

## HIV-1 CO-RECEPTOR TROPISM ASSAYS

Number: 200801-0001

Effective date: 01/09/2008

Revision date: N/A

### Overview

In 1996 scientists discovered that the HIV-1 virus binds with and subsequently infects human CD4 cells through the use of a co-receptor on the cell surface. Different strains of HIV-1 use different co-receptors to enter human CD4 cells. Two main co-receptors have been identified. They are known as CCR5 and CXCR4. Based on co-receptor usage, a new HIV-1 classification was established, i.e., CCR5-tropic, CXCR4-tropic, or dual/mixed tropic.

- CCR5-tropic HIV-1: a virus strain that can only use the CCR5 co-receptor to infect CD4 cells.
- CXCR4-tropic HIV-1 a virus strain that can only use the CXCR4 co-receptor to infect CD4 cells.
- Dual-tropic HIV-1: a virus strain that can use either the CCR5 or CXCR4 co-receptor to infect CD4 cells.

A mixture of CCR5, CXCR4 and dual tropic HIV-1 virus strains may be present in an individual. In this case, the virus is described as being mixed tropic. Currently available tropism assays cannot distinguish between dual-tropic and mixed-tropic; hence the term dual/mixed-tropic is used.

Viral tropism can and frequently does change over the course of the disease. CCR5-tropic virus has been shown to predominate during the early stages of HIV-1 infection. However, over time, CXCR4-tropic HIV-1 (including dual/mixed tropic virus) may emerge in up to half of patients. A relationship has been identified between the viral strain and virulence, and it is clear that CXCR4 co-receptor usage is associated with decreasing immune function and disease progression

Antiretrovirals are medications that are used to keep levels of the HIV virus as low as possible for as long as possible. One of the challenges in treating HIV is that the virus reproduces rapidly and mutates easily. Mutations lead to drug resistance. In order to combat drug resistance, many different classes of antiretrovirals have been developed. Each class of drugs works differently. Recently a new class of antiretrovirals has recently been developed called entry (or fusion) inhibitors. Entry inhibitors act by interfering with the HIV virus's entry into the CD4 cell. There are many steps in the entry process and there are many new entry inhibitors with distinct mechanisms of action being developed. The first FDA-approved entry inhibitor was Fusion® (enfuvirtide). Fusion® interferes with the entry of HIV-1 into CD4 cells by binding to the viral envelope glycoprotein and thereby preventing the fusion of viral and cellular membranes. On August 7, 2007, the FDA approved the first CCR5 entry inhibitor, Selzentry™

(maraviroc). Selzentry™ is indicated for combination antiretroviral treatment in adults infected with only CCR5-tropic HIV-1 detectable virus, who have evidence of viral replication and have HIV-1 strains resistant to multiple antiretroviral agents.<sup>1</sup> Other entry inhibitors, including CXCR4 antagonists, are being developed and will be available in the next few years.

Approximately 40% to 50% of individuals who have used antiretrovirals in the past have dual/mixed tropic virus. Because these are the individuals who will be using the CCR5 entry inhibitor, laboratory testing to determine their tropism is necessary to determine if they will benefit from the drug before it is started. One potential drawback of a tropism assay is that it can fail to detect CXCR4-tropic virus when it makes up less than 10% of the virus population. In addition, patients have been shown to switch viral tropism between the time they have the tropism assay and the time that they begin therapy with an entry inhibitor.

Tropism assays identify whether the virus uses the CCR5 co-receptor, the CXCR4 co-receptor, or a combination of CCR5 and CXCR4 (dual/mixed). Several methods are available to determine HIV tropism including cell-based assays, DNA sequencing and heteroduplex tracking assays. In addition, there are two commercially available tropism assays: Monogram Diagnostics' *Trofile*™ and Pathway Diagnostics' *SensiTrop*™ (available through Quest Diagnostics, Inc.):

- *Trofile*™ was used to determine tropism by Pfizer in all the FDA clinical trials for Selzentry™.
- All existing diagnostic assays and methodologies, including *SensiTrop*™ and *Trofile*™, lack varying degrees of sensitivity and/or specificity.
- There are no published studies comparing *SensiTrop*™ to *Trofile*™.
- The FDA does not regulate the safety or effectiveness of these so-called "in-house or home brewed" tests.

In spite of a well-established relationship between co-receptor use and HIV disease progression, viral tropism is not currently used in the clinical follow-up of HIV-infected patients. The role of tropism assays in clinical practice remains to be established and will most likely depend on commercial availability of CCR5 or CXCR4 antagonists.

## Definitions

**Tropism:** viral tropism refers to the co-receptor used by the virus to enter human CD4 cells. Tropism is defined according to co-receptor usage (e.g. CCR5-tropic virus requires CCR5 to enter and infect the cell).

**Antagonist:** antagonists block the binding of an agonist (an agonist is a substance that binds to a specific receptor and triggers a response in the cell) at a receptor site. Co-receptor antagonists prevent the HIV virus from attaching to CD4 co-receptor.

## Policy

**HIV-1 co-receptor tropism assay requires preauthorization.**

---

<sup>1</sup> The use of a CCR5 targeting entry inhibitor in an individual with dual/mixed tropism allows the virus to switch and promotes the growth of CXCR4. It is thought that a shift from virus using CCR5 to CXCR4 while being treated with CCR5 antagonists could have dire consequences on HIV disease progression. Studies have shown that CXCR4-tropic HIV-1 may lead to faster progression to AIDS.

