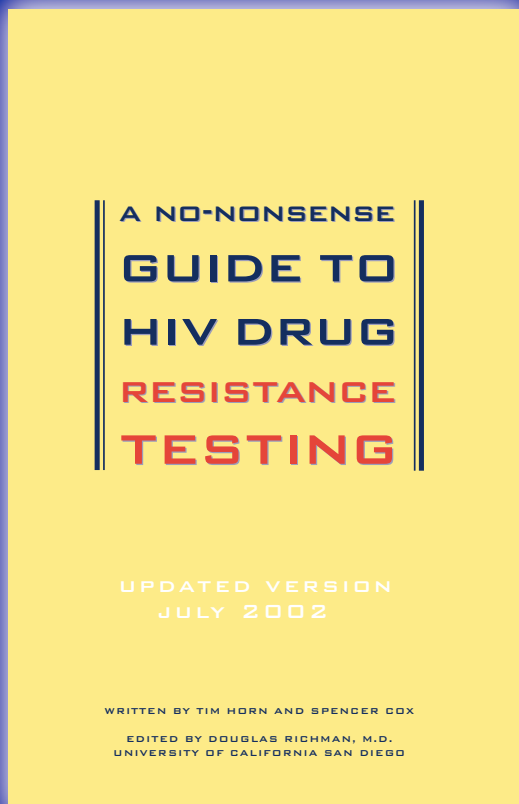


**A NO-NONSENSE
GUIDE TO
HIV DRUG
RESISTANCE
TESTING**

**UPDATED VERSION
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INTRODUCTION

Never before have so many treatment options been available to people living with HIV. More than a dozen anti-HIV drugs are available, which can be combined in a number of different ways. For HIV-positive people, the use of these drugs has translated into health benefits that many experts never thought possible—the possibility of living a healthy life with HIV for many years.

Of course, the availability of new, powerful anti-HIV drugs is just one example of how things have improved in recent years. There are also laboratory tests that have been designed specifically to help HIV-positive people and their health-care providers figure out when—and how best—to use these anti-HIV drugs. The most recent tests to become available are the HIV drug-resistance tests, which are quickly becoming standardized medical procedures for people living with the virus.

HIV drug-resistance tests are proving to be much like viral load tests when those first appeared. In 1996 there was a lot of hope—and confusion—regarding viral load technology and how it could be used to help people living with HIV and to enable their health-care providers to make better treatment decisions. Much of the same optimism and confusion can be found today with respect to HIV drug-resistance tests.

This handbook explains how HIV drug-resistance tests work and what role they might play in improving treatment decisions. The question-and-answer (Q&A) format is designed to answer some of the most frequently asked questions about the tests. Also included is a glossary of terms used in this publication and elsewhere. Finally, a list of additional resources is given at the back of the book.

What is drug resistance?

HIV drug resistance refers to a reduction in the ability of a particular drug or combination of drugs to block reproduction or “replication” of HIV. For people infected with the virus, drug resistance can render drugs less effective or even completely ineffective, thus significantly reducing treatment options.

Resistance typically occurs as a result of changes—called mutations—in HIV’s genetic structure (RNA). Mutations

of RNA lead to alterations in certain proteins, most commonly enzymes, that regulate the production of infectious virus. Mutations are especially common in HIV, as this virus reproduces at an extraordinary rate and does not contain the proteins needed to correct mistakes made during copying of the genetic material. HIV relies on many enzymes—such as reverse transcriptase, integrase, and protease—to replicate inside a human cell. If a mutation of a single site in the reverse transcriptase gene occurs, the change will remain with the virus as long as it replicates or until another copying error alters its form yet again. Some mutations cause the virus

to become so weak that it cannot replicate effectively; other mutations may cause the virus to become even more virulent.

Antiretroviral drugs, generally speaking, disrupt the HIV enzyme’s ability for genetic copying, or making virus that can infect other cells. In a person who takes antiretroviral drugs, most of the HIV are killed or prevented from multiplying further. As a result of random mutations that occur on a daily basis, however, some strains of HIV are naturally resistant to the presence of such drugs. That is why treatment with monotherapy (a single antiretroviral drug) is destined to fail.

