



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

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Drug-Resistance Testing (Last updated July 14, 2016; last reviewed July 14, 2016)

Panel's Recommendations

For Antiretroviral Therapy-Naive Patients:

- HIV drug-resistance testing is recommended for persons with HIV infection at entry into care to guide selection of the initial antiretroviral therapy (ART) regimen (AII). If therapy is deferred, repeat testing may 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).
- In special circumstances (e.g., in patients with acute or recent [early] HIV infection and in pregnant HIV-infected women, ART initiation should not be delayed while awaiting resistance testing results; the regimen can be modified once results are reported (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 should ensure that genotypic resistance testing also includes INSTI genotype testing (BIII).

For Antiretroviral Therapy-Experienced Patients:

- HIV drug-resistance testing should be performed to assist in the selection of active drugs when changing ART regimens in the following patients:
 - In patients with virologic failure and HIV RNA levels >1000 copies/mL (AI).
 - In patients with HIV RNA levels >500 copies/mL but <1000 copies/mL, drug-resistance testing may be unsuccessful but should still be considered (BII).
 - Drug-resistance testing should also be performed when managing suboptimal viral load reduction (AII).
- When a patient experiences virologic failure while receiving an INSTI-based regimen, 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). If more than 4 weeks have elapsed since the ARVs were discontinued, resistance testing may still provide useful information to guide therapy; however, it is important to recognize that previously selected resistance mutations can be missed (CIII).
- Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic response or virologic failure while on first- or second-line regimens (AII).
- The addition of phenotypic to genotypic testing is generally preferred for persons with known or suspected complex drug-resistance mutation patterns (BIII).

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 select treatment strategies. These assays provide information on resistance to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs). In some circumstances, INSTI-resistance tests may need to be ordered separately. Clinicians should check with the testing laboratory. INSTI-resistance testing is particularly important in persons who experience virologic failure while taking an INSTI-containing regimen. Testing for fusion inhibitor resistance can also be ordered separately. Co-receptor tropism assays should be performed when considering the use of a CCR5 antagonist. 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 in relevant viral genes. Most genotypic assays involve sequencing the reverse transcriptase (RT), protease (PR), and integrase (IN) genes to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the gp41 (envelope) gene

associated with resistance to the fusion inhibitor enfuvirtide is also commercially available. Genotypic assays can be performed rapidly and results are available within 1 to 2 weeks of sample collection. Interpreting these 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, IN, 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 consulting with specialists in HIV drug resistance improves virologic outcomes.⁶ Clinicians are thus encouraged to consult a specialist to interpret genotypic test results and design optimal new regimens.

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, interpreting phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC₅₀) associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs.⁷⁻¹¹ Again, consulting with a specialist to interpret test results can be helpful.

Limitations of Genotypic and Phenotypic Assays

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. 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 to note because a wild-type virus often re-emerges as the predominant population in the plasma after drugs that exert selective pressure on drug-resistant populations are discontinued. 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 most valuable when performed before or within 4 weeks after drugs are discontinued (**AII**). Because resistant virus may persist longer in the plasma of some patients, 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 5](#))

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 risk of acquiring drug-resistant virus is related to the

prevalence of drug resistance in HIV-infected persons engaging in high-risk behaviors in a given community. In high-income countries (e.g., the United States, some European countries, Australia, and Japan), approximately 10% to 17% of ART-naive patients have resistance mutations to at least 1 ARV drug.²⁰ Up to 8%, but generally less than 5%, of transmitted viruses will exhibit resistance to drugs from more than 1 class.²⁰⁻²³ Transmitted resistant HIV is generally either NRTI- or NNRTI-resistant. PI resistance is much less common, and to date, transmitted INSTI resistance is rare.²⁴

In persons with acute or recent (early) HIV infection, resistance testing can guide therapy 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 if the patient is willing and able to begin treatment. Once results are reported, the regimen can be modified if warranted (see [Acute and Recent HIV \(Early\) Infection](#)). In the absence of ART, resistant viruses may decline over time to less than the detection limit of standard resistance tests. However, when ART is eventually initiated, even low levels of resistant viruses may still increase the risk of treatment failure.²⁵⁻²⁷ Therefore, if ART is deferred, resistance testing should still be performed during acute HIV infection (**AIII**). In this situation, the genotypic resistance test result may be kept on record until the patient begins ART. Repeat resistance testing at the start of treatment may be considered because a patient may acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of ART (**CIII**).

Interpretation of 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.²⁸⁻³⁰ No prospective trial has addressed whether drug-resistance testing before initiation of therapy confers benefit in this population. However, data from several studies suggest that virologic responses in persons with baseline resistance mutations are suboptimal.^{16-19,31-33} In addition, an analysis of early genotypic resistance testing in treatment-naive HIV-infected patients suggests that baseline testing in this population is cost effective and should be performed.³⁴ 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 over phenotypic testing because of lower cost, more rapid turnaround time, greater sensitivity for detecting mixtures of wild-type and resistant virus, and easier to interpret test results (**AIII**). If therapy is deferred, repeat testing shortly before initiating ART may be considered because the patient may have acquired drug-resistant virus (i.e., superinfection) (**CIII**).

