HIV DRUG RESISTANCE, CD4 AND VIRAL LOAD FACT SHEET

Understanding Drug Resistance

HIV is a smart little virus. Although scientists have spent the last 25 years designing medications to fight it, HIV can learn to adapt and avoid medications. When this happens, we say someone has developed "drug resistance."

How HIV Works

HIV, like all viruses, is a parasite; it needs a human cell in which to reproduce. The first thing HIV does when it enters someone's body is look for a comfortable place to make its home. Its target is the immune system—in particular, cells known as CD4 or helper T cells. The fact that HIV enters these particular cells is bad news, since CD4 cells are what the body uses to fight off infections.

Key Terms Used in This Fact Sheet

Drug resistance: HIV can mutate (change form), resulting in HIV that cannot be controlled with certain medications.

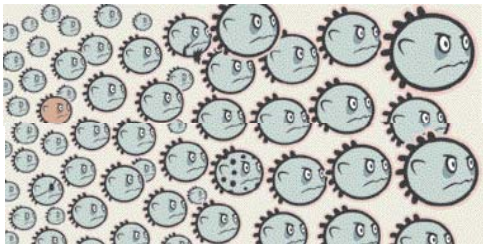
CD4 count: CD4 cells, also called T cells or CD4+ T cells, are white blood cells that fight infection. HIV destroys CD4 cells, making it harder for the body to fight infections. A CD4 count is the number of CD4 cells in a sample of blood.

Viral load: the amount of HIV in a sample of blood.

Once HIV gets inside a CD4 cell, it basically takes control of it and transforms the cell from a disease fighter into a factory whose sole mission is to create as many new copies of HIV as it can. These copies then travel to other CD4 cells, infect them and turn them into HIV factories as well. These factories can produce a billion or more copies of HIV per day. The specific number of HIV copies made each day will depend on how many CD4 cells are infected and producing virus. The level of production can be measured by an infected person's viral load—the lower a person's viral load number, the less HIV is multiplying. Although the parent HIV dies soon after it makes copies of itself, it produces so many copies before it dies that HIV remains a continual danger. While HIV is busily creating copies of itself, it's also destroying the immune system, since soon after it uses CD4 cells to make copies of itself, the CD4 cells die. This explains why, without treatment, someone with HIV may gradually see his or her CD4 count fall. The lower someone's CD4 count is, the more likely he or she will be to get sick.

HIV Mutations

What does all this have to do with drug resistance? The answer is that HIV isn't perfect: While HIV is furiously reproducing, there are bound to be errors. Picture infected CD4 cells as poorly run bug factories that are supposed to make two-eyed blue bugs. Because the factories produce more than a billion of these bugs daily, some bugs won't quite turn out like they're supposed to. Most have two eyes, but some have three. Some are pink and some have spots. The bugs that are different are called "mutants." The changes are called "mutations." HIV mutations occur naturally all the time in everyone with HIV, whether or not they are taking medications. If medications were not needed to treat HIV, mutations wouldn't matter that much, since mutations generally don't make the virus more aggressive.



However, mutations matter because eventually almost everyone with HIV needs treatment. Certain mutations can enable HIV to thrive *despite* the presence of medications in a person's body.

HIV Treatment

Successful HIV treatment usually consists of at least three drugs from two different "classes," or types, of medications. Each class works differently, so that an HIV mutation that makes the virus resistant to one class won't make it resistant to another class. What makes today's HIV treatment so effective is that it is more powerful than ever before, with fewer side effects.

Current treatment combinations can just about stop HIV's ability to reproduce. How will someone know if their HIV is under control? If the medications work well, within about two weeks after starting their first treatment regimen, the amount of HIV in their blood—"viral load"—will decrease dramatically. Within two to six months, they'll probably be told that their HIV is "undetectable." Undetectable simply means that even though they are still HIV positive and can transmit HIV to others, their viral load is now so low that current viral load tests aren't sensitive enough to detect the HIV in their blood. It's sort of like a needle in a haystack—it's there, but hard to find. HIV can't be totally eliminated because it enters the genetic structure of many cells in a person's body, including "reservoirs," such as lymph nodes and spinal fluid, where HIV medications may have a hard time reaching. The great thing about being undetectable is that it signifies that a person's HIV is now under control. The number of CD4 cells in a person's body can begin to grow again and their immune system can recover a nd do its job. With more CD4 cells, the chance of developing opportunistic infections and illnesses is reduced.