FOR PEOPLE INFECTED WITH THE VIRUS, DRUG RESISTANCE CAN RENDER DRUGS LESS EFFECTIVE OR EVEN COMPLETELY INEFFECTIVE, THUS SIGNIFICANTLY REDUCING TREATMENT OPTIONS.

In essence, drug-resistant mutations are an example of Charles Darwin’s principles of evolution. At first, these particular strains of HIV are fewer than the natural and most powerful form of HIV—called the “wild type”—that dominates the population. However, once the wild-type virus is destroyed by the offending drug, the drug-resistant form can reproduce and eventually become the dominant strain, sometimes within as little as a few days. Thus, only the “fittest” survive, as in the Darwinian understanding of natural selection.

What’s with all the strange numbers?

A lot of medical information available to both health-care providers and people living with HIV frequently concerns specific mutations. One example is the classic Epivir (lamivudine; 3TC) mutation: M184V. The 184 refers to the amino acid position on the reverse transcriptase enzyme. The M—which stands for methionine—is the amino acid at position 184 of a wild-type (drug-sensitive) virus’ reverse transcriptase enzyme. The V—which stands for valine—refers to the mutation that results in drug resistance. In other words, the amino acid methionine at position 184 has been replaced by a valine. This change thus prevents an antiretroviral drug from binding with the enzyme to prevent the virus from replicating.

How can drug resistance be measured?

Over the past eight years, a significant number of breakthroughs have been made in understanding the power of antiretroviral drugs against HIV. With the development and availability of viral load tests—such as PCR and bDNA—we can determine from a blood sample how much virus is replicating in the body. If viral load increases substantially while a person is on a combination of antiretroviral drugs, the most likely culprit is drug resistance. Unfortunately, viral load tests cannot determine whether or not HIV is resistant to one drug

in particular or the entire combination. Moreover, in a person with drug-resistant HIV, these tests cannot determine which drug or combination of drugs is likely to be the most effective in the future.

Two general approaches are now used for measuring resistance to HIV drugs. The first is called genotypic testing. Genotypic tests can help determine whether specific genetic mutations are causing drug resistance and drug failure. The second method, called phenotypic resistance testing, is a more direct measure of resistance and, more specifically, of the sensitivity of a person's HIV to particular antiretroviral drugs.

Can you explain more about genotypic tests?

Genotypic resistance testing examines HIV taken from a patient, looking for the presence of specific genetic mutations that are known to cause resistance to certain drugs. For example, it has been well documented by researchers that Epivir is not effective against strains of HIV that have a mutation at a particular position—known as M184V—in their reverse transcriptase enzyme (see “What’s with all the strange numbers?” on page 3). If a genotypic resistance test discovers a mutation at position M184V, chances are that the person’s HIV is resistant to Epivir and is not likely to respond to the drug.

For many drugs—for example, Retrovir (zidovudine; AZT) and protease inhibitors—complex patterns of mutations are required for resistance to occur. Interpretation of these complex patterns can be difficult and incomplete in determining whether or not the virus is sensitive to particular drugs.

A number of laboratories in the United States and Europe offer genotypic resistance testing. The most common method of testing uses PCR technology to make

many copies of, or “amplify,” the HIV genetic material. Once amplified, the genetic sequences of particular viral enzymes—such as reverse transcriptase and protease—can be examined carefully for mutations at any of their positions. Depending on the type and number of mutations found, the laboratory may be able to determine whether someone has developed resistance to a specific drug, since almost all drugs follow a set pattern of mutations. Some drugs have a single pattern of mutation, but others have complex and unpredictable patterns.

For 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. In the absence of therapy, the wild-type virus may outgrow the mutant virus. In turn, the results may not show any drug-resistant mutations; but the mutant virus may still remain at very low numbers in the person’s body and may quickly increase when therapy with the same drugs is restarted.

What are the advantages and limitations of genotypic resistance testing?

Genotypic resistance testing has a few advantages over phenotypic testing, most notably the relative simplicity and speed with which the test can be performed. The testing can take as little as a few days to complete, and because it is less complex, it is somewhat cheaper to perform.