Standard genotypic drug-resistance testing in ARV-naive persons involves testing for mutations in the RT and PR genes. Although reports of transmission of INSTI-resistant virus are rare, as use of INSTIs increases, the potential for transmission of INSTI-resistant virus may also increase. Therefore, when INSTI resistance is suspected, providers should supplement standard baseline genotypic resistance testing with genotypic testing for resistance to this class of drugs (**BIII**).

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are important tools to inform 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.^{6,35-41} In general, these studies found that changes in therapy based on 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.⁴² Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV

regimens because of virologic failure in persons with HIV RNA >1,000 copies/mL (**AI**) (see [Virologic 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 can also 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.⁴³⁻⁴⁵ In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see [Virologic Failure](#)).

Genotypic testing is generally preferred for resistance testing in patients who are on a failing first or second ARV drug regimen and experiencing virologic failure or suboptimal viral load reduction (**AII**). When compared with phenotypic testing, genotypic testing costs less to perform and has a faster turnaround time and greater sensitivity for detecting mixtures of wild-type and resistant virus. In addition, observations show that genotypic and phenotypic assays are comparable predictors of virologic response to subsequent ART regimens.⁴⁶ 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**). **In this circumstance, clinicians should confirm that, when they order a resistance test, their laboratory is testing for INSTI resistance in addition to NNRTI-, NRTI-, and PI-resistance. If INSTI-resistance testing needs to be ordered separately (as is the case in some laboratories), clinicians should request this assay in addition to standard drug-resistance testing.** Addition of phenotypic to genotypic testing is generally indicated for persons with known or suspected complex drug-resistance mutation patterns (**BIII**).

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 genotypic tropism testing should be considered as an alternative phenotypic tropism testing. The same principles regarding testing for co-receptor use also apply to testing when patients exhibit virologic failure on a CCR5 antagonist.⁴⁷ 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](#)).

A next-generation sequencing genotypic resistance assay, which analyzes HIV-1 pro-viral DNA in the host cells, is now commercially available. This test aims to detect archived resistance mutations in patients with HIV RNA below the limit of detection. However, the clinical utility of this assay has yet to be determined.

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 may provide additional information (**BIII**). Optimal prevention of perinatal transmission requires initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

Table 5. Recommendations for Using Drug-Resistance Assays (page 1 of 2)

Clinical Setting/Recommendation	Rationale
Drug-resistance assay recommended	
<p>In acute (early) HIV infection: Drug-resistance testing is recommended (AII). A genotypic assay is generally preferred (AIII). Treatment should not be delayed while awaiting results of resistance testing (AIII).</p> <p>If ART is deferred, repeat resistance testing may be considered when therapy is initiated (CIII). A genotypic assay is generally preferred (AIII).</p>	<p>Drug-resistance testing can determine whether drug-resistant virus was transmitted. The initial regimen can be modified once resistance test results are available. 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>Repeat testing when ART is initiated may 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 to guide selection of initial ART (AII). 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 should supplement standard resistance testing with a specific INSTI genotypic resistance assay (BIII).</p> <p>If therapy is deferred, repeat resistance testing may be considered before initiation of ART (CIII). A genotypic assay is generally preferred (AIII).</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 10% to 17% 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>Genotypic assays provide information on resistance to NRTIs, NNRTIs, PIs, and INSTIs. In some circumstances, INSTI-resistance tests need to be ordered separately (clinicians should check with the testing laboratory).</p> <p>Currently, transmitted INSTI resistance is infrequent, but the risk of a patient acquiring INSTI-resistant strains may be greater in certain known exposure settings.</p> <p>Repeat testing before initiation of ART may 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>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>When virologic failure occurs while a patient is on an INSTI-based regimen, 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>Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to PIs (BIII).</p>	<p>Drug-resistance 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.</p> <p>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>Genotypic assays provide information on resistance to NRTI-, NNRTI-, PI-, and INSTI-associated mutations. In some circumstances, INSTI resistance tests need to be ordered separately (clinicians should check with the testing laboratory).</p> <p>Phenotypic testing can provide additional useful information in patients with complex drug resistance mutation patterns, particularly to PIs.</p>

Table 5. Recommendations for Using Drug-Resistance Assays (page 2 of 2)

Clinical Setting/Recommendation	Rationale
In patients with suboptimal suppression of viral load: Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART (AII).	Testing can determine the role of resistance and thus help the clinician identify 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. However, treatment should not be delayed while awaiting results of resistance testing. The initial regimen can be modified once resistance test results are available.
Drug-resistance assay not usually recommended	
After therapy is discontinued: Drug-resistance testing is not usually recommended more than 4 weeks after ARV drugs are discontinued (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.

Key to Acronyms: ART = antiretroviral therapy; ARV = antiretroviral; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor

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