HIV is a tough little virus. Although scientists have spent the last 25 years designing medications to fight it, HIV can learn to adapt and avoid these medications. When this happens, we say you’ve developed “drug resistance.”

By the time you’ve finished reading this booklet, we hope you’ll have a much better understanding of how resistance works, how your doctors can test for it and what options you have if you find that your HIV is resistant to one or more HIV medications.

How HIV Works

Drug resistance is easier to understand once you know a little bit about 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 your body is look for a comfortable place to make its home. Its target? Your 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 your body uses to fight off infections.
Once HIV gets inside a CD4 cell, it basically hijacks 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 churned out each day will depend on how many CD4 cells are infected and producing virus. The level of production can be measured by your viral load—the lower your 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 your immune system, since soon after it uses your 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 a person’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 you didn’t need medications to treat HIV, mutations wouldn’t matter that much, since mutations generally don’t make the virus more aggressive.
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.

There are now six classes of drugs that stop HIV from multiplying: NNRTIs, NRTIs, protease inhibitors, integrase inhibitors, fusion inhibitors and CCR5 inhibitors. 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 you know your HIV is under control? If your medications work well, within about two weeks after starting your first treatment regimen, the amount of HIV in your blood—your “viral load”—will decrease dramatically. Within two to six months, you’ll probably be told that your HIV is “undetectable.” Undetectable simply means that even though you are still HIV positive and can transmit HIV to others, your viral load is now so low that current viral load tests aren’t sensitive enough to detect the HIV in your 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 your body, including “reservoirs,” such as your 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 your HIV is now under control. The number of CD4 cells in your body can begin to grow again and your immune system can
meds on time and your HIV isn’t already drug resistant. Some HIV always survives, though, including some mutations.

recover and do its job. With more CD4 cells, the chance of developing a host of nasty infections and illnesses is reduced. As long as you keep taking all your medications on time, your 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 you’re on your 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 your viral load as low as you can, even if it’s detectable. A low, stable viral load can still allow you to increase your CD4 count and reduce the chances you’ll become ill.

How Drug Resistance Occurs

HIV medications are best at fighting the regular (“wild-type”)—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 you frequently miss a dose. HIV will grab this opportunity to start making more copies of itself in your CD4 cells. As the amount of HIV in your body increases while you are not taking your medications consistently, so does the amount of mutated HIV—including mutations that make your virus resistant to your medications.

In other words, if you miss doses of your medications too often, you’re effectively training your 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 your body. Once this happens, *no matter how much of that medication you take*, it will no longer have an effect on your HIV. This means you’ve become resistant to that medication. Once your HIV has developed resistance to a medication, it will stay resistant *forever*, since resistant HIV, like wild-type HIV, can remain hidden in some of your cells.
How Does Resistance Affect Your Treatment Options?

Some HIV mutations, as we’ve mentioned, are more dangerous than others. Some will cause resistance to just one drug. But other HIV mutations can cause resistance to two or more drugs—or even to an entire class of drugs.

This is especially true for older NNRTIs. Just one specific type of mutation will make HIV resistant to the NNRTIs Sustiva and Viramune. This is called “cross-resistance” because the drug resistance “crosses over” from one drug to another, in the same way a bug that’s immune to one bug spray might also be immune to other bug sprays.

Sometimes, though, it takes more than one mutation for HIV to become resistant to a drug. This is true for several HIV meds, particularly most of the protease inhibitors and the new second-generation NNRTI Intecelence.
If you do not take your medications on time, mutated HIV can make up a larger and larger percentage of the HIV in your body, and the odds of developing drug resistance will greatly increase.

Resistance to a drug does not automatically mean you can no longer use it. There are different degrees of resistance. Sometimes the medication will still work, just not as well as it used to. How will you know if it’s still worth taking a drug that your HIV has become resistant to? There are many factors for you and your doctor to consider, including which HIV medications you’ve taken in the past, which specific medications your HIV is resistant to, your current CD4 count and viral load, and which medications you haven’t tried yet.