Still, some limitations of genotypic resistance testing are worth noting. Most important, it may be difficult to translate the results of a genotypic resistance test into a meaningful conclusion about the resistance of the virus to drugs. We have learned a lot about the various genetic

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PHENOTYPIC TESTING DIRECTLY MEASURES THE ACTUAL SENSITIVITY OF HIV TO PARTICULAR DRUGS.

mutations that result in antiretroviral drug resistance, but it is also true that we don't know everything about these mutations. It is possible that we have both over- and underestimated the importance of specific mutations and their role in causing drug resistance. Moreover, some genetic mutations have yet to be identified by researchers. Such is the case with older drugs like Videx (didanosine; ddI) and Zerit (stavudine; d4T), and newer drugs like Kaletra (lopinavir/ritonavir) and Viread (tenofovir DF). In people who take these drugs, resistance

certainly does occur. However, researchers are only beginning to determine the exact genetic mutations that cause HIV to become less sensitive to these compounds.

This may also be the case with Retrovir and Epivir. For example, a genotypic resistance test may demonstrate that a person's HIV has several genetic mutations that confer resistance to Retrovir. However, if the person is also taking Epivir—which appears to increase the sensitivity of HIV to Retrovir—such genetic mutations may not accurately reflect the amount of Retrovir resistance.

There is another disadvantage of genotypic resistance testing. The technology used to perform the test does not normally evaluate the genetic structure of small HIV populations found in a blood sample. These small populations—called subpopulations—can contain genetic mutations that do confer drug resistance. For example, there might be a subpopulation of HIV that contains a mutation at position M184V (the mutation that confers 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. Also, genotypic testing may not recognize strains of virus that are resistant to multiple drugs. For instance, if a percentage of this Epivir-resistant population also has genetic mutations that confer complete or partial

resistance to Retrovir and the protease inhibitor Crixivan (indinavir), genotypic resistance testing would probably not recognize this small subpopulation in a blood sample. Should this particular combination of drugs be used, HIV levels may not be suppressed for long.

What about phenotypic testing? How does it work?

Unlike genotypic testing, which looks for particular genetic mutations that confer drug resistance, phenotypic testing directly measures the actual sensitivity of a patient's HIV to particular drugs. To do this, phenotypic 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 IC_{50} or IC_{95} ; IC stands for "inhibitory concentration." Interestingly, this is the method used by researchers to determine whether a drug might be effective against HIV before using it in human clinical trials.

Phenotypic resistance testing of HIV is very similar to methods used to measure antibiotic resistance in bacteria. Sometimes, as in the case of tuberculosis, phenotypic testing of the bacterium determines whether there are any drugs to which it will not respond. This procedure has dramatically improved the ability of health-care providers to treat such infections effectively. Phenotypic testing has now also become a feasible method for measuring resistance to antiviral drugs, as a few companies have developed new tests in which the key portions of HIV genetic material are "inserted" into the shells of laboratory-derived reference strains of HIV. Sensitivity testing is then performed relatively quickly and under more standard conditions.

One of the developers of the newer phenotypic technology takes things a step further by replacing part of the HIV shells with a gene for the enzyme luciferase. With

this enzyme in place, the infected cells glow when the virus successfully reproduces in the laboratory test. Using light sensors, the laboratory can then measure the amount of light produced by the virus in the presence or absence of drugs. Depending on the amount of light produced—when compared to that of a wild-type strain of HIV—the laboratory can determine both the IC_{50} and IC_{95} of the drug.

The concentration of drug necessary to inhibit virus replication is expressed in units called nanomoles (nM). For example, if the IC_{50} 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 fourfold less sensitive to the drug. Unlike genotypic tests, the phenotypic resistance test generally does not require a high viral load, and can be performed on samples with viral loads as low as 500 copies. Like genotypic testing, however, it is recommended that patients be taking antiretroviral therapies at the time of the test.

What are the advantages and limitations of phenotypic resistance testing?

The results of phenotypic tests are easier to interpret than genotypic tests. Because phenotypic testing directly measures the sensitivity of the virus to particular drugs, many researchers and health-care providers have suggested that these tests are more comprehensive and trustworthy than genotypic tests. Phenotypic resistance testing procedures are relatively complex, however, and can take longer than genotypic tests to produce accurate results—from ten days to several weeks. The intricacy of these tests also makes them more expensive.

