

## **UNDERSTANDING RESISTANCE & CROSS-RESISTANCE**

### **1) What is drug resistance?**

- There are many types of germs, or pathogens that can enter the human body. These include viruses, fungi, bacteria, and protozoa. Once inside the body, the primary goal of a germ is to survive and reproduce.
- Pharmaceutical drugs are designed to target these germs and either kill them or prevent them from reproducing inside the body. If a germ continues to reproduce during treatment, it can change itself – or “mutate” – to avoid the drugs. This is called drug resistance.
- When drug resistance occurs, the drug – or combination of drugs – loses its ability to block the germ from reproducing. Over time, the treatment can stop working completely. It is important to prevent germs from reproducing during treatment to prevent drug resistance from occurring.

### **2) How does HIV drug resistance occur?**

- Drug resistance occurs as a result of mutations in HIV’s genetic structure, or genome. HIV’s genome is in the form of RNA, which the virus uses to produce more copies of itself.
- Whenever a life form reproduces, mutations are possible. Human beings and other animals evolved into their present forms because of natural mutations that occurred over many thousands of years. Some mutations offer a survival advantage, and others make the life form less able to survive. This is what is meant by “survival of the fittest.”
- In order to prevent mutations from damaging our cells, our cells do a series of checks to make sure no mistakes have crept in during reproduction. The cells in our body are much more complex than HIV, and our body creates billions of them every day. In fact, every few years we have an almost entirely new body – almost all the cells in our body have died off and been replaced by new copies. But every new cell must have exactly the same DNA as the cells we were born with, or they could not function. Complex mechanisms are used to make sure that each of the 30,000 genes in our DNA is reproduced exactly.
- HIV has only 9 genes and is too simple to have mechanisms to check for errors. So many errors routinely occur – and it is these errors that make it so difficult to control HIV. Mutations are very common in HIV. HIV reproduces at an extremely rapid rate and isn’t able to correct mistakes made when its genetic material (RNA) is copied.

- In order for antiretroviral drugs to be effective, they must first attach themselves to the enzyme they target, or interfere with a specific step of the HIV life cycle. Certain mutations can prevent a drug from binding with the enzyme and as a result make the drug less effective against the virus.
- HIV drug-resistance mutations can occur both before and during therapy.

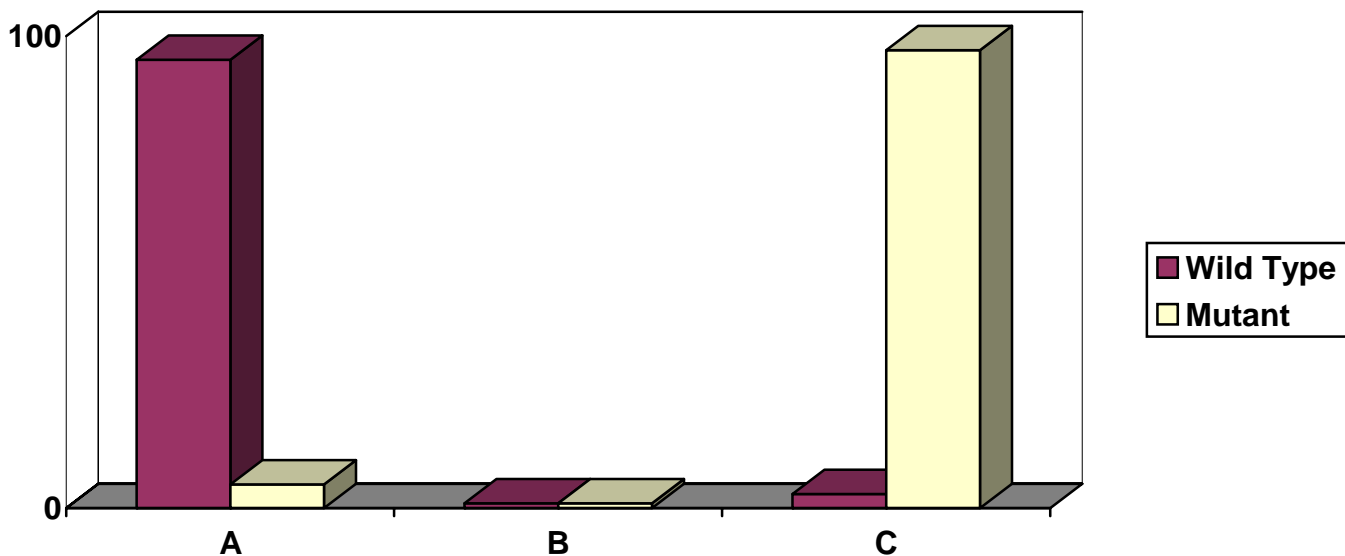
### 3) How do mutations occur before antiretroviral therapy is started?

