Anthem

Clinical UM Guideline

Subject: Tropism Testing for HIV Management
Guideline #: CG-LAB-03
Status: Reviewed

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Description

This document addresses the use of phenotypic co-receptor tropism assay tests in the management of individuals with human immunodeficiency virus type-1 (HIV-1) infection. Phenotypic co-receptor tropism testing with the Trofile® assay (Trofile or Trofile DNA, Monogram Biosciences, Inc., South San Francisco, CA) is performed to identify HIV viral tropism (that is, chemokine receptor 5 [CCR5], chemokine receptor 4 [CXCR4], or dual/mixed-tropic) to assist in the selection of individuals for a CCR5 antagonist.

Clinical Indications

Medically Necessary:

HIV tropism testing with a phenotypic co-receptor tropism assay is considered**medically necessary** in an HIV-1 infected individual for **either** of the following indications:

- Prior to initiating a combination antiretroviral drug regimen with a co-receptor antagonist (CCR5 inhibitor, that is, maraviroc);**or**
- In an individual who has experienced virologic failure while receiving therapy that contains a CCR5 inhibitor.

Not Medically Necessary:

HIV tropism testing with a phenotypic co-receptor tropism assay is considered**not medically necessary** for all other indications, including, but not limited to the following:

- When using other co-receptor (genotypic) assay techniques;**or**
- Repeat HIV tropism testing during co-receptor antagonist treatment or after failure with a co-receptor antagonist;**or**
- To predict disease progression, irrespective of co-receptor antagonist treatment.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When services may be Medically Necessary when criteria are met:

CPT	
87999	Unlisted microbiology procedure [when specified as HIV tropism testing with a phenotypic co-receptor tropism assay]
ICD-10 Diagnosis	
B20	Human immunodeficiency virus [HIV] disease
O98.711	Human immunodeficiency [HIV] disease complicating pregnancy, first trimester
O98.712	Human immunodeficiency [HIV] disease complicating pregnancy, second trimester
O98.713	Human immunodeficiency [HIV] disease complicating pregnancy, third trimester
O98.719	Human immunodeficiency [HIV] disease complicating pregnancy, unspecified trimester
O98.72	Human immunodeficiency [HIV] disease complicating childbirth
O98.73	Human immunodeficiency [HIV] disease complicating the puerperium
Z21	Asymptomatic human immunodeficiency virus [HIV] infection status
Z71.7	Human immunodeficiency virus [HIV] counseling

When services are Not Medically Necessary:
For the procedure code listed above when criteria are not met, or when the code describes a procedure or situation designated in the Clinical Indications section as not medically necessary.

Discussion/General Information

HIV enters cells by a complex process that involves attachment to the CD4 receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cell membranes. The CCR5 co-receptor antagonist (inhibitor) antiretroviral drug, maraviroc (Selzentry®, ViiV Healthcare, Research Triangle Park, NC; Pfizer Manufacturing Deutschland GmbH), prevents HIV entry into target cells by binding to the CCR5 receptor. To date, Selzentry is the only U.S. Food and Drug Administration (FDA) approved CCR5 antagonist agent available to treat CCR5-tropic HIV-1 infection.

The HIV-1 infection, which causes acquired immunodeficiency syndrome (AIDS), 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. Over the course of infection, CXCR4 using HIV-1 clones emerge in some infected individuals. Viruses in many untreated individuals eventually exhibit a shift in co-receptor tropism from CCR5 to either CXCR4 or both CCR5 and CXCR4 (that is, dual- or mixed-tropic; D/M tropic). According to the U.S. Department of Health and Human Services (DHHS, 2023), this shift is temporally associated with a more rapid decline in CD4 T-cell counts. Co-receptor antagonists have been designed to interfere with the interaction between HIV-1 and its co-receptors. When there is documentation, the individual has detectable CXCR4 or D/M-tropic virus, it is assumed that such viruses will always be present. As such, CCR5 co-receptor antagonists will no longer be active for those individuals and should not be used. Additionally, the results of all prior tropism tests should be

obtained, "…and if CXCR4-utilizing or D/M-tropic viruses have ever been detected previously, then *repeat* testing is not necessary and a CCR5 co-receptor antagonist should not be used" (DHHS, 2023).

