Drug-Resistance Testing

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Panel's Recommendations

For Initial Treatment of HIV

- HIV drug-resistance testing is recommended at entry into care for people with HIV to guide the selection of the initial antiretroviral (ARV) regimen (AII). If antiretroviral therapy (ART) is deferred, repeat testing may be considered at the time of ART initiation (CIII).
- Genotypic, rather than phenotypic, testing is the preferred resistance testing to guide therapy in ARV-naive patients (AIII).
- In people with early (acute and recent) HIV infection, in pregnant people with HIV, or in people who will initiate ART on the day of or soon after HIV diagnosis, 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 and protease genes. If transmitted integrase strand transfer inhibitor (INSTI) resistance is suspected or if the person has used long-acting cabotegravir (CAB-LA) as pre-exposure prophylaxis (PrEP) in the past, providers should ensure that genotypic resistance testing also includes the integrase gene (AIII).

For Antiretroviral Therapy–Experienced People

- HIV drug-resistance testing should be performed to assist the selection of active drugs when changing ARV regimens in—
  - People with virologic failure and HIV-RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL, CIII for confirmed HIV RNA 201–500 copies/mL). For people with confirmed HIV-RNA levels >200 copies/mL but <500 copies/mL, drug-resistance testing may be unsuccessful but should still be considered.
  - People with suboptimal viral load reduction (AII).
- Reverse transcriptase and protease genotypic resistance testing should be performed on everyone with virologic failure; integrase resistance testing (which may need to be ordered separately) should be performed on individuals experiencing virologic failure while receiving an INSTI-based regimen (AII).
- For persons taking a non–long-acting ARV regimen, drug-resistance testing in the setting of virologic failure should be performed while the person is still taking their ARV regimen or, if that is not possible, within 4 weeks after discontinuing their ARV regimen (AII). If more than 4 weeks have elapsed since the non–long-acting agents 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 due to lack of drug-selective pressure (CIII).
- Given the long half-lives of the long-acting injectable ARV drugs, resistance testing (including testing for resistance to INSTIs) should be performed in all persons who have experienced virologic failure on a regimen of long-acting CAB and rilpivirine or acquired HIV after receiving CAB-LA as PrEP, regardless of the amount of time since drug discontinuation (AIII).
- Genotypic testing is preferred over phenotypic-resistance testing to guide therapy in people with suboptimal virologic response or virologic failure while on first- or second-line regimens and in people in whom resistance mutation patterns are known or not expected to be complex (AII).
- The addition of phenotypic- to genotypic resistance testing is recommended for people with known or suspected complex drug-resistance mutation patterns (BIII).
- All prior and current drug-resistance test results, when available, should be reviewed and considered when constructing a new regimen for a patient (AIII).

Rating of Recommendations: A = Strong; B = Moderate; C = Weak

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, and clinicians should check this with the testing laboratory. INSTI-resistance testing is particularly important in people who experience virologic failure while taking an INSTI-containing regimen or in those with prior use of injectable long-acting cabotegravir (CAB-LA) (either for treatment of HIV or as pre-exposure prophylaxis [PrEP]). Testing for fusion inhibitor resistance can be ordered separately when needed. There is currently no commercially available resistance test for the CD4 T lymphocyte post-attachment inhibitor ibalizumab, the gp120 attachment inhibitor fostemsavir, or the capsid inhibitor lenacapavir. For a description of co-receptor tropism testing, see Co-Receptor Tropism Assays.

Genotypic Assays

Genotypic assays detect drug-resistance mutations in relevant viral genes; in general, these assays require a plasma viral load of at least 500 to 1,000 copies/mL. Most genotypic assays involve conventional Sanger sequencing of the reverse transcriptase (RT), protease (PR), and integrase (IN) genes of circulating RNA in plasma 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. The Stanford University HIV Drug Resistance Database also provides helpful guidance for interpreting genotypic resistance test results.[1] Various additional tools also are available to assist providers in interpreting genotypic test results.[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 new, optimal ARV regimens.

