Maraviroc Therapy and *CCR5* Genotype

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Maraviroc is used in combination with other antiretroviral agents to treat infection by human immunodeficiency virus type 1 (HIV-1), the virus that causes acquired immune deficiency syndrome (AIDS). Maraviroc is a chemokine receptor antagonist and works by blocking HIV-1 entry into cells.

HIV-1 is classified according to which co-receptors it uses to gain entry in to the cell—either the chemokine receptor 5 (CCR5) or the CXC chemokine receptor 4 (CXCR4). These co-receptors are expressed on different types of cells, and HIV tropism refers to the types of cells and tissues that the virus infects and replicates in. A tropism assay is used to determine which co-receptor HIV-1 uses i.e., whether the virus is CCR5-tropic, CXCR4-tropic, or dual/mixed-tropic (dual refers to HIV-1 that is able to use both receptors, and mixed refers to a mixture of HIV-1 viruses, some of which use CCR5 and others that use CXCR4).

Maraviroc is indicated for treatment of adults with CCR-5 tropic HIV-1 only and is not recommended for adults in whom CXCR4-tropic virus has been detected. The FDA states that tropism testing with a highly sensitive tropism assay is required for the appropriate use of maraviroc (1).

Drug: Maraviroc

Maraviroc is the first FDA-approved drug in a class of HIV drugs called entry and fusion inhibitors. Maraviroc blocks the interaction between HIV-1 and the chemokine receptor CCR5 in healthy immune cells, preventing certain strains (CCR5-tropic) of HIV from entering and infecting the cell. Maraviroc must be taken twice daily, and must always be used with other HIV drugs. Taken in combination with these drugs, maraviroc may lower the HIV virus load in the blood.

Currently, maraviroc is the only CC5R co-receptor inhibitor that has been approved for clinical use (2). It is used to treat HIV-1-infected patients who have a virus that is only able to use CCR5 for entry, and either never received antiretroviral treatment before, or have experienced therapeutic failure following traditional antiretroviral therapies (3). Some of the other CCR5 antagonists under investigation include cenicriviroc, which is

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still in Phase II trials and appears to block an additional receptor, CCR2; and vicriviroc, which was in Phase III trials before being discontinued (4-6).

Maraviroc treatment regimens may be used less often than other regimens. Possible reasons include the requirement to do tropism testing which takes time and is expensive to perform before maraviroc is given (see Genetic Testing), and the large choice of treatment regimens currently available that are generally potent, tolerable, and do not require genotyping prior to use. These treatment regimens include nonnucleoside reverse-transcriptase inhibitor-based, boosted protease inhibitor-based, and integrase inhibitor-based regimens (2, 7).

The entry of HIV-1 in to a host cell is a complex process, which begins when the viral envelope glycoprotein, gp120, binds to the cellular protein, CD4. Binding induces conformational changes in gp120 resulting in the exposure of gp4, another viral envelope protein that helps mediate the interaction between the virus and cellular co-receptors, and the fusion of viral and cellular membranes.

The CD4 count is often used to determine the stages of HIV disease. CD4 is a glycoprotein found on the surface of immune cells such as T helper cells. HIV-1 infection leads to a progressive reduction in the number of T cells that express CD4. A CD4 count of fewer than 200 cells/mm^3 is one of the qualifications for a diagnosis of AIDS (8, 9).

Measurement of the CD4 count is particularly useful before HIV treatment is started because the CD4 count provides information on the overall immune function of the patient. In the United States, antiretroviral therapy is now recommended for all HIV-infected patients regardless of their CD4 count or their viral load (10). In adults who are receiving optimized background treatment for infection with CCR5-using HIV-1, the addition of maraviroc leads to a greater increase in CD4 counts compared to the addition of placebo (1).

HIV-1 most commonly uses either the co-receptors CCR5 or CXCR4 to enter its target cells (11). Maraviroc is an effective antiretroviral agent in individuals who only harbor the CCR5-using virus. It is incapable of inhibiting infection with viruses that do not use CCR5 (i.e., CXCR-using virus, or dual/mixed virus) (1).

Maraviroc is metabolized by the cytochrome P450 system in the liver to inactive metabolites and CYP3A is the major enzyme involved (12). As noted above, maraviroc must be used in combination with other antiretroviral medications; the recommended dosage of maraviroc depends on whether the co-medications are inhibitors or inducers of CYP3A (1).

Gene: *CCR5*

The chemokine (CC motif) receptor 5, CCR5, is mainly found on the surface of white blood cells. Chemokines are a type of cytokine—they are small, secreted proteins that have a crucial role in the inflammatory response by helping immune cells migrate to areas

of tissue damage. Other functions of chemokines include influencing the maturation of various immune cells and promoting the growth of new blood vessels.