The International Antiviral Society-USA Panel updated recommendations for antiretroviral drugs for treatment and prevention of HIV infections in adults (Saag, 2018) state:

> In patients with established HIV, antiretroviral therapy (ART) should be initiated as soon as possible after diagnosis…For virologic failure with more complex treatment history, therapy with at least 2 fully active drugs from different antiretroviral classes, perhaps including maraviroc in the setting of CC chemokine receptor 5 (CCR5)-tropic virus, is recommended.

Maraviroc is the first, and currently the only chemokine co-receptor antagonist drug approved by the FDA to treat CCR5-tropic HIV-1. Maraviroc is a selective, slowly reversible, small-molecule antagonist of the interaction between human cell surface CCR5 and HIV-1 glycoprotein 120 (gp120), necessary for HIV-1 cell infection. Blocking this interaction prevents CCR5-using HIV-1 strains from entry into cells. However, CXCR4-using HIV-1 strains are not prevented. On November 20, 2009, the FDA approved a supplemental new drug application (NDA) to expand the indication for maraviroc to include combination antiretroviral treatment of therapy-naive adults infected with CCR5-tropic HIV-1 virus. The expanded indication is based on safety and efficacy data collected through 96 weeks from the large, double-blind, prospective randomized MERIT trial (Maraviroc versus Efavirenz in Treatment-Naive Patients) which compared combination therapy of maraviroc/zidovudine/lamivudine to the combination therapy regimen of efavirenz/zidovudine/lamivudine (Cooper, 2010; Saag, 2009). In treatment-naive subjects, more subjects treated with maraviroc experienced virologic failure and developed lamivudine resistance compared with efavirenz. Presently, there is no data available in the pediatric population; therefore, maraviroc should not be used in individuals younger than 16 years of age (Selzentry Product Information [PI], 2018).

Tropism Testing

For the clinical studies of individuals with treatment failure, tropism at enrollment and again at baseline was determined using the original phenotypic Trofile assay for 2560 potential enrollees; 56% were CCR5-tropic only and were eligible for the clinical trials. Most other individuals had dual/mixed co-receptor protein HIV infection; CXCR4-infection alone is rare. Of the individuals enrolled, 90% had CCR5-tropic virus at baseline, 4% had dual/mixed tropic virus, and 5% had non-typable virus infection.

Based on information presented to the FDA Antiviral Drugs Advisory Committee and on published assay validation data (Whitcomb, 2007), the original phenotypic Trofile assay had a turnaround time of 14 to 18 days, failed to work in 3%-7% of individuals, and required at least 1,000 copies/mL of HIV RNA. The assay was 100% effective in detecting model CXCR4-tropic or dual/mixed HIV present in a 10% mixture, and 83% effective at a 5% mixture. Validation studies also indicated 100% accuracy of results for 38 samples with known tropism, and 100% reproducibility including repeat assays using multiple operators, instrumentation, reagent lots, and conducted over a 14-day period. No false-positive results were obtained on samples that were HIV-negative but positive for either hepatitis B or C virus.

A more sensitive, second-generation assay replaced the original Trofile assay. The assay examines the complete gp160 coding region of the HIV-1 envelope protein. According to information from Monogram Biosciences, the enhanced sensitivity Trofile can detect CXCR4-tropic virus present at levels less than 0.3% of the total virus population, and at that level of virus, the assay is 100% sensitive. Viral load must be at least 1,000 copies/ml to determine viral tropism. Supportive data, however, have not yet been published. No information could be found on turnaround time; it is assumed to be unchanged from the original assay, that is, 14-18 days.

The enhanced sensitivity Trofile assay became available after week 48 analysis of the phase III treatment-naive MERIT trial (Maraviroc versus Efavirenz in Treatment-Naive Patients); approximately 15% of the subjects identified as CCR5-tropic using the original assay had dual/mixed- or CXCR4-tropic virus by the enhanced sensitivity assay. Reanalysis of the data at week 96 of the MERIT study using the enhanced sensitivity assay screening results reduced the number of maraviroc virologic failures with dual/mixed- or CXCR4-tropic virus to 12 compared to 24 of the 311 subjects when screening with the original Trofile HIV tropism assay (Sierra-Madero, 2010; Selzentry PI, 2018).

