicriviroc

INTRODUCTION

In the early 1990s, prior to effective antiretroviral therapy, it was noted that the presence of HIV-1 capable of inducing syncytium formation in MT-2 cells was associated with an increased risk of clinical progression to AIDS and death (1). As the understanding of HIV-1 entry evolved, it became clear that the switch from a non-syncytium-inducing (NSI) viral phenotype to a syncytium-inducing (SI) phenotype reflected a change in chemokine coreceptor use by the virus. In 1996, several groups discovered that binding of a chemokine coreceptor, either CCR5 or CXCR4, was necessary for HIV-1 entry into the target cell and subsequent infection (2–5). The NSI viral phenotype from earlier observations correlated with the use of CCR5 as the requisite chemokine receptor for HIV-1 entry, and the SI phenotype correlated with the use or partial use of the CXCR4 chemokine receptor (5).

Within 10 years following the discovery of the HIV-1 coreceptor, several CCR5 antagonists were developed and tested as antiretroviral agents in clinical trials. Maraviroc (MVC) was

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approved by the U.S. Food and Drug Administration (FDA) in 2007 for the treatment of HIV infection in individuals “with only CCR5-tropic HIV-1” on the basis of phase III studies demonstrating safety and efficacy (6). Among the 26 approved antiretroviral drugs, MVC is the only HIV-1 drug that targets the host through antagonism of the CCR5 cellular receptor rather than the virus itself. With a new mechanism of action, CCR5 antagonists have activity against HIV-1 that is resistant to other antiretroviral drugs. In addition to HIV-1 therapy, CCR5 antagonists are under investigation for immunomodulatory effects and for HIV-1 prevention.

HIV-1 ENTRY AND CORECEPTOR TROPISM

HIV-1 entry into CD4⁺ T cells is a multiple-step process (7). First, the external envelope glycoprotein (gp120) of HIV-1 binds to the CD4 receptor on the surface of the CD4⁺ T cell. Subsequently, a conformational change in gp120 allows interaction with a chemokine coreceptor (either CCR5 or CXCR4). Binding of the chemokine coreceptor leads to conformational changes in HIV-1 gp41, followed by fusion of the viral membrane and the host cellular membrane and the release of the viral particle contents into the cytoplasm.

A viral strain that uses CCR5 exclusively as the requisite coreceptor for entry is called an R5 virus. Individuals who are homozygous for a gene encoding a nonfunctional CCR5 protein are relatively resistant to HIV-1 infection (8), highlighting the importance of CCR5 for HIV-1 transmission. Some viral strains use the CXCR4 cellular receptor; others can be dual-tropic (use both receptors), and mixed infections can occur in a given patient. Most sexually transmitted HIV-1 strains are R5. In one study of 45 people experiencing acute HIV-1 infection, 55 transmitted viral strains were identified through phylogenetic analysis of viral envelope genes, obtained by single genome amplification of plasma samples. Using phenotypic coreceptor tropism testing, 54 transmitted strains were R5 and 1 was dual-tropic (9).

Viral strains that use the CXCR4 receptor may emerge within weeks after HIV-1 infection. Non-R5 virus was found in 13% of patients experiencing HIV-1 seroconversion (10). The prevalence of non-R5 virus is higher in populations with longer durations of HIV-1 infection (11). For example, 18% of patients with nearly normal CD4⁺ T cell counts who had never received antiretroviral therapy had non-R5 virus as compared to 59% of patients with advanced HIV-1 infection and prior treatment with multiple antiretroviral regimens (Table 1).

CORECEPTOR TROPISM TESTING

Coreceptor tropism testing to document R5 virus only (i.e., no detection of non-R5 virus) is necessary prior to using a CCR5 antagonist as part of a combination antiretroviral therapy regimen (6). The observed efficacy of CCR5 antagonists is partially related to the accuracy of the coreceptor tropism assay used. Viral phenotypic testing was first used to determine eligibility for most of the clinical trials of CCR5 antagonists. When this assay was revised to increase sensitivity for lower levels of X4 or dual-tropic strains, more participants with non-R5 virus at study entry were identified, and observed efficacy results from these studies improved (12, 13). Genotypic assays generally have lower sensitivity for non-R5 virus than phenotypic assays (14). Use of ultradeep genotypic sequencing to assess coreceptor tropism is a promising alternative to phenotypic testing (15).

