

Maraviroc (Celsentri[®]) for Multidrug-Resistant Human Immunodeficiency Virus (HIV)-1

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Summary

- ✓ **Maraviroc belongs to a new class of antiretroviral drugs designed to block entry of HIV-1 into CD4⁺ T-cells via the CCR5 co-receptor. It is indicated for combination therapy in treatment-experienced adults infected with CCR5-tropic HIV-1 that is resistant to multiple antiretroviral agents.**
- ✓ **Results from two randomized controlled trials (RCTs) indicate that in treatment-experienced patients, maraviroc, combined with optimized background therapy (OBT), significantly decreases the level of HIV-1 RNA in the blood (viral load) when compared with OBT alone. The number of patients achieving undetectable viral loads and CD4⁺ cell count increases were also significantly higher in those receiving maraviroc.**
- ✓ **Most patients experiencing treatment failure with maraviroc exhibit tropism changes from CCR5-tropic to CXCR4-using virus, but there is no evidence of disease progression.**
- ✓ **Adverse effects reported with maraviroc include cough, fever, upper respiratory tract infections, rash, muscle and joint pain, abdominal pain, and postural hypotension (dizziness). No significant increases in cardiovascular events, hepatotoxicity, infections or malignancies have been reported with short-term maraviroc therapy. Several post-marketing studies will assess maraviroc's long-term safety for immune function, liver function, malignancy, cardiac events, and risks associated with changes in tropism.**
- ✓ **Results from an ongoing trial in treatment-naïve patients suggest that maraviroc may not be superior in terms of viral suppression to standard therapy, but may significantly increase the number of CD4⁺ T-cells.**

Background

HIV infects and destroys CD4⁺ T-cells during the process of replication.¹ As the virus replicates, CD4⁺ T-cells are progressively depleted, causing immunodeficiency, i.e. acquired immunodeficiency syndrome or AIDS. Despite advances in antiretroviral drugs for HIV infection, the AIDS epidemic claimed 2.9 million lives worldwide in 2006.² Individuals with AIDS are vulnerable to opportunistic infections caused by various pathogens (including *Pneumocystis jiroveci* and cytomegalovirus) and otherwise rare malignancies (such as Kaposi's sarcoma).¹ A major issue with HIV treatment is the emergence of HIV strains with reduced susceptibility to current antiretroviral drugs. The result is uncontrolled HIV replication and disease progression.

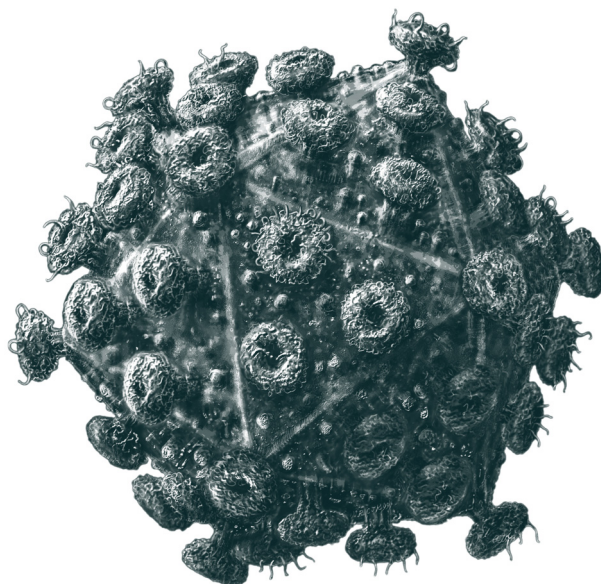


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The HIV Virus

The Technology

Maraviroc belongs to a new class of antiretroviral drugs designed to block entry of HIV-1 into CD4⁺ T-cells via the CCR5 co-receptor.³ Without viral entry, the process of viral replication cannot occur and the number of CD4⁺ T-cells increases, improving immune function.

Maraviroc is indicated in combination with other antiretrovirals for adults infected with CCR5-tropic HIV-1,

who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.³ Maraviroc is not currently indicated for antiretroviral treatment-naïve patients, or for those modifying treatment regimens due to intolerance or toxicity.