Based on the clinical studies used for the FDA approval, and the labeled requirement for tropism testing prior to initiating a course of maraviroc, HIV tropism testing using the Trofile assay is recommended for both treatment-experienced and treatment-naive individuals who are being considered for immediate treatment with maraviroc. Because maraviroc requires twice-daily dosing and requires a tropism assay prior to use, the U.S. Department of Health and Human Services (DHHS) *Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV* (updated 2023) no longer recommends maraviroc for use as initial therapy given that maraviroc has "no virologic benefit when compared with other recommended regimens."

Phenotypic assays are used most often in the clinical trials of CCR5 antagonists, and are considered the "gold standard" for comparison with other methods of tropism testing. Enhancements have allowed detection of a lower threshold of minor CXCR4-using species (Lin, 2009). The Trofile DNA assay test is commercially available to determine the co-receptor tropism (CCR5, CXCR4, or dual/mixed) status of the HIV-1 strain when an individual's HIV-1 viral load is *less than* 1,000 copies/mL. The Trofile DNA is a single cycle pseudovirion-based tropism assay (a proviral DNA tropism assay) that uses the complete gp160 coding region of the HIV-1 virus to evaluate tropism. Instead of using HIV RNA isolated from an individual's plasma as in the Trofile assay, the Trofile DNA assay uses cell associated viral DNA taken from whole blood cells infected with HIV. The turnaround time is unchanged from the original assay (that is, 14-18 days). Testing is by polymerase chain reaction (PCR) amplification and viral culture.

The DHHS updated Guidelines recommends the use of co-receptor tropism assays (including a phenotypic tropism assay) in clinical practice as follows:

- A co-receptor tropism assay should be performed whenever the use of a CCR5 co-receptor antagonist is being considered (Level of Evidence AI);
- Co-receptor tropism testing is also recommended for patients who exhibit virologic failure on a CCR5 antagonist (Level of Evidence BIII);
- A phenotypic tropism assay is preferred to determine HIV-1 co-receptor usage (A1);
- A proviral DNA tropism assay can be utilized for patients with undetectable HIV-1 RNA when CCR5 antagonist is considered for use in a new regimen (e.g., as part of a regimen switch or simplification) (BII).

Note:

- Rating of Recommendations: A = Strong; B = Moderate; C = Optional
- Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion.

The *Antiretroviral Drug for Treatment and Prevention of HIV Infection in Adults - 2018 Recommendations of the International Antiviral Society-USA Panel* (Saag, 2018) states that CCR5 tropism testing results must be confirmed prior to initiating ART that includes maraviroc and at time of virologic failure. The *Primary Care Guidance for Persons with Human Immunodeficiency Virus: 2020 Update by the HIV Medicine Association of the Infectious Diseases Society of America* (Thompson, 2021) agrees with this position and states that tropism testing should be performed if the use of a CCR5 antagonist is being considered or if an individual has exhibited virologic failure while taking a CCR5 antagonist. Furthermore, "routine tropism testing is not recommended prior to initiation of other regimens because of cost and lack of demonstrated benefit."

Definitions

Acquired Immunodeficiency Syndrome (AIDS): A disease of the body's immune system caused by the human immunodeficiency virus (HIV). AIDS is characterized by the death of CD4 cells (an important part of the body's immune system), which leaves the body vulnerable to life-threatening conditions, such as infections and cancers.

Antagonist: Blocks the binding of an agonist (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 the CD4 co-receptor.

CD4 cells: A type of infection-fighting white blood cell that carries the CD4 receptor on its surface; also known as helper T cell or CD4 lymphocyte. CD4 cells coordinate the immune response, which signals other cells in the immune system to perform their special functions. The number of CD4 cells in a sample of blood is an indicator of the health of the immune system. HIV infects and kills CD4 cells, which leads to a weakened immune system.