- Mutations that occur before antiretroviral therapy is started can happen in two ways: natural selection and transmission of drug-resistant virus.
- **Natural selection:** Soon after HIV enters the body, the virus begins reproducing at a rapid rate (up to 10 billion new viruses every day). Even if someone has been infected with HIV that is not resistant to any drugs, HIV makes both perfect copies of itself (wild-type virus) and copies containing errors (mutated virus). In fact, about 90% of the copies HIV makes of itself contain at least one mistake. These mutant viruses are called *variants*. Soon there is not just one type of virus in the body but, instead, a large population of mixed viruses called *quasi-species*.
- Wild-type virus is the most natural and usually the “fittest” virus and, as a result, reproduces the best. Before antiretroviral therapy is started, wild-type virus is the most abundant in the body and dominates in the body. Some mutants are too weak to survive or cannot reproduce. Other mutants are strong enough to reproduce but still are not able to compete with the more “fit” wild-type virus. So, there is more wild-type virus than mutants in the body.
- Some mutants are able to partly, or even fully, resist an antiretroviral drug. This is why people living with HIV should never take just one antiretroviral drug (monotherapy) – resistance can happen very quickly when taking just one drug, and sometimes because of just one mutation. HIV mutations occur randomly and there is no proven way to prevent them from occurring. Variants containing these mutations usually don’t go on to develop additional mutations; doing so compromises their ability to stay alive in the body. So while these variants may be completely resistant to one antiretroviral drug, they are almost always sensitive to other drugs used in a regimen. This is why three-drug regimens work better: a variant may be resistant to one of the drugs but doesn’t stand much of a chance when facing two other drugs that bind to different parts of the virus.
- **Transmission of drug-resistant virus:** If someone who has taken antiretrovirals develops resistance to them and has unprotected sex or shares needles with someone who is not infected with the virus, it’s possible that they can infect their partner with a drug-resistant variant – a strain of HIV containing mutations that causes resistance to one or more antiretroviral.

- If a person is infected with resistant virus, the resistant virus would initially dominate all other viruses that are produced. Over time, wild-type virus will emerge and dominate. But this doesn't mean that the resistant virus is gone; it has merely become a minority member of the entire population of HIV. If the person starts therapy, even years later, the drugs would quickly control the wild-type HIV, but would probably be replaced with the resistant virus already in the body. As a result, the person might have a difficult time reducing viral load or keeping it undetectable.
- According to some studies, between 10% and 30% of all new HIV infections (defined variously as people infected with HIV over the past three years) involve strains resistant to at least one antiretroviral drug or class of drugs. A recent study found that 3% of new HIV infections had resistance to all three classes of antiretrovirals, while other studies showed as many as 11% of new infections being resistant to more than one drug. Resistance to the non-nucleoside reverse transcriptase inhibitors was most common. Researchers expect these rates to increase in the years to come.
- It might also be possible for someone who is already infected with HIV to be infected, again, with a (multiple) drug-resistant strain of HIV. This is sometimes referred to as *reinfection* or *superinfection*. There have now been several reports demonstrating that this is possible, although there is still debate as to how often this occurs in people who have had HIV for longer than a year.

**4) How do mutations occur during antiretroviral therapy?**

- Before antiretroviral therapy is begun, wild-type virus dominates (Figure A), and while there are some mutants, they are far fewer in number and will not usually show up on a resistance test.



