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Maraviroc: The First of a New Class of Antiretroviral Agents

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Maraviroc is the first US Food and Drug Administration–approved drug from a new class of antiretroviral agents that targets a host protein, the chemokine receptor CCR5, rather than a viral target. Binding of maraviroc to this cell-surface protein results in blocking human immunodeficiency virus type 1 (HIV-1) attachment to the coreceptor and prevents the virus from entering $CD4^+$ cells. In this review, we include the details of the discoveries that led to the development of this drug. The drug's pharmacology, including pharmacokinetics and drug interactions, is discussed, as are the clinical efficacy studies that led to licensure. HIV-1 mechanisms of resistance to maraviroc, assays to determine viral coreceptor use (tropism), drug safety, and clinical use of maraviroc are discussed at length.

In August 2007, the US Food and Drug Administration approved the first of a new class of antiretroviral drugs for use in HIV type 1 (HIV-1)–infected persons. Maraviroc, an inhibitor of the interaction between the chemokine receptor CCR5 and HIV-1 gp120, was approved for treatment of patients already experiencing virologic failure because of resistance to other antiretroviral agents.

Inhibition of viral entry is not a new concept. It is, after all, one of the principle mechanisms of viral inhibition by the acquired immune response to infection, and viral entry is the step in viral life cycles that vaccine-induced antibodies are designed to block. Therefore, inhibition of viral entry was a logical target in the case of HIV-1.

When the CD4 receptor was determined to be the primary receptor for HIV-1 binding to $CD4^+$ cells in 1984 [1], there were numerous attempts by researchers and the pharmaceutical industry to develop inhibitors of the binding step. It was apparent from experiments with hybrid murine cells expressing human $CD4^+$ cells that $CD4^+$ cell binding alone did not result in viral entry into cells and that another step was necessary [2]. The coreceptors CCR5 and CXCR4 were discovered a few years later by 2 different research groups [3, 4]. These chemokine receptors were the missing piece of the puzzle that explained viral entry into $CD4^+$ cells, and blocking these cells with their natural ligands (MIP-1α, MIP-1β, and RANTES for CCR5; SDF-1 for CXCR4) resulted in profound inhibition of HIV-1 infection in vitro [5]. Because CCR5 is used by nearly all viral isolates found in new or early infections and is present throughout the course of >50% of infections, this coreceptor presented a potential vulnerability in the viral life cycle. An effort to find effective inhibitors of the interaction between the viral envelope and CCR5 was thus launched by several pharmaceutical companies. The most successful of these efforts resulted in the drugs maraviroc, vicriviroc, and aplaviroc. Aplaviroc development ceased after significant hepatotoxicity became apparent in animal studies. Vicriviroc continues to be in development for treatment-experienced patients. Maraviroc, the first Food and Drug Administration-approved CCR5 inhibitor available for treatment of HIV-1 infection, is the focus of this review. We discuss the structure of this compound and its pharmacokinetics, antiviral potency, potential impact on the host immune response, resistance, efficacy in clinical trials, and safety. We hope to provide some perspective on its clinical utility within the field of the currently available antiretroviral drugs.

THE TARGET

The HIV-1 coreceptors CXCR4 and CCR5 belong to the G protein–coupled receptor superfamily, which is estimated to include >1000 different proteins, and are important targets for drug discovery in many disease states [6]. CCR5 is an especially interesting target, because the genetic absence of surface-expressed CCR5 in δ32 homozygous genotype populations results in almost complete resistance to HIV-1 infection [7]. This ab-

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sence seems to have few deleterious consequences for the host, although there is now a fairly strong association between homozygosity for the deletion mutation and risk of symptomatic West Nile virus infection [8].

DRUG DISCOVERY

Pfizer scientists screened their library of compounds, using a chemokine radioligand binding assay to identify a small-molecule CCR5 ligand. The imidazopyridine UK107,543 was one of the most potent lead compounds identified and was the starting point of an intensive medicinal chemistry program, which included parallel screening to optimize the binding potency, antiviral activity, absorption, pharmacokinetics, and specificity for CCR5. The result of this massive effort was maraviroc [9]. Maraviroc was found to have potent in vitro antiviral activity against all CCR5-tropic HIV-1 viruses tested, including 43 primary isolates from various clades and diverse geographic origin (mean MIC_{90}, 2.0 nmol/L). Maraviroc was also active against 200 clinically derived HIV-1 envelope pseudoviruses, 100 of which were from viruses resistant to existing drug classes [9].