Chemokine receptor 5 (CCR5): A protein on the surface of some immune system cells. Along with CXCR4, it is one of two co-receptors that HIV can use along with the CD4 receptor to bind to and enter host cells.

Co-receptor: A protein on the surface of a cell that serves as a second binding site for a virus or other molecule. Although the CD4 protein is HIV's primary receptor, the virus must also bind to either the CCR5 or CXCR4 co-receptor to get into a host cell.

Human Immunodeficiency Virus (HIV): The virus that causes Acquired Immunodeficiency Syndrome (AIDS). HIV is in the retrovirus family and is responsible for most HIV infections throughout the world.

Treatment-experienced: A term used to describe HIV-infected individuals who are currently being treated with anti-HIV drugs or who have taken anti-HIV drugs in the past.

Treatment failure: A broad term that describes failure of an anti-HIV treatment to adequately control the HIV infection. The three types of HIV treatment failure are virologic, immunologic, and clinical failure. Factors that contribute to treatment failure include poor adherence, drug resistance, and drug toxicity.

Treatment-naïve: A term used to describe HIV-infected individuals who have never taken anti-HIV drugs.

Viral load (VL): The amount of HIV RNA in a blood sample, reported as the number of HIV RNA copies per milliliter of blood plasma; also known as HIV RNA. The VL provides information about the number of cells infected with HIV and is an important indicator of HIV progression and of how well treatment is working.

Viral tropism: Refers to which type of co-receptor HIV uses when binding to a cell during infection. HIV can bind to the CXCR4 co-receptor (X4-tropic) or to the CCR5 co-receptor (R5-tropic) on a cell surface. Although the virus often prefers one co-receptor to the other, it also can be dual/mixed-tropic HIV that can bind to either co-receptor. Viral tropism may switch, or change from preference for one co-receptor to the other, during the course of an HIV infection.

Virologic failure: The inability of anti-HIV drug treatment to reduce the viral load or to maintain suppression of the viral load. Virologic failure is the most common type of treatment failure and may lead to immunologic and clinical failure.

References

Peer-Reviewed Publications:

1. Cooper DA, Heera J, Goodrich J, et al. Maraviroc versus efavirenz, both in combination with zidovudine-lamivudine, for the treatment of antiretroviral-naive subjects with CCR5-tropic HIV-1 infection. J Infect Dis. 2010; 201(6):803-813.
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12. Sierra-Madero J, Di Perri G, Wood R, et al. Efficacy and safety of maraviroc versus efavirenz, both with zidovudine/lamivudine: 96-week results from the MERIT study. HIV Clin Trials. 2010; 11(3):125-132.
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Government Agency, Medical Society, and other Authoritative Publications:

1. Aves T, Tambe J, Siemieniuk RA, Mbuagbaw L. Antiretroviral resistance testing in HIV-positive people. Cochrane Database Syst Rev. 2018; 11:CD006495.
2. Kityo C, Thompson J, Nankya I, et al; Europe Africa Research Network for Evaluation of Second-line Therapy (EARNEST)Trial Team. HIV drug resistance mutations in non-B subtypes after prolonged virological failure on NNRTI-based first-line regimens in sub-Saharan Africa. J Acquir Immune Defic Syndr. 2017; 75(2):e45-e54.
3. Saag MS, Benson CA, Gandhi RT, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2018 recommendations of the International Antiviral Society-USA Panel. JAMA. 2018; 320(4):1-18.
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Websites for Additional Information

1. U.S. Department of Health and Human Services (DHHS). AIDS*info* Glossary. Available at: https://clinicalinfo.hiv.gov/en/glossary. Accessed on August 8, 2023.