- Soon after antiretroviral therapy is started, the amount of both wild-type and mutant virus in the body is reduced dramatically (Figure B). Unfortunately, no antiretroviral drug – or combination of drugs – is able to completely stop HIV from reproducing. In other words, there is always a small population of virus in the body that continues reproducing, despite the presence of antiretroviral
- Wild-type virus is the most sensitive to antiretroviral drugs. Because of this, HIV mutants in the body have a survival advantage over wild-type virus once anti-HIV drugs are taken. If antiretroviral drugs are not able to completely suppress HIV, mutants can become the dominant strain of HIV (Figure C).
- If a person with resistant virus stops all antiretrovirals, their viral population will soon revert to a state that appears similar to Figure A. In reality, however, the resistant virus created earlier still exists, and will quickly reappear once the person restarts HAART. This is why resistance testing is best done while on medication.
- Resistant virus usually persists for life, and once an individual becomes resistant to a drug, that drug will most likely never be useful for that person again.
- Over time, variants accumulate additional mutations. Some of these mutations will harm the virus while others will further limit a drug's ability to stop it from reproducing. Once the virus has accumulated enough mutations, the antiretroviral drugs lose their ability to bind to it and prevent it from reproducing. As the drugs become weaker, the amount of drug-resistant virus in the body increases, causing an undetectable viral load to become detectable again and increase over time. Should the drug-resistant virus continue to reproduce, it can acquire even more mutations to resist the antiretroviral drugs completely. But, as mentioned earlier, sometimes a single mutation can lead to complete resistance against a drug.
- Mutations that emerge during therapy can be divided into two groups: *primary mutations* and *secondary mutations*. Each antiretroviral drug is associated with at least one primary mutation. This mutation is of greatest concern, as they are the ones that cause the greatest amount of drug resistance. Secondary mutations do not cause drug resistance unless a primary mutation is present. If both primary and secondary mutations are present, drug resistance can become more complicated.
- While primary and secondary mutations can cause the virus to become resistant to anti-HIV drugs, they usually have a negative effect on the power of the virus. This is why some people who are experiencing an increase in their viral load might not see a decrease in their CD4+ cell counts, at least not at first. In other words, the virus loses its ability to cause damage to the immune system if it contains drug-resistance mutations. However, some studies show that certain primary and secondary mutations can cause the virus to regain its power and, quite possibly, become even more powerful than wild-type virus. In turn, most experts recommend switching therapies before the virus accumulates any additional mutations.

- *Cross-resistance* can also occur during therapy. When HIV becomes resistant to one drug, it can automatically become resistant to other drugs in the same class. For example, the K103N mutation seen in some people's virus after taking Sustiva can automatically cause that virus also to be resistant to both Viramune and Rescriptor. Even if the person hasn't yet taken Viramune or Rescriptor, he or she will likely be cross-resistant to the drug and will not likely benefit from it.
- The key to avoiding the accumulation of mutations that cause resistance and cross-resistance is to keep the amount of virus in the body as low as possible, for as long as possible.

### 5) What are some of the factors that contribute to the accumulation of drug-resistance mutations during therapy?

- Don't forget the golden rule: the less virus there is in the body, the less likely it is that the virus will continue reproducing and mutating. A powerful antiretroviral regimen is the most effective way to keep the level of virus low – preferably undetectable (<50 copies/mL) – and to delay additional mutations from occurring.
- Monotherapy (taking just one anti-HIV drug – the standard until the early '90s), didn't work because it lowered viral loads by only 70%. This left 30% of the virus in the body to mutate and become resistant, usually within a very short period of time. Taking two drugs lowered viral loads by 90-95%, but resistance still emerged. In most people, three or even four drugs are needed, since a three-drug combination can lower viral loads up to 99.9%. If virus levels can be kept that low, a combination could work for many years.
- There are a number of factors that can prevent an antiretroviral drug regimen from being as powerful as it can be. These include:

**Poor adherence or compliance.** In order for antiretroviral drugs to work correctly, they must be taken exactly as prescribed. This means taking the correct number of pills each day, being careful to take them a certain number of hours apart, while at the same time following dietary requirements (see "poor absorption" below).