CLINICAL TRIALS

Table 2 summarizes key clinical trials of CCR5 antagonists.

Maraviroc (MVC)

MVC is the only CCR5 antagonist FDA-approved for the treatment of HIV-1 infection, based on demonstrated safety and efficacy in pivotal studies of HIV-infected patients. Following demonstration of in vitro HIV-1 activity and short-term safety and tolerability in HIV-uninfected individuals, this small-molecule CCR5 antagonist was studied in two parallel randomized placebo-controlled phase IIa studies (16). A total of 63 HIV-infected asymptomatic patients demonstrated to have R5 virus only were enrolled and were randomized to receive MVC monotherapy over 10 days in 10 different dosing groups.

In a combined analysis, all MVC groups demonstrated a greater decrease in HIV-1 RNA level than the placebo groups. At MVC doses of 100 mg twice daily and above, subjects experienced a viral load reduction of >1 log copies/ml. MVC was generally well tolerated with few treatment-emergent adverse events. The investigators concluded they had demonstrated proof of concept that targeting the CCR5 receptor with MVC was associated with an antiviral effect and called for further clinical evaluation.

Two parallel phase III placebo-controlled studies of MVC versus optimized therapy in viremic antiretroviral treatment-experienced patients (the MOTIVATE studies) were next designed to assess the efficacy and safety of MVC given once or twice daily when added to optimized background therapy in patients with R5 virus only who had experienced failure on three classes of antiretroviral drugs or demonstrated drug-resistant virus (17, 18). The MOTIVATE 1 and 2 studies enrolled a total of 1,049 patients who were randomized to receive MVC once or twice daily or matching placebo, together with an antiretroviral regimen selected and optimized on the basis of treatment history and genotypic and phenotypic drug resistance testing. The dose of MVC depended on the other antiretroviral drugs used in the regimen. Notably, agents that were investigational at the time, including darunavir, etravirine, and raltegravir, were not permitted in the background antiretroviral regimen.

At 48 weeks in the two studies, the mean change in HIV-1 RNA was greater with MVC once daily (-1.6 – -1.7 log copies/ml) and twice daily (-1.8 – -1.9 log copies/ml) compared to placebo (-0.80 log copies/ml). The proportion of subjects with HIV-1 RNA suppressed to <50 copies/ml was 42%–47% in the MVC arms compared to 16%–18% in the placebo arms. The change in CD4⁺ T cell counts from baseline was $+113$ – 128 cells/ μ l in the MVC arms compared to $+54$ – 69 cells/ μ l in the placebo arms. There was no statistically significant difference in adverse events between the study groups. The investigators concluded that MVC resulted in significantly greater virologic suppression and CD4⁺ T cell increases than placebo and was generally well tolerated. These pivotal studies supported FDA approval of the drug in 2007. Two-year results from the MOTIVATE studies demonstrated durable treatment responses and no new safety issues (19).

Another important study of MVC enrolled treatment-experienced patients with dual- or mixed-tropic (non-R5) HIV-1 (20). A total of 167 patients with non-R5 virus were randomized to receive optimized background antiretroviral therapy plus either MVC once or twice daily or placebo. At 24 weeks, mean HIV-1 RNA changes (log copies/ml) were -0.9 (MVC once daily), -1.2 (MVC twice daily), and -1 (placebo) with no statistically significant difference between MVC and placebo. Mean CD4⁺ T cell count changes were $+60$ cells/ μ l (MVC once daily), $+62$ cells/ μ l (MVC twice daily), and $+36$ cells/ μ l (placebo). The investigators concluded that although MVC did not confer significant virologic benefit in this study population with non-R5 virus, the drug was not associated with a CD4⁺ T cell count decline. Overall, this study failed to support the use of MVC in HIV-infected patients with dual- or mixed-virus (non-R5) infection.

