



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

Downloaded from <http://aidsinfo.nih.gov/guidelines> on 8/17/2016

Visit the *AIDSinfo* website to access the most up-to-date guideline.

Register for e-mail notification of guideline updates at <http://aidsinfo.nih.gov/e-news>.

## 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](http://www.iasusa.org/resistance_mutations)).<sup>1</sup> 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.<sup>2-5</sup> Clinical trials have demonstrated that consulting with specialists in HIV drug resistance improves virologic outcomes.<sup>6</sup> 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 [IC<sub>50</sub>]) is calculated, and the ratio of the IC<sub>50</sub> of test and reference viruses is reported as the fold increase in IC<sub>50</sub> (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 IC<sub>50</sub>) associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs.<sup>7-11</sup> 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.<sup>12-14</sup> 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.<sup>15</sup> 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).<sup>16-19</sup> 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.<sup>20</sup> Up to 8%, but generally less than 5%, of transmitted viruses will exhibit resistance to drugs from more than 1 class.<sup>20-23</sup> Transmitted resistant HIV is generally either NRTI- or NNRTI-resistant. PI resistance is much less common, and to date, transmitted INSTI resistance is rare.<sup>24</sup>

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.<sup>25-27</sup> 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.<sup>28-30</sup> 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.<sup>16-19,31-33</sup> 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.<sup>34</sup> 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.<sup>6,35-41</sup> 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.<sup>42</sup> 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.<sup>43-45</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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
<b>Drug-resistance assay recommended</b>	
<p><b>In acute (early) HIV infection:</b> Drug-resistance testing is recommended <b>(AII)</b>. A genotypic assay is generally preferred <b>(AIII)</b>. Treatment should not be delayed while awaiting results of resistance testing <b>(AIII)</b>.</p> <p>If ART is deferred, repeat resistance testing may be considered when therapy is initiated <b>(CIII)</b>. A genotypic assay is generally preferred <b>(AIII)</b>.</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><b>In ART-naive patients with chronic HIV infection:</b> Drug-resistance testing is recommended at entry into HIV care to guide selection of initial ART <b>(AII)</b>. A genotypic assay is generally preferred <b>(AIII)</b>.</p> <p>If an INSTI is considered for an ART-naive patient <b>and</b> transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay <b>(BIII)</b>.</p> <p>If therapy is deferred, repeat resistance testing may be considered before initiation of ART <b>(CIII)</b>. A genotypic assay is generally preferred <b>(AIII)</b>.</p> <p>If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed <b>(AI)</b> (see <a href="#">Co-receptor Tropism Assays</a>).</p>	<p>Transmitted HIV with baseline resistance to at least 1 drug is seen in <b>10% to 17%</b> 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><b>In patients with virologic failure:</b> Drug-resistance testing is recommended in patients on combination ART with HIV RNA levels &gt;1,000 copies/mL <b>(AI)</b>. In patients with HIV RNA levels &gt;500 copies/mL but &lt;1,000 copies/mL, testing may not be successful but should still be considered <b>(BII)</b>.</p> <p>A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second regimens <b>(AII)</b>.</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 <b>(AII)</b>.</p> <p>If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed <b>(AI)</b> (see <a href="#">Co-receptor Tropism Assays</a>).</p> <p>Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns, particularly to PIs <b>(BIII)</b>.</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
<b>In patients with suboptimal suppression of viral load:</b> Drug-resistance testing is recommended in patients with suboptimal viral load suppression after initiation of ART ( <b>AII</b> ).	Testing can determine the role of resistance and thus help the clinician identify the number of active drugs available for a new regimen.
<b>In HIV-infected pregnant women:</b> Genotypic resistance testing is recommended for all pregnant women before initiation of ART ( <b>AIII</b> ) and for those entering pregnancy with detectable HIV RNA levels while on therapy ( <b>AI</b> ).	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. <b>However, treatment should not be delayed while awaiting results of resistance testing. The initial regimen can be modified once resistance test results are available.</b>
<b>Drug-resistance assay not usually recommended</b>	
<b>After therapy is discontinued:</b> Drug-resistance testing is not usually recommended more than 4 weeks after ARV drugs are discontinued ( <b>BIII</b> ).	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.
<b>In patients with low HIV RNA levels:</b> Drug-resistance testing is not usually recommended in patients with a plasma viral load <500 copies/mL ( <b>AIII</b> ).	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