- Skipping doses or not taking medication correctly can cause the *trough level* of an antiretroviral drug to decrease in the body. The trough level refers to the amount of drug left in a person's body just before another dose of the drug is taken by mouth. (See *chart in Module #9*.) If the trough level becomes too low, there may still be enough drug in the body to control wild-type HIV (which is most sensitive to the drugs), but not enough to control the variants. If the variants are able to keep reproducing, they will soon outnumber wild-type virus and become the dominant virus in the body.

- According to a few research reports, a person with HIV must be more than 95% adherent with his or her antiretroviral drug regimen in order for it to continue working properly. This means missing less than one dose a month.

**Poor absorption.** Not only must antiretroviral drugs be taken on schedule, they also need to be absorbed effectively into the bloodstream. A drug that is not absorbed properly can result in trough levels that are too low and, ultimately, allow HIV reproduction and the accumulation of drug-resistance mutations.

- Some drugs have specific dietary requirements. For example, people taking Videx shouldn't eat anything 1/2 hour before or 2 hours after taking it. Conversely, Prezista should be taken with a meal, or within two hours of a meal. If dietary requirements are not followed while taking any of these drugs, drug levels in the body will decrease.
- People with HIV can also experience diarrhea and vomiting. These can cause antiretroviral drugs to be expelled from the gut too quickly, reducing the amount of drug absorbed into the bloodstream.

**Varying pharmacokinetics.** Pharmacokinetics is a term used by researchers to describe how a drug is absorbed, distributed, metabolized, and removed from the body. Pharmacokinetics are measured by checking drug levels in blood that is drawn over various periods of time.

- Even though two people might receive the exact same dose of a drug, the amount of drug may be higher in one person's bloodstream than in the others. Factors that can contribute to this difference include their body weight, height, and age. Some people process, or metabolize, drugs faster or slower than others do. This can speed up – or slow down – the rate at which a drug is cleared from the body.
- It is important to remember that a drug's correct dose, as approved by the FDA, is determined in clinical trials based on the average dose found to be safe and effective. In other words, some people may be able to keep their viral load undetectable using lower doses of the drug, while some people might require higher doses of the drug to keep their viral load undetectable. Healthcare providers can perform blood tests to measure the amount of drug in their patients' bodies. This is called *therapeutic drug monitoring* (TDM) and it may help determine whether or not a person has a correct trough level of each medication to ensure that viral load remains low or undetectable.

## 6) Does a rebound in *viral load* mean that drug resistance has occurred?

- Figuring out if an antiretroviral drug regimen is not working properly can be determined in three ways:
  - 1) A viral load that fails to go undetectable within the first few months of therapy.
  - 2) A viral load that 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).
  - 3) A detectable viral load continues increasing, even though antiretroviral drug therapy is still being taken.
- While viral load can help determine whether or not an antiretroviral drug regimen is still working correctly, it cannot explain why a regimen is no longer working the way it should.
- A detectable or increasing viral load does not necessarily mean that drug-resistance mutations have occurred. A detectable viral load may be due to poor adherence or poor absorption. While these can eventually lead to the emergence of drug-resistance mutations, viral load can become detectable before they develop. Thus, it is important to act quickly and determine the reason why viral load is increasing soon after it becomes detectable.
- If resistance mutations have developed, viral load tests cannot determine whether or not the virus is resistant to one specific drug or the entire regimen. Moreover, in a person with drug-resistant HIV, viral load testing cannot determine which drug or combination of drugs is likely to be the most effective in the future.
- To look for drug resistance, there are two tests, or assays, available to people living with HIV and their healthcare providers. The first is called genotypic testing. Genotypic tests can help determine whether specific mutations known to lead to drug resistance are present. The second method, called phenotypic testing, is a more direct measure of resistance and, more specifically, the sensitivity of a person's HIV to particular antiretroviral drugs.

