GENOTYPIC DRUG RESISTANCE TESTING IN HIV MANAGEMENT

Policy Number: PDS - 009
Effective Date: January 1, 2015

Table of Contents

GUIDELINES 1
BACKGROUND 2
CLINICAL EVIDENCE 3
Guidelines and Recommendations 4
US FOOD AND DRUG ADMINISTRATION (US FDA) 5
CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS) 5
APPLICABLE CODING 5
REFERENCES 6
POLICY HISTORY/REVISION HISTORY 7

INSTRUCTIONS FOR USE
Physician Decision Support (PDS) is a lab ordering tool operated by BeaconLBS. This Clinical Guideline supports the Questions and Answers that appear in PDS for tests referenced in this document. UnitedHealthcare reserves the right, in its sole discretion, to modify its Clinical Guidelines as necessary. This Clinical Guideline is provided for informational purposes. It does not constitute a Medical Policy or medical advice.

GUIDELINES

Genotypic drug resistance testing for HIV infected patients is recommended in the following situations:

- When the newly diagnosed or chronically infected patient (child or adult) enters care, whether treatment is initiated at that time or deferred.
- If therapy is deferred, consideration should be given to repeat testing before therapy is initiated.
- For the selection of a new drug regimen in the setting of virologic failure (resistance testing should be performed while the patient is still on the failing regimen or within 4 weeks of discontinuation of the regimen).
- In pregnancy, genotypic testing is recommended prior to initiation of therapy and for those entering pregnancy with a detectable viral load. Additionally:

- Resistance testing is not recommended when the plasma viral load is below 500 copies/mL by plasma RNA HIV testing; plasma levels of 500-1000 copies/mL are required for adequate amplification.
These recommendations are based on current guidelines from the United States Department of Health and Human Services, International AIDS Society-USA Panel,1 Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children, Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission, and the HIV Medicine Association of the Infectious Diseases Society of America.1-5

BACKGROUND

Human Immunodeficiency Virus (HIV) enters the host and moves to the lymphatics where it replicates in CD4+ cells. It uses reverse transcriptase to transcribe its RNA into DNA before integrating into host DNA. Retroviruses are known to replicate with a high rate of mutation, and due to the genetic diversity of HIV, drugs targeting replication steps will be met with viral evolution. When resistant strains selectively emerge in the setting of antiretroviral therapy, the term acquired resistance is used. When antiretroviral resistance is transmitted from one person to another, the term primary or transmitted drug resistance is used. Antiretroviral resistance may be the result of a number of mutations, but in some cases, it can result from a single point mutation.

The first case of antiretroviral resistance was reported in 1989,6 and by 1995, an expert panel of physicians was selected by the International AIDS Society to establish guidelines for HIV drug therapy for patients in developed countries.1 This panel convenes regularly to update clinical guidelines. In the year 2000, the panel’s guidelines changed to identify drug resistance testing as standard of care for HIV,7 and this recommendation holds in the most recent panel guidelines.1 The move toward this recommendation in 2000 was based on retrospective and prospective studies of the clinical utility of resistance testing.

There are two main types of resistance testing: genotypic testing and phenotypic testing. In genotypic testing, PCR is used to amplify the reverse transcriptase, protease, and integrase genes of HIV-1. These regions are sequenced and compared to wild type reference sequences. A rules-based algorithm is used to make a prediction of susceptibility based on the mutations identified. In contrast, phenotypic testing is a direct measure of drug susceptibility. In phenotypic testing, the amplified regions of the patient’s virus are used to produce a recombinant virus that is grown in the presence of ARVs. The growth of the patient’s (recombinant) virus is compared to that of a wild type reference strain and a ratio is determined with defined cutoffs for determining susceptibility. Virtual phenotyping is a quantitative prediction of drug susceptibility. In this methodology, a patient’s genotype is compared to a wild type reference strain. A prediction of phenotypic drug susceptibility is then made by using a phenotype/genotype correlative database.

