HIV Drug Resistance

The widespread availability of effective antiretroviral therapy has made the fight against HIV much easier. But treatment still involves challenges, including drug resistance. Fortunately, modern HIV medications are more potent, and the virus is not able to defeat them as easily, but it is still important to take your meds every day and receive the recommended monitoring tests to ensure
that your treatment is working.

What is drug resistance?

Drug resistance refers to the ability of viruses or bacteria to continue multiplying despite the presence of drugs that usually kill them. In the case of HIV, drug resistance occurs when the virus develops mutations, or changes in its genetic code. These changes can alter HIV proteins—including the reverse transcriptase, protease and integrase enzymes that the virus uses to replicate—in ways that make them nonresponsive to drugs. Untreated or inadequately treated HIV replicates rapidly and can quickly develop mutations that confer resistance.

How does drug resistance occur?

Drug-resistance mutations can occur both before and during HIV treatment. In some cases, people acquire a strain of HIV that already has these mutations. This is known as transmitted drug resistance. It can happen, for example, if the virus was transmitted from a person who is on treatment but not taking the meds consistently. It is estimated that 5% to 25% of transmitted HIV is already drug resistant.

In other cases, people initially have nonresistant, or “wild type,” HIV that later develops resistance. This is known as acquired drug resistance. This is most likely to happen if a person on treatment does not maintain optimal adherence, meaning they do not always take their meds on schedule as prescribed. This allows the virus to replicate and develop new resistance mutations over time.

Resistance mutations can also evolve if a person is using only one drug that is active against the virus, known as monotherapy. This is why HIV treatment requires combination therapy using two or more drugs that work in different ways. People who used first-generation antiretrovirals one at a time as they became available often developed resistance, but it is less likely with modern treatment.

It is also possible, but less common, for people taking pre-exposure prophylaxis (PrEP) to develop drug resistance. While Truvada (tenofovir disoproxil fumarate/emtricitabine), Descovy (tenofovir alafenamide/emtricitabine) or Apretude (long-acting cabotegravir) can prevent HIV on their own, they are not strong enough to suppress the virus after infection. If a person acquires HIV despite using PrEP—for example, if they don’t take it consistently—and it is not diagnosed quickly, the virus can replicate and develop resistance mutations.

What factors contribute to drug resistance?

If there’s one golden rule of antiretroviral therapy, it’s that the lower a person’s viral load while on treatment, the less likely it is that the virus will mutate and develop resistance. A number of factors can lead to a detectable viral load, including:

Poor adherence: In order for HIV medications to work as they should, they must be taken as prescribed. Most HIV meds must be taken every day, though the new long-acting regimen Cabenuva (injectable cabotegravir plus rilpivirine) is administered once a month. Missing doses can lead to low drug levels in the body, which allows the virus to resume replication and
accumulate resistance mutations as it multiplies. Tell your health care provider if you are having trouble maintaining good adherence. Some regimens are more convenient than others, and some drugs are more “forgiving” of occasional missed doses.

Poor absorption: Not only do HIV drugs need to be taken on schedule, they also must be absorbed effectively into the bloodstream. Medications that are not absorbed properly can result in drug levels that are too low to fully control the virus. Certain drugs must be taken with food or on an empty stomach to be absorbed properly. Vomiting and diarrhea can cause drugs to be expelled from the gut too quickly, before they’re absorbed.

Pharmacokinetics: Pharmacokinetics is the scientific term for how a drug is absorbed, distributed, broken down and eliminated from the body. Interactions between drugs is one factor that can interfere with absorption. Some HIV medications require a booster to maintain high enough levels in the body (for example, protease inhibitors boosted with ritonavir or cobicistat). Be sure that your doctor about knows about all the medications you are taking, including prescription drugs, over-the-counter medications, herbal remedies and supplements.

What are the consequences of resistance?

When resistance occurs, your drugs may stop working, which allows HIV to resume replication. This can lead to disease progression and raises the risk of HIV transmission. What’s more, some mutations confer cross-resistance to all or most other drugs in the same class, which can limit future treatment options. Certain medications, however, are less susceptible to resistance if you occasionally miss a dose; these drugs are said to have a high barrier to resistance.

