

Understanding Drug Resistance

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The widespread availability of antiretroviral therapy has made the fight against HIV a great deal easier. But like a horse without a rider, these medications can't go the distance alone. Working closely with your doctor, you'll need to choose and monitor your treatment carefully. This is because of obstacles that can arise before and during treatment—one of the most important is HIV drug resistance.

Fortunately, we now know a lot about how to reduce the risk of drug resistance and treat drug-resistant virus. We also have access to important technologies that look for drug-resistant virus and help us make important treatment decisions. These drug-resistance tests have become a routine part of HIV care.

This lesson explains what drug resistance is and how drug-resistance tests work, including the role they play in improving the success of antiretroviral therapy.

What Is HIV drug resistance?

In simple terms, drug resistance refers to the ability of disease-causing germs—such as bacteria and viruses—to continue multiplying despite the presence of drugs that usually kill them.

With HIV, drug resistance is caused by changes (mutations) in the virus's genetic structure. These mutations can lead to changes in certain proteins, most commonly enzymes, that help HIV reproduce (replicate).

Mutations are very common in HIV. This is because HIV replicates at an extremely rapid rate and does not contain the proteins needed to correct the mistakes it makes during copying.

Mutations occur randomly, on a daily basis, but many are harmless. In fact, most mutations

actually put HIV at a disadvantage—they reduce the virus's "fitness" and slow its ability to infect CD4 cells in the body. However, a number of mutations can actually give HIV a survival advantage when HIV medications are used, because these mutations can block drugs from working against the HIV enzymes they are designed to target. These are the mutations we are concerned about when we talk about drug resistance.

HIV relies on many enzymes to replicate inside a human cell. It also relies on proteins, including gp41, to latch on to CD4 cells and infect them. Mutations can occur in any of these parts of the virus and cause drug resistance:

- **Reverse transcriptase:** nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) target this enzyme.
- **Integrase:** Integrase inhibitors target this enzyme.
- **Protease:** Protease inhibitors target this enzyme.
- **gp41:** Fusion inhibitors target this protein on HIV's outer wall.

For people infected with HIV, drug resistance can render drugs less effective or even completely ineffective, thus significantly reducing treatment options.

How does it occur?

HIV drug-resistance mutations can occur both before and during HIV treatment. Here's a look at how this happens:

- **Transmission of drug-resistant HIV.** Many HIV-positive people now take HIV drugs. If someone has developed resistance to one or more of these HIV drugs and has unprotected

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sex or shares needles with someone who is not infected with the virus, it is possible that they can infect their partner with a drug-resistant variant—a strain of HIV containing mutations that can cause resistance.

In the United States and other countries where HIV treatment is widely used, between 5 percent and 20 percent of new HIV cases involve strains of the virus that are resistant to at least one HIV medication.

- **During treatment.** Even if someone is infected with HIV that doesn't contain drug-resistance mutations ("wild-type" virus), genetic changes still occur over time, even before treatment is started. This ends up creating a large mixture of virus in the body. Some of these variants contain the necessary mutations that can partially, or fully, resist an antiretroviral drug—which explains why one-drug treatment (monotherapy) should never be used to treat HIV.

Soon after combination HIV drug treatment is started, the amount of wild-type virus is dramatically reduced. However, if the amount of virus isn't pushed down and kept at very low levels, HIV variants can continue replicating, acquiring additional mutations. And once the virus has accumulated enough mutations, a high level of resistance to the drugs being used can occur, causing viral load to increase and CD4 cells to drop.

A major concern with these mutations is that they can result in cross-resistance. This means that HIV resistance to one drug can automatically become resistant to other drugs in the same class. For example, if you're on a drug regimen that contains the NNRTI Sustiva and your virus becomes resistant to it, chances are that your virus is also resistant to the NNRTIs Viramune and Rescriptor, even though you haven't taken these drugs.

What factors contribute to resistance during treatment?

If there's one "golden rule" of antiretroviral therapy, it is: the lower the viral load while on treatment, the less likely it is that the virus will continue reproducing and mutating. A powerful HIV regimen is the most effective way to keep the level of virus low—prefer-

ably "undetectable" (<50 copies/mL as measured by a sensitive viral load test)—and to delay additional mutations from occurring.