Checking for Resistance

How do you find out if your virus is resistant to any of your current medications? One way is by monitoring your viral load every three to four months. This will allow you and your doctor to see how the HIV in your body is responding to treatment.
Let’s say, for instance, that you’re on treatment and your viral load begins to increase steadily. This could mean that one or more of your medications have lost some, or even all, of their power because some of your virus has become resistant to them. Your doctor will check for drug resistance using a “resistance test.” A resistance test examines the HIV in your body and finds out whether your HIV is resistant to any of the currently available medications. (For more on the different types of resistance tests available, see page 14.)

**Resistance Testing: Finely Targeting Your Drugs**

HIV resistance testing has become the standard of care for HIV-positive people. It is recommended in all U.S. and international HIV treatment guidelines for both adults and children. What is the goal of resistance testing? To determine how much of your HIV has mutated and whether these mutations affect the activity of one or more of your HIV medications. Resistance testing is done by studying a sample of your blood using specialized lab equipment.

You and your doctor can use the results of these tests to select the HIV medications most likely to be effective against your virus. Keep in mind that resistance testing may not detect all mutated HIV. Researchers are also still working to identify all the different HIV mutations that cause resistance to HIV medications. Nevertheless, resistance tests are an essential part of HIV treatment.
Using a resistance test, your doctor can take a closer look at the HIV in your body to see whether it’s developed mutations that will make it resistant to one or more HIV meds.

Who Should Get a Resistance Test?

People Who Have Never Taken HIV Medications

How is it possible to be resistant to HIV medications before you’ve even taken them? Unfortunately, it’s easier than you might think. In the United States, an average of 7% to 19% of newly infected people have mutations that are associated with drug resistance to at least one drug—and, in some cases, to a whole class of medications.

How does this happen? The person you got HIV from may have been on HIV treatment, and his or her virus became resistant to one or more medications. Transmitted along with HIV was their resistance to certain drugs. If you were infected within the last several years, taking a resistance test before beginning HIV
treatment will reveal whether you have HIV that is resistant to any HIV medications.

However, if you were infected more than a few years ago, or if you are not sure when you were infected, current resistance tests may not be able to provide a completely accurate result. This is because, after a few years, without HIV treatment, wild-type HIV will reproduce more than the drug-resistant virus you were originally infected with, and that wild-type HIV will once again become the most common type of HIV in your body.

Currently available resistance tests are not sensitive enough to detect mutations when they are present in small numbers in your body; they are most likely still there, but in low numbers.

So, for example, if you got HIV from a person who had resistance to Sustiva (this drug is one of the three drugs in Atripla), and a few years went by before you started taking HIV medications, a resistance test may not note that you have any
In people who are infected with drug-resistant HIV, the majority of the HIV in their bodies will be mutated. One or more of these mutations will prevent HIV meds from working as well as they should.

mutations to Sustiva. But if you then start to take Sustiva, the Sustiva-resistant virus in your body will once again thrive.

While these tests may not detect resistance in people who were infected several years ago, it’s still best to get one as soon as possible after you’re diagnosed. If the test does find resistance, this information will be extremely helpful when it comes time to choose your first treatment regimen.

**People Whose Viral Load Rises While on Treatment**

If you’re currently receiving HIV treatment and your viral load rises sharply, this could indicate that you’re experiencing what your doctor might call “treatment failure.” Although it sounds worse than it actually is, it could mean that your HIV has grown resistant to one or more of the medications you’re taking.

However, a rising viral load can signify other things as well. Your body could be reacting to a recent vaccination or an infection. Or, a new HIV drug you just started taking could be interacting with
other drugs you’re taking, making your treatment less powerful.

Once your doctor rules out all these other possibilities, and *before you stop or change treatment*, it’s critical to *immediately* get a resistance test. This way you can learn *which* drug is failing to keep your HIV under control and switch medications if necessary.

Quick timing is essential because once you stop or change medications, your drug-resistant HIV may become harder to detect, since many mutations thrive only when you’re taking the medication they’re resistant to. When not taking medications, wild-type HIV will become the most numerous type of HIV in your body and mutated HIV will be more difficult to measure.