## References

- Hirsch MS, Gunthard HF, Schapiro JM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. *Clin Infect Dis*. Jul 15 2008;47(2):266-285. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18549313](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18549313).
- Flandre P, Costagliola D. On the comparison of artificial network and interpretation systems based on genotype resistance mutations in HIV-1-infected patients. *AIDS*. Oct 24 2006;20(16):2118-2120. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17053360](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17053360).
- Vercauteren J, Vandamme AM. Algorithms for the interpretation of HIV-1 genotypic drug resistance information. *Antiviral Res*. Sep 2006;71(2-3):335-342. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16782210](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16782210).
- Gianotti N, Mondino V, Rossi MC, et al. Comparison of a rule-based algorithm with a phenotype-based algorithm for the interpretation of HIV genotypes in guiding salvage regimens in HIV-infected patients by a randomized clinical trial: the mutations and salvage study. *Clin Infect Dis*. May 15 2006;42(10):1470-1480. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16619162](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16619162).
- Torti C, Quiros-Roldan E, Regazzi M, et al. A randomized controlled trial to evaluate antiretroviral salvage therapy guided by rules-based or phenotype-driven HIV-1 genotypic drug-resistance interpretation with or without concentration-controlled intervention: the Resistance and Dosage Adapted Regimens (RADAR) study. *Clin Infect Dis*. Jun 15 2005;40(12):1828-1836. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15909273](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15909273).
- Tural C, Ruiz L, Holtzer C, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. *AIDS*. Jan 25 2002;16(2):209-218. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11807305](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11807305).
- Lanier ER, Ait-Khaled M, Scott J, et al. Antiviral efficacy of abacavir in antiretroviral therapy-experienced adults harbouring HIV-1 with specific patterns of resistance to nucleoside reverse transcriptase inhibitors. *Antivir Ther*. Feb

2004;9(1):37-45. Available at

[http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15040535](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15040535).

8. Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. *J Infect Dis*. Mar 1 2004;189(5):837-846. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=14976601](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14976601).
9. Flandre P, Chappey C, Marcelin AG, et al. Phenotypic susceptibility to didanosine is associated with antiviral activity in treatment-experienced patients with HIV-1 infection. *J Infect Dis*. Feb 1 2007;195(3):392-398. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17205478](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17205478).
10. Naeger LK, Struble KA. Food and Drug Administration analysis of tipranavir clinical resistance in HIV-1-infected treatment-experienced patients. *AIDS*. Jan 11 2007;21(2):179-185. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17197808](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17197808).
11. Naeger LK, Struble KA. Effect of baseline protease genotype and phenotype on HIV response to atazanavir/ritonavir in treatment-experienced patients. *AIDS*. Apr 4 2006;20(6):847-853. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16549968](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16549968).
12. Verhofstede C, Wanzeel FV, Van Der Gucht B, De Cabooter N, Plum J. Interruption of reverse transcriptase inhibitors or a switch from reverse transcriptase to protease inhibitors resulted in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. *AIDS*. Dec 24 1999;13(18):2541-2546. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10630523](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10630523).
13. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS*. Dec 22 2000;14(18):2857-2867. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11153667](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11153667).
14. Devereux HL, Youle M, Johnson MA, Loveday C. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS*. Dec 24 1999;13(18):F123-127. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10630517](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10630517).
15. Benson CA, Vaida F, Havlir DV, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. *J Infect Dis*. Nov 1 2006;194(9):1309-1318. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17041858](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17041858).
16. Little SJ, Holte S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med*. Aug 8 2002;347(6):385-394. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=12167680](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12167680).
17. Borroto-Esoda K, Waters JM, Bae AS, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. *AIDS Res Hum Retroviruses*. Aug 2007;23(8):988-995. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17725415](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17725415).
18. Pozniak AL, Gallant JE, DeJesus E, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes—a 96-week analysis. *J Acquir Immune Defic Syndr*. Dec 15 2006;43(5):535-540. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17057609](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17057609).
19. Kuritzkes DR, Lalama CM, Ribaldo HJ, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. *J Infect Dis*. Mar 15 2008;197(6):867-870. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18269317](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18269317).
20. World Health Organization. WHO HIV Drug Resistance Report 2012. Geneva, Switzerland. Available at <http://www.who.int/hiv/pub/drugresistance/report2012>. Accessed May 13, 2016.
21. Yanik EL, Napravnik S, Hurt CB, et al. Prevalence of transmitted antiretroviral drug resistance differs between acutely and chronically HIV-infected patients. *J Acquir Immune Defic Syndr*. Oct 1 2012;61(2):258-262. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22692092>.
22. Agwu AL, Bethel J, Hightow-Weidman LB, et al. Substantial multiclass transmitted drug resistance and drug-relevant polymorphisms among treatment-naive behaviorally HIV-infected youth. *AIDS Patient Care STDS*. Apr 2012;26(4):193-196. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22563607>.
23. Castor D, Low A, Evering T, et al. Transmitted drug resistance and phylogenetic relationships among acute and early

HIV-1-infected individuals in New York City. *J Acquir Immune Defic Syndr*. Sep 1 2012;61(1):1-8. Available at <http://www.ncbi.nlm.nih.gov/pubmed/22592583>.

