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## HIV Drug Resistance

You might think that HIV drug resistance is a complicated subject and less important than other aspects of HIV treatment. However, resistance is the main reason that prevents HIV drugs from being effective for life. New forms of triple drug therapy make the HIV virus undetectable by viral load tests in more than 90% of patients who take their medications as prescribed. However, with time, the virus can adapt to these drugs. In other words, it develops resistance. This article explains how drug resistance works and looks at ways to prevent it.

### How do HIV drugs work?

In HIV infection, the virus multiplies very quickly in the body. This is called “viral replication”. An HIV+ person not on drug treatment can have millions of copies of HIV virus circulating in their body. The HIV virus replicates, on average, several thousand times a day. More than an estimated 10 billion new viruses are therefore produced each day in an untreated individual. This viral replication can be measured through a viral load test, which counts the number of HIV viruses in one millilitre (mL) of blood.

If your viral load is below 30,000, replication is considered low. If, on the other hand, it is above 100,000, it is considered high. When it multiplies, the HIV virus destroys immune cells called “CD4 cells.” The more the virus multiplies, the higher the viral load will increase and the faster the CD4 cell count will decline. When the CD4 cell count declines quickly (for example, to below 350), triple therapy may be suggested by your doctor.

The objective of triple therapy is to prevent the virus from replicating. When the virus is present in very small numbers (fewer than 50 copies per mL), its replication is no longer detectable by the viral load test. In other words, replication has become undetectable. Triple therapy usually makes the viral load undetectable in less than six months. To achieve this level of replication control, the physician must generally prescribe a combination of at least three drugs (triple therapy) that blocks the viral replication mechanism. If fewer than three drugs are prescribed, the HIV virus will not only manage to adapt to the drugs, but it will also multiply.

### What is resistance?

Resistance occurs when the virus manages to multiply even when drug levels in the blood are normally considered sufficient to block viral replication. This means that the virus has adapted to the drugs and the viral load becomes detectable again, despite the triple therapy.

### How does the virus adapt to drugs?

When a drug is effective, the virus inside cells is “dormant” and does not replicate, or replicates very little. However, when the blood drug levels are too low, the virus starts to multiply again at a rate of millions or even billions of copies a day. When it replicates, the virus makes mistakes, or “genetic mutation” occurs (i.e. changes take place in the virus structure). Some of these mutations allow the virus to adapt to the drugs. Through natural selection, the better-adapted viruses (those that can reproduce in the presence of drugs) will quickly replace the viruses that are sensitive to the drugs (those that cannot replicate in the presence of drugs). The better-adapted viruses are said to have become resistant to the drugs.

The yellow line represents the blood drug level after dosing. The drug is to be taken every 12 hours. In this example, a dose is taken at 8 a.m. and 8 p.m.

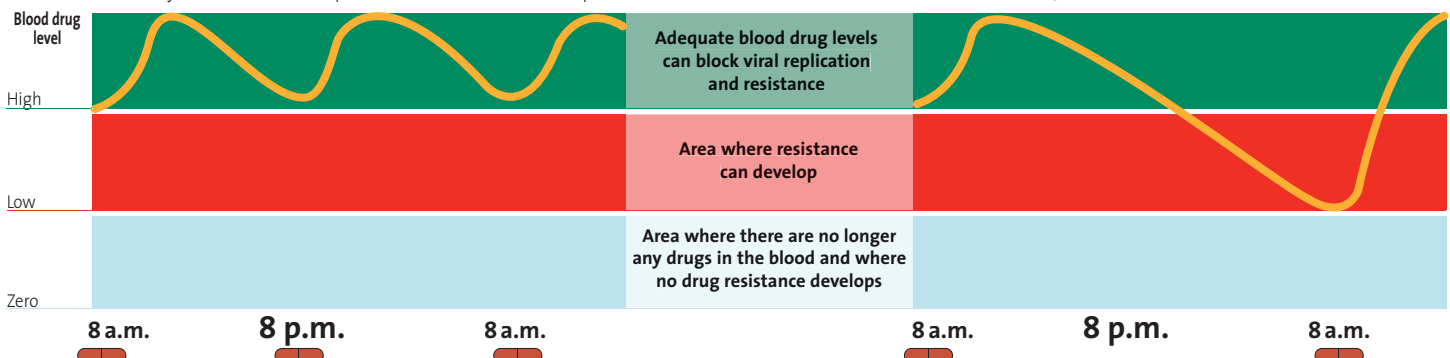


Figure 1

In this example, the second dose, scheduled for 8 p.m., was missed and taken the next morning. In the meantime, the blood drug level has fallen too low to block viral replication, thus allowing the virus to adapt to the drug.