**People Who Need to Change Medications Due to Side Effects**

Let’s say you’ve been on HIV medications and, due to side effects, you need to change one or more drugs. If your viral load is above 1,000 copies, you should get a resistance test. Once again, make sure you get the test *before you stop or change treatment*. The test may help you be sure that a new medication will work at its full power.

If you have a viral load below 1,000 at the time you decide to switch medications, though, a resistance test might not be ordered because even though drug resistance mutations may be present, they are more difficult to reliably find when someone’s viral load drops below 1,000.

**Pregnant Women**

To avoid passing HIV to their babies, it’s best for pregnant women with HIV to make sure they have an undetectable viral load. If you’re pregnant and getting HIV treatment but you have a detectable viral load, resistance testing may help figure out which drugs aren’t working and which will have the best chance of preventing your baby from getting HIV.
There are currently two basic types of resistance tests: genotypic and phenotypic tests. Experts recommend a genotypic test if you have recently been infected or have used only a few HIV medications. U.S. HIV treatment guidelines say that for people who have taken a large number of medications, it may be best to take both a genotypic and phenotypic test. Another option is to take what is called a “virtual phenotype,” a type of genotypic test that gives you genotypic results and then plugs these results into a comprehensive database to provide results similar to a phenotypic test.

Keep in mind, however, that your doctor may be limited in the number and type of resistance tests he or she can order for you, depending on the clinic’s policy and on how you pay for your treatment. Medicaid, private health insurance policies and state HIV/AIDS Drug Assistance Programs (ADAPs) may limit coverage to only a few tests a year and may even specify whether a genotypic, phenotypic or virtual phenotypic test is allowed.

**Genotypic Tests**

With a genotypic test, a blood sample containing your HIV is examined to see if there are any mutations. The test results will pinpoint the exact HIV genes where the mutation or mutations occur. Once mutations are found, they are compared to a long list of mutations known to cause resistance to HIV medications.

This is the least expensive of all the resistance tests, costing about $350, and the results are usually available within two to three weeks. Genotypic tests are most easily interpreted when only a few mutations are expected. Your doctor would not expect to see
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 found in people who are taking medications such as Atripla, Sustiva and Viramune. 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 your medications work.
many mutations if you’ve never taken HIV medications before, or if you’ve only taken a few. But if you have been on many regimens or you are on a regimen containing protease inhibitors, the number of mutations may be high. In such cases, both a genotypic and phenotypic test may be useful.

**Interpreting Genotypic Test Results**

The challenge in resistance testing isn’t spotting the HIV mutations—it’s figuring out what each mutation means. Just because you have a mutation does not necessarily mean you should switch HIV medications. It’s much more complex than that, especially if you have many different HIV mutations.

For instance, for people with five or six mutations, the mutations may work together to make HIV partially—or even completely—resistant to a single medication or to an entire class of drugs. In other cases, a single mutation may make HIV resistant to one drug, but simultaneously make it more sensitive to another drug. As you can see, it can get complex. Plus, several companies make genotypic tests, with some variations in how each test works. However, the more experience a doctor and a laboratory have in using resistance tests, the more effectively they can interpret these tests. Deciding whether to switch medications because of resistance will depend on your treatment history and which treatment options are still available to you.

**Phenotypic Tests**

Phenotypic tests look for drug resistance in a completely different way from genotypic tests. Instead of finding specific mutations, they measure the ability of someone’s HIV to reproduce in the presence of HIV medications.

To do this, blood samples containing your HIV are divided into many test tubes, each of which includes increasing doses of a given
HIV medication. Laboratory technicians then carefully study the samples to see how your HIV reacts. By doing this, the lab workers can calculate how much of each HIV medication would be needed to keep your HIV from reproducing. The lab workers then compare these amounts to the amount of each drug needed to stop wild-type HIV from reproducing. As you can imagine, this test is more expensive than a genotypic test (it costs around $750 to $1,200) and results can take up to a month to get back.