HIV-1 variants differ in their use of co-receptors for entry.⁴ Variants may exclusively use the CCR5 co-receptor (CCR5-tropic or R5 viruses) or exclusively use the CXCR4 co-receptor (CXCR4-tropic or X4 viruses).⁴ Variants that use either receptor (i.e., a mixture of R5 and X4 virus) are termed dual-tropic or R5X4 viruses.⁴ In the early, asymptomatic stage of infection, approximately 85% of patients are infected with CCR5-tropic virus.⁵ In contrast, the proportion of treatment-experienced patients exclusively infected with CCR5-tropic virus (i.e., potential candidates for maraviroc) is only 50% to 60%.⁵ The appearance of CXCR4-tropic virus in treatment-experienced patients has been linked with faster progression to AIDS.^{6,7}

A tropism test to confirm a patient is infected exclusively with CCR5-tropic virus must be conducted prior to initiation of therapy with maraviroc.³ The Trofile™ assay is currently the only CCR5 tropism test available. The assay can be reliably performed on plasma samples containing $\geq 1,000$ copies/mL HIV-1 RNA and can detect X4 variants present at greater than 5% to 10% of the plasma viral population.⁵

Regulatory Status

Maraviroc (brand name Celsentri® in Canada and Europe, Selzentry® in the US) is manufactured by Pfizer Inc.³ Maraviroc was approved by Health Canada in September 2007.³ It was also approved in the US and in Europe in 2007.^{8,9} Currently, Canadian patients can receive maraviroc through an expanded access program (EAP) sponsored by Pfizer.⁸

The Trofile™ tropism assay (Monogram Biosciences, Inc.) has Clinical Laboratory Improvement Amendment certification in the US, but has not been approved by the US Food and Drug Administration (FDA) as a test kit. The Trofile™ assay is not currently licensed by Health Canada but is currently being covered by Pfizer as part of the EAP.⁸

Patient Group

In 2005, approximately 58,000 Canadians were living with HIV/AIDS, a 16% increase from the 2002 estimate of 50,000.¹⁰ An estimated 2,300 to 4,500 new

infections occurred in Canada in 2005.¹⁰ Prevalence will likely increase as new infections continue to occur and as new treatments prolong survival. Consequently, the number of patients who have HIV strains resistant to existing antiretroviral drugs is also likely to increase.

Current Practice

Currently available antiretroviral drugs cannot eradicate HIV. Therefore, prolonged suppression of the virus in order to restore and preserve immunologic function, improve quality of life, and avoid HIV-associated morbidity and mortality is the focus of HIV treatment.^{1,11,12} Two surrogate markers, the plasma HIV-1 RNA (or viral load) and the CD4⁺ cell count, are routinely used in practice. The CD4⁺ cell count serves as an indicator of immune function. In general, the CD4⁺ cell count should be determined every three to six months, and therapy with antiretrovirals should be initiated when the CD4⁺ cell count falls in the 200 to 350 cells/ μ L range.^{1,11} Plasma HIV-1 RNA is an important indicator of treatment efficacy and should be measured four weeks after initiating therapy, two to eight weeks after treatment modifications, and every three to four months once viral load is undetectable (<50 copies/mL).^{1,11} One major goal of antiretroviral therapy is to achieve and maintain an undetectable viral load within three to four months of therapy initiation.^{1,11} For patients who are experiencing failure with their current regimen due to drug resistance, the goal is to select a regimen with at least two active antiretroviral drugs based on resistance testing.^{1,11} When viral suppression to undetectable levels is not possible in treatment-experienced patients, the aim of treatment is to preserve immune function and limit disease progression.^{1,11}

Several classes of antiretroviral drugs are available. Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs) act on intracellular viral enzymes important for replication.¹³ Highly active antiretroviral therapy (HAART) with regimens consisting of a combination of these drugs (generally two NRTIs plus a NNRTI or PI) has effectively reduced viral load and prolonged survival of patients with HIV.¹ However, the inconvenience of some of these drug regimens (e.g., high pill burden, frequent dosing, gastrointestinal side effects) and short- and long-term drug toxicity (including metabolic complications, pancreatitis, hepatotoxicity, peripheral neuropathy, and bone marrow suppression) often result in poor adherence to therapy, which promotes viral resistance.¹⁴ Six years after starting HAART, approximately 10% to 20% of

patients are estimated to have viral strains resistant to all three drug classes.¹⁵ Furthermore, sequential HAART regimens have been shown to be progressively less durable for viral suppression.¹⁶