## 7) What is genotypic testing?

- Genotypic resistance testing examines the actual structure – or genotype – of an individual's HIV (a standard blood sample is all that is required). The HIV is examined for the presence of specific mutations that are known to cause resistance to certain drugs. The HIV genome is a chain of amino acids that has been extensively studied. Researchers know which amino acid exists at each point, or *codon*, along this chain in wild-type virus.
- An example: The M184V mutation is responsible for causing resistance to Efavirenz. The 184 refers to the codon in the reverse transcriptase enzyme. In this case, the amino acid methionine (M) at position 184 has been replaced by valine (V). This

change prevents Epivir from binding with the enzyme to prevent the virus from reproducing. Since Emtriva will also not work against virus with the M184V mutation, two drugs are now ruled out, even if only one of them was used.

- For many drugs, including the protease inhibitors, complex patterns of mutations are required for resistance to occur
- To conduct a genotypic test, laboratories use PCR technology to make many copies of, or "amplify," the HIV genetic material. Once amplification has been completed, the genetic sequences of particular viral enzymes – such as reverse transcriptase and protease – can be examined carefully for mutations. Depending on the type and number of mutations found, the laboratory can determine whether someone has developed resistance to a specific drug, since almost all drugs follow a set pattern of mutations.
- There are actually two types of genotypic tests: point-mutation assays and sequencing assays. Sequencing assays look for any mutation in either the reverse transcriptase or protease enzymes. Point-mutation assays look for key mutations in these enzymes that are known to cause drug resistance. Most laboratories use point-mutation assays, as they are easier (and cheaper) to perform and their results are easier to interpret.
- For most genotypic tests to be accurate, they generally require the use of a blood sample from a person who is actively taking antiretroviral medication and has a viral load higher than 1,000 copies/mL. Some can be used if a person's viral load is higher than 500 to 600 copies/mL.
- If therapy is stopped before blood is drawn for a genotypic test, the wild-type virus in the body may outgrow the mutant virus. In turn, the results may not show any drug-resistant mutations, but the drug-resistant strain may still remain at very low numbers in the person's body and may quickly increase when therapy with the same drugs is restarted.
- Genotypic resistance testing can take a week or two to complete. A single genotypic test can cost between \$300 and \$500. These tests are often covered by Medicare, Medicaid, and/or ADAP.

## **8) How are genotypic test results reported?**

When a genotypic testing report comes back from the lab, it contains a listing of the mutations that were found in the virus' reverse transcriptase and protease enzymes.

- While researchers have identified a number of mutations that can cause drug resistance, they don't know everything there is to know about these mutations. We know that some combination of mutations causes the virus to become more resistant

to antiretroviral drugs than other combinations of mutations. Researchers are still trying to determine which sequences of mutations are the most important.

- Mutations known to cause resistance to Retrovir and Epivir can be misleading. For example, a genotypic resistance test may show that a person's HIV has several genetic mutations that cause resistance to Retrovir. However, if the person is also taking Epivir – which appears to increase HIV's sensitivity to Retrovir – such genetic mutations may not accurately reflect the amount of Retrovir resistance.
- Another limitation: genotypic tests do not evaluate the genetic structure of small HIV populations found in a blood sample. For example, there might be a population of HIV that contains a mutation at position M184V (the mutation that causes resistance to Epivir). Unless this particular strain accounts for more than 20% of the HIV population found in a blood sample, chances are that it will not be recognized by the test. So, a genotype test can tell which drugs will *not* work, not which drugs will work.