Like genotypic testing, phenotypic tests are limited in their ability to assess the drug sensitivity of HIV subpopulations. Again, this may prevent such tests from

producing an accurate estimate of HIV's ability to respond—especially for long periods of time—to specific antiretroviral drugs.

Another challenge with phenotypic testing is understanding 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? Research in drug resistance, specifically in clinical trials of antiretroviral drugs, has begun to improve the understanding of these levels.

Can phenotypic and genotypic testing be used together?

Yes. As explained above, each type of test has its limitations. Identifying genetic mutations with genotypic tests may not accurately predict HIV's sensitivity to a particular drug; however, the lack of specific levels of resistance that are associated with treatment failure for all drugs that are based on clinical data tends to limit the results of phenotypic tests. Using both tests together could certainly help deal with some of the limitations of each test administered individually.

Both tests are slightly limited in their ability to measure subpopulations of potentially drug-resistant HIV. Using both tests together may not necessarily overcome this obstacle. However, as technology improves, this problem will be diminished. Some companies have already discovered new ways to make tests more sensitive, increasing the usefulness of resistance testing at all stages of treatment.

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How can these tests help decide on an initial treatment regimen?

Based on what is known about HIV's error-prone replication process (see above), we can assume that all patients have at least a few subpopulations of HIV that are resistant to individual drugs. 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. After all, the purpose of combination therapy is to serve as a multipronged attack on such strains.

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A potential threat, however, is the *transmission* of multiple-drug-resistant strains of HIV. Multiple-drug-resistant HIV (MDR-HIV) is defined as a strain of the virus that has limited or no sensitivity to several antiretroviral drugs. Such viruses usually emerge in HIV-infected people who were not prescribed drugs in the optimal way or who were not able to adhere to the challenging demands of drug-taking schedules. People harboring such virus can then transmit it to others.

Some researchers have found that HIV is either partially or fully resistant to one or more of the commonly used antiretrovirals in between 10% and 30% of newly infected people. Such cases are likely to increase dramatically in the near future.

For instance, in a study from San Diego, California, published in 1999 in the *Journal of the American Medical Association* (*JAMA*), 141 patients who had become infected with HIV in the previous year and had received less than seven days of anti-HIV treatment were tested for drug resistance. Some degree of resistance to at least one anti-HIV drug was found in 36 patients, or more than 25% of

the study participants. Two percent of patients had high levels of resistance to at least one drug.

In another study conducted in New York and also published in a 1999 issue of *JAMA*, eighty newly HIV-infected people were tested for drug resistance. About 27% of the patients had some evidence of drug resistance, and resistance to several drugs was found in almost 4% of participants.

Although presently neither genotypic nor phenotypic testing is being used by many health-care providers routinely for this purpose, recently released federal guidelines state that use of resistance testing should be considered in selecting an initial treatment regimen. However, it is still not known how long drug-resistant virus can be detected in the bloodstream after someone becomes infected with the virus. It is also not known what the long-term consequences are for someone who is infected with MDR-HIV.

How can these tests help in choosing a new treatment regimen when an old one fails?

Drug failure is loosely defined as an increase in viral load, a decrease in T-cell counts, and/or signs of physical disease progression in people who are on combination antiretroviral therapy. Although drug failure can also be used to describe the experience of people who must stop their medication because of intolerable side effects, it is most often associated with the presence of genetic mutations and decreased drug sensitivity.

Viral load tests are likely to remain the most important tool for determining whether or not drug failure is occurring. Drug-resistance tests, on the other hand, can play an invaluable role in helping doctors and their

patients understand why failure has occurred and what treatment options are still available.

Are any results available from clinical studies?

A number of clinical studies of drug-resistance testing are currently being conducted in the United States and abroad. The results of many studies have already been presented, both at major medical conferences and in medical journals.