The compound has a molecular weight of 514 g/mol and is a moderately lipophilic (log D7.4 value, 2.1) and basic (pKa, 7.3) molecule [10]. Maraviroc is sold under the trade name Selzentry (Celcentri outside the United States) and is available as film-coated tablets for oral administration containing either 150 mg or 300 mg. It is 75.5% plasma protein bound in humans. The volume of distribution of maraviroc is ~194 L.

Absorption of maraviroc is rapid but variable, with the time to maximum absorption generally being 1–4 h after receipt of the drug. After a 10-day course of monotherapy with maraviroc, the mean viral load reductions were similar at all dosages: the mean viral load reductions were 1.42 $\log_{10}$ copies/mL (range, 1.04–1.84 $\log_{10}$ copies/mL) with a dosage of 100 mg twice daily, 1.45 $\log_{10}$ copies/mL (range, 0.90–1.71 $\log_{10}$ copies/mL) with a dosage of 150 mg twice daily, 1.35 $\log_{10}$ copies/mL (range, 0.95–1.62 $\log_{10}$ copies/mL) with a dosage of 300 mg once daily, and 1.60 $\log_{10}$ copies/mL (range, 0.78–2.42 $\log_{10}$ copies/mL) with a dosage of 300 mg twice daily [11].

Coadministration of a 300-mg tablet with a high-fat breakfast reduced the maraviroc maximum concentration (C_{max}) and total drug exposure (area under the curve [AUC]) by 33% in healthy volunteers. The results were somewhat different in HIV-1–infected patients. Twice daily and once daily administration of the drug and the effect of food were compared for response to treatment in HIV-1–infected volunteers. There was no difference in reduction in viral load at day 11 between groups given a dosage of 150 mg twice daily and those given a dosage of 300 mg once daily or between groups given a dosage of 150 mg twice daily with food and those given treatment who fasted. With a dosage of 150 mg twice daily, food reduced the C_{max} by 60% and the AUC by ~50%, with no effect on trough concentrations (C_{min}) and no significant impact on viral load reduction. However, there were no food restrictions in the clinical studies that demonstrated the efficacy and safety of maraviroc; thus, no food restrictions were placed on the drug at licensing.

The pharmacokinetics of oral maraviroc are not dose proportional over the dose range. The absolute bioavailability is 23% for a 100-mg dose and is predicted to be 33% for a 300-mg dose [12].

The elimination half-life after a single 300-mg oral dose is 10.6 ± 2.7 h. The terminal half-life of maraviroc after administration of an oral dose to achievement of a steady state in healthy subjects was 14–18 h. The C_{max} is 144 ± 51 ng/mL, and the AUC is 537 ± 133 ng-h/mL. Recent results from a pharmacokinetic study of genital tract secretions and vaginal tissue in healthy, uninfected women who received a standard oral dosage of 300 mg of maraviroc twice daily for 7 days indicated that the AUC in cervicovaginal fluid was >4-fold higher than that in plasma; in vaginal tissue, the AUC was almost double that in plasma [13]. The concentration in cervicovaginal fluid at 72 h after the last dose was roughly equal to plasma concentrations at 12 h after the last dose. These results suggest that maraviroc may be a useful component of pre-exposure prophylaxis or microbicide strategies in HIV-1 prevention.

Maraviroc is a substrate for p-glycoprotein, which limits intracellular concentrations of the drug. It is also a substrate for CYP3A4 and, therefore, requires adjustment in the presence of inhibitors, such as ritonavir, or inducers, such as efaverenz and etravirine.

The majority of the drug (~75%) is excreted in the feces, whereas ~20% is excreted in urine [10]. Approximately 33% of the drug is excreted unchanged. The remainder is excreted as inactive metabolites. No dose adjustment is necessary for renal or hepatic impairment [12], although some accumulation of the drug may occur in persons with moderate-to-severe renal insufficiency (renal clearance, <50 mL/min) or hepatic insufficiency [12]. Occupancy of CCR5 receptors by maraviroc was studied in HIV-1–infected patients and was found to be >80% just before readministration at a steady state. Five days after discontinuation of the drug, the receptors remained >60% occupied, which may account for an observed delay in viral load rebound after drug discontinuation [11].