24. Doyle T, Dunn DT, Ceccherini-Silberstein F, et al. Integrase inhibitor (INI) genotypic resistance in treatment-naive and raltegravir-experienced patients infected with diverse HIV-1 clades. *J Antimicrob Chemother*. Nov 2015;70(11):3080-3086. Available at <http://www.ncbi.nlm.nih.gov/pubmed/26311843>.
25. Johnson JA, Li JF, Wei X, et al. Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naive populations and associate with reduced treatment efficacy. *PLoS Med*. Jul 29 2008;5(7):e158. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18666824](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18666824).
26. Simen BB, Simons JF, Hullsiek KH, et al. Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naive patients significantly impact treatment outcomes. *J Infect Dis*. Mar 1 2009;199(5):693-701. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19210162](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19210162).
27. Paredes R, Lalama CM, Ribaud HJ, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. *J Infect Dis*. Mar 2010;201(5):662-671. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=20102271](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=20102271).
28. Smith DM, Wong JK, Shao H, et al. Long-term persistence of transmitted HIV drug resistance in male genital tract secretions: implications for secondary transmission. *J Infect Dis*. Aug 1 2007;196(3):356-360. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=17597449](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17597449).
29. Novak RM, Chen L, MacArthur RD, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. *Clin Infect Dis*. Feb 1 2005;40(3):468-474. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15668873](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15668873).
30. Little SJ, Frost SD, Wong JK, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. *J Virol*. Jun 2008;82(11):5510-5518. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=18353964](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18353964).
31. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA*. Jul 14 2004;292(2):180-189. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15249567](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15249567).
32. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med*. Jul 15 2004;351(3):229-240. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=15247339](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15247339).
33. Pillay D, Bhaskaran K, Jurriaans S, et al. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. *AIDS*. Jan 2 2006;20(1):21-28. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16327315](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16327315).
34. Sax PE, Islam R, Walensky RP, et al. Should resistance testing be performed for treatment-naive HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis*. Nov 1 2005;41(9):1316-1323. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16206108](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16206108).
35. Cingolani A, Antinori A, Rizzo MG, et al. Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). *AIDS*. Feb 15 2002;16(3):369-379. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11834948](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11834948).
36. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet*. Jun 26 1999;353(9171):2195-2199. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10392984](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10392984).
37. Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beinr Community Programs for Clinical Research on AIDS. *AIDS*. 2000;14(9):F83-93. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10894268&dopt=Abstract](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10894268&dopt=Abstract).
38. Cohen CJ, Hunt S, Sension M, et al. A randomized trial assessing the impact of phenotypic resistance testing on antiretroviral therapy. *AIDS*. Mar 8 2002;16(4):579-588. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11873001](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11873001).
39. Meynard JL, Vray M, Morand-Joubert L, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral

- therapy after treatment failure: a randomized trial. *AIDS*. Mar 29 2002;16(5):727-736. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=11964529](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=11964529).
40. Vray M, Meynard JL, Dalban C, et al. Predictors of the virological response to a change in the antiretroviral treatment regimen in HIV-1-infected patients enrolled in a randomized trial comparing genotyping, phenotyping and standard of care (Narval trial, ANRS 088). *Antivir Ther*. Oct 2003;8(5):427-434. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=14640390](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14640390).
  41. Wegner SA, Wallace MR, Aronson NE, et al. Long-term efficacy of routine access to antiretroviral-resistance testing in HIV type 1-infected patients: results of the clinical efficacy of resistance testing trial. *Clin Infect Dis*. Mar 1 2004;38(5):723-730. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=14986258](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=14986258).
  42. Palella FJ, Jr., Armon C, Buchacz K, et al. The association of HIV susceptibility testing with survival among HIV-infected patients receiving antiretroviral therapy: a cohort study. *Ann Intern Med*. Jul 21 2009;151(2):73-84. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=19620160](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19620160).
  43. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. *JAMA*. Jan 12 2000;283(2):229-234. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10634339](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10634339).
  44. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. Trilege (Agence Nationale de Recherches sur le SIDA 072 Study Team). *JAMA*. Jan 12 2000;283(2):205-211. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=10634336](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10634336).
  45. Machouf N, Thomas R, Nguyen VK, et al. Effects of drug resistance on viral load in patients failing antiretroviral therapy. *J Med Virol*. May 2006;78(5):608-613. Available at [http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list\\_uids=16555280](http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16555280).
  46. Anderson JA, Jiang H, Ding X, et al. Genotypic susceptibility scores and HIV type 1 RNA responses in treatment-experienced subjects with HIV type 1 infection. *AIDS Res Hum Retroviruses*. May 2008;24(5):685-694. Available at <http://www.ncbi.nlm.nih.gov/pubmed/18462083>.
  47. Lewis M MJ, Simpson P, et al. Changes in V3 loop sequence associated with failure of maraviroc treatment in patients enrolled in the MOTIVATE 1 and 2 trials. Presented at: 15th Conference on Retroviruses and Opportunistic Infections. 2008. Boston, Massachusetts.