To date, several retrospective and prospective studies have been completed. In a prospective study, volunteers are enrolled specifically to assess the effects of a particular treatment, medical procedure, or test. A retrospective study is an analysis of data from a study that has already been completed. And while several retrospective studies have demonstrated that drug-resistance tests were very useful, the best way to determine if these assays will work in the real world is by conducting prospective studies.

In mid-1999, results from the first prospective study involving genotypic resistance testing were published in the journal *Lancet*. In the study, which was conducted in France, HIV-positive people who were seeing their viral load increase while on a triple-drug regimen were randomly assigned to one of two groups. Only those in group B (65 people in total) were permitted to make treatment changes based on the results of resistance testing; patients in group A (43 people in total) determined which salvage therapy they should take based on viral load only.

After three months, the people in group B had viral loads that were significantly lower than those in group A (-1.04 vs. -0.46 log, respectively). After six months of therapy, people in group B were almost twice as

likely to have undetectable viral loads (32% vs. 14%, respectively). According to the team of researchers conducting the study, these results suggest that drug-resistance testing was of significant help in determining which drugs should be used in a salvage regimen to yield more effective results. The team also acknowledges that the results are from a relatively small, short-term study and that much more information is needed from additional clinical trials.

With respect to phenotypic testing, the results from the first prospective study were published in a March 2002 edition of the medical journal *AIDS*. Similar to the prospective genotypic testing study discussed above, HIV-positive people who were failing an anti-HIV drug combination were randomized to one of two groups: one group (142 patients in total) was permitted to pick a new combination of drugs based on the results of phenotypic resistance testing, whereas volunteers in the second group (130 patients in total) determined which treatments they should switch to based on the anti-HIV drugs they had tried in the past.

Using a conservative type of data analysis—called the intent-to-treat analysis—patients who were permitted to use phenotypic testing appeared to do better than those who simply chose new drugs based on their treatment history. Overall, 38% of patients who used phenotypic testing to plan a new drug regimen had undetectable viral loads (<400 copies/mL) after 16 weeks on their new combination. Among patients not permitted to use phenotypic resistance testing, only 22% had undetectable viral loads after four months.

SOME RESEARCHERS HAVE FOUND THAT HIV IS EITHER PARTIALLY OR FULLY RESISTANT TO ONE OR MORE OF THE COMMONLY USED ANTIRETROVIRALS IN BETWEEN 10% AND 30% OF NEWLY INFECTED PEOPLE. SUCH CASES ARE LIKELY TO INCREASE DRAMATICALLY IN THE NEAR FUTURE.

Would it be necessary to switch every drug?

In the recent past, it was recommended that anyone who appeared to be failing a particular combination should switch to an entirely new batch of drugs. This, of course, was frustrating, as many HIV-positive people did not have three or more untried drugs from which to choose. It was also a potentially wasteful decision for those who did have several remaining options. Why toss out a drug that may, in fact, still be effective against HIV?

WITH DRUG RESISTANCE TESTING, IT MIGHT BE POSSIBLE TO WEED OUT THE INEFFECTIVE DRUG OR DRUGS IN A GIVEN COMBINATION.

With drug-resistance testing, it is possible to weed out the ineffective drug or drugs in a given combination. For example, in a study published in *JAMA* in January 2000 involving people taking an antiretroviral combination of Crixivan, Retrovir, and Epivir, 17 patients experienced viral load increases while receiving therapy. Although it would make sense to blame such viral load increases on multiple-drug resistance, resistance tests demonstrated that 14 patients had developed resistance to Epivir only; HIV in these patients could generally still be blocked by Crixivan.

Do most experts recommend these 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.

Where can I get these tests?

Resistance tests are generally available through various clinical reference laboratories and hospitals. Genotypic tests typically cost between \$300 and \$500, whereas phenotypic tests cost between \$700 and \$900. Your health-care provider can request these tests through the laboratory he or she uses to check your viral load and T-cells, or directly through a resistance testing laboratory.

Will insurance cover the cost of resistance testing?

Yes. However, insurance coverage varies depending on where you live. Medicaid, Medicare, ADAP and most private insurance providers have coverage policies for drug-resistance testing. Local AIDS service organizations can help obtain information about the availability of government-funded programs to pay for resistance tests.