FCHP will cover an HIV-1 co-receptor tropism assay when all of the following criteria are met:

- The plan member is 18 years of age or older and has documented resistance to multiple antiretroviral agents, and
- The plan member is being considered for combination antiretroviral therapy which will include a co-receptor antagonist and the results of the co-receptor tropism assay will be used to evaluate the plan member's likely benefit from the co-receptor antagonist, and
- The plan member's viral load is at least 1,000 copies/ml (this is necessary to determine viral tropism).

### Exclusions

1. Repeat HIV-1 co-receptor tropism assays are not covered.
2. HIV-1 co-receptor tropism assays are not covered for monitoring HIV disease progression or for assessing early failure of co-receptor antagonist therapy.

### Codes

Codes	Number	Description
CPT	84999	Unlisted chemistry procedure

### References

1. Poveda E, Briz V, Quinines-Mateu M, Soriano V. HIV Tropism: Diagnostic Tools and Implications for Disease Progression and Treatment with Entry Inhibitors. *AIDS* 2006;20(10):1359-1367.
2. Selzentry™ (Pfizer, Inc. NY, NY) Full Prescribing Information. Issued August 2007. Available at: [http://media.pfizer.com/files/products/uspi\\_maraviroc.pdf](http://media.pfizer.com/files/products/uspi_maraviroc.pdf).
3. Skrabal K, Low AJ, Dong W, Sing T, Cheung PK, Mammano F, Harrigan PR. Determining Human Immunodeficiency Virus Co-receptor Use in a Clinical Setting: Degree of Correlation Between Two Phenotypic Assays and a Bioinformatic Model. *J Clin Microbiol* 2007 Feb;45(2):279-284.
4. Whitcomb JM, Huang W, Fransen S, Limoli K, Toma J, Wrin T, Chappey C, Kiss LDB, Paxinos EE, Petropoulos CJ. Development and Characterization of a Novel Single-Cycle Recombinant-Virus Assay To Determine Human Immunodeficiency Virus Type 1 Coreceptor Tropism. *Antimicrobial Agents and Chemotherapy* 2007 Feb;51(2):566-575.
5. Arasteh K, Stocker H. Tropism Switch in Patients Infected with HIV-1 and Its Clinical Implications for the Treatment with CCR5-Receptor Inhibitors. *Eur J Med Res* 2007;12:397-402.
6. Hoffman C. The Epidemiology of HIV Coreceptor Tropism. *Eur J Med Res* 2007;12:385-390.
7. Lorenzen T, Stoehr A, Walther I, Plettenberg A. CCR5 Antagonists in the Treatment of Treatment-Experienced Patients Infected with CCR5 Tropic HIV-1. *Eur J Med Res* 2007;12:419-425.
8. van Lunzen J. How Will CCR5 Antagonists Influence the Recommendations for the Antiretroviral Treatment of HIV-1 Infection? *Eur J Med Res* 2007;12:435-440.
9. Mueller MC, Bogner JR. Treatment with CCR5 Antagonists: Which Patient May Have a Benefit? *Eur J Med Res* 2007;12:441-452.

10. Foeglein A, Walter H. Determination of HIV-1 Coreceptor Tropism in Clinical Practice. *Eur J Med Res* 2007;12:473-482.
11. Braun P, Wiesmann F. Phenotypic Assays for the Determination of Coreceptor Tropism in HIV-1 Infected Individuals. *Eur J Med Res* 2007;12:463-472.
12. Sierra S, Kaiser R, Thielen A, Lengauer T. Genotypic Coreceptor Analysis. *Eur J Med Res* 2007;12:453-462.
13. Briz V, Poveda E, Soriano V. HIV Entry Inhibitors: Mechanisms of Action and Resistance Pathways *J Antimicrob Chemotherapy* 2006;57:619-627.

### Products to which this policy applies

- ⊕ FCHP Direct & Select Care
- ⊕ FHLAC Indemnity
- ⊕ Fallon Preferred Care
- ⊕ MassHealth
- ⊕ Non-Group: FCHP Independent Care, Direct Enrollment, & Bill-at-Home
- ⊕ Fallon Senior Plan™

### Committee review dates

Technology Assessment Subcommittee: 01/08/2008, 02/26/2008

Technology Assessment Committee: 04/08/2008

#### IMPORTANT NOTE

**Not all services are covered for all commercial products or employer groups.** Even though this policy may indicate that a particular service or supply is considered covered, this conclusion is not based upon the terms of your particular benefit plan. Each benefit plan contains its own specific provisions for coverage and exclusions. Not all benefits that are determined to be medically necessary will be covered benefits under the terms of your benefit plan. You need to consult the Evidence of Coverage to determine if there are any exclusions or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and your plan of benefits, the provisions of your benefits plan will govern. However, applicable state mandates will take precedence with respect to fully insured plans and self-funded non-ERISA (e.g., government, school boards, church) plans. Unless otherwise specifically excluded, Federal mandates will apply to all plans. With respect to Medicare and Medicaid members, this policy will apply unless Medicare and Medicaid policies extend coverage beyond this Medical Policy.