**Interpreting Phenotypic Test Results**

Unlike genotypic tests, which spot specific HIV mutations known to confer resistance to medications, phenotypic tests try to measure how well the medications actually work on your virus. For instance, if a phenotypic test shows that the normal dose of Epivir would have to be increased 100 times in order to stop your HIV from reproducing, we say it has “100-fold resistance.” This would mean that your HIV is extremely resistant to Epivir, though this does not mean that the dose of Epivir should be increased. Resistance tests are not used to determine doses of medications.

Note that each drug and its fold change needs to be interpreted separately. A two-fold increase in the amount of medication needed to stop HIV reproduction would be considered high resistance for some drugs, such as Viread. For Kaletra, however, it means no resistance. It’s your doctor’s job to know how many “folds” of resistance your virus could have and still be treated effectively with a particular drug. Your doctor will also have to take into consideration how many HIV medications you’ve already been on, how successful each regimen was and the results of previous resistance tests.

Researchers are still studying how resistant HIV needs to be to make a medication completely ineffective, so your doctor might not be able to give you a definitive answer based on the results of a phenotypic test.
Another limit of phenotypic tests is that they only look at how your HIV reacts to one drug at a time. It’s still a technical challenge to measure the effect of drug combinations. Most people on HIV treatment are taking three or more medications at the same time, which can make the interpretation of any resistance test complicated. Be sure your doctor has experience in using these tests, or can get expert advice. Phenotypic tests may be especially useful when unusual mutations are found, or when newly available medications are being used.

**Virtual Phenotypic Tests**

A third type of resistance test is called a virtual phenotype. The virtual phenotypic test is, in many ways, a combination of a genotypic and a phenotypic test, but it can cost more than a genotype. Like a genotypic test, results are available within two to three weeks.

With this test, you can find out how likely it is that each of your mutations will be resistant to HIV medications—which is exactly what a conventional phenotypic test finds, only you and your doctor don’t have to actually get a phenotypic test. Plus, because the computer database used by this test is always updated with new test results from around the world, the results of a virtual phenotypic test are continually being refined and improved.

**Interpreting Virtual Phenotypic Test Results**

Once you take this test, you’ll receive both a genotypic test result and a phenotypic analysis. In many ways, virtual phenotypic tests are just like conventional phenotypic tests: the amount of resistance is described in “fold changes,” the results are easier to understand than genotypic test results and the test is ideal for people who have a complicated mix of mutations.

The virtual phenotypic test is different than a phenotypic test
A sample of your blood is taken and a genotypic test is done. The genotypic test determines which specific HIV mutations are in your body.

The results of your genotypic test are entered into a computer program. The program searches a massive database that’s filled with resistance test results from thousands of other people. All of these people got not only a genotypic test, but a phenotypic test as well.

The computer program searches the database looking for genotypic test results that are similar to yours. Once it finds them, it then looks at the phenotypic test results for those people.

The computer program analyzes the phenotypic test results, and spits out a report that tells your doctor what your phenotypic test results would have been if you had gotten one.

because your results are compared to hundreds of sample viruses with the same mutation, which may provide a more helpful prediction of the level of resistance than conventional phenotypic tests. A virtual phenotypic test, however, might not be as good as a conventional phenotypic test for figuring out whether your HIV is resistant to new medications. In addition, if you have any unusual HIV mutations, this test may have trouble figuring out whether they’re drug resistant.
Meet the Mutations: A Class-by-Class Breakdown

**Nucleoside Reverse Transcriptase Inhibitors (NRTIs)**

Researchers have identified 34 or so mutations that make HIV resistant to one or more NRTIs. The effects of these mutations can be complicated. The M184V mutation, for example, will make HIV resistant to Epivir and Emtriva, but it will also make HIV more vulnerable to Retrovir and Viread. This is why it’s important to have detailed knowledge of how mutations impact your treatment regimen.

**Non- Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**

Researchers have identified 19 or so mutations that make HIV resistant to one or more NNRTIs. A single mutation, K103N, will make you highly resistant to Sustiva and Viramune. Even if you don’t have the K103N mutation, a combination of other mutations can also make your HIV resistant to NNRTIs.