MVC also was evaluated as first-line treatment in the MERIT (maraviroc versus efavirenz in treatment-naïve patients) study (12). A total of 917 patients with R5 virus only (demonstrated by the original phenotypic tropism assay) were randomized to receive zidovudine/lamivudine in combination with either MVC 300 mg once or twice daily or efavirenz at standard dose. An interim analysis conducted after 205 patients had been receiving their study drug for at least 16 weeks demonstrated 78% (MVC once daily) versus 88% (efavirenz) patients had HIV-1 RNA suppressed to <400 copies/ml with an adjusted difference of -10.5%. Because this difference fell below the prespecified noninferiority threshold of 10%, the Data and Safety Monitoring Board recommended the once-daily MVC arm be discontinued.

A total of 721 remaining subjects were included in the 48-week analysis demonstrating that 71% in the MVC 300 mg twice-daily group had HIV-1 RNA <400 and 65% had <50 copies/ml, whereas in the efavirenz group, 73% had HIV-1 RNA <400 and 69% had <50 copies/ml. With a noninferiority threshold of -10%, the investigators concluded that MVC was noninferior to efavirenz with respect to the <400 copies/ml endpoint, but not the <50 copies/ml endpoint. In addition, more MVC subjects discontinued because of lack of efficacy (12% versus 4%), but fewer discontinued for adverse events (4% versus 14%), and fewer who experienced virologic failure developed resistance to lamivudine (17% versus 38%) compared to efavirenz. Interestingly, mean CD4⁺ T cell counts increased from baseline statistically significantly more with MVC than efavirenz.

Using a newer enhanced phenotypic tropism assay, baseline samples from the MERIT study were rerun. An additional 107 patients (15%) were found to have non-R5 virus at baseline and would have been excluded from the study. In a post hoc analysis of the subjects with R5 virus only demonstrated using the enhanced tropism assay, the response in the once-daily MVC arm no longer exceeded the prespecified threshold with 82% (MVC once-daily) versus 86% (efavirenz) of subjects with HIV-1 RNA <400 copies/ml. Reanalyzing the primary study endpoint, 68% in both the MVC twice-daily and efavirenz groups had HIV-1 RNA suppressed to <50 copies/ml, fulfilling the criterion for noninferiority. Week 96 observations showed durability of both virologic and CD4⁺ T cell responses in both the MVC and efavirenz groups (21).

A single case of possible MVC-induced hepatotoxicity with allergic features prompted inclusion of a black-box warning in the prescribing information (6). However, a cross-protocol analysis of 96-week data from the MVC clinical development program in both treatment-naïve and -experienced subjects revealed no significant imbalance in hepatic toxicity between MVC and control groups (22). Concerns about CCR5 antagonists and malignancy also were addressed in a cross-protocol analysis of phase II and III studies of MVC that demonstrated malignancy rates in the MVC arms actually were numerically lower than in the comparator arms (23).

INVESTIGATIONAL CCR5 ANTAGONISTS

Aplaviroc (APL)

Following demonstration of in vitro HIV-1 activity, the small-molecule CCR5 antagonist APL was first tested in a clinical study of 40 HIV-infected subjects with R5 virus only, CD4⁺ T cell nadir >200 cells/μl and HIV-1 RNA >5,000 copies/ml (24). Subjects were randomized to receive APL monotherapy in one of four dosing groups. Mean HIV-1 RNA changes (log copies/ml) at nadir were: -0.5 (200 mg daily), -1.2 (200 mg twice daily), -1.0 (400 mg once daily), -1.7 (600 mg twice daily), and -0.1 (placebo). APL was generally well tolerated with no drug-related discontinuations.

Two follow-up phase II studies randomized treatment-naïve patients with R5 virus only to receive zidovudine/lamivudine together with either APL versus efavirenz (25) or APL versus lopinavir/ritonavir (26). Both studies were terminated prematurely after a mean 14 weeks because of severe hepatotoxicity in two subjects receiving APL. They developed grade 3–4 increases in both alanine aminotransferase and bilirubin, and one of them went on to develop hepatic necrosis (27). These cases, coupled with a case of serious hepatotoxicity seen in a phase III study of APL in treatment-experienced patients, led to discontinuation of clinical development of APL. Although the etiology of the hepatotoxicity was uncertain, experts felt it was more consistent with an idiosyncratic drug reaction rather than a class effect for CCR5 antagonists.

