



HIV DRUG RESISTANCE AND DRUG RESISTANCE TESTING

What is HIV Drug Resistance?

Antiretroviral Therapy (ART) has been an important tool to help reduce transmission of the Human Immunodeficiency Virus (HIV). A CDC study published in 2015 showed that ART recipients who achieved viral suppression had a 94% lower HIV transmission rate compared to those with undiagnosed HIV infections.¹



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While the use of antiretroviral (ARV) drugs have been shown to be effective in controlling the proliferation of the HIV virus and prolonging the survival of those infected through viral suppression, it has also created opportunities for drug resistance to develop.²

Drug resistance develops when mutations in HIV strains occur, so that previously effective HIV medication is no longer successful in suppressing viral loads.³ The existence of HIV drug resistant strains poses a problem in controlling both individual viral suppression and the spread of these strains within a population.² The ability of drug resistant strains to render first-line treatments ineffective can severely challenge current efforts to fight HIV/AIDS if spread widely.⁴

HIV Drug Resistance in the United States

According to the Department of Health and Human Service (DHHS), 10% - 17% of patients with HIV infections who have not started ART (ART-naïve), are resistant to at least one 1 ART drug.⁵ A literature review published in 2012 looked at 45 studies (42 in the United States and 3 in Canada) conducted between 1993 and 2008. Results showed that out of 8,718 ARV-naïve individuals, about 12.9% carried a drug resistant strain of HIV.⁶ Similarly, a study conducted by the Center for AIDS Research looked at 14,111 ARV-naïve individuals in the United States from 2003 – 2008. According to the study, the prevalence of genotypic resistance to at least one drug was 14.2%.⁷

HIV Drug Resistance Testing

HIV drug resistance testing has been developed to evaluate the susceptibility of HIV strains to individual ARV drugs.² There are two different types of HIV drug resistance tests that are typically used, genotypic assays and phenotypic assays. Genotypic assays determine if certain viral genes have developed drug resistance mutations. Phenotypic assays test a virus' ability to grow in varying ARV drug concentrations.^{2,5}

In collaboration with



Generally speaking, genotypic assays are more commonly used because of its lower cost, wider availability, and shorter time needed to get results. Phenotypic assays are useful in providing information for better interpreting results from genotypic assays and for designing new drugs. In addition, phenotypic testing is clinically useful in detecting HIV strains with uncommon drug resistance mutations.⁸

Drug resistance testing is important, especially for those who have not started ART. The test can help determine if someone has a drug resistant strain of HIV, thus informing the course of treatment. HIV drug resistance testing can also inform how drug resistance may have contributed to virologic failure and will aid the clinician in selecting an appropriate treatment regimen for the individual.⁵

Drug Resistance Testing Recommendations

Current HIV drug resistance testing recommendations from the DHHS vary by the individual and their clinical situation. The recommendations on what type of test to use range from using only a genotypic assay, to using a mix of phenotypic and genotypic assays, or using assays that are specific to some drug classes, such as integrase strand transfer inhibition (INSTI) genotypic resistance assays and co-receptor tropism assays.⁵

Current guidelines strongly recommend a co-receptor tropism assay if a patient is considered for the use of a CCR5 antagonist for treatment.⁹ While the choice of HIV drug resistance assay may vary by patient, clinicians should keep in mind that drug resistance testing may not be useful for certain patient populations. This is the case for individuals with low plasma viral loads, because the viral number may not be high enough for detection.

Another case where drug resistance testing may not be effective is in individuals who have discontinued their therapy, since there is a lack of drug pressure to select for the survival and proliferation of the drug resistant species.¹⁰

Table 1 summarizes drug resistance assay recommendations and rationale for different patient populations according to their clinical condition.

