

Overview

Useful For

Identification of HIV-1 genotypic alterations in the integrase region of HIV-1 to predict antiretroviral drug resistance in HIV-1-infected patients receiving integrase strand transfer inhibitors (ie, bictegravir, cabotegravir, dolutegravir, elvitegravir, raltegravir)

Guiding initiation or change of drug combinations for the treatment of HIV-1 infection

Testing Algorithm

See [HIV Treatment Monitoring Algorithm](#) in Special Instructions.

Special Instructions

- [HIV Treatment Monitoring Algorithm](#)

Method Name

Reverse Transcriptase Polymerase Chain Reaction (RT-PCR)/DNA Sequencing

NY State Available

Yes

Specimen

Specimen Type

Plasma EDTA

Ordering Guidance

This test is intended to be used to monitor known HIV-positive infections. It is not intended for primary detection of HIV infections.

Shipping Instructions

Ship frozen on dry ice. If shipment will be delayed for more than 5 days, freeze specimen at -70 degrees C (up to 35 days) until shipment on dry ice.

Specimen Required

Supplies: Aliquot Tube, 5 mL (T465)

Collection Container/Tube: Lavender top (EDTA)

Submission Container/Tube: Plastic vial (polypropylene preferred)

Specimen Volume: 2.2 mL

Collection Instructions: Centrifuge and aliquot plasma per collection tube manufacturer's instructions for use (eg, centrifuge and aliquot within 2 hours of collection for BD Vacutainer tubes).

Additional Information: To ensure a minimum HIV-1 RNA amount (at least 500 copies/mL), the preferred blood volume must be submitted. Testing may be canceled if the specimen supplied is inadequate.

Reject Due To

Gross hemolysis OK
Gross lipemia OK

Specimen Minimum Volume

1.2 mL

Specimen Stability Information

| Specimen Type | Temperature | Time | Special Container |
|---------------|--------------------|---------|-------------------|
| Plasma EDTA | Frozen (preferred) | 35 days | |
| | Refrigerated | 5 days | |

Clinical & Interpretive

Clinical Information

Antiviral resistance may compromise highly active antiretroviral therapy (HAART) in HIV-1-infected patients receiving HAART. When combination therapy fails, detection and analysis of HIV genotypic variants can guide necessary changes to antiretroviral therapy and decrease HIV-1 viral load, thereby improving patient outcome.

HIV-1 is an RNA virus that infects cells and is then converted to complementary DNA (cDNA) by the action of the viral reverse transcriptase (RT). RT has little proofreading capacity and therefore incorporates errors in the proviral DNA. These errors are transcribed into infectious viral particles when the proviral DNA is transcribed into RNA. Similarly, the enzyme protease catalyzes a polyprotein to produce peptides necessary for active viral replication. Although HAART (combinations of nucleoside analogs, nonnucleoside agents, protease inhibitors, and/or integrase strand transfer inhibitors) may be effective in reducing viral load, genotypic alterations arising in drug-targeted HIV loci due to selective pressure from antiviral therapy can result in antiviral resistance that may compromise such therapy.

Amplification and analysis of drug-targeted HIV-1 sequences allow identification of changes in nucleotide sequence and

associated amino acid codons that may cause antiviral drug resistance. Such genotypic changes are identified by comparing the sequence data of the patient's HIV-1 strain to that of a wild-type HIV-1 strain. The significance of these genotypic alterations in relation to antiviral resistance is then determined by a set of interpretive rules developed and used by the Stanford HIVdb Program Genotypic Resistance Interpretation Algorithm (<http://sierra2.stanford.edu/sierra/servlet/JSierra>) for final interpretation.

In the Stanford HIVdb program, genotypic alterations are categorized and interpreted according to phenotypic antiviral susceptibility tests performed using the ViroLogic PhenoSense assay (Monogram Biosciences Inc) or a HeLa-CD4 reporter gene assay. Each alteration is assigned a drug penalty score and the total score generated from all of the alterations relevant to the specific antiviral drug is used to estimate the level of resistance to that drug. These interpretive rules may be updated periodically by the Stanford HIVdb Team after reviewing newly published data on HIV-1 genotypic drug resistance variants.

Reference Values

Not applicable

Interpretation

Detectable HIV-1 genotypic alterations conferring resistance to an antiviral drug are reported as amino acid codon changes (eg, N155H), along with associated resistance interpretations for the current FDA-approved integrase strand transfer inhibitors (bictegravir, cabotegravir, dolutegravir, elvitegravir, and raltegravir).

Susceptible (SUSC) indicates that the genotypic alterations present in patient's HIV-1 strain have not been associated with resistance to the specific drug (Stanford HIVdb total score 0 to 9).

Potential Low-Level Resistance (PLR) indicates that genotypic alterations detected have been associated with possible reduction in susceptibility to the specific drug (Stanford HIVdb score 10 to 14).

Low-Level Resistance (LR) indicates that genotypic alterations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 15 to 29).

Intermediate Resistance (IR) indicates that genotypic alterations detected have been associated with reduction in susceptibility to the specific drug (Stanford HIVdb score 30 to 59).

High-Level Resistance (HR) indicates that genotypic alterations detected have been associated with maximum reduction

in susceptibility to the specific drug (Stanford HIVdb score > or =60).

Unable to Genotype indicates that viral target sequences are of poor quality to reliably determine antiviral resistance. This result may be due to low viral load, ambiguous or incomplete viral target sequences, presence of polymerase chain reaction (PCR) inhibitors, and/or alterations in the PCR or sequencing primer binding regions.