Vicriviroc (VCV)

VCV is a small-molecule CCR5 antagonist that completed testing in phase I–III clinical studies of HIV-infected individuals but subsequently was withdrawn from further clinical development. Following in vitro studies demonstrating virologic activity and pharmacokinetic studies in HIV-uninfected individuals, the first study of VCV in HIV-infected individuals enrolled 48 patients with R5 virus only who were randomized to sequential groups of VCV at doses of 10, 25, and 50 mg twice daily or matching placebo for 14 days (28). HIV-1 RNA reductions (log copies/ml) at 14 days were significantly greater in the VCV groups: the reported changes were -0.9 (10 mg), -1.5 (25 mg), and -1.6 (50 mg) compared to $+0.1$ in the placebo group. VCV demonstrated a half-life of 28–33 h, supporting once-daily dosing, and was generally well tolerated.

ACTG A5,211 was a phase II study of VCV in 118 treatment-experienced individuals with R5 virus only (29). Patients were randomized to receive VCV at 5, 10, or 15 mg once daily (or matching placebo) added to a ritonavir-containing regimen for 14 days, and then the background antiretroviral regimen was optimized on the basis of treatment history and drug resistance testing. Ritonavir was required by the trials to enhance the pharmacokinetic profile of VCV. At 14 days, HIV-1 RNA (log copies/ml) changed in the VCV groups: -0.9 (5 mg), -1.1 (10 mg), and -1.9 (15 mg). There was no change in the placebo group. The Study Monitoring Committee recommended discontinuation of the 5-mg dose early because of suboptimal potency. At 24 weeks, the primary endpoint of the study, the change in HIV-1 RNA (log copies/ml) was -1.5 (VCV 10 mg) and -1.7 (VCV 15 mg) compared to placebo (-0.3). VCV was generally well tolerated, although notably 6 malignancies were reported in the VCV groups versus 2 in the placebo group. Three-year follow-up demonstrated durable virologic suppression in 49% of the 52 subjects who had HIV-1 RNA <50 copies/ml by week 24, with a total of 12 patients on VCV experiencing malignancies versus 1 among placebo patients (30).

A follow-up phase II study of VCV (VICTOR-E1) in 114 treatment-experienced individuals randomized patients to receive higher doses of VCV: 20 mg or 30 mg once daily (versus matching placebo) added to an optimized, ritonavir-containing antiretroviral regimen (31). At week 48, HIV-1 RNA levels were <50 copies/ml in 53% of the 20-mg VCV group, 56% of the 30-mg VCV group, and 14% of the placebo group. Adverse events were comparable across the groups, and no malignancies occurred in the VCV groups.

A third phase II study enrolled 92 treatment-naïve patients with R5 virus only who were randomized initially to receive VCV 25, 50, or 75 mg once daily or placebo for 14 days (32). Ritonavir was not used in this study; thus, higher doses were required. At 14 days, mean HIV-1 RNA (log copies/ml) decreased significantly more in the VCV groups: changes were -0.9 (25 mg), -1.2 (50 mg), and -1.3 (75 mg) compared to -0.1 (placebo). At that point, subjects receiving VCV added zidovudine/lamivudine, and subjects initially receiving placebo started a three-drug regimen of zidovudine/lamivudine and efavirenz. Interim

reviews by the Data and Safety Monitoring Board demonstrated higher rates of virologic failure with VCV 25 mg and 50 mg (but not 75 mg) compared to the efavirenz group, and the study was terminated.

Two parallel phase III studies of VCV in treatment-experienced patients with R5 virus only enrolled a total of 721 patients (15). Subjects designed an optimized ritonavir-containing antiretroviral regimen that could include the newly approved antiretroviral drugs darunavir and/or raltegravir, and then were randomized 2:1 to receive VCV 30 mg once daily or matching placebo. In all, 61% of subjects took an optimized background regimen that included at least three fully active drugs. At 48 weeks, the primary endpoint of the study, the proportion of subjects with HIV-1 RNA <50 copies/ml, was not significantly different in the two groups: 64% (VCV) versus 61% (placebo). Thus, VCV failed to demonstrate significant additional antiretroviral activity over that of the highly active optimized background regimen. In a post hoc analysis in the 261 patients with two or fewer active drugs in the background regimen, significantly more patients randomized to VCV (70%) suppressed HIV-1 RNA to <50 copies/ml than those on placebo (55%). In September 2010, the study sponsor announced termination of further development of VCV because of suboptimal virologic activity in phase II and III studies.