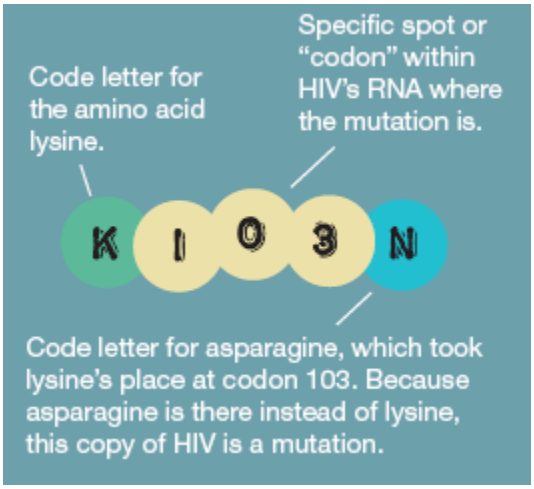
As long as a person keeps taking all their medications on time, their chances of remaining undetectable are excellent. In addition, with HIV's reduced ability to multiply, there are fewer opportunities for HIV mutations to be made. Of course, if someone is on their third, fourth or fifth regimen, and have many drug resistant mutations, reaching an undetectable viral load is sometimes difficult, if not impossible. Fortunately, many recent studies show there's a benefit to keeping a person's viral load as low as possible, even if it's detectable. A low, stable viral load can still allow a person to increase their CD4 count and reduce the chances they will become ill.

How Drug Resistance Occurs

HIV medications are best at fighting the regular — not the mutated—virus. Although most HIV mutations are harmless, sometimes HIV can get lucky: If a mutation differs in just the right way, it can render an HIV medication useless. If this happens, we say that HIV is "resistant" to that medication. Suppose someone frequently misses a dose. HIV will grab this opportunity to start making more copies of itself in their CD4 cells. As the amount of HIV in their body increases while they are not taking their medications consistently, so does the amount of mutated HIV—including mutations that make their virus resistant to their medications.

In other words, if the person misses doses of their medications too often, they're effectively training their mutated, drug-resistant HIV to survive better. The mutated virus may begin to make more and more copies of itself, and could eventually become the most common type of HIV in their body. Once this happens, *no matter how much of that medication they take*, it will no longer have an effect on their HIV. This means they've become resistant to that medication. Once their HIV has developed resistance to a medication, it will stay resistant *forever*, since resistant HIV, like regular HIV, can remain hidden in some of their cells.

What Exactly Is a Mutation? And What Are All Those Numbers About?



To make it easier to work with HIV resistance tests, researchers have a shorthand system for naming HIV mutations.

An HIV "mutation" is actually just a slight change in a specific section of HIV's RNA, the genetic code that provides all the instructions for how HIV works. Mutations occur naturally, not just in HIV, but in other viruses as well—not to mention within the cells of every other living thing, humans included. Every HIV mutation is given a unique name to help researchers identify it.

Let's look at K103N, the most common mutation. The number in the middle is called a "codon"—it identifies the specific position within HIV's RNA where the mutation is located. The first letter stands for the amino acid that is normally found at that position in wild-type HIV; the last letter stands for the amino acid that's there instead (which is the mutation).

So, in the case of K103N, we have a mutation at codon 103 in HIV's reverse transcriptase gene. In that particular spot, the amino acid K (which stands for lysine) has been replaced by the amino acid N (which stands for asparagine), which makes that particular copy of HIV into a mutation. It just so happens that this particular mutation, K103N, is one of the worst mutations to have, since it makes HIV highly resistant to many of the approved drugs in the NNRTI class. Not all mutations, of course, are so dangerous. Most mutations will have no impact at all on how well someone's medications work.

HIV Monitoring Tests

The CD4 Count Test

This test, also known as a "T-cell count test," gives an indication of the number of CD4 cells in a person's bloodstream. The more CD4 cells a person has, the stronger their immune system is.

A normal CD4 count for someone without HIV is usually between 500 and 1,600. Experts generally agree that when someone's CD4 count goes below 350, they're at a high risk for developing potentially dangerous illnesses.

Healthy	500 - 1,660
Borderline Low	350 - 500
Low	200 - 350
Extremely Dangerous	0 - 200

The Viral Load Test

Viral load tests provide an estimate of how much HIV is circulating in someone's blood. A viral load test measures the amount of HIV in a small amount (milliliter, or mL) of blood. Current viral load tests can detect as few as 50 copies of HIV per milliliter of blood. When a viral load test indicates that someone has fewer than 50 copies/mL of HIV, their health care provider will tell them that their viral load is "below the limit of detection," or "undetectable."