

# **Test Specific Guidelines**

# HIV Tropism Testing for Maraviroc Response

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## Introduction

HIV tropism testing for maraviroc response is addressed by this guideline.

## Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

<u>Procedures addressed by this guideline</u>	<u>Procedure codes</u>
<u>HIV-1 Tropism Genotyping, Common</u>	<u>87901</u>
<u>HIV-1 Tropism Genotyping, Other</u>	<u>87906</u>
<u>HIV-1 Tropism Phenotyping</u>	<u>87999</u>

## What Is HIV Tropism Testing for Maraviroc Response?

### Definition

HIV tropism testing is used to help determine an individual's response to maraviroc (Selzentry®). Maraviroc is only effective against CCR5-tropic HIV-1.

### Human Immunodeficiency Virus (HIV)

HIV replicates itself in humans by infecting T-cells with CD4 receptors (often called CD4 cells). HIV-1 enters the CD4 cell by binding one of two cell surface co-receptors: CCR5 or CXCR4.<sup>1,2</sup>

#### Tropism classifications

Tropism is the ability of HIV-1 virus to use one or both of these co-receptors. There are three main tropism classifications:<sup>3</sup>

CCR5 tropism (R5-tropic) — HIV-1 virus that only infects cells with the CCR5 co-receptor.

CXCR4 tropism (X4-tropic) — HIV-1 virus that only infects cells with the CXCR4 co-receptor.

**Dual or mixed tropism (D/M-tropic) — HIV-1 virus populations that can use either co-receptor to infect cells.**

### **Tropism Classification Changes**

**CCR5-tropic virus predominates in early infection and treatment naïve patients.<sup>1-3</sup>**

**CXCR4 tropism increases both as the disease progresses and with treatment.<sup>1</sup> In later infection, CXCR4 tropism emerges in about 20% of treatment naïve patients.<sup>3</sup>**

**Treatment-experienced patients have up to a 50% chance for the presence of CXCR4-tropic virus.<sup>1</sup>**

### **Treatment**

**Maraviroc is an antiretroviral drug that selectively binds to the CCR5 co-receptor. This blocks CCR5-tropic HIV-1 from binding to the co-receptor and entering the cell.<sup>4</sup>**

#### **Contraindication**

**Maraviroc is effective only against CCR5-tropic HIV-1. Patients with viruses using both the CXCR4 and CCR5 receptors (dual/mixed tropic) do not respond virologically to maraviroc.<sup>4</sup> Therefore, maraviroc is not indicated for CXCR4-tropic or dual or mixed-trophic HIV-1 infections.<sup>4</sup>**

#### **Clinical resistance**

**Virologic failure on maraviroc can result from outgrowth of undetected CXCR4 virus as a result of maraviroc treatment.<sup>4</sup>**

## **Test Information**

### **Introduction**

**HIV tropism testing may include phenotype testing or genotyping assays.**

### **When to Test**

**HIV tropism testing should be performed before maraviroc therapy is initiated. Maraviroc should only be used in adults with CCR5-tropic HIV-1 infections based on those results.<sup>2,4</sup>**

**Testing may also be considered for patients with treatment failure on maraviroc. Treatment failure is often associated with a switch to CXCR4 tropism.<sup>5</sup>**

### **Phenotype Testing (Trofile®)**

**Phenotype testing was the first method available and is most widely recommended.<sup>2,6</sup> Phenotyping works by exposing cell lines with CCR5 or CXCR4 co-receptors to virus made with a patient's HIV-1 genes that control tropism. The**

virus' ability to infect each cell line is assessed based on the expression of a reporter gene.<sup>2,7</sup> Patients enrolled in maraviroc clinical trials were screened using the Trofile phenotype assay.<sup>7,8</sup> A newer, more sensitive version of the assay was subsequently released.<sup>9</sup>

## Genotyping Assays

There are two genotypic assays used for tropism.