A next-generation sequencing genotypic resistance assay that analyzes HIV-1 proviral DNA in host cells is now commercially available. This test aims to detect archived resistance mutations in patients with HIV RNA below the limit of detection or with low-level viremia.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of ARV drugs. RT, PR, and, more recently, IN and envelope gene 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_{50}]) is calculated, and the ratio of the IC_{50} of test and reference viruses is reported as the fold increase in IC_{50} (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 can be complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) associated with drug failure, although clinically significant fold increase cutoffs have been described 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 <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 discontinuation of drugs that exert selective pressure on drug-resistant populations. As a consequence, the proportion of virus with resistance mutations can decrease to below the 10% to 20% threshold.[12-14] In the case of some oral ARV drugs, this reversion to predominantly wild-type virus can occur in the first 4 to 6 weeks after the drugs are discontinued. However, with injectable agents with prolonged half-lives (e.g., cabotegravir [CAB] and rilpivirine [RPV]), drug pressure may persist for prolonged periods. 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, for persons taking a non–long-acting ARV regimen, drug-resistance testing in the setting of virologic failure should be performed while the person is still taking their ARV regimen or, if that is not possible, within 4 weeks after discontinuing their ARV regimen **(AII).** If more than 4 weeks have elapsed since the non–long-acting agents 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 due to lack of drug-selective pressure **(CIII).** Given the long half-lives of the long-acting injectable ARV drugs, resistance testing (including testing for resistance to INSTIs) should be performed in all persons who have experienced virologic failure on a regimen of long-acting CAB and RPV or acquired HIV after receiving CAB-LA as PrEP, regardless of the amount of time since drug discontinuation **(AIII).** However, the absence of detectable resistance in patients not currently on antiretroviral therapy (ART) must be interpreted with caution when designing subsequent ARV regimens. Importantly, in addition to considering prior ART history, prior genotypic- or phenotypic-resistance test results should be obtained from old records when possible. Because the most current drug-resistance test may not be able to detect resistance mutations that were previously detected, these prior test results are clinically important and should be reviewed and considered when designing a new ARV regimen **(AIII).**

A next-generation sequencing genotypic assay that analyzes HIV-1 proviral DNA may provide additional information on drug resistance in patients with low levels of plasma HIV RNA or in patients whose levels are below the limit of detection **(CIII).** However, these assays might miss some or all previous drug-resistance mutations, and they should be interpreted with caution. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Clinical Practice (See Table 5 Below)

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 ART.[16-19] The risk of acquiring drug-resistant virus is related to the prevalence of drug resistance in people with HIV who engage in high-risk behaviors within a given community. The prevalence of resistance and mutations by ARV drug class depends upon the population being studied (e.g., people with previous ARV exposure vs. ARV-naive people), geography, and ARV class available in the region.[20] Pre-existing HIV drug resistance before initiation of ART is recognized as an issue for both high- and low-income countries. The prevalence of transmitted drug resistance (TDR) in high-income countries ranges from 9% to 14% and varies by country.[21-23] Pre-treatment drug resistance—defined by the World Health Organization to include people exposed to ARVs prior to initiating first-line therapy (e.g., for PrEP or for the prevention of perinatal transmission)—exceeds 10% in many countries.[20] In most TDR surveys, NNRTI resistance and NRTI resistance are the most common mutation class types detected, followed by PI- and INSTI-resistance mutations, respectively.[21-23]

Resistance testing can guide therapy selection to optimize virologic response in all people starting ART **(AII).** A genotypic assay is preferred for this purpose **(AIII).** In early (acute and recent) HIV infection, in pregnant people with HIV, or in people willing and able to initiate ART on the day or soon after HIV diagnosis, treatment initiation should not be delayed pending resistance testing results. Once results are reported, the regimen can be modified if warranted (see Early [Acute and Recent] HIV Infection) **(AIII).** 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.[24-26] Therefore, if ART is deferred, resistance testing should still be performed at the time of entry into care to optimize the chance of capturing transmitted resistance **(AIII).** In this situation, the genotypic resistance test result should be used for regimen selection in the future when the person begins ART. If a person received CAB-LA as part of ART or PrEP, genotypic resistance testing should include the IN gene.

