HIV Genotype and Phenotype Testing

Introduction

HIV genotype and phenotype testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

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Development of drug resistance to antiretroviral therapy

Human immunodeficiency virus (HIV) replicates rapidly, particularly in response to antiretroviral (ARV) therapies.

These replications are a result of substitutions in the viral protease, reverse transcriptase, or integrase enzymes which are targeted by various ARV drugs that can
lead to drug-resistant mutations (quasi species). These mutations lead to virologic
treatment failure.

Because of the rapidity of these replications, highly active antiretroviral therapy
(HAART) has been designed to use treatments with multiple mechanisms of action in
order to reduce mutations and the development of drug-resistant variants. The drug
included in this regimen include, but are not limited to, nucleoside reverse transcriptase
inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease
inhibitors (PIs), integrase inhibitors, and fusion inhibitors.

**Effectiveness of HAART**

The effectiveness of HAART in suppressing HIV replication for prolonged periods has
allowed HIV to be considered a chronic, rather than a fatal, disease.

However, drug failure continues to occur because HAART regimens do not completely
suppress replication in all cases. Other factors, such as nonadherence, inadequate
potency of treatment, or suboptimal drug levels may play a part in drug failure.

Historically, the initiation of, or a change in, ARV therapy has been based on HIV
ribonucleic acid (RNA) levels and CD4 cell counts, both of which are essential
components of the clinical management of HIV. Because treatment decisions can
irrevocably alter an individual's response to future therapy, clinicians can also utilize
genotypic or phenotypic assays as additional clinical tools for selecting safe and
efficacious treatment regimens.

**Test information**

**Introduction**

HIV phenotype and genotype testing may include genotypic resistance assays,
phenotypic resistance assays, or virtual phenotyping.

**Genotypic resistance assays**

Genotypic resistance assays look for mutations that are present in HIV genes (e.g.,
reverse transcriptase [RT], protease, fusion, or integrase enzymes). Some assays
sequence the entire gene, while others use probes to detect mutations that are known
to produce drug resistance.

Advantages of genotyping over phenotyping are a shorter turnaround time (1-2 weeks
compared to 2-3 weeks) and lower cost.

**Phenotypic resistance assays**

Phenotypic resistance assays measure the ability of the virus to replicate in vitro in the
presence of an ARV drug. The medical literature, the federal government and medical
society guidelines all support the use of HIV genotyping and/or phenotyping to identify
drug-resistant viruses and assist with selecting the most appropriate ARV drugs for an individual.

**Virtual phenotyping**

Virtual phenotyping is a modified genotypic test that looks for mutations in the genetic structure of the HIV virus. When mutations are found, the information is entered into a database that contains data on thousands of HIV samples. If the genotype of the virus being studied matches a genotype in the database, the assumption is that the phenotype will also match.

Virtual phenotyping is not a direct measure; rather, it is a prediction based on genotypic analysis and database matching. Current clinical practice guidelines do not provide specific guidance about the role of virtual phenotyping in HIV resistance testing. However, based on current clinical practice, it appears there is correlation between genotypic interpretation and virtual phenotypic results—particularly when the drug(s) used in HAART have been on the market long enough for the correlative database to garner enough matching genotypes and phenotypes to provide accurate phenotypic results.

As a result, the value of virtual phenotyping is limited when evaluating newer and experimental drugs because there are fewer matching genotypes and phenotypes in the correlative database.

**Guidelines and evidence**

**Introduction**

This section includes relevant guidelines and evidence pertaining to HIV genotype and phenotype testing.

**Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents**

A Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS, 2016) recommends:

- “HIV drug-resistance testing is recommended in persons with HIV infection at entry into care regardless of whether antiretroviral therapy (ART) will be initiated immediately or deferred.” [Evidence level AII]
  - “If therapy is deferred, repeat testing should be considered at the time of ART initiation.” [Evidence level CIII]
- “Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients.” [Evidence level AIII]
• “HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ARV regimens in persons with virologic failure and HIV RNA levels >1,000 copies/mL.” [Evidence level A1]
  o “In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered.” [Evidence level BII].
• “Drug-resistance testing should also be performed when managing suboptimal viral load reduction.” [Evidence level AII]
• “Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens.” [Evidence level AII]
• “The addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to protease inhibitors (PIs).” [Evidence level BIII]
• “Genotypic resistance testing is recommended for all pregnant women before initiation of ART…” [Evidence level AII]
  o “…and for those entering pregnancy with detectable HIV RNA levels while on therapy.” [Evidence level A1]

Infectious Diseases Society of America

Infectious Diseases Society of America (IDSA, 2013) guidelines agree that HIV resistance testing should be done routinely upon initiation of care and/or at the start of ART therapy initiation as well as in patients experiencing virologic failure:

• “Because drug-resistant virus can be transmitted from one person to another, all patients should be assessed for transmitted drug resistance with an HIV genotype test upon initiation of care.” [Strong recommendation, high quality evidence].
• “If therapy is deferred, repeat testing at the time of antiretroviral therapy (ART) initiation should be considered because of the potential for superinfection.” [Weak recommendation, low quality evidence]
• “Resistance testing is also indicated for patients who are experiencing virologic failure to guide modification of ART.” [Strong recommendation, high quality evidence]

International Antiviral Society–USA Panel

International Antiviral Society–USA Panel (IAS-US, 2012) recommendations contain similar guidance on genotype testing:

• “Baseline genotypic testing for resistance should be performed in all treatment-naive patients...” [Evidence level Alla]
  o “…and in cases of confirmed virologic failure.” [Evidence level Ala]
• “A new regimen should be constructed using resistance testing (both past and present), treatment history and consideration of tolerability and adherence issues.” [Evidence level Ala]

Criteria

Medically Necessary

HIV genotyping is considered medically necessary and, therefore, covered for any of the following:

• For resistance testing at baseline for individuals with acute HIV infection, regardless of whether ARV therapy is initiated or deferred.
• To guide therapy in ARV-naive individuals with chronic HIV infection, regardless of whether ARV is initiated or deferred.
• For all pregnant women prior to initiation of therapy and for those entering pregnancy with detectable HIV RNA levels while on therapy.
• To assist in the selection of active drugs when changing ARV regimens in individuals with virologic failure or suboptimal response on their first or second regimens.
• For individuals with known or suspected complex drug-resistance patterns.

HIV phenotyping is considered medically necessary and, therefore, covered when genotypic results do not allow for drug selection in either of the following instances:

• To assist in the selection of active drugs when changing ARV regimens in individuals with virologic failure or suboptimal response on their third and subsequent regimens, or if the individual had initially acquired a multidrug-resistant virus.
• For individuals with known or suspected complex drug-resistance patterns.

Virtual phenotyping should be used with discretion as a testing option with respect to newer drugs used in antiretroviral therapy (ART) because there are typically fewer matching genotypes and phenotypes in the correlative database.

• Standard phenotyping should be used in these circumstances.

Not Medically Necessary

HIV genotyping and phenotyping performed at the same time is duplicative and is considered not medically necessary and, therefore, not covered.
References

Introduction

These references are cited in this guideline.


2. AIDSinfo. Adult and Adolescent Guidelines: Drug Resistance Testing


38. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department