EFFECT OF CONCOMITANT TREATMENT ON THE PHARMACOKINETICS OF MARAVIROC

Because maraviroc is a substrate of CYP3A and Pgp, its pharmacokinetics are likely to be modulated by inhibitors and inducers of these enzymes and transporters. The CYP3A and/or Pgp inhibitors ketoconazole, lopinavir plus ritonavir, ritonavir, saquinavir, and atazanavir all increased the C_{max} and AUC of maraviroc. The CYP3A inducers rifampin and efavirenz decreased the C_{max} and AUC of maraviroc. Tipranavir plus ri-

tonavir (net CYP3A inhibitor and Pgp inducer) did not affect the steady-state pharmacokinetics of maraviroc. Neither trimethoprim-sulfamethoxazole nor tenofovir altered the pharmacokinetics of coadministered maraviroc. The recommended drug administration schedules are listed in table 1.

RESISTANCE

Resistance to maraviroc can occur in either of the 2 following ways: (1) mutations can develop that allow HIV-1 to use CXCR4 coreceptors (i.e., a change in tropism) or (2) mutations can develop that allow HIV-1 to continue using the CCR5 coreceptors, despite blockade by maraviroc. A change in tropism is of particular concern, because the presence of virus that can use the CXCR4 coreceptor has been associated with a more rapid decrease in $CD4^+$ lymphocyte count and faster disease progression [14, 15]. The frequency with which coreceptor switching occurs is unknown. Switching involves the development of multiple mutations throughout gp160, with resulting lowered replication capacity (i.e., fitness) and less efficient use of both CCR5 and CXCR4 [16].

The main mechanism of resistance to maraviroc appears to be the ability of the virus to use maraviroc-bound (inhibitor-bound) CCR5 coreceptors as a result of selection of multiple mutations in the V3 loop of gp120 [17]. The in vitro result of resistance is a "plateau effect" seen on susceptibility curves plotting the percentage of HIV-1 inhibition against increasing concentrations of maraviroc. In other words, increasing concentrations of maraviroc do not increase the percentage of viral inhibition, because maraviroc-resistant HIV-1 can bind to CCR5 in both its normal conformation and its maraviroc-bound conformation. The height of the plateau is dependent on the relative affinity of HIV-1 for inhibitor-bound versus free CCR5; the greater the affinity for maraviroc-bound CCR5, the lower the height of the plateau [17].

There appears to be little intrinsic resistance to maraviroc [9] and no cross-resistance with the fusion inhibitor enfuvirtide, which selects for mutations in the gp41 region of the viral envelope complex [18]. Maraviroc has good activity at baseline against both subtypes B and non–subtype B virus [9]; subtype differences were not associated with differences in virologic failure rates in a recently completed clinical trial [19].

TROPISM

Maraviroc has activity against HIV-1 that is exclusively CCR5 tropic. Thus, determination of tropism is necessary before initiation of therapy with the drug. The most widely used assay for determination of tropism is the Trofile assay, which is available only through Monogram Biosciences, at a cost of ~US$1800. This assay has the ability to detect minority (CXCR4) variants with a sensitivity of 100% when the percentage of minority variants is at least 10% and with a sensitivity of 85% when the percentage of minority variants is 5% [20]. Although work continues on development of reliable V3 genotyping algorithms for prediction of tropism, currently available V3 genotyping algorithms have been shown to be inadequate for prediction of CXCR4 coreceptor use [21], especially with non–subtype B virus [22]. Recently presented data concluded that the Trofile assay detected substantially more CXCR4-using viruses than did another commercially available assay, the SensiTropassay, although formal sensitivity analyses were not performed [23].

The issue of detecting minority variants is especially important, because preexisting minority variants that are not detected at baseline have been shown to be correlated with treatment failure in persons receiving maraviroc [24, 25]. An improved version of the Trofile assay is being developed and has been shown to detect preexisting minority variants that are not detected with the currently available Trofile assay [26]. In a recent analysis of persons enrolled in a phase II trial of vicriviroc (AIDS Clinical Trials Group 5211), 22% of persons classified at baseline as infected with CCR5-tropic virus by the standard Trofile assay were found to be infected with dual- and/or mixed-tropic virus when the enhanced assay was used for the same baseline specimens [26]. The enhanced assay is likely to be available commercially within the next 6–12 months.

