



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Drug-Resistance Testing (Last updated February 12, 2013; last reviewed February 12, 2013)

Panel's Recommendations

- 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 (AII). If therapy is deferred, repeat testing should be considered at the time of ART initiation (CIII).
- Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral (ARV)-naive patients (AIII).
- Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the reverse transcriptase (RT) and protease (PR) genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is a concern, providers may wish to supplement standard genotypic resistance testing with an INSTI genotype test (CIII).
- 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 (AI). In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII).
- Drug-resistance testing should also be performed when managing suboptimal viral load reduction (AII).
- In persons failing INSTI-based regimens, genotypic testing for INSTI resistance should be performed to determine whether to include a drug from this class in subsequent regimens (AII).
- Drug-resistance testing in the setting of virologic failure should be performed while the person is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy (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 (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) (BIII).
- Genotypic resistance testing is recommended for all pregnant women before initiation of ART (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI) (see the [Perinatal Treatment Guidelines](#) for more detailed discussion).

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

Genotypic and Phenotypic Resistance Assays

Genotypic and phenotypic resistance assays are used to assess viral strains and inform selection of treatment strategies. Standard assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Testing for integrase and fusion inhibitor resistance can also be ordered separately from several commercial laboratories. Co-receptor tropism assays should be performed whenever the use of a CCR5 antagonist is being considered. Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-receptor use is now commercially available (see [Co-receptor Tropism Assays](#)).

Genotypic Assays

Genotypic assays detect drug-resistance mutations present in relevant viral genes. Most genotypic assays involve sequencing of the RT and PR genes to detect mutations that are known to confer drug resistance. Genotypic assays that assess mutations in the integrase and gp41 (envelope) genes are also commercially available. Genotypic assays can be performed rapidly and results are available within 1 to 2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations selected by different antiretroviral (ARV) drugs and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains an updated list of significant resistance-associated mutations in the RT, PR, integrase, and envelope genes (see

http://www.iasusa.org/resistance_mutations).¹ The Stanford University HIV Drug Resistance Database (<http://hivdb.stanford.edu>) also provides helpful guidance for interpreting genotypic resistance test results. Various tools to assist the provider in interpreting genotypic test results are now available.²⁻⁵ Clinical trials have demonstrated that consultation with specialists in HIV drug resistance improves virologic outcomes.⁶ Clinicians are thus encouraged to consult a specialist to facilitate interpretation of genotypic test results and design of an optimal new regimen.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT and PR gene sequences and, more recently, integrase and envelope sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits viral replication by 50% (i.e., the median inhibitory concentration [IC₅₀]) is calculated, and the ratio of the IC₅₀ of test and reference viruses is reported as the fold increase in IC₅₀ (i.e., fold resistance).

Automated phenotypic assays that can produce results in 2 to 3 weeks are commercially available, but they cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC₅₀) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs.⁷⁻¹¹ Again, consultation with a specialist to interpret test results can be helpful.

Further limitations of both genotypic and phenotypic assays include lack of uniform quality assurance testing for all available assays, relatively high cost, and insensitivity to minor viral species. Despite being present, drug-resistant viruses that constitute less than 10% to 20% of the circulating virus population will probably not be detected by commercially available assays. This limitation is important because after drugs exerting selective pressure on drug-resistant populations are discontinued, a wild-type virus often re-emerges as the predominant population in the plasma. As a consequence, the proportion of virus with resistance mutations decreases to below the 10% to 20% threshold.¹²⁻¹⁴ In the case of some drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. Prospective clinical studies have shown that despite this plasma reversion, re-initiation of the same ARV agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and that the virus present at failure is derived from previously archived resistant virus.¹⁵ Therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued (**AII**). Because resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing done 4 to 6 weeks after discontinuation of drugs may still detect mutations. However, the absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens.