This table is adapted from the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents.¹⁰



Table 1: HIV Drug Resistance Assay Recommendations

PATIENT POPULATION AND CLINICAL CONDITION	RECOMMENDED ASSAY(S)	ADDITIONAL EXPLANATION ON RECOMMENDED ASSAYS
Patients with acute or recent (early) HIV infection:		
<ul style="list-style-type: none"> ▣ Individuals who start ART immediately 	Genotypic assay	<ul style="list-style-type: none"> ○ HIV drug resistance testing can help determine if the individual was infected with an HIV drug resistant strain.
<ul style="list-style-type: none"> ▣ Individuals who defer ART 	Genotypic assay	<ul style="list-style-type: none"> ○ Treatment should not be deferred while waiting for drug resistance test results, since course of treatment may be altered once test results become available. ○ Repeated drug resistance testing should be considered once the individual starts ART.
ART-naïve patients with chronic HIV infection:		
<ul style="list-style-type: none"> ▣ Individuals who start ART immediately 	Genotypic assay	<ul style="list-style-type: none"> ○ Genotypic assays can provide information on various drug classes, however, sometimes the INSTI drug resistance test needs to be ordered separately. This should be done especially when the clinician is concerned that the patient may have INSTI resistance. ○ Repeated drug resistance testing should be considered prior to starting ART. ○ Individuals who are considered for the use of CCR5 antagonists in their treatment regimen should use the co-receptor tropism assay to test if treatment is appropriate for the patient.
<ul style="list-style-type: none"> ▣ Individuals who defer ART 	Genotypic assay	
<ul style="list-style-type: none"> ▣ Individuals who are considered for INSTI drug class 	Genotypic assay supplemented with specific INSTI genotypic resistance assay	
<ul style="list-style-type: none"> ▣ Individuals who are considered for a CCR5 antagonist drug class 	Co-receptor tropism assay	
Patients with virologic failure:		
<ul style="list-style-type: none"> ▣ Individuals with failure on first or second regimen 	Genotypic assay	<ul style="list-style-type: none"> ○ HIV drug resistance testing can provide valuable information to help the clinician understand the reason for virologic failure and inform the selection of course of treatment. ○ Patient should be tested for drug resistance when they are still taking prescribed drugs, if this is not possible, testing should be done within 4 weeks of discontinuing treatment. ○ Genotypic assays can provide information on various drug classes, however, sometimes the INSTI drug resistance test needs to be ordered separately. This should be done especially when the clinician is concerned that the patient may have INSTI resistance. ○ In patients with complex drug resistance patterns, phenotypic assays can supplement genotypic assays to provide additional information, especially for protease inhibitor drug class.
<ul style="list-style-type: none"> ▣ Individuals on INSTI-based regimen 	INSTI-specific genotypic resistance assay	
<ul style="list-style-type: none"> ▣ Individuals who are considered for a CCR5 antagonist drug class 	Co-receptor tropism assay	
<ul style="list-style-type: none"> ▣ Individuals with known or suspected complex drug resistance patterns 	Genotypic assay supplemented with phenotypic assay	
Patients with suboptimal suppression of viral load:		
[See recommendations for patients with virologic failure]		<ul style="list-style-type: none"> ○ HIV drug resistance testing can provide valuable information to help clinicians understand the reason for virologic failure and inform the selection of course of treatment.
HIV-infected pregnant patients:		
<ul style="list-style-type: none"> ▣ Individuals who have not started ART 	Genotypic assay	<ul style="list-style-type: none"> ○ HIV drug resistance testing can help clinicians in selecting the optimal course of treatment for the patient, so that the mother can achieve maximal viral suppression to prevent perinatal transmission of HIV. ○ Treatment should not be deferred while waiting for drug resistance test results, since course of treatment may be altered once test results become available.
<ul style="list-style-type: none"> ▣ Individuals who are entering pregnancy with detectable HIV RNA levels while on therapy 	Genotypic assay	

*Adapted from Department of Health and Human Service's Panel on Antiretroviral Guidelines for Adults and Adolescents – Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. Recommendations as of July 14, 2016.⁹

Preventing HIV Drug Resistance – A Role for Everyone

HIV Positive Patients on ART

For patients who are receiving treatment, research has shown that non-adherence to HIV medication increases the risk of developing HIV drug resistance. However, the relationship between drug adherence and the probability of developing drug resistance follows a bell shaped curve, where the highest levels of adherence results in the lowest threat of resistance because high drug adherence prevents viral replication, thus decreasing the chance of a drug resistant mutation.⁴

Those at the lowest levels of adherence have a lower chance of developing resistance, because there is inadequate selective drug pressure for the proliferation of the resistant viral strain.⁴ It is the individuals who are in the mid-range of adherence who are at highest risk for developing drug resistance because of a complex environment that favors the drug resistant strain.⁴ Thus it is important for patients to adhere to their drug regimen. Research suggests that although patients at the lowest levels of adherence have lower chances of a drug resistant mutation, even relatively small degrees of non-adherence in those who have started ART can substantially increase the risk of developing drug resistance.^{4,11}