EFFICACY

The efficacy of maraviroc was established in 2 concurrently conducted clinical trials involving HIV-1–infected, antiretroviral-experienced persons with persistent viremia (Maraviroc Plus Optimized Therapy in Viremic Antiretroviral Treatment Experienced Patients [MOTIVATE] 1 and 2) [27, 28]. The 2 trials differed primarily by the geographic location of participants. In a combined analysis of the 2 trials, maraviroc together with optimized background therapy (OBT) resulted in an ~1 $\log_{10}$ decrease in HIV-1 RNA levels, compared with OBT only [29]. Approximately 2.5 times as many persons receiving maraviroc achieved HIV-1 RNA levels <50 copies/mL, compared with those not receiving maraviroc (44% vs. 17%). The increase in $CD4_+$ cell count also was higher in those receiving maraviroc (120 cells/μL vs. 61 cells/μL). The use of enfuvirtide did not appear to increase the virologic response among those receiving maraviroc; to our knowledge, this was the first time that enfuvirtide did not increase the virologic response rate in recent clinical trials involving antiretroviral-experienced persons. However, an analysis based on previous use of enfuvirtide has yet to be completed and published. Moreover, although a recent meta-analysis of phase II and III clinical trials involving antiretroviral-experienced persons found CCR5 inhibitors to be associated with an enhanced $CD4^+$ cell count response, independent of the degree of virologic suppression [30], it is unclear whether this effect is durable or clinically relevant. Indeed, the

Table 1. Recommended dosing regimen for maraviroc with concomitant medications.

Concomitant drug effect	Concomitant medication examples	Dosage
No net alteration in metabolism	Tipranavir plus ritonavir, nevirapine, all NRTIs, and enfuvirtide	300 mg BID
CYP3A inhibitors (with or without a CYP3A inducer)	Ritonavir, all boosted protease inhibitors (except tipranavir plus ritonavir), delavirdine, ketoconazole, itraconazole, clarithromycin, nefazadone, and telithromycin	150 mg BID
CYP3A inducers alone	Efavirenz, etravirine, rifampin, carbamazepine, phenobarbital, and phenytoin	600 mg BID

NOTE. No dose adjustment is necessary or recommended for renal or hepatic impairment, although the safety and efficacy of maraviroc have not been studied sufficiently in persons with renal or hepatic impairment. BID, twice daily; NRTI, nucleoside analogue reverse-transcriptase inhibitor.

increase in circulating $CD4^+$ cell count may be attributable to decreased trafficking to tissues (and increased endothelial demargination) as a result of the blocking of CCR5 [31].

In the MOTIVATE trials, maraviroc was generally well tolerated; the percentage of treatment discontinuations because of toxicity was the same in the maraviroc plus OBT arm and in the OBT only arm (5% in each arm). Deaths were somewhat more frequent among those receiving maraviroc than among those receiving OBT only (1.8% vs. 1.0%). However, none of the deaths were judged to be due to maraviroc. It is worth noting that the population studied in the MOTIVATE trials had advanced HIV-1 infection (median $CD4^+$ cell count, <200 cells/μL), with >65% of participants receiving $\leq$2 active drugs as background therapy. Approximately 50% of persons screened for the MOTIVATE trials were found to be infected with dual- and/or mixed-tropic virus and, thus, were not eligible for participation [27, 28].

The percentage of persons infected with virus that is exclusively CCR5 tropic has been shown to decrease with decreasing $CD4^+$ cell count [32] and with years of antiretroviral experience [33] (from 80%–90% in antiretroviral-naive persons to $\geq$50% in antiretroviral-experienced persons [34]). Therefore, the potential usefulness of maraviroc might be expected to be greater for antiretroviral-naive persons. The efficacy of maraviroc in antiretroviral-naive persons was studied in the MERIT trial (multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagnoist, maraviroc vs. efavirenz, both in combination with Combivir [zidovudine/lamivudine], for the treatment of antiretroviral-naive subjects infected with R5 HIV-1) [35]. In this trial, 740 persons infected with CCR5-tropic HIV-1 were randomized 1:1 to receive either maraviroc or efavirenz, each in combination with zidovudine plus lamivudine. The median $CD4^+$ cell count at entry into the trial was ~250 cells/μL.