Use of Resistance Assays in Clinical Practice (See [Table 4](#))

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial antiretroviral therapy (ART).¹⁶⁻¹⁹ The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in HIV-infected persons engaging in high-risk behaviors in the community. In the United States and Europe, recent studies suggest that the risk that transmitted virus will be resistant to at least one ARV drug is in the range of 6% to 16%.²⁰⁻²⁵ Up to 8%, but generally less than 5% of transmitted viruses will exhibit resistance to drugs from more than one class.^{24, 26-28}

If the decision is made to initiate therapy in a person with early HIV infection, resistance testing at baseline

can guide regimen selection to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AII)**. A genotypic assay is preferred for this purpose **(AIII)**. In this setting, treatment initiation should not be delayed pending resistance testing results. Once results are obtained, the treatment regimen can be modified if warranted (see [Acute and Recent HIV Infection](#)). In the absence of therapy, resistant viruses may decline over time to less than the detection limit of standard resistance tests, but when therapy is eventually initiated, resistant viruses even at a low level may still increase the risk of treatment failure.²⁹⁻³¹ Therefore, if therapy is deferred, resistance testing should still be done during acute HIV infection **(AIII)**. In this situation, the genotypic resistance test result may be kept on record until the patient is to be started on ART. Repeat resistance testing at the time treatment is started should be considered because it is possible for a patient to acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of ART **(CIII)**.

Performing drug-resistance testing before ART initiation in patients with chronic HIV infection is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure. It is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier.³²⁻³⁴ No prospective trial has addressed whether drug-resistance testing before initiation of therapy confers benefit in this population. However, data from several, but not all, studies suggest that virologic responses in persons with baseline resistance mutations are suboptimal.^{16-19, 35-37} In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed.³⁸ Therefore, resistance testing in chronically infected persons is recommended at the time of entry into HIV care **(AII)**. Although no definitive prospective data exist to support the choice of one type of resistance testing over another, genotypic testing is generally preferred in this situation because of lower cost, more rapid turnaround time, the assay's ability to detect mixtures of wild-type and resistant virus, and the relative ease of interpreting test results **(AIII)**. If therapy is deferred, repeat testing soon before initiation of ART should be considered because the patient may have acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

Standard genotypic drug-resistance testing in ARV-naïve persons involves testing for mutations in the RT and PR genes. Although transmission of integrase strand transfer inhibitor (INSTI)-resistant virus has rarely been reported, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, when INSTI resistance is suspected, providers may wish to supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs **(CIII)**.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding treatment decisions for patients who experience virologic failure while on ART. Several prospective studies assessed the utility of resistance testing to guide ARV drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both.^{6, 39-45} In general, these studies found that changes in therapy that were informed by resistance testing results produced better early virologic response to salvage regimens than regimen changes guided only by clinical judgment.

In addition, one observational cohort study found that performance of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival.⁴⁶ Thus, resistance testing is recommended as a tool in selecting active drugs when changing ARV regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)** (see [Virologic and Immunologic Failure](#)). In persons with HIV RNA >500 copies/mL but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**. Drug-resistance testing in persons with a plasma viral load <500 copies/mL is not usually recommended because resistance assays cannot be consistently performed given low HIV RNA levels **(AIII)**.

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination ART is, for certain patients, associated with resistance to only one component of the regimen.⁴⁷⁻⁴⁹ In this situation, substituting individual drugs in a failing regimen may be a possible option, but this concept will require clinical validation (see [Virologic and Immunologic Failure](#)).

In patients who are on a failing first or second ARV drug regimen and experiencing virologic failure or suboptimal viral load reduction, genotypic testing is generally preferred for resistance testing **(AII)**. This is based on the fact that, when compared with **phenotypic testing**, genotypic testing costs less to perform, has a faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus. **In addition, observations show that the assays are comparable predictors of virologic response to subsequent ART regimens.**⁵⁰

Addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns, particularly to PIs **(BIII)**.

