

Evidence Based Guideline

Laboratory Testing for HIV Tropism

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Description of Procedure or Service

The human immunodeficiency virus (HIV-1), which causes acquired immunodeficiency syndrome, uses co-receptor proteins (either CCR5 or CXCR4) on the surface of target cells to enter and infect the cells. The most commonly transmitted strains of HIV-1 bind to CCR5 and are said to have “tropism” for CCR5-expressing cells. Dual or mixed (D/M) tropic viruses can bind to either receptor type. It is estimated that around 85% of treatment-naïve patients harbor CCR5-tropic virus only, around 15% harbor D/M virus, and less than 1% are infected with CXCR4-tropic virus alone. CXCR4-tropic virus is associated with immunosuppression and later stages of disease. New, experimental drugs, termed co-receptor antagonists, have been designed to interfere with the interaction between HIV-1 and its co-receptors.

Maraviroc (Selzentry™, Pfizer) is the first co-receptor antagonist to be approved by the U.S. Food and Drug Administration (FDA). Maraviroc is a selective, slowly reversible, small-molecule antagonist of the interaction between human cell surface CCR5 and HIV-1 gp120, also necessary for HIV-1 cell infection. Blocking this interaction prevents CCR5-tropic HIV-1 entry into cells. However, CXCR4-tropic HIV-1 entry is not prevented. According to the label, maraviroc, in combination with other antiretroviral agents, is indicated for adult patients who:

- are treatment experienced, or
- are treatment naïve (approved as of November 24, 2009);
- are infected with only CCR5-tropic detectable HIV-1;
- have evidence of viral replication.

The FDA-approved full prescribing information for the drug states that “Tropism testing must be conducted with a highly sensitive and specific tropism assay that has demonstrated the ability to identify patients appropriate for [maraviroc] use.” This is because efficacy was not demonstrated in a Phase II study of maraviroc in patients with D/M or CXCR4-tropic HIV-1. Due to potential adverse effects (hepatic and cardiotoxicity), maraviroc should only be used in indicated patients.

HIV tropism testing is available by either phenotypic or genotypic methods. Tropism testing with a phenotypic assay, a cellular-based assay that functionally determines tropism, is available with the enhanced sensitivity Trofile™ (Monogram Biosciences, South San Francisco, CA) assay. This phenotypic assay uses virus stocks pseudotyped with envelope sequences derived from patient plasma to infect cell lines engineered to express CCR5 or CXCR4 HIV-2 co-receptors. Other phenotypic assays have been developed (e.g., in Europe) but commercial availability in the United States is uncertain. Genotypic tropism testing, which infers tropism on the basis of sequencing data, was first available with the SensiTrop assay. However, the SensiTrop assay has been discontinued and replaced by assays from other commercial and laboratory sources. For example, Quest Diagnostics Inc. offers the HIV-1 Coreceptor Tropism test, which is based on heteroduplex analysis of PCR-amplified and sequenced regions of the HIV-1 envelope V3 loop.

*****Note: This Evidence Based Guideline is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

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HIV tropism testing with the phenotypic assay may be appropriate for selecting patients for treatment with HIV co-receptor antagonists such as maraviroc. Patients indicated for testing:

- have evidence of viral replication, and
- have failed multiple antiretroviral treatment regimens, or
- are treatment naïve.

Medical Evidence regarding Laboratory Testing for HIV Tropism indicates it is not recommended in the following situations

HIV tropism testing using other assay techniques is not recommended

HIV tropism testing without immediate plans to prescribe HIV co-receptor antagonists such as maraviroc is not recommended

Repeat HIV tropism testing during co-receptor antagonist treatment or after failure with co-receptor antagonists is not recommended.

HIV tropism testing to predict disease progression (irrespective of co-receptor antagonist treatment) is not recommended.

Rationale

HIV-1 viral load is a strong prognostic indicator of HIV disease progression, and suppression of viral load is a critical goal of antiretroviral therapy. Viral rebound (virologic failure) is typically followed by a reduction in CD4 cell count (immunologic failure), and if not adequately addressed by changes in treatment, by HIV-related events (clinical progression). Thus, success of any antiretroviral treatment regimen is monitored by measuring HIV-1 RNA level and CD4 cell count; significant changes direct patient management.

Viral strains transmitted in vivo are almost always CCR5-tropic by current assay methods, even when the source virus contains a CXCR4-tropic component. Over time and more often after antiretroviral treatment, detectable CXCR4-tropic virus emerges in about half of patients and is associated with rapid CD4 cell depletion and clinical disease progression. However, patients whose infection remains predominately CCR5-tropic can also experience disease progression. Whether the emergence of CXCR4-tropic virus is a cause or a consequence of immunologic deterioration is unknown. Using tropism monitoring to direct antiretroviral therapy has not been established.

A concern regarding treatment with CCR5 co-receptor antagonists is that small, undetectable populations of CXCR4-tropic virus would be enriched and accelerate disease progression. However, in a randomized, placebo-controlled phase II study of maraviroc treatment of patients with dual/mixed-tropic infections, there was no evidence of significantly decreased CD4 cell count nor of increased viral load or disease progression in maraviroc-treated individuals. Additional study of tropism switching is needed in ongoing clinical trials of HIV-1 co-receptor antagonists. Recently, the association of CXCR4 tropism (defined with the Trofile assay) with clinical progression has been shown to be independent of CD4 cell count and HIV-1 RNA level (adjusted hazard ratio 3.82, 95% CI: 1.69–8.60, p=0.001 compared to patients with CCR5-tropic infection only). However, there currently is no recommended management change based on a CCR5 to CXCR4 tropism switch during treatment with maraviroc. Treatment failure is detected by increased viral load and decreased CD4 cell count, indicating that maraviroc treatment can be discontinued. As more co-receptor antagonists become available, however, tropism monitoring may signal impending need to change from one to another to maintain viral control. Studies will be needed to support improved outcomes with additional tropism monitoring compared to standard monitoring of viral load and CD4 cell count alone.

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Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

Billing/Coding/Physician Documentation Information

This guideline may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable codes: no specific code

Scientific Background and Reference Sources

Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1-139. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

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(2):566-75

Philpott SM. HIV-1 coreceptor usage, transmission, and disease progression. *Curr HIV Res* 2003; 1(2):217-27

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.49, 12/11/08

Senior Medical Director review 10/2009

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.49, 12/10/09

Policy Implementation/Update Information

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| 11/9/09 | New evidence based guideline developed. HIV tropism testing with the phenotypic assay may be appropriate for selecting patients for treatment with HIV co-receptor antagonists such as maraviroc. Patients indicated for testing have failed multiple antiretroviral treatment regimens and have evidence of viral replication. (adn) |
| 3/16/10 | Specialty Matched Consultant Advisor Panel review 2/11/10. Description section updated. Evidence Based Guideline revised to read: HIV tropism testing with the phenotypic assay may be appropriate for selecting patients for treatment with HIV co-receptor antagonists such as maraviroc. Patients indicated for testing: have evidence of viral replication, and have failed multiple antiretroviral treatment regimens, or are treatment naïve. Also revised the Not Recommended section to read. "HIV tropism testing using other assay techniques is not recommended. HIV tropism testing without immediate plans to prescribe HIV co-receptor antagonists such as maraviroc is not recommended. Repeat HIV tropism testing during co-receptor antagonist treatment or after failure with co-receptor antagonists is not recommended. HIV tropism testing to predict disease progression (irrespective of co-receptor antagonist treatment) is not recommended." (adn) |

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