The MERIT trial was designed as a noninferiority trial using a covirologic end point, with the lower 95% CI boundary required to be no greater than 10% lower to support the claim of noninferiority. For the covirologic end point of HIV-1 RNA level <400 copies/mL, the lower confidence interval boundary was −9.5% (favoring efavirenz); for the covirologic end point of HIV-1 RNA level <50 copies/mL, the lower confidence interval boundary was −10.9% (also favoring efavirenz). Therefore, the claim of noninferiority of maraviroc as a component of initial therapy, compared with efavirenz, could not be supported. The difference in the percentage of persons achieving an HIV-1 RNA level of <50 copies/mL was particularly striking among those who entered the trial with HIV-1 RNA levels $\geq$100,000 copies/mL (66.6% vs. 59.6%, favoring efavirenz). It should be noted that the $CD4^+$ cell count response was at least as good with maraviroc as it was with efavirenz and that maraviroc was well tolerated. Nevertheless, the results of the MERIT trial do not support the use of maraviroc as therapy for antiretroviral-naive persons.

The efficacy of maraviroc was also studied in a population of persons who were infected with virus that was dual and/or mixed tropic for the CCR5 and CXCR4 coreceptors [36]. In the study, 158 antiretroviral-experienced persons were randomized 1:2 to receive OBT only or OBT plus maraviroc. There were no safety, virologic, or immunologic outcome differences noted after 48 weeks of therapy. In other words, maraviroc was of no benefit to this population of persons infected with dual- and/or mixed-tropic virus.

MALIGNANCIES AND OTHER SERIOUS ADVERSE EVENTS

There has been some concern that CCR5 blockade may result in decreased immune surveillance and a subsequent increased risk of development of malignancies (e.g., lymphomas). In addition, genetic deficiency of the CCR5 coreceptor is an important risk factor for the development of symptomatic West Nile virus infection [8]. To date, there has been no suggestion from clinical trials data that the incidence of either lymphomas or West Nile virus infection is increased among those receiving maraviroc. The incidence of infections overall also was not increased among those receiving maraviroc in clinical trials; there was an increase in the incidence of herpes virus infections (11.4 vs. 8.2 cases per 100 person-years of exposure), upper respiratory tract infections (36.9 vs. 27.1 cases per 100 person-years of exposure), sinusitis (10.6 vs. 7.3 cases per 100 person-years of exposure), and influenza (2.7 vs. 1.0 cases per 100

person-years of exposure) and a decrease in the incidence of pneumonia (3.4 vs. 10.4 cases per 100 person-years of exposure) among those receiving maraviroc [12]. In addition, there was 1 case of possible maraviroc-induced hepatotoxicity with allergic features in an HIV-1–negative volunteer [12], but there was nothing to suggest that maraviroc was similar in this respect to the discontinued CCR5 coreceptor antagonist aplaviroc [37]. There was an increase in the number of hepatic adverse events seen in individuals who received maraviroc in clinical trials, although there was no overall increase in the number of serious (grade 3 or 4) abnormalities in liver function among individuals who received the drug [12]. Nevertheless, there is a "black box" warning about hepatotoxicity in the package insert for maraviroc [12]. Only ~6% of persons who received maraviroc in clinical trials were coinfected with hepatitis C virus, and another 6% were positive for hepatitis B surface antigen; thus, little is known about the safety of maraviroc in these populations.

SUMMARY

Maraviroc is a promising new antiretroviral agent that does not have any cross-resistance with drugs from other classes. The drug has proven to be useful when combined with other antiretroviral agents for treatment of antiretroviral-experienced persons infected with CCR5-tropic HIV-1. Clinical experience is still limited, especially with regard to safety data and the assessment of risk of malignancies. Dosing is somewhat complicated (table 1), and there are many potential and actual drug-drug interactions. It is unclear whether enfuvirtide will be of added benefit to patients receiving maraviroc. The Trofile assay for tropism should be performed before initiation of therapy with maraviroc. Because of the risk of under-detection of dual- and/or mixed-tropic virus, maraviroc should be used with at least 2 other fully active drugs. Maraviroc is not approved for use in antiretroviral-naive persons and, on the basis of the results of the MERIT trial, should not be used solely with nucleoside analogue reverse-transcriptase inhibitors as active agents. Finally, data on the pharmacokinetics of maraviroc in the female genital tract suggest that the drug may prove to be useful in future strategies for HIV-1 prevention.