**Protease Inhibitors (PIs)**

Researchers have identified around 40 mutations associated with PIs. The good news? Most of these mutations contribute to resistance, but only in small ways. Although a single mutation can cause resistance to one PI, no single mutation has yet occurred that causes resistance to all PIs. The bad news? These small mutations can add up: It takes only three specific mutations to make HIV resistant to most PIs. To avoid this, researchers are examining ways to closely monitor the concentration of PIs in your body. If the concentration seems to be a little on the low side, a doctor would “boost” the PI up to a higher level. This would not only reduce the number of mutations occurring, but, of course, would reduce the amount of HIV in your body as well.
**Fusion Inhibitors**

Resistance to the only approved drug in this class, Fuzeon, is still being studied. Ten mutations are known to cause resistance to Fuzeon, but they do not affect sensitivity to other medications in other classes. There is also a special genotypic resistance test that can detect Fuzeon resistance. It looks for mutations in a different part of HIV RNA.

**Integrase Inhibitors**

These drugs block the entry of HIV into human DNA, the irreversible step of HIV infection. Resistance to integrase inhibitors seems to be somewhat similar to that of protease inhibitors, where one of three recognized changes gives significant resistance, and then additional mutations give high-level resistance. One inhibitor, Isentress, is available now, but at least two others are under development, one of which is expected to work if Isentress resistance has developed.

**CCR5 Inhibitors**

Most HIV strains use the CXCR4 co-receptor and the CCR5 co-receptor to enter a CD4 cell. Selzentry (the only approved CCR5 inhibitor) works by preventing HIV from using the CCR5 co-receptor to enter CD4 cells. Resistance to Selzentry can sometimes occur if the virus learns to use the CCR5 co-receptor *despite* the presence of Selzentry. However, more often, CCR5 inhibitors fail if an HIV strain appears that can enter the CD4 cell using the CXCR4 co-receptor instead of the CCR5 co-receptor (this HIV strain is known as X4-tropic or dual-tropic). You must take a special test called a tropism test before you can use Selzentry. You should also take this test if Selzentry stops working for you in order to determine whether your strain of HIV has changed.
As you can see, resistance is not easy to deal with. The best approach is to make an effort to avoid it. Fighting the HIV in your body requires a total commitment to taking your medications exactly as they are prescribed. If you give it room to grow, HIV will eventually become resistant to every single HIV medication. Your job is to make sure HIV never gets that opportunity. What can you do?

Don’t skip doses. Missing only a few doses a month could cause resistance to occur.

Don’t let yourself run out of medications. Fill all the prescriptions your doctor gives you ASAP.

Try to take your medications at the times recommended by your doctor. For example, if you’re told to take a medication twice a day, that means you should take your doses about 12 hours apart.

Pay close attention to food requirements: If you’re asked to take a medication with a meal, make sure you always do so, or it might not work as well.

Don’t have unprotected sex with other HIV-positive people—it could expose you to another strain of HIV that is resistant to one or more of your medications (this is called “superinfection”).

If you are getting medical care from other physicians in addition to your HIV doctor, and you are prescribed medications for other reasons, make sure that you tell them which HIV medications you are taking. Be sure to also tell them about any other medications, vitamins or natural supplements you are taking. Even garlic supplements can potentially change the effectiveness of your HIV medications, so the more your HIV doctor knows about everything you are taking, the better.

Keep in mind that no HIV medication or combination of medications is capable of shutting down HIV reproduction completely. The best medications can do is dramatically slow it down. Taking your medication exactly as directed keeps a consistently high level of the medication in your bloodstream and throughout your body. While these powerful drugs are in your body, HIV will have a very difficult time reproducing, and mutations will be much less likely to occur.
The Bottom Line

Although our knowledge of HIV drug resistance has grown tremendously in the past few years, there’s a lot left for us to learn about how HIV mutations occur and the effect they have on each different HIV medication. Likewise, HIV drug resistance testing is a developing technology; improvements are being made all the time. As the accuracy of resistance testing advances, it will allow better targeting of HIV treatment.