Other Investigational CCR5 Antagonists

Cenicriviroc (TBR-652) is a small-molecule CCR5 antagonist that also uniquely acts as a CCR2 antagonist in vitro, with consequent potential to decrease inflammation. The compound demonstrated short-term virologic activity in HIV-infected subjects with R5 virus only. Decreases in HIV-1 RNA of up to 1.8 copies/ml were reported, as well as reductions in mean levels of monocyte chemotactic protein-1 (MCP-1), a marker of inflammation, in two of five dosing groups (33). PF-232,798 is a small-molecule CCR5 antagonist that demonstrates in vitro activity against MVC-resistant HIV-1 strains and has reached clinical development (34).

In addition to the small-molecule CCR5 antagonists, CCR5 monoclonal antibodies have been tested in clinical studies. With a different mechanism of action, these compounds demonstrate virologic synergy when combined with CCR5 antagonists and also activity against HIV-1 strains resistant to the small-molecule CCR5 antagonists (35, 36). PRO 140 is a CCR5 monoclonal antibody that has been tested in HIV-infected patients with R5 virus only, administered intravenously or subcutaneously for single or multiple doses, given weekly or every other week. PRO 140 demonstrated HIV-1 RNA reductions up to 1.8 log copies/ml and was generally well tolerated (37, 38). A second CCR monoclonal antibody, HGS004, administered as a single dose intravenously at one of five doses to 63 HIV-infected subjects with R5 virus only, demonstrated HIV-1 RNA decreases of up to 1.0 copies/ml at the higher doses tested and was generally well tolerated (39). Other CCR5 antagonists are in preclinical development.

VIROLOGIC FAILURE OF CCR5 ANTAGONISTS

Virologic failure can be defined as incomplete suppression of HIV-1 RNA or rebound of HIV-1 viremia after successful suppression of HIV-1 RNA. Virologic failure on CCR5 antagonists can occur through two different mechanisms. More commonly, in patients with R5 virus only, non-R5 virus can emerge after virologic failure on a CCR5 antagonist. This does not appear to coincide with a rapid clinical progression of HIV disease (30, 40, 41). The less common mechanism of virologic failure is characterized by a decrease in the maximal percent inhibition for the CCR5 antagonist on phenotypic resistance assays (30, 41). This means that the replication of resistant virus in an in vitro system is only partially suppressed at maximal concentrations of the CCR5 antagonist. This implies that the resistant

virus can utilize CCR5 with a bound antagonist to enter the cell. Typically, resistance to other antiretroviral medications is characterized as a change in the 50% inhibitory concentration rather than the maximal percent inhibition.

RECOMMENDATIONS OF CURRENT GUIDELINES

U.S. Department of Health and Human Services (DHHS) Antiretroviral Treatment Guidelines for initial therapy designate MVC with zidovudine/lamivudine as an “acceptable regimen” and MVC with either tenofovir/emtricitabine or abacavir/lamivudine as regimens that “may be acceptable but more definitive data are needed” in patients with R5 virus only (42). Further, the guidelines state that treatment-experienced patients with R5 virus only can consider adding or substituting MVC in a regimen as an option among antiretroviral drugs that demonstrate activity against drug-resistant viral strains. The International Antiviral Society–USA guidelines designate a MVC-based regimen as an “alternative” initial regimen but note the limited clinical experience in treatment-naïve patients (43). These guidelines go on to suggest that “strategically, [MVC] may be more useful in treatment-experienced patients or when primary [transmitted] drug resistance is present....” MVC is not listed in either the current European AIDS Clinical Society treatment guidelines (44) or the World Health Organization treatment guidelines (45).