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References

1. Dalgleish AG, Beverley PC, Clapham PR, et al. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. Nature **1984**; 312:763–7.
2. Tersmette M, van Dongen JJ, Clapham PR, et al. Human immunodeficiency virus infection studied in CD4-expressing human-murine T-cell hybrids. Virology **1989**; 168:267–73.
3. Alkhatib G, Combadiere C, Broder CC, et al. CC CKR5: a RANTES, MIP-1α, MIP-1β receptor as a fusion cofactor for macrophage-tropic HIV-1. Science **1996**; 272:1955–8.
4. Oberlin E, Amara A, Bachelerie F, et al. The CXC chemokine SDF-1 is the ligand for LESTR/fusin and prevents infection by T-cell-line-adapted HIV-1. Nature **1996**; 382:833–5.
5. Oravecz T, Pall M, Norcross MA. Beta-chemokine inhibition of monocytotropic HIV-1 infection: interference with a postbinding fusion step. J Immunol **1996**; 157:1329–32.
6. Tilakaratne N, Sexton PM. G-protein-coupled receptor-protein interactions: basis for new concepts on receptor structure and function. Clin Exp Pharmacol Physiol **2005**; 32:979–87.
7. Samson M, Libert F, Doranz BJ, et al. Resistance to HIV-1 infection in Caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. Nature **1996**; 382:722–5.
8. Lim JK, Louie CY, Glaser C, et al. Genetic deficiency of chemokine receptor CCR5 is a strong risk factor for symptomatic West Nile virus infection: a meta-analysis of 4 cohorts in the US epidemic. J Infect Dis **2008**; 197:262–5.
9. Dorr P, Westby M, Dobbs S, et al. Maraviroc (UK-427,857), a potent, orally bioavailable, and selective small-molecule inhibitor of chemokine receptor CCR5 with broad-spectrum antihuman immunodeficiency virus type 1 activity. Antimicrob Agents Chemother **2005**; 49:4721–32.
10. Walker DK, Abel S, Comby P, Muirhead GJ, Nedderman AN, Smith DA. Species differences in the disposition of the CCR5 antagonist, UK-427,857, a new potential treatment for HIV. Drug Metab Dispos **2005**; 33:587–95.
11. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. Nat Med **2005**; 11:1170–2.
12. Selzentry full prescribing information. LAB-0357-1.0. New York: Pfizer Labs, **2007**. Available at: http://media.pfizer.com/files/products/uspi_maraviroc.pdf. Accessed 29 May 2008.
13. Dumond J, Patterson K, Pecha A, et al. Maraviroc pharmacokinetics in blood plasma, genital tract fluid and tissue in healthy female volunteers [abstract 135LB]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.
14. Shankarappa R, Margolick JB, Gange SJ, et al. Consistent viral evolutionary changes associated with the progression of human immunodeficiency virus type 1 infection. J Virol **1999**; 73:10489–502.
15. Goetz M, Leduc R, Kostman J, et al. Relationship between HIV coreceptor tropism and disease progression in persons with untreated chronic HIV infection [abstract TUPEB092]. In: Program and abstracts of the 4th International AIDS Society Conference (Sydney, Australia). Stockholm, Sweden: International AIDS Society, **2007**.
16. Pastore C, Ramos A, Mosier DE. Intrinsic obstacles to human immunodeficiency virus type 1 coreceptor switching. J Virol **2004**; 78: 7565–74.
17. Westby M, Smith-Burchnell C, Mori J, et al. Reduced maximal inhibition in phenotypic susceptibility assays indicates that viral strains resistant to the CCR5 antagonist maraviroc utilize inhibitor-bound receptor for entry. J Virol **2007**; 81:2359–71.
18. Xu L, Pozniak A, Wildfire SA, et al. Emergence and evolution of enfuvirtide resistance following long-term therapy involves heptad repeat 2 mutations within gp41. Antimicrob Agents Chemother **2005**; 49: 1113–9.
19. Heera J, Saag M, Ive P, et al. Virological correlates associated with treatment failure at week 48 in the phase 3 study of maraviroc in treatment-naïve patients [abstract 40LB]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.
20. Whitcomb JM, Huang W, Fransen S, et al. Development and characterization of a novel single-cycle recombinant-virus assay to determine human immunodeficiency virus type 1 coreceptor tropism. Antimicrob Agents Chemother **2007**; 51:566–75.
21. Low AJ, Dong W, Chan D. Current V3 genotyping algorithms are