Figure 2

## How can we prevent the development of resistant viruses?

Resistance usually results from viral replication in the presence of drugs. You must therefore not give viral replication any chance to take place. If there is no replication, genetic mutations are not possible and the virus cannot develop resistance (green area, figure 1, front page).

If there are no drugs in the blood, resistance does not usually develop, since the virus does not have to adapt to them (blue area, figure 1 front page). The virus can, however, multiply very quickly in the absence of drugs and lead to a weakened immune system and disease progression.

When the virus multiplies in the presence of low drug levels, it can adapt and develop resistance (red area, figure 1, front page).

## When will the virus multiply in the presence of drugs?

The HIV virus can multiply in the presence of drugs. Here are a few examples:

- **If a given therapy is not strong enough.** For example, instead of taking at least three drugs at the same time, the patient takes only one or two. With some exceptions, at least three drugs are prescribed at the same time to treat HIV infection.
- **If the drugs are not taken on a regular basis.** The virus should never be in the presence of inadequate drug levels. Since it can multiply very quickly, it can replicate within only a few hours if drug levels are inadequate (red area, figure 2, front page). If a dose of a prescribed drug is skipped, then the drug will be slowly eliminated from the blood. After a period of 8 to 24 hours, depending on the case, the blood's drug level is not high enough to prevent viral replication but is high enough to enable resistant viruses to develop (red area, figure 2, front page).
- **If the drugs are stopped.** Some drugs, such as efavirenz (Sustiva) and nevirapine (Viramune), are eliminated from the blood more slowly than others. These drugs can remain in the blood for a few days, while other triple therapy components are eliminated in a few

hours. In such conditions, the virus is in the presence of just one drug for a few hours, which allow for the development of resistant strains.

- **If dietary restrictions are not adhered to.** Some drugs should be taken with food, others on an empty stomach. If the recommendations are not followed, the drug may not be properly absorbed in the gastrointestinal tract, and its blood level may not be high enough to prevent viral replication and the development of resistance.
- **If there are interactions between your drugs or between your drugs and some over-the-counter products** (e.g. some natural products or heartburn medications). These products can lower the blood levels of some HIV drugs and cause resistance to develop. You should tell your doctor or pharmacist about all the medications or natural products you are taking, to ensure that there are no interactions.
- **Resistance can nonetheless occur, despite good treatment compliance.** Although rare, this can be due to genetic factors that modify absorption and blood drug levels.

## Why do HIV drugs have to be taken every day?

The best way to prevent drug resistance is to take your medications as prescribed, not forgetting a single dose, taking them at the specified times, and adhering to your dietary restrictions, if any. Some drugs need to be taken every 8 hours, others every 12 hours and still others every 24 hours. In general, following the dosing recommendations prevents the development of resistance.

It is important to choose a treatment that is well suited to your lifestyle. If you have to stop taking your medications, talk to your doctor about the best way to end your triple therapy. You can also talk to your pharmacist or any other health care provider about the various ways to ensure treatment adherence (i.e. taking all of your pills at the specified times every day as prescribed by your doctor).

## What if the drugs stop working?

There is a blood sample-based resistance test. The sample is obtained when the viral load becomes detectable and when there is reason to believe that resistance is the main culprit. The test identifies the drugs to which the virus has become resistant. When the virus adapts to a given drug, this can undermine the effectiveness of the other drugs in the same class. If drug resistance develops, it is usually irreversible.

Once resistance occurs, you may be able to switch to other drugs or to another class of drugs. In such cases, the resistance test can help the physician choose an appropriate alternative treatment. Sometimes, increasing the dose of a given drug can help the body fight HIV resistance. But since the number of drugs available is limited, the best way to fight resistance is to prevent it.

## How to avoid resistance

To avoid resistance, we must first understand how it occurs, then prevent the HIV virus's adaptation mechanisms. This requires motivation, a commitment to your treatment, and support. Do not hesitate to ask for help if taking your treatment seems to be getting more difficult or too much of a hassle, or if side effects prevent you from properly adhering to your treatment regimen.

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