OTHER USES FOR CCR5 ANTAGONISTS

CD4⁺ T Cell Recovery

A meta-regression of phase II and III clinical trials of investigational antiretroviral agents found that clinical trial arms containing a CCR5 antagonist had a 30-cells/μl higher CD4⁺ T cell increase than arms not containing a CCR5 antagonist when controlling for differing rates of virologic suppression (46). Similarly, greater CD4⁺ T cell recovery was also observed in the phase III trial comparing combination regimens with MVC versus efavirenz, a non-nucleoside reverse transcriptase inhibitor, for initial antiretroviral therapy of HIV-infected patients (12). Although MVC did not meet prespecified criteria for noninferiority in the original analysis of virologic suppression to efavirenz in that study, subjects receiving MVC had a significantly greater CD4⁺ T cell rise 48 weeks after randomization than those receiving efavirenz, 170 versus 144 cells/μl (+26 cells/μl, 95% CI 7–46) (12). These observations prompted several small clinical trials that tested whether adding MVC to a suppressive antiretroviral regimen would lead to CD4⁺ T cell count increases in patients with suboptimal responses. Ultimately, two of these studies did not find a significant gain with MVC (47, 48); other studies are in progress.

Suppression of Immune Activation

Several investigators have explored the effect of MVC on persistent immune activation associated with chronic HIV-1 infection. The persistently elevated levels of immune activation and inflammation in HIV-infected persons treated with antiretroviral therapy may explain the greater prevalence of cardiovascular, hepatic, and renal diseases, neurocognitive dysfunction, and non-AIDS-related malignancies in this population (49–54). One single-arm trial found that adding MVC reduced markers of immune activation and reduced T cell apoptosis (50); these changes partially reversed after discontinuation of MVC. However, a small randomized clinical trial did not confirm this effect and suggested that MVC may actually increase immune activation (49). In the trial comparing MVC and efavirenz for initial antiretroviral therapy, MVC was associated with a faster decline in markers of immune activation (55). Further studies are needed to evaluate the effect of CCR5 antagonists on immune activation as well as the clinical relevance of this finding.

HIV-1 Prevention

CCR5 antagonists are appealing as candidates for prevention of HIV-1 infection from a mechanistic point of view because these compounds act prior to HIV-1 entering the target cell. In macaque models, an investigational CCR5 antagonist that is not being developed clinically, CMPD 167, administered either topically intravaginally (56) or orally (57), prevented infection with simian immunodeficiency virus (SIV). MVC prevented SIV infection when administered vaginally to macaques (58) and prevented HIV-1 infection when administered orally in a humanized mouse model (59).

Given that safety will be of paramount importance in administering antiretroviral agents to HIV-uninfected individuals for prevention, the approved drug MVC, with a number of years of available clinical experience and safety data (22, 23), has clear advantages over any investigational CCR5 antagonist. In addition, pharmacokinetic studies demonstrate orally administered MVC concentrates in the genital tract, with levels in vaginal secretions three times that of blood plasma (60) and levels in rectal tissue 7.5–26 times that of blood plasma (61). Further supporting a role for MVC in HIV-1 prevention is the fact that the drug is uncommonly used as HIV treatment, and consequently, MVC-resistant viral strains are uncommonly transmitted. Studies evaluating MVC either as a topical microbicide or oral agent for pre-exposure prophylaxis (PrEP) are planned.

Glossary

R5 virus	An HIV viral strain that uses CCR5 as the requisite coreceptor for entering a CD4+ T cell. For a given patient, “R5 virus only” means that only viruses using CCR5 were found on coreceptor tropism testing. “R5 virus only” generally corresponds to the nonsyncytium-inducing virus phenotype based on HIV growth in the MT-2 cell assay
Non-R5 virus	Viral strains that use CXCR4 as the requisite coreceptor for entering a CD4+ T cell. Most often, this occurs as a mixed infection; coreceptor tropism testing will find viral strains that use CCR5 or both CXCR4 and CCR5. Rarely, patients can harbor viral strains that only use CXCR4. Non-R5 virus generally corresponds to the syncytium-inducing virus phenotype based on HIV growth in the MT-2 cell assay
Maraviroc (MVC)	an FDA-approved CCR5 antagonist
Aplaviroc (APL)	an investigational CCR5 antagonist that was withdrawn from clinical development over concerns about hepatotoxicity
Vicriviroc (VCV)	an investigational CCR5 antagonist that was withdrawn from clinical development after completing phase III efficacy trials