Most chemokines have four characteristic cysteine residues in a conserved location, and they are classified into four families by the location of the first two cysteine residues: CXC, CC, C, and CX3C. For example, members of the "CC" cytokine family have two adjacent cysteine residues near their amino terminus.

The receptors for chemokines are G-protein coupled, seven-transmembrane domain receptors. Two of these receptors, CCR5 (binds CC chemokines) and CXCR4 (binds CXC chemokines), are also co-receptors used by HIV to enter into human white blood cells. CCR5 is expressed on fewer cells (e.g., specific T cells, precursor cells and dendritic cells) than CXCR4 (e.g., most immune cells, vascular endothelial cells and neurons).

HIV-1 virus that uses the CCR5 co-receptor (CCR5-tropic) is more commonly found in the early stages of infection. It is also more common in individuals who have yet to receive treatment, and at least half of all infected individuals harbor only CCR5-tropic viruses throughout the course of infection. The CXCR4-tropic virus is more commonly found during later stages of disease and in individuals who have received HIV treatment. The presence of CXCR4-tropic virus is a predictor of lower CD4 count, a higher viral load, and a more rapid progression to AIDS (8).

A variant of *CCR5*, *CCR5-Δ32*, contains a 32-base pair deletion and codes for a nonfunctional receptor that hinders the entry of CCR5-tropic virus in to cells. Individuals who have two copies of this allele are highly resistant to HIV infection, and although individuals who have one copy of the allele remain susceptible to HIV infection, the progression of HIV to AIDS is delayed (13).

The *CCR5-Δ32* allele occurs at high frequency in European Caucasians (5%–14%) but is mostly absent among African, Native American, and East Asian populations. This has led to suggestions that at some point in history, the allele conferred a survival advantage (14). Possible causes of a positive selection pressure include protection against the bubonic plague (*Yersinia pestis*) or smallpox (*Variola virus*) during the Middle Ages. However, other studies have found that the CCR5-Δ32 allele arose long before this time and underwent neutral evolution (15).

Genetic Testing

Testing of the HIV-1 virus (i.e., the virus, not the patient) should be carried out prior to initiation of treatment with maraviroc. A tropism assay is needed to identify individuals with CCR5-tropic HIV-1. The assay must be highly sensitive to detect low levels of CXCR4-tropic viruses. Maraviroc should not be prescribed if non-CCR5 variants (CXCR4-tropic or dual/mixed-tropic) are detected (1, 12).

HIV tropism can be determined by phenotype or genotype testing. Phenotypic assays can be performed using plasma RNA (if viral load is greater than 1000 copies/ml) or cell-associated DNA (if viral load is less than 1000 copies/ml). Phenotypic assays use

replication-defective laboratory viruses that carry the complete cloned viral envelope proteins gp120 and gp41 derived from the patient. Phenotypic assays measure the ability of these pseudoviruses to infect CD4+ target cells that express either CCR5 or CXCR4 (10).

Genotyping methods are used to predict which co-receptors on the cell are used by the virus rather than directly assessing tropism. Genotyping methods involve sequencing the third variable region (V3) of gp120 and using algorithms to predict co-receptor usage.

While phenotypic assays are still considered to be the gold standard, the use of genotyping to determine patient eligibility for maraviroc is increasing because of the lower cost, greater accessibility, and faster turnaround of results compared to other methods (16, 17). Although there are still discrepancies between the results from phenotypic assays and the easier genotypic assays, the correlation between genotypic assays and the clinical efficacy of maraviroc is improving (18).

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): The following points should be considered when initiating therapy with maraviroc:

- Adult patients infected with only CCR5-tropic HIV-1 should use maraviroc.
- Tropism testing must be conducted with a highly sensitive tropism assay that has demonstrated the ability to identify patients appropriate for use of maraviroc. Outgrowth of pre-existing low-level CXCR4- or dual/mixed-tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure on maraviroc.
- Use of maraviroc is not recommended in subjects with dual/mixed- or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a Phase 2 study of this patient group.

Please review the complete therapeutic recommendations that are located here: (1).

The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

Nomenclature

Allele name	Other name(s)	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CCR5delta32		NM_000579.3:c.554_585del32 NM_001100168.1:c.554_585del32	NP_000570.1:p.Ser185Ilefs NP_001093638.1:p.Ser185Ilefs	rs333

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

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Tests in GTR by Gene

CCR5 gene