Unfortunately, there are a number of factors that can prevent an HIV drug regimen from being as powerful as it can be. These include:

- **Poor treatment adherence:** In order for HIV drugs to work correctly, they must be taken exactly as prescribed. Skipping doses or not taking your medication correctly can cause the amount of an HIV drug to decrease in the bloodstream. If the drug level becomes too low, HIV can reproduce more freely and accumulate additional mutations.

There are a number of reasons why someone might struggle with treatment adherence, including side effects, a hectic schedule or forgetfulness. If you've been having difficulty adhering to your drug regimen, it's nothing to be embarrassed about—be sure to tell your doctor so that you can up with solutions, which might include simplifying your treatment.

- **Poor absorption:** Not only must HIV drugs be taken on schedule, they also need to be absorbed effectively into the bloodstream. A drug, or combination of drugs, that is not absorbed properly can result in levels in the bloodstream that are too low and, ultimately, allow HIV reproduction and the accumulation of drug-resistance mutations. Certain drugs have dietary requirements, which can affect absorption. People with HIV can also experience diarrhea and vomiting, which can cause HIV drugs to be expelled from the gut too quickly and affect absorption.

- **Varying pharmacokinetics:** Pharmacokinetics is the scientific term used by researchers to mean how a drug is absorbed, distributed, broken down, and removed from the body. Interactions between drugs—including common HIV medications—can be a major problem in this regard. For example, if the NRTI Viread (tenofovir) is combined with the protease inhibitor Reyataz (atazanavir), blood levels of Reyataz can fall to dangerously low levels. This is why the protease inhibitor Norvir (ritonavir), which boosts Reyataz levels in the bloodstream, must be used if Viread is also prescribed.

There are many drug interactions like this. Be sure that your doctor knows all of the medications you are taking, including prescription drugs, over-the-counter remedies and nutritional supplements.

Do I have drug resistance?

Viral load is one of the best tools available to determine if HIV treatment is working. An undetectable viral load is an excellent sign that treatment is working correctly. Viral load can also show when treatment isn't working properly:

- Your viral load fails to go undetectable within the first several months of starting a new HIV drug regimen.
- Your viral load goes from being undetectable to detectable (note: A one-time “blip” in viral load is not usually a sign that a drug regimen is no longer working).
- Your detectable viral load continues increasing, even though you are still taking your prescribed HIV drug regimen.

While viral load can help you determine if your drug regimen isn't working effectively, it cannot explain why this is happening. This is where drug-resistance testing comes in. These tests can help you and your doctor determine if your virus has become resistant to the medications you're taking—or if you haven't yet started treatment yet, help figure out if you were infected with a drug-resistant strain of HIV that might affect your selection of medications.

When should drug-resistance tests be used?

HIV treatment guidelines, including those produced by the U.S. Department of Health and Human Services (HHS) and the International AIDS Society-USA (IAS-USA), recommend drug-resistance testing for all HIV-positive people. Here's a look at when these tests should be used:

- **When HIV is first diagnosed.** Knowing if you've been infected with a drug-resistant strain of HIV—and which drugs your virus is resistant to—can be very helpful. For the most accurate results, you should be tested for HIV drug resistance soon after you are diagnosed as HIV positive, even if you won't be starting treatment for several months or years (the information will be recorded in your medical file

and help guide treatment when the time comes).

It is important to note, however, that drug-resistance testing does not always produce accurate results when used in this manner. Soon after a drug-resistant strain enters the body, it begins reproducing. Over time, a wild-type strain of HIV can emerge, forcing the drug-resistant strain(s) to go into hiding and escape detection using drug-resistance testing. In other words, testing may not produce reliable information if too much time has passed since infection occurred.

- **If treatment doesn't appear to be working.** If viral load fails to become undetectable after a new treatment regimen is started, or becomes detectable again after a period of being undetectable, drug-resistance testing may help determine the cause. For best results, the test should be conducted while you are on your regimen—provided that your viral load is detectable—or within four weeks of discontinuing treatment.

If no drug resistance is found, the problem might be poor adherence, absorption difficulties or drug–drug interactions. It is best to remedy these problems before resistance mutations develop. If drug resistance is found, these tests can help determine which medications have stopped working for you (people rarely develop resistance to all three or four drugs being taken) and also help figure out which medications to switch to.