inadequate for predicting X4 co-receptor usage in clinical isolates. AIDS **2007**; 21:F17–24.
22. Garrido C, Roulet V, Chueca N, et al. Evaluation of eight different bioinformatics tools to predict viral tropism in different HIV-1 subtypes. J Clin Microbiol **2008**; 46:887–91.
23. Tressler R, Valdez H, van der Ryst E, et al. Comparison of results from the SensiTrop™ vs Trofile™ assays on 100 samples from the maraviroc expanded access program [abstract 920a]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.
24. Westby M, Lewis M, Whitcomb J, et al. Emergence of CXCR4-using human immunodeficiency virus type 1 (HIV-1) variants in a minority of HIV-1 infected patients following treatment with the CCR5 antagonist maraviroc is from a pretreatment CXCR4-using virus reservoir. J Virol **2006**; 80:4909–20.
25. Lewis M, Simpson P, Fransen S, et al. CXC44-using virus detected in patients receiving maraviroc in the phase III studies MOTIVATE 1 and 2 originates from a pre-existing minority of CXCR4-using virus [abstract 56]. In: Program and abstracts of the XVI International HIV Drug Resistance Workshop (St. Michael, Barbados). **2007**.
26. Reeves J, Han D, Wilkin T, et al. An enhanced version of the Trofile HIV co-receptor tropism assay predicts emergence of CXCR4 use in ACTG5211 vicriviroc trial samples [abstract 869]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.
27. Nelson M, Fätkenheuer G, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in viremic, ART-experienced patients infected with CCR5-tropic HIV-1 in Europe, Australia, and North America: 24 week results [abstract 104aLB]. In: Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections (Los Angeles). **2007**.
28. Lalezari J, Goodrich J, DeJesus E, et al. Efficacy and safety of maraviroc plus optimized background therapy in viremic ART-experienced patients infected with CCR5-tropic HIV-1: 24week results of a phase 2b/3 study in the US and Canada [abstract 104bLB]. In: Program and abstracts of the 14th Conference on Retroviruses and Opportunistic Infections (Los Angeles). **2007**.
29. Hardy D, Reynes J, Konourina I, et al. Efficacy and safety of maraviroc plus optimized background therapy in treatment-experienced patients with CCR5-tropic HIV-1: 48-week combined analysis of the MOTIVATE studies [abstract 792]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.
30. Wilkin T, Ribaudo H, Gulick R. The relationship of CCR5 inhibitors to CD4 count changes: a meta-analysis of recent clinical trials in treatment-experienced subjects [abstract 800]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.
31. Glass WG, Lim JK, Cholera R, et al. Chemokine receptor CCR5 promotes leukocyte trafficking to the brain and survival in West Nile virus infection. J Exp Med **2005**; 202:1087–98.
32. Van Rij RP, Hazenberg MD, van Benthem BH, et al. Early viral load and $CD4^+$ T cell count, but not percentage of $CCR5^+$ or $CXCR4^+$ $CD4^+$ T cells, are associated with R5-to-X4 HIV type 1 virus evolution. AIDS Res Hum Retroviruses **2003**; 19:389–98.
33. Johnston ER, Zijenah LS, Mutetwa S, et al. High frequency of syncytium-inducing and CXCR4-tropic viruses among human immunodeficiency virus type 1 subtype C–infected patients receiving antiretroviral treatment. J Virol **2003**; 77:7682–8.
34. Hoffmann C. The epidemiology of HIV coreceptor tropism. Eur J Med Res **2007**; 12:385–90.
35. Saag M, Ive P, Heera J, et al. A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Combivir (zidovudine/lamivudine), for the treatment of antiretroviral-naive subjects infected with R5 HIV 1: week 48 results of the MERIT study [abstract WESS104]. In: Program and abstracts of the 4th International AIDS Society Conference (Sydney, Australia). Stockholm, Sweden: International AIDS Society, **2007**.
36. Goodrich JM, Saag M, van der Ryst E, et al. 48-Week safety and efficacy of maraviroc, a novel CCR5 antagonist, in combination with optimized background therapy (OBT) for the treatment of antiretroviral-experienced patients infected with dual/mixed-tropic HIV-1 [abstract LB-2]. In: Program and abstracts of the 2007 Annual Meeting of the Infectious Diseases Society of America (San Diego). Arlington, VA: Infectious Diseases Society of America, **2007**.
37. Nichols WG, Steel HM, Bonny T, et al. Hepatotoxicity observed in clinical trials of aplaviroc (873140). Antimicrob Agents Chemother **2008**; 52:858–65.