Recently, the addition of second-generation PIs such as tipranavir and darunavir has helped individuals with multidrug-resistant HIV achieve viral suppression.¹⁴ However, both drugs have the potential for significant adverse effects, long-term toxicities, and drug interactions. Enfuvirtide (T-20), a fusion inhibitor that blocks entry of HIV-1 into CD4⁺ T-cells, is used in treatment-experienced patients with few remaining options.¹⁷ While enfuvirtide is generally well tolerated, it can only be administered by twice daily subcutaneous injections, and most patients experience injection site reactions.¹⁴

The Evidence

Approval of maraviroc was based on unpublished safety and efficacy data from two identical RCTs (Table 1).^{18,19} The studies were designed to reflect a heavily treatment-experienced HIV-1-infected population with evidence of HIV-1 replication despite ongoing antiretroviral therapy. MOTIVATE-1 (n=585) was conducted in the US and Canada and MOTIVATE-2 (n=464) studied patients in Europe, Australia, and North America. Investigators selected optimized background therapy (OBT) based on treatment history and tolerability, as well as drug resistance testing carried out at screening. OBT was administered as open-label therapy not provided by the sponsor. Baseline characteristics (including plasma HIV-1 RNA, CD4⁺ cell count, and resistance to different classes of antiretrovirals) were well balanced among the maraviroc (once or twice daily dosing) and placebo arms.⁵ Approximately 41% of the subjects exhibited a screening viral load $\geq 100,000$ copies/mL and 43% were also being treated with enfuvirtide.³ Of note, no patients were treated with darunavir (the studies were conducted prior to its approval) and only 10% were using tipranavir as part of their antiretroviral regimen. Of the 1,042 patients with CCR5-tropic virus at screening, 79 (7.6%) had CXCR4-tropic or dual-tropic virus at baseline, illustrating the background change in tropism over a four-to six-week period prior to administration of maraviroc.⁵

Forty-eight week results revealed that treatment with maraviroc once or twice daily significantly improved viral suppression when compared with OBT alone.^{18,19} The percentage of patients achieving undetectable viral

loads and the increase in CD4⁺ cell count were also significantly higher for those receiving therapy with maraviroc.^{18,19} In all three treatment arms, patients with lower screening viral load (<100,000 copies/mL), or those using enfuvirtide for the first time, were more likely to achieve undetectable levels of virus.^{18,19} In two-thirds of patients, failure of viral suppression with maraviroc was associated with the detection of CXCR4-using (i.e., CXCR4- or dual-tropic) virus.^{3,20} Treatment failure in those with CCR5-tropic virus occurred as a result of phenotypic and genotypic resistance to maraviroc and resistance to OBT.²¹ Time to failure with CXCR4-using virus was approximately 30 days shorter than that for CCR5-tropic virus.²⁰ A clonal analysis revealed that CXCR4-using virus emerged from a low level of pre-existing CXCR4-using virus not detected by the tropism assay prior to treatment, and was not due to a co-receptor switch from CCR5-tropic virus to CXCR4-using virus.²² All patients who were found to have CXCR4-using virus during the study and for whom tropism data was available at follow-up (approximately 68% of the patients) reverted to exhibiting CCR5-tropic virus after treatment with maraviroc was discontinued.²⁰ Selection for CXCR4-using virus was not associated with any short-term adverse events or disease progression.^{3,20} Furthermore, even with the emergence of CXCR4-using virus, patients failing on maraviroc had a larger mean increase in CD4⁺ cell count from baseline (47 and 57 cells/ μ L for once or twice daily dosing, respectively) compared with 24 cells/ μ L for all treatment failures (regardless of tropism) on placebo.¹⁹

Similar results have been observed in an RCT to determine the safety and efficacy of maraviroc in 186 patients infected with CXCR4-using virus.²³ Results show that although viral load did not differ significantly after 48 weeks of treatment with maraviroc when compared with OBT alone, patients treated with maraviroc experienced a larger increase in CD4⁺ cell counts (65 and 78 cells/ μ L for once or twice daily dosing, respectively) compared with 51 cells/ μ L for placebo.²³ There was no increased risk of infection or disease progression in patients receiving maraviroc. The possibility of immunological benefit regardless of tropism underscores the importance of evaluating if and when testing for tropism is necessary. Whether this increase in CD4⁺ cell count is sustained and proves to be clinically significant remains to be determined.