### 9) What is phenotypic testing?

- Unlike genotypic testing, which looks for particular genetic mutations that causes drug resistance, phenotypic testing directly measures the sensitivity – or phenotype – of a patient's HIV in response to particular antiviral drugs.
- Phenotypic resistance tests measure the concentration of a drug required to inhibit viral replication in the test tube by a defined amount such as 50% or 95%. This is called IC50 or IC95. IC stands for *inhibitory concentration*. In other words, a laboratory conducting a phenotypic test is trying to determine the amount of drug needed to stop HIV from reproducing. If it only takes a standard amount of the drug – a concentration equal to those used by HIV-positive people – HIV is not resistant to the drug. If higher amounts of the drug are needed to stop HIV from reproducing, HIV is considered to be resistant to the drug being tested.
- The concentration of drug necessary to inhibit virus replication is expressed in units called nanomoles (nM). For example, if the IC50 of the wild-type virus is 100nM and that of the test virus is 400nM, the test virus is considered to be fourfold resistant to the drug being tested. In other words, HIV in the patient is four times less sensitive to the drug.
- Unlike genotypic tests, the phenotypic resistance test generally does not require a high viral load. Like genotypic testing, however, it is recommended that patients be taking antiretroviral therapies at the time blood is drawn for the test.
- Because phenotypic testing directly measures the sensitivity of the virus to particular drugs, some researchers believe that these tests are more comprehensive and trustworthy than genotypic tests.

- Phenotypic resistance testing procedures are relatively complex and can take longer than genotypic tests to produce accurate results – from ten days to several weeks. They are also more expensive than genotypic tests. A single phenotypic test can cost between \$700 and \$900, although these tests are also often covered by Medicare, Medicaid, and/or ADAP.
- Phenotypic tests cannot evaluate the sensitivity of small HIV populations found in a blood sample. For example, there might be a population of HIV that is not sensitive to Efavir. Unless this particular strain accounts for more than 10% to 20% of the HIV population found in a blood sample, chances are that it will not be recognized by the test. As with genotypic tests, a phenotype test can only tell which drugs will *not* work – it cannot ensure that a drug will work against a person's virus.
- Another challenge is that researchers still do not fully understand what level of resistance translates into a failure of treatment. For example, a five-, six-, or sevenfold reduction in the sensitivity of HIV to a protease inhibitor is considered "moderate." But is there a significant difference between a fivefold reduction and a sevenfold reduction? Researchers are still trying to figure out what level of resistance determines that a drug is no longer useful.

#### **10) What about using genotypic and phenotypic tests together?**

- Using both tests together could certainly help deal with some of the weaknesses of each test administered individually. However, this can be very expensive and time consuming.
- Two tests combine genotypic testing results with phenotypic testing results. These tests first analyze HIV's genotype. They then compare this result to a database of thousands of matched genotypes and phenotypes, and predict the drugs that the current sample might be sensitive or resistant to.

#### **11) Can drug-resistance tests be used before someone starts antiretroviral therapy for the first time?**

- Yes. Since many people are now being infected by virus that is already drug-resistant, most providers do a baseline genotype before therapy is started. And even if someone is infected with wild-type virus, it is safe to assume that all they have at least a few forms of HIV that are resistant to individual drugs before therapy is started. However, these strains are often too limited in number and strength to compete with wild-type virus, and they stand a good chance of being killed off by initiating combination antiretroviral therapy. In other words, genotypic or phenotypic testing might not provide an accurate picture of drug resistance before therapy is started.
- Drug-resistance tests might prove to be useful for people infected with multiple-drug-resistant (MDR) strains of HIV. Soon after an MDR strain enters the body, it begins

reproducing. Over time, a wild-type strain of HIV emerges and dominates the viral population. Thus, in order for drug-resistance tests to be used, blood will probably need to be drawn soon after infection takes place, usually within a few weeks after initial infection. Unfortunately, only a small percentage of people know when they are infected or immediately go to see a healthcare provider. For some people, genotype testing may identify some resistant virus up to three years after initial infection.