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SUMMARY POINTS

1. HIV-1 uses the CCR5 or CXCR4 cellular receptor as a requisite coreceptor for entry into CD4⁺ T cells.
2. CCR5 antagonists inhibit HIV-1 entry by blocking the interaction of HIV-1 with CCR5.
3. **R5 virus** predominates in early HIV-1 infections; **non-R5 virus** is more common in patients with long-standing HIV-1 infection, especially those failing prior antiretroviral regimens.
4. Coreceptor tropism testing to document “R5 virus only” is necessary before treating with a CCR5 antagonist.
5. Maraviroc (MVC) is the only FDA-approved CCR5 antagonist.
6. Clinical trials show that MVC is safe and effective at suppressing HIV-1 viremia in patients with R5 virus only.
7. Two investigational CCR5 antagonists entered clinical trials but were withdrawn owing to hepatotoxicity (aplaviroc) and suboptimal virologic activity (vicriviroc). Additional CCR5 antagonists are under investigation.
8. Future studies will explore the use of CCR5 antagonists both for immunomodulatory effects and HIV prevention.

Table 1

Coreceptor tropism in different HIV-infected populations

Population (reference)	Acute seroconversion (10)	Early-stage HIV-1 infection (11)	Chronic HIV-1 infection, prior to ART initiation (11)	Highly treatment-experienced, initiating a new ART regimen (11)
Number tested	69	314	1,451	391
Median CD4 count (cells/ μ l)	N/A	629	238	104
Proportion with R5 virus (only)	87%	82%	73%	37%
Proportion with non-R5 virus:				
Dual-tropic virus or mixed infection	13%	18%	27%	59%
X4 virus (only)	0%	0%	0.3%	4%

N/A, not available.

Table 2

Key clinical trials of CCR5 antagonists for HIV-1 infection

Study	Design	Comparison	Sample size	Average baseline CD4 cell count	Results	Conclusions
<i>Antiretroviral-experienced patients (reference)</i>						
MOTIVATE (16, 17)	Two phase III randomized double-blind placebo-controlled trials	MVC once daily versus MVC twice daily versus placebo, each with an optimized background ART regimen	1,049 HIV-1-infected adults with R5 virus	169 cells/ μ l	HIV-1 RNA <50 copies/ml (48 weeks): 42% (once-daily MVC), 47% (twice-daily) and 16% (placebo)	MVC associated with significantly better virologic suppression rates in patients with prior ART experience who harbor R5 virus
Study 1029: MVC in patients with non-R5 virus (20)	Phase II randomized double-blind placebo-controlled trial	MVC once daily versus MVC twice daily versus placebo, each with an optimized background ART regimen	167 HIV-infected adults with non-R5 virus	<50 cells/ μ l	Change in plasma HIV-1 RNA (log copies/ml at 24 weeks): -0.91 (once-daily MVC), -1.20 (twice-daily MVC), -0.97 (placebo)	MVC not associated with virologic activity in patients harboring non-R5 virus
VICTOR-E3 and E4 (15)	Two phase III randomized double-blind placebo-controlled trials	VCV once daily versus placebo, each with an optimized background ART regimen	721 HIV-infected adults with R5 virus	221–287 cells/ μ l	HIV-1 RNA <50 copies/ml (48 weeks): 64% (VCV) and 61% (placebo)	VCV not associated with additional virologic activity in patients with prior ART experience who harbor R5 virus taking an optimized background ART regimen. This was likely due to the high virologic efficacy of the background ART regimen
<i>Antiretroviral-naïve patients</i>						
MERIT (12)	Phase III randomized double-blind placebo-controlled trial	MVC once daily versus MVC twice daily versus zidovudine/lamivudine	614 HIV-1-infected adults with R5 virus after reanalysis with more sensitive assay	236 cells/ μ l (MVC twice daily) and 254 (efavirenz)	HIV-1 RNA <50 copies/ml (48 weeks): 68% (MVC twice daily) and 68% (efavirenz)	Twice daily MVC was noninferior to efavirenz in suppressing replication of HIV infection; MVC once daily was stopped early because of poor efficacy; on reanalysis, once daily MVC achieved virologic suppression rates only slightly less than efavirenz

Abbreviations: ART, antiretroviral therapy; MVC, maraviroc; VCV, vicriviroc.