Inconclusive indicates inability of the assay to reliably determine antiviral resistance because of the presence of PCR inhibitors, alterations in the PCR or sequencing primer binding regions, or ambiguous or incomplete viral target sequences that did not allow reliable analysis to determine antiviral resistance.

Cautions

Due to the complexity of the results generated, the International Antiviral Society-USA Panel recommends expert interpretation of genotyping and phenotype test results for patient care management. A patient's response to antiviral therapy depends on multiple factors, including the percentage of a patient's viral population that is drug resistant, patient compliance with the prescribed drug therapy, patient access to adequate care, drug pharmacokinetics, and drug interactions. Drug resistance test results should be interpreted only in conjunction with clinical presentation and other laboratory markers when making therapeutic decisions.

Absence of resistance to a drug does not rule out the presence of reservoirs of drug-resistant virus in the infected patient.

The HIV-1 genotypic test is not a direct measure of drug resistance. Although genotypic testing can detect variants in the relevant HIV-1 genome, the significance of these variants requires careful interpretation to predict drug susceptibility. This assay's ability to amplify the target and detect genotypic alterations is poor and unreliable when the plasma HIV-1 viral load is less than 500 copies/mL. Specimens submitted for this test should contain at least 500 copies/mL of HIV-1 RNA.

This assay has been optimized for genotypic analysis of HIV-1 group M, subtype B, which includes the majority of HIV-1 strains infecting patients in the United States and Europe. HIV-1 groups N and O, and some group M, non-B subtypes may not be detected using this assay, and the significance of variants and drug resistance variant interpretation for these other groups and subtypes of HIV-1 is unknown.

The genotypic alteration database and interpretive rules used by the Stanford HIVdb Program Genotypic Resistance Interpretation Algorithm for final interpretation are updated periodically. Therefore, the test results may not necessarily

include all of the drug-related variants described in the current medical literature.

Possible causes of treatment failure other than the development of drug resistance include poor adherence to medication regimen, drug potency, and individual variation in pharmacokinetics (eg, inadequate phosphorylation of nucleosides).

Clinical Reference

1. Ceccherini-Silberstein F, Cento V, Calvez V, Perno CF: The use of human immunodeficiency virus resistance tests in clinical practice. *Clin Microbiol Infect.* 2010;16:1511-1517
2. Taylor BS, Olender SA, Tieu HV, Wilkin TJ: CROI 2016: Advances in antiretroviral therapy. *Top Antivir Med.* 2016;24(1):59-81
3. Gunthard HF, Calvez V, Paredes R, et al: Human immunodeficiency virus drug resistance: 2018 Recommendations of the International Antiviral Society-USA Panel. *CID.* 2018;68:177-187
4. Saag MS, Gandhi RT, Hoy JF, et al: Antiretroviral drugs for treatment and prevention of HIV infection in adults: 2020 recommendations of the International Antiviral Society-USA Panel. *JAMA.* 2020;324(16):1651-1669
5. Panel on Antiretroviral Guidelines for Adults and Adolescents: Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV. NIH; Updated June 3, 2021 Accessed July 8, 2021. Available at <https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines>

Performance

Method Description

This assay uses a modified method of the ViroSeq HIV-1 Integrase Genotyping Kit (Abbott Molecular Inc.). HIV-1 RNA in a given human plasma specimen is extracted and purified by a manual method. The entire HIV-1 integrase sequence is amplified to generate a 1100-base pair (bp) product, which serves as a template for 4 sequencing primers designed to generate an assembled consensus sequence of approximately 900 bp in length. The ViroSeq Integrase Software version 1.0.0 is used to assemble, edit, and analyze alterations within this consensus sequence by comparing it to a known reference (wildtype) HIV-1 sequence. Manual review of all resistance-related codons (see table below) as defined by <http://hivdb.stanford.edu/DR/INIResiNote.html> is performed using ViroSeq Integrase Software v1.0.0 and each consensus sequence is analyzed by the Stanford HIVdb Program Genotypic Resistance Interpretation Algorithm (<http://sierra2.stanford.edu/sierra/servlet/JSierra>) for final interpretation of antiviral drug resistance. (Unpublished Mayo method)

| Antiretroviral resistance-associated codon positions for HIV-1 Integrase | | | | | |
|--|----|-----|-----|-----|-----|
| 50 | 95 | 128 | 145 | 151 | 193 |

| | | | | | |
|----|-----|-----|-----|-----|-----|
| 51 | 97 | 138 | 146 | 153 | 230 |
| 54 | 114 | 140 | 147 | 155 | 232 |
| 66 | 119 | 142 | 148 | 157 | 263 |
| 68 | 121 | 143 | 149 | 163 | - |

PDF Report

No

Specimen Retention Time

2 months

Performing Laboratory Location

Rochester

Fees & Codes
Test Classification

This test was developed, and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. This test has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information

87906

LOINC® Information

| Test ID | Test Order Name | Order LOINC Value |
|---------|-------------------------------------|-------------------|
| HIVI | HIV-1 Genotypic Integrase Resist, P | 72560-6 |

| Result ID | Reporting Name | LOINC® |
|-----------|-------------------------------------|---------|
| 63247 | HIV-1 Genotypic Integrase Resist, P | 83325-1 |
| 44168 | Integrase mutations | 61199-6 |
| 44169 | Dolutegravir | 72857-6 |
| 44170 | Elvitegravir | 72526-7 |
| 44171 | Raltegravir | 72525-9 |
| 603221 | Bictegravir | 90080-3 |
| 44172 | HIVI_SEQ: | 90903-6 |
| 614988 | Cabotegravir | 96566-5 |