## **12) Can drug-resistance tests be used to choose a new drug regimen after an initial one fails?**

- Yes. As discussed in Question 6, viral load tests can help determine whether or not drug failure is occurring. Drug resistance tests, on the other hand, may play an invaluable role in helping healthcare providers and their patients understand why failure has occurred and what treatment options are still available.
- If viral load fails to become undetectable or becomes detectable again after a period of being undetectable, drug-resistance testing may help determine the cause. If no mutations are present (using genotypic assays) or the HIV is still sensitive to the drugs being used (using phenotypic assays), the problem might be poor adherence/compliance or poor absorption. It is best to remedy these problems before resistance mutations develop.
- If mutations are found or HIV is determined to be losing sensitivity to the drugs being used, drug-resistance tests can help determine which of the remaining antiretroviral drugs might be effective against the virus.
- If drug-resistance tests are not used, it is recommended that anyone who appears to be failing a particular combination should switch to an entirely new batch of drugs. This can be frustrating, as many HIV-positive people do not have three or more untried drugs from which to choose. It may also be a wasteful decision for those who do have several remaining options.
- There have been a number of studies demonstrating that both genotypic tests and phenotypic tests can help patients and their healthcare providers choose a new regimen after an initial regimen has failed. Patients who use drug-resistance tests may be able to keep their viral load undetectable for a longer period of time than those who do not use the tests.
- With drug resistance testing, it may be possible to weed out the ineffective drug or drugs in a given combination. Especially for patients with few options, it's important to know if resistance has developed to all of their drugs or if some can still be used.
- Drug-resistance testing can also help determine what can be done about partial resistance. For example, a phenotypic test might determine that HIV is partially – as opposed to completely – resistant to a certain protease inhibitor (e.g., Crixivan). In this case, it might be possible to simply add another drug (e.g., a low dose of

Ritonavir) to increase the levels of Crixivan in the body. By increasing the levels of Crixivan, there is more drug available to combat the partially resistant virus.

### 13) Do specialists recommend drug-resistance tests?

- Yes. Two important groups of medical experts now recommend that drug resistance tests be used in helping HIV-positive people plan their treatment regimens, especially if a switch in therapies is needed. One group that recommends drug resistance testing is the United States Department of Health and Human Services (DHHS), a branch of the federal government that oversees public health in the United States. A second group that recommends these tests is the International AIDS Society-USA (IAS-USA), a private medical organization made up of many leading HIV/AIDS experts in the United States and elsewhere.

### 14) 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 as much as possible about anti-HIV drugs.** The more people with HIV know, the easier it will be to make treatment choices that can help avoid drug resistance.
  - **Start treatment with a powerful anti-HIV regimen.** The current standard of care is to begin with a regimen that has a strong chance of fully suppressing the virus. The sooner an undetectable viral load is achieved, the better
  - **Be sure to follow instructions.** As discussed in Question 5, it is very important that HIV-positive people take their antiretroviral medication exactly as prescribed. Missing doses, not taking the right number of pills, or eating when pills need to be taken on an empty stomach, can affect the amount of the drug in the body, cause drug-resistance mutations to develop, and lead to an increase in viral load.
  - **Good communication with a healthcare provider.** HIV-positive people should understand their healthcare provider's instructions on how antiretroviral medication should be taken. Asking questions and reporting any problems to a healthcare provider are important for avoiding drug resistance.
  - **Regular viral load testing matters.** An increasing viral load is often the first sign that drug resistance is developing. Monitoring viral load regularly is a good way to guard against drug resistance.

Both New York State's ADAP (AIDS Drug Assistance Program) and Medicaid programs cover up to a total of three genotypic and/or phenotypic tests a year. A laboratory that's approved by ADAP and Medicaid must perform the tests. LabCorp, Quest, Specialty, and Virologic Labs do both phenotypic and genotypic testing.

### Resistance Tests in Use

#### **Genotype Tests**

- GeneSeq HIV (ViroLogic)
- GenotypR Plus (Specialty Labs)
- HIV GenoSure (LabCorp)
- TruGene (Bayer) \*
- ViroSeq (Abbott) \*

#### **Phenotype Tests**

- Antivirogram (Virco)
- Phenoscript (Specialty Labs)
- PhenoSense HIV (Virologic)

#### **Combined Genotype and Phenotype Test**

- PhenoSense GT (Virologic)

#### **Virtual Phenotype Tests**

- GenoSure Plus (Labcorp)
- VircoType (Virco)

*\* FDA approved*

*Special thanks to Tim Horn*