The first assesses the V3-coding region of the HIV-1 envelope gene (the third variable loop, V3) which is the primary determinant of tropism. Quest Diagnostics' website states that sensitivity to detect X4 virus in 90% of dual-mixed samples is 18% X4 at a viral load of 25,000 copies/mL and 6% X4 at a viral load of 100,000 copies/mL. The genotyping assay assesses part of the HIV-1 envelope gene (the third variable loop, V3) that is the primary determinant of tropism. If the plasma viral load is <1,000 copies/ml, sufficient viral RNA may not be amplified to perform a standard tropism test.<sup>9</sup>

The second, HIV-1 proviral DNA genotypic tropism testing, is available for patients with HIV RNA <1,000 copies/mL or undetectable plasma viral load. These assays evaluate HIV-1 proviral DNA integrated within infected cells for CXCR4-utilizing viral strains.<sup>10,11</sup>

## Guidelines and Evidence

### Introduction

This section includes relevant guidelines and evidence pertaining to HIV tropism testing for maraviroc response.

### Department of Health and Human Services Panel

The Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS, 2021) recommended:<sup>2</sup>

"A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered." [Evidence level AI]

"Co-receptor tropism testing is recommended in patients who exhibit virologic failure on a CCR5 antagonist." [Evidence level BIII]

"A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage." [Evidence level AI]

"A genotypic tropism assay should be considered as an alternative test to predict HIV-1 co-receptor usage." [Evidence level BII]

"A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when a CCR5 antagonist is considered for use in a new regimen (e.g., as part of a regimen switch or simplification)." [Evidence level BII]

**“.Compared to genotypic testing, phenotypic testing has more evidence supporting its utility. Therefore, a phenotypic test for co-receptor usage is generally preferred [Evidence level AI]. However, because phenotypic testing is more expensive, requires more time to perform, and may have logistic challenges, a genotypic test to predict HIV-1 co-receptor usage should be considered as an alternative test” [Evidence level BII]**

### **Infectious Diseases Society of America**

**The Infectious Diseases Society of America (IDSA, 2020) guidelines agreed that tropism testing should be done before starting any CCR5 antagonist. IDSA also stated patients who exhibit virologic failure while taking a CCR5 antagonist may also be considered for tropism testing.<sup>6</sup>**

### **U.S. Food and Drug Administration**

**Maraviroc (Selzentry®) has been approved for use in treatment-experienced patients 16 years of age and older with only CCR5-tropic HIV-1 virus and evidence of replication despite the use of several other antiretroviral therapies.<sup>4</sup> Regarding tropism testing, maraviroc product labeling stated:<sup>4</sup>**

**“Tropism testing must be conducted with a highly sensitive tropism assay that has demonstrated the ability to identify patients appropriate for SELZENTRY use.”**

**“Use of SELZENTRY 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.”**

## **Criteria**

### **Introduction**

**Requests for HIV tropism testing for maraviroc response are reviewed using these criteria.**

### **CCR5 Tropism Testing**

**CCR5 tropism testing is considered medically necessary for the following individuals:**

**Individuals with HIV-1 infection considering a CCR5 inhibitor, OR**

**Individuals taking a CCR5 inhibitor who experience treatment failure**

## **References**

### **Introduction**

**These references are cited in this guideline.**

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**Armand-Ugon M, Moncunill G, Gonzalez E, et al. Different selection patterns of resistance and cross-resistance to HIV-1 agents targeting CCR5. *J Antimicrob Chemother.* Mar 2010;65(3):417-424.**

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**Recordon-Pinson P, Soulie C, Flandre P, et al. Evaluation of the genotypic prediction of HIV-1 coreceptor use versus a phenotypic assay and correlation with the virological response to maraviroc: the ANRS GenoTropism study. *Antimicrob Agents Chemother.* Aug 2010;54(8):3335-3340.**

**Quest Diagnostics. HIV-1 Coreceptor Tropism, Ultradeep Sequencing Test Summary. Available at: <http://education.questdiagnostics.com/faq/FAQ86v1>.**

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