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.[27-29] Though no prospective trial has directly addressed whether drug-resistance testing before initiation of therapy confers benefit in this population, data from several studies, including one prospective clinical trial, suggest that virologic responses in people with baseline resistance mutations are suboptimal.[16-19 30-34] In addition, an analysis of early RT and PR genotypic resistance testing in ARV-naive people suggests that baseline testing in this population is cost effective and should be performed.[35] Therefore, resistance testing in people with chronic HIV 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, faster turnaround time, greater sensitivity for detecting mixtures of wild-type and resistant virus, and easier interpretation of 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).**[36] Standard genotypic drug-resistance testing in ARV-naive people 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 also may increase. The prior use of CAB-LA for PrEP also may increase the risk of INSTI resistance at the time of HIV diagnosis. When INSTI resistance is possible, providers should supplement standard, baseline, genotypic resistance testing with genotypic testing of the IN gene, which may need to be ordered separately **(AIII).**

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA in host cells can be considered in people with baseline HIV RNA <1,000 copies/mL or when conventional HIV RNA drug-resistance testing is unsuccessful **(CIII).** As outlined above, the results should be interpreted with caution, as this assay might miss some or all previously existing drug-resistance mutations.

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 have assessed the utility of resistance testing to guide ARV drug selection in patients who experience virologic failure. These studies involved genotypic assays, phenotypic assays, or both.[6 37-43] In general, these studies found that changes in therapy based on resistance test 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 the use of genotypic drug-resistance testing in ART-experienced patients with detectable plasma HIV RNA was independently associated with improved survival.[44] Thus, resistance testing is recommended as a tool for selecting active drugs when changing ARV regimens because of virologic failure in people with HIV RNA >200 copies/mL (**AI** for >1,000 copies/mL, **AIII** for 501–1,000 copies/mL, **CIII** for confirmed HIV RNA 201–500 copies/mL) (see Virologic Failure). In people with HIV RNA >200 copies/mL but <500 copies/mL, testing may be difficult to obtain outside of a research setting, but it still should be considered. Conventional drug-resistance testing in people with plasma viral loads <200 copies/mL **is not recommended** because of unclear benefits and since drug-resistance assays cannot be consistently performed at very low HIV-RNA levels **(AIII).**

Resistance testing also can help to guide treatment decisions for patients with suboptimal viral load reduction **(AII).** Virologic failure in the setting of ART is, for certain patients, associated with resistance to only one component of the regimen.[45-47] In this situation, substituting individual drugs in a failing regimen may be an option, but this concept will require clinical validation (see Virologic Failure).

Genotyping is preferred for resistance testing in patients who experience virologic failure or suboptimal viral load reduction while on a first or second ARV drug regimen and in patients in whom resistance mutation patterns are known or not expected to be complex (i.e., mutations that are straightforward, usually limited in number, and/or those that have clear significance) **(AII).** Often in these situations, the mutation patterns detected can be interpreted by algorithms used to predict the impact of subsequent regimens on virologic response. For patients with extensive treatment history, complex mutational patterns may occur. In such situations, the interpretation of complex genotypes and the impact of the mutation pattern on subsequent treatment regimens can be challenging. For these individuals, phenotypic-resistance testing may provide additional helpful information **(BIII).** Rather than only predicting the impact of the detected mutations, these assays can measure *in vitro*

the actual fold change in drug susceptibility, as well as the actual impact of mutation combinations and interactions on each drug under consideration.

