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Resistance [1]

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Table of Contents

- What Is Resistance?
- What Causes Resistance?
- Cross-Resistance and Sequencing
- How Do I Know if I Have Drug Resistance?
- Resistance Testing
- Preventing Resistance

What Is Resistance?

HIV drugs are designed to keep your viral load [2] under control by preventing the virus from reproducing (or making copies of itself). Sometimes HIV changes, or mutates as it makes copies of itself. These changes may allow the virus to overcome the effects of a drug and keep reproducing. When this happens, we say that HIV has developed resistance to that drug.

Resistance is a major challenge in HIV treatment. Resistance decreases the ability of HIV drugs to control your virus and reduces your treatment options. The best way to prevent resistance is to stick closely (adhere) to your HIV drug regimen. With good adherence [3], resistance is less likely to develop. This gives your current drugs the best chance of working and will keep more treatment options open to you in the future.

What Causes Resistance?

After infecting a CD4 cell [4] (disease-fighting white blood cell), HIV makes many new copies of itself that infect other CD4 cells. This process happens very quickly ? HIV can make billions of new viruses every day. When making new viruses, HIV must copy its genetic information. Copying happens so fast that mistakes are made. These mistakes are called mutations, and they occur randomly.

Some mutations are harmless. They produce weak viruses that cannot infect other CD4 cells. Other mutations can cause big problems ? they allow the virus to reproduce even when it is exposed to certain HIV drugs. If a drug does not work against a mutated virus, that virus will reproduce rapidly. This causes your viral load to go up, and it may be necessary to change drugs to get HIV back under control.

The main reason to use a combination of HIV drugs instead of just one is to block reproduction at several points in HIV's lifecycle [5]. A combination of drugs aimed at several different targets is much better at preventing HIV reproduction than one alone. With less reproduction, viral load is lower, and mutations and resistance are less likely to occur.

Cross-Resistance and Sequencing

Cross-resistance happens when certain mutations cause resistance not just to one drug, but to an entire class of drugs. There are five classes of HIV drugs:

- Nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) such as Retrovir (zidovudine) and Ziagen (abacavir)
- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as Sustiva (efavirenz) and Viramune (nevirapine)
- Protease Inhibitors (PIs) such as Reyataz (atazanavir) and Prezista (darunavir)
- Entry inhibitors such as Selzentry (maraviroc) and Fuzeon (enfuvirtide)
- Integrase inhibitors such as Isentress (raltegravir)

Cross-resistance is more likely to happen in some classes than others. For example, resistance to the NRTI Retrovir also causes resistance to many of the other NRTIs. Resistance to one NNRTI also leads to resistance to most of the other NNRTIs. This may limit your choices when it is time to pick a new combination of HIV drugs.

If you are starting a treatment regimen for the first time, it is important to ask your health care provider about alternatives (a "plan B") in case the current regimen does not work for you. Thinking ahead will help to ensure that you have several good drug choices in the future.

How Do I Know if I Have Drug Resistance?

Resistance is common and can be transmitted with the virus. Between five and 20 percent of newly-infected people are infected with strains of the virus that are resistant to at least one HIV medication. This means that some newly-infected people, who have never taken any drugs, already have drug-resistant HIV and have a more limited selection of HIV treatments to choose from. People living with HIV (HIV+) who have already received HIV therapy are even more likely to have resistant virus and fewer drug choices.

The best way to tell if you have drug resistance is to have regular viral load tests. If your HIV drugs are working well to control your virus, your viral load should be "undetectable" ? so low that the test cannot detect any virus in your blood. If you are taking HIV drugs and your viral load does not become undetectable or goes up after you have been taking the drugs for a while, your virus may have developed drug resistance.

If this happens, it is important that you have a drug resistance test. These tests can help you

and your health care provider determine if your virus has become resistant to the HIV drugs you are taking and pick new drugs that will work better.