- **During pregnancy.** If you are HIV positive and become pregnant, the most effective way to reduce the risk of transmitting the virus to your baby is to get your viral load undetectable and keep it there—at least until your baby is born. Drug-resistance testing before and during treatment can help achieve this important goal.

Which Tests Are Available?

Generally speaking, there are two types of drug-resistance tests available to HIV-positive patients: genotypic and phenotypic assays. Because genotypic testing provides results in one to two weeks—compared to the two-, three- or four-week turnaround associated with phenotypic testing—it is the preferred choice for patients who have yet to start treatment.

Among patients who have used multiple drugs in the past, interpreting the results of both tests together may be most useful. One company, Monogram Biosciences, will phenotype and genotype a blood sample and provide the results of both tests on the same lab report—called PhenoSense GT.

What Is genotypic testing?

These tests examine the actual genetic structure—of HIV taken from a patient (a standard blood sample is all that is required). The HIV is examined for the presence of specific genetic mutations that are known to cause resistance to certain drugs.

An example: Researchers know that the NRTIs Epivir and Emtriva are not effective against forms of HIV that contain the mutation “M184V” in its reverse transcriptase gene. If a genotypic resistance test discovers a mutation at position M184V, chances are that the person’s HIV is resistant to Epivir and Emtriva and is not likely to respond to either of these drugs.

For many drugs, including the protease inhibitors and other NRTIs, complex patterns of mutations are required for resistance to occur. In this way, interpreting the results of genotypic testing can be tricky, given that different mutations—and different combinations of mutations, especially in patients with a lot of treatment experience—can mean different things. However, as knowledge of mutations and their different patterns has grown considerably over the past several years, laboratories are able to provide accurate and useful information to physicians.

Examples of available genotypic tests include: Bayer Health Diagnostics’ HIV-1 TrueGene, Celera Diagnostics/Abbott Laboratories’ ViroSeq, Lab-Corp’s GenoSure (Plus) and Monogram Biosciences’ GeneSeq.

To learn more about the specific mutations and genotyping, we recommend Stanford University’s HIV Drug Resistance Database website (<http://hivdb.stanford.edu/>). They maintain detailed lists of the various mutations associated with resistance to each of the approved antiretrovirals, along with an interactive tool that you and your doctor can use to double-check your genotypic testing results.

What Is phenotypic resistance testing?

Unlike genotypic testing, which looks for particular

genetic mutations that cause drug resistance, phenotypic testing directly measures the behavior—or phenotype—of a patient’s HIV in response to particular antiretrovirals. Because of the way phenotypic tests work and the results they provide, many experts believe that these tests are more comprehensive and trustworthy than genotypic tests, especially when testing samples from patients who have tried and failed a number of HIV drugs in the past.

Using the simplest terms, phenotypic testing is performed by placing samples of a patient’s HIV in test tubes with each HIV drug to observe how the virus reacts. The ability of the virus to grow (or not grow) in the presence of each drug is evaluated. The virus is exposed to varying strengths, or concentrations, of each drug. The ability of the patient’s virus to grow in the presence of the drugs is compared with some wild-type virus that is known to be 100 percent susceptible to all HIV drugs. The comparison between the patient’s virus and the wild-type virus provides the phenotyping results.

These results tell doctors how much of a particular drug is needed to reduce HIV replication. In other words, the laboratory conducting a phenotypic test is trying to determine the amount, or concentration, of drug needed to stop HIV from reproducing.

For example, if four times as much of the NRTI Ziagen (abacavir) is needed to control HIV replication, the virus is said to have “fourfold resistance” to the drug. If seven times as much Ziagen is needed, the virus is sevenfold resistant to the drug.

When phenotypic tests first became available, interpreting these fold changes was difficult. It wasn’t clear what a fold change meant in terms of the virus being fully sensitive, less sensitive, or not sensitive to a specific HIV drug. As a result, companies conducting phenotypic tests began working closely with researchers to better understand fold changes and what they really mean in terms of resistance to available medications. After several years of extensive research, these companies have developed “clinical cutoffs”—an important component of phenotypic testing that allows for much easier interpretation of fold changes as they relate to the sensitivity of HIV to many of the available medications.