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 ARV regimens.[48] In patients who experience virologic failure while on INSTI-based regimens or in those with prior INSTI exposure, including to CAB-LA for HIV treatment or prevention, 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 people with known or suspected complex drug-resistance mutation patterns **(BIII).**

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for patients who are experiencing treatment failure and for whom conventional HIV RNA genotypic drug-resistance testing is unsuccessful or unavailable due to low HIV-RNA levels **(CIII).** As outlined above, results should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations.

When the use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed **(AI)** (see Co-Receptor Tropism Assays).

Use of Resistance Assays for Optimizing Antiretroviral Regimen in People With Viral Suppression

In the past decade, simpler, more potent, and better-tolerated ARV drugs have become available and new ARV drugs will likely continue to emerge. Switching individual or multiple ARV drugs in a regimen is sometimes considered for patients with suppressed viral load to simplify a regimen, avoid drug interactions or toxicity, or for other reasons. If a patient's viral load is suppressed, standard drug-resistance testing will not be successful.

The next-generation sequencing genotypic resistance assay that analyzes proviral DNA can be considered for these individuals, particularly if complex or semi-complex pre-existing resistance is suspected. In individuals who have experienced no prior virologic failures and who are on their first or second regimen, or who have genotypic testing results from when they had prior virologic failures, the use of the proviral DNA genotypic test is unlikely to provide additional useful information. However, in individuals who have experienced multiple prior failures, have a prolonged history of prior ARV regimens, and/or for whom prior genotypic resistance test results are not available, it may be appropriate to utilize proviral DNA genotypic testing **(CIII).** When such testing is obtained, results should be combined with all prior genotypic and phenotypic test results to construct a cumulative genotype, which incorporates all current and previously detected drug-resistance mutations. Results from proviral DNA genotypes should be interpreted with caution, as these assays might miss some or all previously existing drug-resistance mutations. The usefulness of these assays in the clinic is still under investigation and has yet to be fully determined.