Now that drug-resistance tests have been recommended by the DHHS and IAS-USA and have become accepted as standardized medical procedures, it is likely that more insurance companies and other third-party reimbursement programs will pay for the tests.

GLOSSARY

Adherence: The degree to which a patient exactly follows a prescribed treatment regimen. Poor adherence may negatively impact a drug's effectiveness. Compliance is an alternate term.

Amino Acid: A nitrogen-containing molecule that serves as a building block for proteins, including enzymes, muscles, and structural molecules.

Antiretroviral: A substance that stops or suppresses the activity of a retrovirus such as HIV. AZT, ddC, ddI and d4T are examples of antiretroviral drugs.

Assay: A test.

bdNA (branched DNA): A test for measuring the amount of HIV and other viruses in the blood. Test results are reported in numbers of virus particle equivalents per milliliter of plasma. *See also* PCR.

Codon: A three-nucleotide genetic subunit that determines which amino acid is placed at one point in a protein chain. Mutations at specific HIV codons are associated with changes in the amino acid sequence of HIV's proteins and enzymes. Such mutations can cause HIV to become resistant to antiretroviral drugs.

Cross-Resistance: The phenomenon by which HIV and other disease-causing organisms become resistant to more than one drug after a single therapy. For example, people who develop resistance from taking one protease inhibitor are likely to be cross-resistant to other drugs in the same class.

DNA (Deoxyribonucleic Acid): A double-stranded molecule that makes up the chromosomes in the center of a cell and carries information in the form of genes.

Enzyme: A cellular protein whose shape allows it to hold together several other molecules in close proximity to each other. Enzymes also induce chemical reactions in other substances.

First-Line Treatment: The best starting therapy for someone who has never received therapy before. Because of the potential for the development of cross-resistance by HIV and other microbes, the choice of first-line medication(s) affects the efficacy of subsequent therapies.

Gene: A unit of DNA in the chromosomes that determines the structure of a specific protein or enzyme. Genes regulate the metabolism of individual cells and the development and specialization of body cells and tissues.

Genotype: The genetic makeup of an individual organism, determined by the sequence of nucleotides in its genes. *See also* Phenotype.

Genotypic Assay: A blood test that determines the genetic sequences of an organism. Frequently performed in HIV to establish whether certain mutations conferring drug resistance are present. *See also* Phenotypic Assay; Resistance.

HAART (Highly Active Antiretroviral Therapy): Potent antiretroviral treatment usually including a combination of three or more drugs whose purpose is to reduce viral load to undetectable levels.

IC (Inhibitory Concentration): The amount of drug in the blood needed to suppress the reproduction of a disease-causing microorganism such as HIV. For example, IC₉₅ is the drug level needed to block 95% of HIV's normal replication; IC₅₀ is the drug level needed to block 50% of HIV's normal replication.

NNRTI (Non-Nucleoside Reverse Transcriptase Inhibitor): A member of a class of compounds—including efavirenz, delavirdine, and nevirapine—that act directly to combine with and block the action of HIV’s reverse transcriptase to prevent viral RNA from being converted into DNA and integrated into the uninfected cell’s nucleus. NNRTIs have suffered from HIV’s ability to mutate rapidly and become resistant to their effects.

Nucleoside: The molecular units that serve as the building blocks of DNA and RNA, the genetic material found in living organisms.

Nucleoside Analog [Nucleoside Reverse Transcriptase Inhibitor (NRTI)]: A type of antiviral drug, such as AZT, ddI, ddC, d4T, 3TC, or abacavir, whose structure constitutes a defective version of a natural nucleoside. Like NNRTIs, these drugs block the viral enzyme responsible for converting HIV-RNA into DNA, ultimately preventing the cell from becoming infected.

PCR (Polymerase Chain Reaction): A sensitive test that amplifies DNA. PCR is a critical part of tests for viral load, genotyping, and phenotyping.

Phenotype: The functional capabilities and outward appearance of a microorganism. It is the physical expression of the genotype.

Phenotypic Assay: A test that measures the sensitivity of HIV to specific antiretroviral drugs. It is considered more of a direct measure of HIV drug resistance than genotypic tests. *See also* Genotypic Assay.