Index

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

History

Status	Date	Action
Reviewed	11/09/2023	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Discussion/General Information, References and Websites for Additional Information sections.
Reviewed	11/10/2022	MPTAC review. Updated Discussion/General Information, References and Websites for Additional Information sections.
Reviewed	11/11/2021	MPTAC review. Updated References section.
Reviewed	11/05/2020	MPTAC review. References were updated. Reformatted Coding section.
Reviewed	11/07/2019	MPTAC review. References were updated.
Reviewed	01/24/2019	MPTAC review. Updated Discussion, References, and Websites for Additional Information sections.
Revised	03/22/2018	MPTAC review. The document header wording updated from “Current Effective Date” to “Publish Date.” Clarified wording in Clinical Indications section and throughout document (changed coreceptor to co-receptor). Updated Discussion, References, Definitions, and Websites for Additional Information sections.
Reviewed	05/04/2017	MPTAC review. Updated Discussion, References and Websites for Additional Information sections.
Reviewed	05/05/2016	MPTAC review. Updated Discussion and References sections. Removed ICD-9 codes from Coding section.
Reviewed	05/07/2015	MPTAC review. Updated Description, Discussion, and References sections.
Revised	05/15/2014	MPTAC review. Revised criterion to include the Trofile DNA test. Updated the Description, Coding, Discussion, Definitions, References, Websites for Additional Information, and Index sections.
Reviewed	05/09/2013	MPTAC review. Minor format changes. Updated Discussion, References, and Websites for Additional Information sections.
Reviewed	05/10/2012	MPTAC review. Updated Description, Discussion, Coding and References.
	01/01/2012	Updated Coding section with 01/01/2012 CPT changes.
Revised	05/19/2011	MPTAC review. Revised criterion to clarify that HIV tropism testing is medically necessary in an individual prior to initiating a combination antiretroviral drug regimen with a co-receptor antagonist, and in an individual who has experienced virologic failure while receiving therapy that contains a CCR5 inhibitor. Removed not medically necessary statement for co-receptor tropism assay testing in the absence of antiretroviral treatment failure. Updated Discussion and References. Added Definitions and Websites for Additional Information.

Revised	05/13/2010	MPTAC review. Revised document title to Tropism Testing for HIV Management. Revised Clinical Indications, removing indications for phenotypic and genotypic assays used in HIV-1 management other than the co-receptor tropism assay test, Trofile™. Updated Discussion/General Information, Coding, References, and Index.
Revised	08/27/2009	MPTAC review. Revised/clarified medically necessary criteria for genotypic and phenotypic assays for drug resistance testing and for tropism testing with the co-receptor tropism assay based on DHHS guidelines. Clarified not medically necessary criterion for use of other co-receptor (genotypic) assay techniques. Updated Discussion and References.
Revised	05/21/2009	MPTAC review. Revisions as follows: 1) Subject/title to Phenotypic and Genotypic Assays in HIV Management; 2) Medically necessary criteria for HIV-treated individuals who have experienced virologic failure during antiretroviral therapy (ART), adding “defined as HIV RNA levels ≥500 but <1,000 copies/mL;” and criterion for testing pregnant women; 3) Revised not medically necessary criterion for individuals who have plasma HIV RNA levels of <500 copies/mL. Updated Discussion and References.
Revised	05/15/2008	MPTAC review. Revised/renamed document number to CG-LAB-03. Addition of medically necessary and not medically necessary criteria for HIV tropism testing with the co-receptor assay (Trofile™). Discussion, Coding, and References updated.
Revised	11/29/2007	MPTAC review. Addition of medically necessary criteria for HIV drug resistance testing through phenotype and genotype assays: In individuals with recently acquired HIV infection; and, in individuals with established HIV infection prior to initiating ART. Addition of timeframe criterion: HIV resistance testing is considered not medically necessary in individuals greater than four weeks after discontinuation of ART. Discussion and References updated.
Revised	12/07/2006	MPTAC review. Clarification of when concurrent genotypic and phenotypic assays are medically necessary. Concurrent genotypic and phenotypic testing is considered not medically necessary in all other situations. Coding updated; removed CPT 0023T deleted 12/31/2005.
Revised	09/14/2006	MPTAC review. Added concurrent testing by genotypic and phenotypic assay is duplicative. Updated References.
	01/01/2006	Updated Coding section with 01/01/2006 CPT/HCPCS changes
	11/22/2005	Added reference for Centers for Medicare and Medicaid Services (CMS) – National Coverage Determination (NCD).
Revised	09/22/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.			No document
WellPoint Health Networks, Inc.	12/02/2004	2.12.03	Phenotypic and Genotypic Resistance Assays in HIV Management

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