How do I know if I have drug resistance?

A viral load test often gives the first indication of drug resistance. If your viral load does not drop soon after starting therapy or if it starts going up while on treatment, it may be due to resistance. On the other hand, if your viral load is undetectable, that means the virus is not replicating because your meds are doing their job unhampered by resistance. A rising CD4 count is another, usually later, sign that your treatment may not be working properly.

While viral load can help determine if your drug regimen isn’t working, it cannot explain why this is happening. This is where resistance testing comes in. These tests can help your doctor determine whether your virus has become resistant to the medications you’re taking. And if you haven’t yet started treatment or are looking to switch regimens, resistance testing can help determine which medications are most likely to work well.

There are two types of resistance test:

Genotypic tests: This type of test examines HIV’s genetic sequence, or genotype, to see whether it contains mutations known to be associated with drug resistance. Specifically, the tests look for changes in HIV’s reverse transcriptase, protease and integrase enzymes. For example, the nucleoside reverse transcriptase inhibitors lamivudine and emtricitabine are not active against HIV
that contains a mutation dubbed M184V in the reverse transcriptase enzyme. If this mutation is present, a person is less likely to respond to either of these drugs. Some drugs, including protease inhibitors, require patterns of multiple mutations for resistance to occur, so interpreting genotypic tests can be tricky. To learn more about specific resistance mutations, see Stanford University’s HIV Drug Resistance Database.

Phenotypic tests: This type of test directly measures the behavior, or phenotype, of HIV in the presence of specific medications. A sample of HIV from a blood test is exposed to various concentrations of different drugs in a laboratory to see whether the virus can still replicate. Its ability to do so is compared against wild-type virus that is known to be fully susceptible to all antiretrovirals. Phenotypic resistance is often expressed in fold changes. For example, if four times as much of a particular drug is needed to control HIV replication, the virus is said to have “fourfold resistance” to that drug.

Genotypic tests are easier, quicker and cheaper, but phenotypic tests can be more accurate under certain circumstances. For a person with newly diagnosed HIV who is starting treatment for the first time, genotypic testing is usually sufficient. HIV treatment guidelines from the U.S. Department of Health and Human Services (DHHS) recommend genotypic testing when a person enters HIV care to guide the selection of the first treatment regimen. However, therapy should not be delayed while awaiting test results; a standard regimen can be started right away and adjusted later if needed.

Genotypic tests are also preferred for people with suboptimal response or virological failure while on their first or second regimen. The tests should be done while the person is still on the failing regimen; however, testing might not yield reliable results if viral load is detectable but low. Phenotypic testing, in contrast, is preferred for people with known or suspected complex drug-resistance mutation patterns, which is often the case for heavily treatment-experienced individuals.

How can I avoid drug resistance?
People with HIV can take a number of steps to reduce the likelihood of developing drug resistance:

- Learn about HIV treatment and the available options. The more you know, the easier it will be to make treatment choices that help you avoid resistance.
- Start treatment with a potent antiretroviral regimen, which offers the best chance of fully suppressing the virus and preventing the development of resistance.
- When switching treatments, pick a potent new regimen that also meets your needs for convenience and tolerability.
- Take your HIV medications exactly as directed every day or, if you use Cabenuva, every month.
- Get regular monitoring tests, including viral load and CD4 count measurements, to ensure that
Your treatment is working.

Today’s antiretrovirals are very effective, and newer meds, such as integrase inhibitors, have a high barrier to resistance. Most people starting treatment for the first time can find a regimen that keeps their viral load suppressed over the long term, which minimizes the risk of drug resistance. Putting together an effective regimen is more challenging for heavily treatment-experienced people—especially those who used less potent drugs early in the epidemic—but most can still get their HIV under control. Communicate with your health care providers and let them know if you’re having trouble taking your meds as directed, as poor adherence is the biggest risk factor for drug resistance.

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