While resistance tests are extremely helpful, there are still a lot of kinks to work out. One of the biggest kinks is that resistance tests aren’t fortune-tellers. Although they can identify weaknesses in medications you are currently taking or considering taking, they can’t guarantee how well a new medication will work. But resistance tests are still effective tools for spotting HIV mutations and figuring out which HIV medications are, and aren’t, likely to work for you. They provide a lot of valuable information that you and your doctor can use to figure out the next step your treatment should take.

Hopefully, this booklet has given you a better idea of how resistance happens, how you can avoid it, how doctors can test for it and what it means to have drug-resistant HIV. The more you know about resistance, the easier it’ll be to work with your doctor to figure out your best course of treatment—and the better your chances of staying healthy far into the future.
These are the genotypic resistance test results for Bob S. (not his real name), a 45-year-old man diagnosed with HIV in 1999. When Bob was first diagnosed, his CD4 count was 20 and his viral load was 240,000. He also was dealing with MAC, a serious illness caused by common bacteria.

Gerald Pierone Jr., M.D., started Bob on Epivir, Zerit and Viramune. Bob’s CD4 count rose from 20 to 100 and his viral load ranged from 3,000 to 5,000 over the course of the year. These lab results were good, but not good enough.

A resistance test in 2000 showed that Bob’s HIV had developed resistance to several of his medications, as well as cross-resistance to medications he hadn’t even been given yet. Dr. Pierone prescribed a new regimen of Epivir, Zerit and the powerful protease inhibitor Kaletra. Bob stayed on this regimen for almost three years, but his CD4 count barely crept up to 200 and his viral load never became undetectable. He had also developed fat loss in his face and peripheral neuropathy, a painful, burning sensation in his extremities.

So, in June 2004, Dr. Pierone did a genotypic resistance test. This test suggested resistance to all of the available protease inhibitors except for Reyataz. Bob’s HIV was also sensitive to Viread. The best solution, Dr. Pierone decided, was to prescribe a four-drug regimen of Epivir, Reyataz, Norvir and Viread. However, despite this switch, Bob’s viral load remained in the 1,000 to 2,000 range and his CD4 count didn’t move from 200.

In July 2005, another resistance test showed that Bob’s HIV was sensitive to Aptivus, which had recently been approved. So, in October 2005, Bob was switched to Truvada (a combination of Viread and Emtriva), Norvir and Aptivus. Soon after, for the first time, Bob’s viral load dropped to an undetectable level and his CD4 count climbed to 322, higher than it had ever been before. In addition, Bob’s peripheral neuropathy completely resolved and his facial thinning improved.
The resistance test showed that Bob’s HIV had developed resistance to Reyataz, so Dr. Pierone took Bob off of this drug but kept him on Viread because his HIV was still sensitive to this drug.

Although Bob’s HIV was also susceptible to Lexiva, Dr. Pierone decided that given Bob’s treatment history, his HIV was likely to be more sensitive to Aptivus.
These are the phenotypic resistance test results for Janet H. (not her real name), a 53-year-old woman living with HIV since 1985. Janet tried many treatment regimens and nearly a dozen different HIV medications; some worked well for a while, but eventually they had difficulty lowering her viral load, which hovered between 10,000 and 40,000.

By 2001, Janet’s health was declining. Since starting her latest regimen—a combination of Epivir, Ziagen, Agenerase and Kaletra—she had developed frequent sinus infections, lipodystrophy (abnormal fat changes) around her abdomen, diarrhea and nausea. Eventually, the side effects were just too much; Janet told her doctor, Cal Cohen, M.D., that she had to stop her medications.

Before she did so, Dr. Cohen ordered two resistance tests. The first, a genotypic test, found a large number of mutations that suggested her HIV was resistant to NRTIs and protease inhibitors. The second, a phenotypic test, added more information. It found that Janet’s HIV was resistant to every NRTI and protease inhibitor available in 2001, except one: Retrovir.

Even worse, while Janet was off her medications, her CD4 count dropped to 10 and her viral load skyrocketed to more than a million. It was time for a new regimen, and fast. But which medications to choose?