The study population in the MOTIVATE trials was predominantly male (89%) and Caucasian (84%).⁵ It is not clear if the safety and efficacy data from these studies are generalizable to other populations including

Table 1: Summary of efficacy data for maraviroc in treatment-experienced HIV-1 infected patients

	MOTIVATE-1 48-week Results¹⁸	MOTIVATE-2 48-week Results¹⁹
Study Design	Randomized, placebo-controlled, double-blind Inclusion criteria: Patients ≥ 16 years infected with CCR5-tropic HIV-1, viral load ≥ 5000 copies/mL despite at least 6 months of prior therapy, resistance to at least one antiretroviral drug from each of the three classes (NRTI, NNRTI, and at least 2 PI). Patient stratification: Enfuvirtide use in OBT and HIV-1 RNA <100,000 copies/mL or ≥ 100,000 copies/mL at screening. Treatment: Maraviroc* once or twice daily, plus OBT versus placebo plus OBT. Primary outcome: Mean reduction in HIV-1 RNA from baseline. Secondary outcomes: Percentage of patients with undetectable HIV-RNA, change in CD4 ⁺ cell count from baseline, HIV-1 tropism at baseline and at time of failure, safety and tolerability of maraviroc.	
Mean Change in HIV-1 RNA from Baseline (Log¹⁰ copies/mL)	Placebo -0.80 Maraviroc once daily -1.66 Difference from placebo -0.85 (97.5% CI: -1.22, -0.49) Maraviroc twice daily -1.82 Difference from placebo -1.02 (97.5% CI: -1.39, -0.66)	Placebo -0.76 Maraviroc once daily -1.72 Difference from placebo -0.96 (97.5% CI: -1.38, -0.54) Maraviroc twice daily -1.87 Difference from placebo -1.11 (97.5% CI: -1.52, -0.70)
Patients with HIV-1 RNA <50 copies/mL	Placebo 16% Maraviroc once daily 42% (p<0.0001 versus placebo) Maraviroc twice daily 47% (p<0.0001 versus placebo)	Placebo 18% Maraviroc once daily 45% (p<0.0001 versus placebo) Maraviroc twice daily 45% (p<0.0001 versus placebo)
Mean Change in CD4⁺ Cell Count from Baseline (cells/μL):	Placebo +54 Maraviroc once daily +113 Difference from placebo +59 (95% CI: +34, +84) (p<0.0001 versus placebo) Maraviroc twice daily +122 Difference from placebo +68 (95% CI: +44, +93) (p<0.0001 versus placebo)	Placebo +69 Maraviroc once daily +121 Difference from placebo +52 (95% CI: +23, +81) (p=0.0005 versus placebo) Maraviroc twice daily +128 Difference from placebo +59 (95% CI: +30, +87) (p<0.0001 versus placebo)

*Dose of 150 mg once or twice daily was given with PI (excluding tipranavir/ritonavir) and/or delavirdine; otherwise 300 mg once or twice daily was used.

OBT=Optimized Background Therapy consisting of 3-6 antiretroviral agents ± low dose ritonavir

the elderly, children or adolescents (<16 years), and pregnant women. Further trials are needed to assess which populations should use maraviroc, which antiretrovirals should be used in combination with maraviroc in these populations, and the frequency of drug resistance.

Adverse Effects

Forty-eight week data from the MOTIVATE trials indicate that the incidence and severity of infections (including AIDS-defining opportunistic infections), cardiac events, hepatotoxicity, laboratory abnormalities (including abnormalities in liver enzymes), malignancies, and death were comparable among treatment arms.^{18,19,24} The most common adverse reactions (>8% incidence) – which occurred at a higher

frequency with maraviroc compared to placebo – were cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms (muscle and joint pain), abdominal pain, and dizziness.³ Overall, the short-term safety profile for maraviroc is promising in light of evidence of adverse effects associated with other investigational CCR5 antagonists. The development of aplaviroc was discontinued due to severe hepatotoxicity, and there is some evidence of an increased risk of malignancies with vicriviroc (currently in phase 3 development).^{6,25} The long-term effect of maraviroc on immune function, hepatotoxicity, cardiovascular risks, and incidence of malignancy remains to be determined.