Currently, genotypic testing is the preferred method of determining resistance for patients on first or second regimens.7 While genotypic tests have a faster turnaround time and are less expensive than phenotypic tests, in some specific situations; the addition of phenotypic testing is useful, including cases of complex mutation patterns.2

Optimal therapy targets an increase in CD4 cell count of 50-100 cells/mm3 per year and a viral load of less than 200 copies/mL.2 Of the two monitoring tests, CD4 count and plasma HIV viral load, viral load is considered the stronger indicator of virologic failure. In previous years, any detectable viral load was considered evidence of virologic failure. However, viral blips and assay variability are less likely to confound the results if the cut-off set point for viral load is measurably higher than the detectable limit.2 For this reason, when the confirmed viral load is greater than 200 copies/mL, virologic failure is said to exist. Once virologic failure has been confirmed, resistance testing, as defined previously, should be carried out.1
Although there are many factors including adherence issues, problems with drug metabolism, and coinfection that can contribute to virologic failure, resistance to antiretroviral therapy is an important cause of virologic failure. Consequently, resistance testing is a key laboratory tool in the clinical management of the HIV-positive patient.

**CLINICAL EVIDENCE**

A recent estimate of the prevalence of transmitted drug resistance in newly diagnosed patients is 14.6% although lower rates have been reported globally.\(^8\),\(^9\) Whether a single variant or multiple resistant variants are transmitted may depend in part on the mode of viral transmission with high risk behaviors increasing the chance of transmitting multiple resistant variants.\(^10\),\(^11\) A study of newly diagnosed HIV patients in the United States looked at the prevalence of transmitted resistance to three antiretroviral classes (NNRTIs, NRTIs, and PIs). The study reported transmitted resistance prevalences of 7.8%, 5.6% and 4.5% for the three classes, respectively. In the same study, the prevalence of resistance to a single class of antiretroviral drugs (12.1%) was greater than that for two (1.9%) or three (0.7%) drug classes.\(^5\) Research has also shown that resistance to one drug in a failing regimen does not necessitate abandoning all the drugs in that regimen. For example, it may be acceptable to continue using the protease inhibitor in a failing regimen if susceptibility to that protease inhibitor is maintained, as identified by resistance testing.\(^1\)

Randomized, prospective, controlled trials have shown that genotypic testing improves response to therapy in patients with virologic failure on a combined antiretroviral regimen. In the VIRADAPT pilot study, 65 patients failing a combination regimen had their subsequent regimen selected with data from resistance testing and 43 patients failing a combination regimen had their subsequent regimen selected based on clinical guidelines alone without resistance testing. HIV RNA levels were monitored, and at month 6, plasma load decreased 1.15 log copies/ml in the group whose regimen was selected on the basis of resistance testing and 0.67 log copies/ml in the control group (p=0.05).\(^12\) In the GART study of 153 patients with virologic failure after a combination regimen, viral suppression was achieved in 34% of patients receiving genotypic resistance testing for subsequent regimen selection compared to 22% in patients with a subsequent regimen determined by clinical judgment alone.\(^13\)

A meta-analysis of randomized clinical trials that enrolled patients with virologic failure reported that when treatment was based on resistance testing results, virologic suppression at 3 months was achieved in 42.6% of patients compared with 33.2% in those whose regimen was determined by clinical judgment in the absence of resistance testing.\(^14\)

Genotypic resistance testing has been found to be cost-effective in studies using a measure of cost-effectiveness in dollars per quality-adjusted life-year gained.\(^15\),\(^16\) These large studies compared genotypic resistance testing to expert opinion alone using data from the Swiss HIV Cohort Study with over 14,000 enrolled patients\(^15\) and from the Multicenter AIDS Cohort Study.\(^15\)

There are numerous reviews of resistance testing in the literature that address topics including methods, clinical utility,\(^17\),\(^18\) and recent advances.\(^19\) In addition, numerous clinical guidelines for the selection and monitoring of HIV therapy have been established by the United States Department of Health and Human Services and other expert panels.\(^1\)-\(^5\)
Guidelines and Recommendations