Use of Resistance Assays in Pregnancy

In pregnancy, the goal of ART is to rapidly and maximally reduce plasma HIV RNA in order to provide optimal maternal therapy and to prevent perinatal transmission of HIV. Genotypic resistance testing is recommended for all pregnant people with HIV 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 prompt initiation of ART pending resistance testing results. Once the results are available, the ARV regimen can be changed as needed.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
In Early (Acute and Recent) HIV 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).	Drug-resistance testing can determine whether drug-resistant virus was transmitted or acquired while using PrEP. The initial ARV regimen can be modified, if necessary, 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.
If ART is deferred, repeat resistance testing may be considered when therapy is initiated (CIII). A genotypic assay is generally preferred (AIII).	Repeat testing when ART is initiated may be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
Before ART Initiation in Patients With Chronic HIV Drug-resistance testing is recommended at entry into HIV care to guide the selection of initial ART (AII). A genotypic assay is generally preferred (AIII). Treatment should not be delayed while awaiting results of resistance testing (AIII).	Transmitted HIV with baseline resistance to at least one drug is seen in 9% to 14% of patients, and suboptimal virologic responses may be seen in patients with baseline resistance mutations to ARVs in the prescribed regimen. Some drug-resistance mutations can remain detectable for years in untreated patients with chronic HIV.
If transmitted INSTI resistance is a concern, providers should supplement standard resistance testing with a specific INSTI genotypic resistance assay, which may need to be ordered separately (AIII). Given the prolonged half-lives of long-acting injectable ARV drugs, INSTI-resistance testing should be considered in all people with HIV who previously received CAB-LA for PrEP, regardless of the time since drug discontinuation (AIII).	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). Currently, transmitted INSTI resistance is infrequent, but the risk of a patient acquiring INSTI-resistant strains may be greater in certain known exposure settings. INSTI-resistance testing should be ordered for all people with prior exposure to INSTIs for PrEP.
For pregnant people or if ART will be initiated on the day of or soon after HIV diagnosis, treatment can be initiated prior to receiving resistance testing results.	If necessary, the ARV regimen can be modified once resistance test results are available.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
If therapy is deferred, repeat resistance testing may be considered before initiation of ART (CIII). A genotypic assay is generally preferred (AIII).	Repeat testing before initiation of ART may be considered, because the patient may have acquired a drug-resistant virus (i.e., a superinfection). 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.
If use of a CCR5 antagonist is being considered, a co-receptor tropism assay should be performed (AI).	See Co-Receptor Tropism Assays section.
In Patients With Virologic Failure Drug-resistance testing is recommended in patients on combination ART with HIV-RNA levels >200 copies/mL (AI for >1,000 copies/mL, AIII for 501–1,000 copies/mL) and a confirmed HIV RNA 201–500 copies/mL (CIII). In patients with confirmed HIV-RNA levels between 201–500 copies/mL, testing may not be successful but should still be considered.	Drug-resistance testing can help determine the role of resistance in virologic failure and maximize the clinician's ability to select active drugs for the new regimen. Resistance testing for HIV-RNA levels 201–500 copies/mL may need to be conducted within a research setting.
Resistance testing should be done while the patient is taking ART or, if that is not possible, within 4 weeks after discontinuation of non–long-acting ARV drugs (AII). If >4 weeks have elapsed, resistance testing may still be useful to guide therapy; however, previously-selected mutations can be missed due to lack of drug-selective pressure (CIII).	The absence of detectable resistance in such patients must be interpreted with caution when designing subsequent ARV regimens, as mutations may decay with time.
A standard genotypic resistance assay is generally preferred for patients experiencing virologic failure on their first or second ARV regimens and for those with expected noncomplex resistance patterns (AII).	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.
All prior and current drug-resistance testing results should be reviewed and considered when designing a new ARV regimen for a patient experiencing virologic failure (AIII).	Drug-resistance mutations may decay with time, and mutations detected in prior resistance tests may not be detected in current tests, though they remain clinically relevant.
When virologic failure occurs in a patient on an INSTI-based regimen or in a patient with a history of INSTI use, genotypic testing for INSTI resistance should be performed to determine whether to include drugs from this class in subsequent regimens (AII).	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).
Adding phenotypic testing to genotypic testing is generally preferred in patients with known or suspected complex drug-resistance patterns (BIII).	Phenotypic testing can provide additional useful information in patients with complex drug-resistance mutation patterns.
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 in suboptimal viral suppression, and it can help the clinician identify the number of active drugs available in the current ARV regimen and assess the need for a new regimen.

Table 5. Recommendations for the Use of Drug-Resistance Assays

Clinical Setting and Recommendation	Rationale
In Pregnant People With HIV Genotypic resistance testing is recommended for all pregnant people before initiation of ART (AIII) and for those entering pregnancy with detectable HIV-RNA levels while on therapy (AI).	The goals of ART in pregnant people with HIV are to achieve maximal viral suppression for treatment of maternal HIV and to prevent perinatal transmission of HIV. Genotypic resistance testing will assist the clinician in selecting the optimal ARV 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, if needed.
In Patients With Undetectable Viral Load or Low-Level Viremia Who Are Planning to Change Their ARV Regimen HIV-1 proviral DNA resistance assays may be useful in patients with HIV RNA below the limit of detection or with low-level viremia, where a HIV-RNA genotypic assay is unlikely to be successful (CIII).	This test may provide information about previously circulating resistant viral variants that are archived within proviral DNA. These assays may miss some or all prior resistance mutations that have occurred within the viral quasi-species and, therefore, they should be interpreted with caution. The clinical utility of HIV-1 proviral DNA assays has not been fully determined.

Key: ART = antiretroviral therapy; ARV = antiretroviral; CAB-LA = cabotegravir long-acting; INSTI = integrase strand transfer inhibitors; NNRTI = non-nucleoside reverse-transcriptase inhibitors; NRTI = nucleoside reverse-transcriptase inhibitors; PI = protease inhibitor; PrEP = pre-exposure prophylaxis

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