Protease: An enzyme that triggers the breakdown of proteins. HIV’s protease enzyme breaks apart long strands of viral protein into the separate proteins constituting the viral core and the enzymes it contains.

HIV protease acts as new virus particles are budding off a cell membrane.

Protease Inhibitor (PI): A drug that binds to and blocks HIV protease from working, thus preventing the production of new functional viral particles. Examples include saquinavir, ritonavir, indinavir, nelfinavir, and amprenavir.

Protein: Large molecules made up of long sequences of amino acids. Some hormones and all enzymes and cellular structural components are proteins.

Resistance: Reduction in an organism’s sensitivity to a particular drug. Resistance is thought to result mainly from a genetic mutation. In HIV, such mutations can change the structure of viral enzymes and proteins so that an antiviral drug can no longer bind with them. Resistance detected by searching a pathogen’s genetic makeup for mutations believed to confer lower susceptibility is called genotypic resistance. Resistance found by successfully growing laboratory cultures of the pathogen in the presence of a drug is called phenotypic resistance.

RNA (Ribonucleic Acid): A single-stranded molecule composed of nucleotide sequences. It is similar in basic structure to half of the double-stranded DNA. In cells, RNA transmits the code from the DNA-based genes that instructs the cells’ chemical machinery to produce structural proteins and enzymes. In retroviruses, RNA is the sole repository of the viral genes.

Sensitivity: The degree to which an organism is affected by a drug. *See also* Resistance.

Wild-Type Virus: Naturally occurring HIV with an optimal genetic makeup and no laboratory-induced mutational defects. The term also refers to HIV that has not been exposed to antiviral drugs and therefore has not accumulated mutations conferring drug resistance.

RESOURCE GUIDE

To learn more about HIV-drug resistance testing, contact one of the national AIDS/HIV referral organizations listed below. These organizations can either provide information directly or refer you to a local AIDS/HIV service organization that specializes in health-care counseling. Moreover, several of the listed organizations produce free or low-cost treatment-related publications for people with AIDS/HIV.

National AIDS Hotline

1-800-342-AIDS

Provides information and referrals on all aspects of HIV/AIDS treatment and services. Open 24 hours a day, 365 days a year.

AIDS Education Global Information System (AEGIS)

www.aegis.org

Provides highly comprehensive, up-to-date news and information about HIV/AIDS and all other HIV/AIDS-related information from around the world.

AIDS Treatment Information Service (ATIS)

www.hivatis.org

1-800-HIV-0440

Provides federally approved treatment guidelines for AIDS and HIV.

AIDS Treatment Data Network (ATDN)

www.atdn.org

1-800-734-7104

Provides information, counseling, and case management for men, women, and children with HIV, and those coinfecting with hepatitis C. Simple-language English and Spanish materials are available.

AIDSMeds.com

www.aidsmeds.com

Provides complete and up-to-date information about HIV treatment and topics surrounding treatment, including resistance testing, treatment failure, structured treatment interruptions, and more.

The Body

www.thebody.com

Provides a variety of up-to-date information about HIV and AIDS, including general HIV education, treatment, policy and activism, and more.

New Mexico AIDS Info Net

www.aidsinonet.org

Provides HIV/AIDS education fact sheets in both English and Spanish on a variety of topics, including basics of HIV/AIDS, prevention, treatment, and more.

Physicians' Research Network (PRN)

www.prn.org

1-212-924-0857

Publishes an on-line and printed version of *The PRN Notebook*, a tri-monthly review of research reports and information for physicians and other health-care providers.

Project Inform Treatment Information Hotline

www.projinf.org

1-800-822-7422

Provides information on AIDS/HIV treatments and can refer callers to local AIDS/HIV service organizations that specialize in treatment information dissemination.

Treatment Action Group (TAG)

www.aidsinfonyc.org/tag/index.html

1-212-253-7922

A treatment advocacy organization that publishes research reports, position papers, and a monthly newsletter.

Community AIDS Treatment Information

Exchange (CATIE)

www.catie.ca

Toll-free in Canada: 1-800-263-1638

Provides treatment and other medical related information to both patients and health-care providers in Canada.

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