Pre-Exposure Prophylaxis (PrEP) Users

The rollout of PrEP has raised concern in that it could contribute to the spread of HIV drug resistance. Research done through mathematical modelling has shown that the duration and extent of PrEP exposure in HIV infected individuals is a major determinant in the development of HIV drug resistance.^{12,13} This can promote the occurrence of HIV drug resistance in situations where PrEP is initiated in people where acute HIV infection is not recognized.¹⁴

Non-adherence to PrEP may also be a problem, as poorly adherent users lack the protection of PrEP, and may become infected while at a higher risk of developing resistance.¹¹ While PrEP shows promise in preventing new HIV infections, the benefits may be offset by HIV drug resistance.¹¹ To prevent the development of HIV drug resistance through the use of PrEP, it is important to integrate HIV testing with PrEP implementation programs to monitor PrEP candidates for HIV infection and drug resistance, as well as emphasize to PrEP candidates the importance of adherence.¹²

Providers

According to the CDC's recommendations for HIV prevention with adults and adolescents with HIV, providers should inform their patients about the benefits of drug adherence. This includes discussing how not taking ART as prescribed can lead to consequences such as developing HIV drug resistance and transmitting it to others.¹⁵ In addition, providers should provide adherence monitoring to identify patient adherence patterns. This would be helpful to determine if the patient would require a behavioral intervention or change in regimen.¹⁶

Examples of behavioral interventions to improve adherence include case management, reminder devices, directly observed therapy, etc.¹⁶ In addition, if a provider is able to better understand a patient's adherence, a drug regimen can be prescribed that is suited to how well the patient adheres. However, more research is needed to better understand adherence-resistance relationships for different classes of drugs, so that providers can prescribe the most appropriate treatment regimen based on patient profile.^{16,17}

Providers are also encouraged to consult HIV clinical care or HIV-specific virology experts when interpreting results from HIV drug resistance tests. Results from a randomized multi-center trial testing, whether a combination of genotypic testing and expert advice improves virologic outcomes, showed that patients experienced better outcomes when their clinicians optimized their treatment with an expert.¹⁸

Public Health and Research

HIV drug resistance databases have been developed to collect and study HIV drug resistant strains. These databases are helpful in interpreting HIV drug resistance test results, and help researchers link sequence data to other forms of data for each strain.^{19, 20} These databases are also important for surveillance and characterizing the epidemiology of HIV drug resistance nationally and globally.^{21, 22}

Databases include: Stanford's HIV Drug Resistance Database (<http://HIVdb.Stanford.edu>), HIV French Resistance - National Agency for AIDS Research (www.HIVFrenchResistance.org), International Antiviral Society – USA (IAS-USA) HIV Drug Resistance Mutations (www.IASUSA.org), Los Alamos National Laboratory HIV Database (www.HIV.lanl.gov).

While there have been many advances in the fight against the HIV/AIDS epidemic in the past few decades, HIV drug resistance continues to pose a challenge for individuals and whole populations. In order to stop the spread of HIV drug resistant strains, it is essential for providers, patients, and public health professionals to be vigilant in regards to treatment and adherence, and to closely monitor potential development and spread of HIV drug resistant strains through testing.

Building Organizational Capacity

The CDC-funded HIV CBA center at CAI can help conduct an assessment of your organizational needs, identify resources, plan for implementation and provide you with training and capacity building support that leads to successful program for high-impact HIV prevention through ART adherence, thus contributing to the prevention of drug resistance. The HIV CBA Center is able to shape trainings and technical assistance to the specific needs of your health care organization.

The approach includes capacity building for providers and support staff in areas such as:

- ⦿ Behavioral Change & Motivational Interviewing
- ⦿ HIV Treatment Adherence
- ⦿ Anti-Retroviral Treatment and Access to Services (ARTAS)
- ⦿ Identifying Early Red Flags for Abandoning Care & Poor Adherence
- ⦿ PrEP – Pre-Exposure Prophylaxis

For more information on how to obtain our capacity building services to incorporate into your Health Care Organization, visit www.hivcbacenter.org.

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