Dr. Cohen decided on a regimen of Epivir, Retrovir, Kaletra and two new drugs: Viread (which had been approved that year) and Fuzeon (at that time, still an experimental drug from a new class of HIV medications). His hope was that, even though Janet’s HIV was resistant to some of the medications in the regimen, they would still be powerful enough to help, especially when mixed with those new medications.

Dr. Cohen was right: Janet’s viral load dropped to about 10,000, where it remained for two years. Her CD4 count rose from 10 to 319. Although her new regimen wasn’t able to completely stop HIV from reproducing, it was able to do so enough to allow her immune system to recover and her health to improve.

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<td>Highest viral load: 1,208,084</td>
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<td>Current CD4 count: 319</td>
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A Closer Look: Phenotypic resistance test

Patient: Janet H.
Doctor: Cal Cohen, M.D.

Lowest CD4 count: 10
Highest viral load: 1,208,084
Current CD4 count: 319
Current viral load: 10,000

CAL COHEN, M.D., M.S.
Harvard Medical School, Boston, Mass.
From this test, it appears Janet doesn’t have many treatment options left. Of all of the HIV medications available when this test was taken in 2001, Retrovir was the only one left that Janet’s HIV seemed to be vulnerable to. Luckily, at that time there were new drugs available to her.

“Susceptibility” is a measurement of how vulnerable HIV is to each HIV medication. The normal susceptibility range indicates how vulnerable HIV without mutations is to each drug. The green bar for Retrovir indicates that Janet’s HIV is at least as susceptible to Retrovir as a virus with no HIV mutations.
Kyle C. (not his real name) has been on HIV treatment for a long time. His first regimen consisted of only Epivir and Retrovir. After two years on that regimen, he switched to his first triple-drug regimen: Combivir (a combination of Retrovir and Epivir) and Sustiva. At the time this resistance test was taken, Kyle was taking Epivir, Videx, Norvir and Invirase.

Although Kyle’s overall health was good, his CD4 count was 287 and his viral load was 34,500, which indicated that his HIV medications weren’t suppressing HIV as well as they should. His doctor, Mark Holodniy, M.D., ordered a virtual phenotypic test.

This test found that Kyle’s HIV was highly resistant to many HIV medications: Epivir and Emtriva (both NRTIs), every NNRTI available at that time and many protease inhibitors, especially if given unboosted. To some medications, such as Videx, Ziagen, unboosted Crixivan or Prezista, Kyle’s virus had developed some, but not complete, resistance. Other drugs remain fully active, such as the NRTIs Retrovir, Zerit and Viread. The protease inhibitors Crixivan, Invirase, Kaletra and Aptivus retained full activity, but only when boosted with Norvir. Although Kyle was on a regimen containing boosted Invirase, predicted on this test to have Maximal Response, his medications did not fully suppress HIV. This could be for several reasons, including the possibility that Kyle was finding it difficult to take all his medications on time.

Based on the results of the test, Dr. Holodniy prescribed a new regimen: Epzicom, Viread and Kaletra. Six months later, Kyle was doing extremely well: His CD4 count was up from 287 to 361, and his viral load became undetectable.
The test predicts which drugs are likely to work best for Kyle’s virus (Maximal Response), which drugs the virus has developed some degree of resistance to (Reduced Response) and which drugs the virus is highly resistant to (Minimal Response).

Kyle’s HIV is 43.6 fold resistant to Epivir. This means that when the laboratory technicians did the test, they had to use 43.6 times the normal amount of Epivir for it to be effective against Kyle’s virus. Of course Kyle does not have to take 43.6 times more pills; this number just indicates that his virus is highly resistant to Epivir.

Aptivus and Prezista had not been available to the general public when this resistance test was taken.

The location of the white square within the color gradient indicates the degree of susceptibility Kyle’s HIV has to a particular drug: green indicating hardly any resistance, green-to-orange indicating some resistance, orange-to-red indicating increasing resistance, and red indicating high resistance.
How Do You Make Sense of Drug Resistance?

- Begin by talking to your health care professional.
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