The FDA's approval of maraviroc specified several post-marketing commitments, including studies to assess long-term safety regarding immune function, liver

function, malignancy, cardiac events (including risk for arrhythmia and myocardial infarction), and risks associated with switches in tropism.⁵ Two non-randomized, open-label trials are also evaluating the safety and tolerability of maraviroc in a broader patient population.^{26,27}

Administration and Cost

Maraviroc is available as 150 mg and 300 mg oral tablets.³ It can be taken with or without food and is given twice daily in combination with other antiretroviral medications. The recommended starting dose is 300 mg twice daily. A starting dose of 150 mg twice daily should be given when combined with drugs that inhibit the liver enzyme responsible for its metabolism [e.g., protease inhibitors (excluding tipranavir), delavirdine, ketoconazole], and a starting dose of 600 mg twice daily should be given with drugs that induce its metabolism (e.g., efavirenz, rifampin).³ There are currently no contraindications to treatment with maraviroc, but it should be used with caution in patients at increased risk for cardiovascular events or with pre-existing liver disease. Dosing adjustment recommendations for patients with renal and hepatic impairment have not been established.³

The Canadian price for maraviroc is approximately \$33 per day, which is similar to darunavir (\$28 per day) and tipranavir (\$33 per day), but less than half the cost of enfuvirtide (\$80 per day).^{8,28,29} In the US, the price for maraviroc is US\$29 per day and the approximate cost for the Trofile™ tropism assay is US\$2,000.³⁰ The cost-effectiveness of using maraviroc in combination with other antiretroviral medications has not yet been studied.

Concurrent Developments

In October 2007, raltegravir (Isentress™) was approved by the FDA for use in combination with other antiretroviral agents in treatment-experienced patients resistant to multiple drug classes.³¹ Raltegravir belongs to a new class of antiretroviral agents which inhibit the insertion of HIV DNA into human DNA by the viral integrase enzyme.³¹ It will not require a tropism test, and costs US\$27 per day.³² Several other investigational antiretrovirals to treat resistant HIV-1 strains are under development.^{25,33} Phase 3 trials are underway for vicriviroc (another CCR5 co-receptor antagonist) and etravirine (a second-generation NNRTI) in treatment-experienced patients. Etravirine is already available to patients in an expanded access program.²⁵ New antiretroviral drugs or drug classes in

phase 2 development include maturation inhibitors (bevirimat), integrase inhibitors (elvitegravir), cholesterol-dependent entry inhibitors (SP01A), a CD4-specific monoclonal antibody (TNX-355), and CCR5 co-receptor antagonist (INCB9471). Second generation NNRTIs (rilpivirine) and NRTIs (apricitabine, elvucitabine) are also in phase 2 development.

Rate of Technology Diffusion

Current evidence indicates that only approximately 40% to 50% of treatment-experienced patients exclusively carry CCR5-tropic virus and, thus, may be candidates for therapy with maraviroc.⁵ Until other tropism assays become available, the cost and turnaround time for shipment to the US (three to five weeks) for the Trofile™ assay may serve as a barrier to the use of maraviroc. Several other tropism assays are in development, but are not yet commercially available.^{34,35} An ongoing study is assessing alternative surrogate markers for the tropism assay.³⁶

The use of maraviroc in treatment-naïve patients is also under investigation. The MERIT study is an ongoing RCT assessing the efficacy of maraviroc versus efavirenz in 721 treatment-naïve patients also treated with zidovudine and lamivudine.³⁷ Results at 48 weeks show that the number of patients who achieve HIV-1 RNA <50 copies/mL is comparable between the two groups (65.3% for patients receiving twice-daily maraviroc versus 69.3% for patients receiving efavirenz). The once-daily maraviroc arm was discontinued due to inferior efficacy. Although these response rates are similar, they did not meet the pre-specified criteria for non-inferiority of maraviroc at <50 copies/mL. More patients discontinued in the maraviroc twice daily arm due to lack of efficacy compared with efavirenz (11.9% versus 4.2%). However, maraviroc was associated with a significantly greater increase in mean CD4⁺ cell count from baseline (a difference of 26 cells; 95% CI: 7-46). Maraviroc was also better tolerated than efavirenz with fewer discontinuations due to adverse events (4.1% versus 13.6%) and half as many patients taking maraviroc (1.7%) experienced AIDS-defining events, such as infection or malignancy, compared with those taking efavirenz (3.3%).³⁷ Maraviroc is also being investigated in a phase 2 RCT for rheumatoid arthritis in patients receiving methotrexate.³⁸

Implementation Issues

It is not yet known which antiretroviral combinations should be used with maraviroc. The economic and

clinical utility of the Trofile™ test and other tropism assays still needs to be determined. Recommendations regarding when or how frequently to test for tropism changes during treatment have yet to be established. Further evidence is also needed on maraviroc's long-term efficacy and safety to support the extension of its use in treatment-naïve individuals infected with resistant HIV-1 strains, or in those intolerant to standard antiretroviral therapy.

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