*Department of Health and Human Services*\(^2\)

In 2013, the Department of Health and Human Services released the following recommendations\(^3\):

- Drug resistance testing should be performed when the HIV patient enters care, when therapy is initiated or modified, and when virologic failure is identified or if otherwise clinically indicated. If testing was done at entry into care, but treatment deferred, resistance testing at initiation of therapy should be considered.
- Resistance testing is not recommended if therapy is modified due to toxicity or regimen simplification in the setting of viral suppression.
- Genotypic testing is the preferred assay for treatment-naïve patients, patients with suboptimal virologic response or virologic failure on first and second line regimens.
- In pregnancy, genotypic resistance testing is recommended before initiation of therapy, and for those who enter pregnancy while on therapy but who have detectable HIV RNA

*International AIDS Society-USA Panel*\(^3\)

The 2012 International AIDS Society-USA Panel made the following recommendations\(^4\):

- Genotypic drug resistance testing should be performed in all treatment-naïve HIV patients.
- Drug resistance testing is recommended when virologic failure is identified, and preferably before the failing regimen is discontinued.
- Resistance testing (recent and past), treatment history, and tolerability and adherence issues should be considered when constructing a new antiretroviral regimen

*Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children*\(^3\)

In 2012, the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children made the following recommendations\(^3\):

- Drug resistance testing should be performed in all treatment-naïve children. Genotypic resistance testing is preferred.
- Drug resistance testing should be performed in the setting of virologic failure while the patient is still on the failing regimen or within 4 weeks of its discontinuation.
- Phenotypic resistance testing should be performed in the setting of complex drug mutation resistance patterns.
- Interpretation of resistance tests should be done in consultation with a pediatric HIV infection specialist.

*Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission*\(^4\)

In 2012, the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission updated its guidelines to include the following recommendations\(^4\):

- Drug resistance testing should be performed in all pregnant women before initiating treatment or when modifying antiretroviral regimens in those whose viral load is above the threshold for resistance testing.
- Drug resistance testing should be performed in all pregnant women on antiretroviral therapy with persistently detectable HIV RNA or suboptimal viral suppression.
**HIV Medicine Association of the Infectious Disease Society of America**

In 2013, the HIV Medicine Association of the Infectious Diseases Society of America published new primary care guidelines for the management of HIV infected patients. Those guidelines included the following recommendations for HIV genotype testing:

- Genotypic drug resistance testing should be performed when the HIV patient enters care. If therapy is deferred, drug resistance testing should be repeated at the time of initiation of treatment due to the possibility of superinfection with another mutated strain or strains.
- Drug resistance testing should be performed when virologic failure is identified. In persons failing integrase strand transfer inhibitor (INSTI)--based regimens, genotypic testing for INSTI resistance should be ordered.
- Drug resistance therapy is recommended prior to the initiation of therapy in infants and children.

### US FOOD AND DRUG ADMINISTRATION (US FDA)

There are several HIV genotyping assays available that are FDA approved.

### CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

For Medicare populations, CMS does not pay for screening procedures (tests) performed in the absence of signs or symptoms. (Section 1862(a)(7) of the Social Security Act)

There are several CMS policies that apply to HIV Testing (Prognosis, including Monitoring). In some cases, CMS reimbursement is limited to FDA approved and “home-brew” tests only.

Additionally, there may be a limit to the number of assays per patient per 12 month time period. Physicians should consult their state’s regulations.

### APPLICABLE CODING

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>87901</td>
<td>Infectious agent genotype analysis by nucleic acid (DNA or RNA), HIV 1, reverse transcriptase and protease</td>
</tr>
<tr>
<td>87900</td>
<td>Infectious agent drug susceptibility phenotype prediction using regularly updated genotypic bioinformatics</td>
</tr>
<tr>
<td>87906</td>
<td>Infectious agent genotype analysis by nucleic acid (DNA or RNA), HIV 1, other regions</td>
</tr>
</tbody>
</table>
REFERENCES


<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
</table>