Returning to the example of Ziagen, using Monogram Bioscience’s PhenoSense HIV assay, the lower clinical cutoff is 4.5-fold resistance and the upper

clinical cutoff is 6.5-fold resistance. In other words, HIV that is fourfold resistant to Ziagen is still technically sensitive to the drug, whereas HIV that is sevenfold resistant to Ziagen means that the virus is much less sensitive to the drug and, as a result, not a good treatment choice.

As for fold changes that fall between the lower and upper cutoffs, this means partial resistance (the higher the fold change, the less sensitive HIV is to the drug being used). While it is always best to use antiretrovirals that your virus is fully sensitive to, it is sometimes necessary to use (or reuse) medications your HIV is partially resistant to.

Each HIV drug has different clinical cutoffs, which can be confusing. To help make sense of these cutoffs and to make it easier for health care providers to interpret the results, laboratories conducting these tests provide detailed reports for every test conducted.

There are two “conventional” phenotypic tests available: Monogram Bioscience’s PhenoSense assay and Virco Lab’s Antivirogram. Both tests evaluate the fold changes for all of the available NRTIs, Protease Inhibitors, and NNRTIs. Monogram Biosciences has a separate phenotypic assay, called PhenoSense Entry, which tests HIV’s sensitivity to the entry inhibitor Fuzeon.

Another test is Virco Lab’s vircoTYPE HIV-1 assay. This is actually a “predictive” phenotypic test, using genotypic testing results to figure out what the virus’s phenotype is, without actually performing a pheno-

typic test. To do this, labs use genotyping testing to determine if an HIV sample has mutations known to cause drug resistance. Once the genotype has been determined, the laboratory searches a database maintained by Virco containing the genotypes of several thousand HIV samples collected from other patients. It then retrieves the phenotypes—the fold changes—that correspond to these samples, averages the information together and predicts the drugs that the current sample will be more or less sensitive to.

It is important to note that Monogram Biosciences and Virco calculate their cutoffs differently. As a result, the cutoffs determined for one company’s test (e.g., PhenoSense) do not apply to the cutoffs determined for the other company’s test (e.g., vircoTYPE).

How Can Drug Resistance Be Avoided?

There are a number of steps that HIV-positive people can take to prevent—or at least slow down—the development of resistance:

- **Learn all you can about HIV treatment and the available options.** The more you know, the easier it will be to make treatment choices that help you avoid drug resistance. Reading the information on this website about HIV medicine is a good first step.
- **Start treatment with a powerful HIV regimen.** Your first shot at HIV treatment is probably your best chance at fully suppressing the virus and preventing the development of drug resistance.



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The PhenoSense lab report also includes information on an HIV sample’s replication capacity (RC). RC measures how well a patient’s virus is able to replicate compared to a wild-type reference virus. Generally speaking, wild-type virus replicates the best inside the human body. When the virus accumulates drug-resistance mutations, it allows the virus to continue replicating in the presence of HIV treatment. However, these mutations can affect HIV’s fitness—its ability to cause damage to the immune system at the same rate as wild-type HIV.

Knowing HIV’s RC may help to determine when to delay, start, switch or interrupt therapy. For example, in highly treatment-experienced patients with multi-drug resistance, viruses with low RC values may be associated with stable or increasing CD4 counts, which reduces the need for changing a regimen. However, more information from clinical trials is needed to better understand how best to use RC in making such treatment decisions.

- **Be sure to follow instructions.** It is very important that HIV-positive people take their HIV medications exactly as prescribed. Missing doses and not taking the right number of pills can cause viral load to increase and cause drug-resistance mutations to develop.
- **Communicate with your doctor.** Knowing how to take your medicine properly and reporting any problems to your doctor are important for avoiding drug resistance.
- **Monitor the effects of your treatment.** This means keeping an eye on your viral load and other lab tests after you begin treatment and for as long as you remain on therapy. Every three months is a standard recommendation. Often an increasing viral load—or a viral load that fails to go undetectable—is the first sign that drug resistance is developing. Monitoring viral load is a good way to guard against drug resistance.

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