Resistance Testing

According to guidelines [6] put out by the US Department of Health and Human Services (DHHS), resistance testing is recommended for:

- People who have just become infected with HIV, whether or not they are going to take HIV drugs right away
- People who have never taken HIV drugs and are starting to receive medical care, whether or not they are going to take HIV drugs right away
- People who have never been on HIV drugs and are planning to start
- People who are on HIV drugs and see their viral load go up (usually over 1,000 copies/mL)
- People who have recently started HIV drugs and their viral load is not coming down enough
- HIV+ pregnant women

Resistance testing is not usually recommended for:

- People who have stopped HIV drugs for four weeks or more
- People with a viral load below 500 copies

There are several ways to test for resistance:

- **Genotype test**
  This test uses HIV from your blood to check for mutations ? changes in the virus' genetic sequence or genetic code ? associated with drug resistance. This is the preferred test for those whose HIV drugs fail to bring their viral load down enough and for pregnant women with detectable virus while on treatment.
- **Phenotype test**
  This test exposes your virus to many HIV drugs in a test tube to determine which ones still work against your HIV. This is the preferred test for people with complex drug-resistance patterns.
- **Virtual phenotype test**
  This is a genotype test that goes one step further ? it takes your genotype, finds similar genotypes in a database, and uses their phenotypic test results to predict which drugs will be effective against your virus (and its mutations)

In most cases, the genotype is the preferred test. For people who have been on HIV treatment before and may have HIV that is resistant to a number of different drugs, including protease inhibitors, the phenotype test may be done in addition to the genotype. Resistance tests are helpful when choosing a drug regimen. The tests are only a guide, however. Other factors, such as past medications, side effects, and adherence should be taken into account as well.

Preventing Resistance

The best way to avoid resistance is to follow your medication regimen closely. It is important not to skip doses. Also, try to take your medications at the same time every day. If you

maintain good adherence [3], you give your HIV drugs the best chance to work and yourself the best chance to live in good health.

Although resistance may seem overwhelming, remember that you have the power to help prevent it. If you follow your medication schedule, the virus will not reproduce as quickly. And if it is not reproducing, it can not make the changes that lead to resistance.

Tags:

- women and HIV drug resistance [7]
- women and HIV resistance [8]
- HIV drug resistance [9]
- HIV resistance [10]
- HIV resistance testing [11]
- resistance testing [12]
- phenotype [13]
- genotype [14]
- drug resistance [15]
- cross resistance [16]

Additional Resources

Drug Resistance and Resistance Testing (CATIE) [17]
Drug Resistance (AIDSmap) [18]
HIV Drug Resistance (WHO) [19]
Understanding Drug Resistance (AIDSmeds) [20]
HIV Resistance Testing (The AIDS InfoNet) [21]
A Guide to HIV Drug Resistance (The Body) [22]
HIV Drug Resistance Database (Stanford) [23]
Drug Resistance Testing (NIH guidelines) [24]

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Links:
[1] http://www.thewellproject.org/hiv-information/resistance
[2] http://www.thewellproject.org/hiv-information/women-and-viral-load
[3] http://www.thewellproject.org/hiv-information/adherence-0
[4] http://www.thewellproject.org/hiv-information/understanding-cd4-cells-and-cd4-cell-tests
[5] http://www.thewellproject.org/hiv-information/hiv-drugs-and-hiv-lifecycle
[6] http://www.thewellproject.org/hiv-information/hiv-treatment-guidelines
[7] http://www.thewellproject.org/tags/women-and-hiv-drug-resistance
[8] http://www.thewellproject.org/tags/women-and-hiv-resistance
[9] http://www.thewellproject.org/tags/hiv-drug-resistance
[10] http://www.thewellproject.org/tags/hiv-resistance
[11] http://www.thewellproject.org/tags/hiv-resistance-testing
[12] http://www.thewellproject.org/tags/resistance-testing
[13] http://www.thewellproject.org/tags/phenotype
[14] http://www.thewellproject.org/tags/genotype
[15] http://www.thewellproject.org/tags/drug-resistance
[16] http://www.thewellproject.org/tags/cross-resistance
[17] http://www.catie.ca/en/practical-guides/hiv-drug-treatment/appendices/e
[18] http://www.aidsmap.com/resources/treatmentsdirectory/Drug-resistance/page/1280050/
[19] http://www.who.int/hiv/topics/drugresistance/en/
[20] http://www.aidsmeds.com/articles/Resistance_7509.shtml
[21] http://aidsinfonet.org/fact_sheets/view/126?lang=eng
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[23] http://hivdb.stanford.edu/
[24] http://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv-guidelines/6/drug-resistance-testing