In patients failing INSTI-based regimens, testing for INSTI resistance should be **performed** to determine whether to include drugs from this class in subsequent regimens **(AII)**; genotypic testing is preferred for this purpose.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)**. **Phenotypic co-receptor tropism assays have been used in clinical practice. A genotypic assay to predict co-receptor use is now commercially available and is less expensive than phenotypic assays. Evaluation of genotypic assays is ongoing, but current data suggest that such testing should be considered as an alternative assay. The same principles regarding testing for co-receptor use also apply to testing when patients exhibit virologic failure on a CCR5 antagonist.**⁵¹ Resistance to CCR5 antagonists in the absence of detectable CXCR4-using virus has been reported, but such resistance is uncommon (see [Co-receptor Tropism Assays](#)).

Use of Resistance Assays in Pregnant Women

In pregnant women, the goal of ART is to maximally reduce plasma HIV RNA to provide optimal maternal therapy and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant women before initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AI)**. Phenotypic testing in those found to have complex drug-resistance mutation patterns, particularly to PIs, may provide additional information **(BIII)**. Optimal prevention of perinatal transmission may require initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

Table 4. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
<p>In acute HIV infection: Drug-resistance testing is recommended regardless of whether antiretroviral therapy (ART) is initiated immediately or deferred (AII). A genotypic assay is generally preferred (AIII).</p> <p>If ART is deferred, repeat resistance testing should be considered at the time therapy is initiated (CIII). A genotypic assay generally is preferred (AIII).</p>	<p>If ART is initiated immediately, drug-resistance testing can determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or to modify or change regimens if results are obtained after treatment initiation.</p> <p>Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.</p> <p>If ART is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time ART is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).</p>
<p>In ART-naive patients with chronic HIV infection: Drug-resistance testing is recommended at entry into HIV care, regardless of whether therapy is initiated immediately or deferred (AII). A genotypic assay is generally preferred (AIII).</p> <p>If therapy is deferred, repeat resistance testing should be considered before initiation of ART (CIII). A genotypic assay is generally preferred (AIII).</p> <p>If an INSTI is considered for an ART-naive patient and transmitted INSTI resistance is a concern, providers may supplement standard resistance testing with a specific INSTI genotypic resistance assay (CIII).</p> <p>If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed (AI) (see Co-receptor Tropism Assays)</p>	<p>Transmitted HIV with baseline resistance to at least 1 drug is seen in 6% to 16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug-resistance mutations can remain detectable for years in untreated, chronically infected patients.</p> <p>Repeat testing before initiation of ART should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection).</p> <p>Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus.</p> <p>Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.</p> <p>(see Co-receptor Tropism Assays)</p>
<p>In patients with virologic failure: Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels >1,000 copies/mL (AI). In patients with HIV RNA levels >500 copies/mL but <1,000 copies/mL, testing may not be successful but should still be considered (BII).</p> <p>A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens (AII).</p> <p>In patients failing INSTI-based regimens, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens (AII).</p> <p>If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed (AI) (see Co-receptor Tropism Assays).</p> <p>Addition of phenotypic assay to genotypic assay is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to protease inhibitors (PIs) (BIII).</p>	<p>Testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug-resistance testing should be performed while the patient is taking prescribed ARV drugs or, if not possible, within 4 weeks after discontinuing therapy.</p> <p>Genotypic testing is preferred to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant HIV.</p> <p>Standard genotypic drug-resistance assays test only for mutations in the RT and PR genes.</p> <p>Phenotypic testing can provide additional useful information in patients with complex drug-resistance mutation patterns, particularly to PIs.</p>

Table 4. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended in patients with suboptimal suppression of viral load after initiation of ART (AII) .	Testing can help determine the role of resistance and thus assist the clinician in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women before initiation of ART (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI) .	The goal of ART in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug-resistance assay not usually recommended	
After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after discontinuation of ARV drugs (BIII) .	Drug-resistance mutations may become minor species in the absence of selective drug pressure, and available assays may not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL (AIII) .	Resistance assays cannot be consistently performed given low HIV RNA levels.

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