

Switching HIV Treatment

Let's face it. No one drug or combination regimen is going to work for everyone forever. Some people, especially those who start treatment promptly using modern <u>antiretrovirals</u>, can stay on their first regimen for a long time. But others are unable to keep their viral load suppressed or have trouble tolerating side effects—or they may simply want a new regimen that contains fewer drugs, has a lower pill burden or requires less frequent dosing.

The good news is that treatment options have expanded and improved in recent years. Maintenance therapy—simplified regimens that aim to maintain existing viral suppression—are now a switch option for some people who have achieved a stable undetectable viral load on a standard three-drug regimen. With a better understanding of <u>drug resistance</u> and the development of new medications that can treat drug-resistant virus, most people with HIV can keep the virus under control over the long term.

Why switch medications?

Whether you've just started antiretroviral therapy or have been on treatment for years, the following are some reasons for switching medications.

- Viral load is not fully suppressed. Inability to achieve or maintain an undetectable viral load is less common with modern antiretrovirals, but some people are still taking older drugs or using combinations that are less potent.
- Inadequate CD4 cell recovery. Some people who adhere well to treatment and have a fully suppressed viral load still may not see their CD4 count increase to a normal level, which could leave them vulnerable to opportunistic illnesses.
- Difficulty taking meds regularly. Some people have trouble maintaining <u>good adherence</u> to their treatment regimen. Some medications are more convenient to take, and some are more "forgiving" of an occasional missed dose.
- Too many pills or too frequent dosing. Most people with HIV can now use single-tablet regimens, or single pills containing two or more drugs that are taken just once a day. In addition, there are

now a long-acting injectable medications that can be administered every other month or even less often.

- Short-term and long-term side effects. If side effects are having a negative effect on quality of life, it may be possible to switch to medications that are better tolerated. Short-term side effects may include nausea, diarrhea and difficulty sleeping. Examples of longer-term effects include weight gain, increased cholesterol or glucose levels, kidney damage and bone loss.
- Drug interactions. Some antiretrovirals can interact with medications for other conditions. Some people living with HIV, for example, need treatment for other infections, such as hepatitis B or C. As people age, they are more likely to develop chronic conditions, such as high blood pressure or diabetes, that require additional medications. Drug interactions are most likely when a regimen includes ritonavir or cobicistat to boost other antiretrovirals. Newer HIV meds, in particular integrase inhibitors, are less likely to interact with other medications.
- Swallowing, food or fluid needs. Some people have difficulty swallowing larger pills. Some medications must be taken on an empty stomach, which may cause nausea or vomiting. Others must be taken with food, which can make timing inconvenient.
- Pregnancy. Some HIV medications have been more extensively studied for use during pregnancy. Ideally, an appropriate regimen should be planned before conception and monitored throughout pregnancy to protect the health of the mother and reduce the risk of transmitting HIV to the baby.
- Medication cost or insurance issues. Some HIV meds cost less than others, and an increasing number of older drugs are available as less expensive generic versions. Some people with HIV face insurance restrictions that limit their choice of medications.

What is treatment failure?

Treatment failure simply means that some of the medications in a regimen are not doing their job. Virological failure means that a regimen is not able to maintain viral suppression. If your viral load does not fall to an undetectable level while on treatment—or if it does not stay down—you are at risk for disease progression and could transmit the virus to others. Virological failure often occurs because the virus has mutated, or changed at the genetic level, enough to lose susceptibility to a drug. Usually, the <u>CD4 count</u> rises as viral load falls because HIV is no longer killing these cells. The count typically rises by 50 to 200 cells, on average, during the first year on treatment. But older people and those who started treatment with a very low CD4 count may take longer to see this level of improvement, and some people never experience adequate CD4 cell recovery despite having a stable undetectable viral load. This is known as immunological failure. If your CD4 count stays too low, you remain at risk for opportunistic illnesses.

How do I know if my treatment is working?

The best way to tell whether your medications are working is to measure the amount of HIV in the blood. This is known as the <u>viral load</u>, or HIV RNA level. In regular HIV care, an undetectable viral load generally means that the number of copies of HIV in a small sample of blood is below 50. But highly sensitive tests used for research can measure much lower levels. The lower the viral load, the less risk for disease progression, and studies show that people with a viral load below 200 do not transmit HIV through sex.

It is important to have your viral load checked after you first start treatment or switch to a new regimen to determine whether the new meds are working. The Department of Health and Human Services treatment guidelines recommend viral load testing two to eight weeks after starting treatment or switching drugs. Once viral load is suppressed, testing should be repeated every three to four months. People who have a stable undetectable viral load for a year or more can cut back to testing every six months.

Your treatment might not be working if your viral load does not begin to decline soon after starting or switching treatment—most people will see a substantial drop within the first few months—or if it does not fall below 50 copies within a year.

Another warning sign is an undetectable viral load that becomes detectable again. This could mean you are not taking your medications consistently or your HIV has become resistant to the drugs. However, it is important to look at trends over time rather than one measurement. A single detectable viral load, known as a "blip," could be the result of a lab error or could be a temporary rise—for example, if you recently had a flu or received a vaccine. A single low-level blip is usually nothing to worry about, but if two consecutive tests show a rising viral load, it might be time to adjust your regimen.

What causes treatment failure?

Treatment failure can have several causes, all of which can be addressed by switching to a new regimen.

• Weak drugs. Certain HIV drugs or combinations are not as potent as others. This is especially true of older medications. Modern antiretroviral regimens can keep HIV under control in most

people, but those with a very high viral load may need to start treatment with more potent regimens.

- Poor absorption. Absorption refers to how much of a drug is taken up into the bloodstream and distributed throughout the body. Some meds must be taken on an empty stomach or with food to ensure that they're absorbed properly. In some cases, taking other medications around the same time as HIV drugs can affect absorption. Vomiting or diarrhea after taking your meds can also lead to poor absorption.
- Drug interactions. Some HIV medications are broken down in the body by a liver enzyme that
 also metabolizes many other commonly used medications. This competition can either increase
 or decrease the level of antiretrovirals or other medications in the blood. Regimens that include
 ritonavir or cobicistat—drugs that boost the level of certain other antiretrovirals—are especially
 prone to drug interactions. Tell your provider about all the medications you are taking, including
 prescription drugs, over-the-counter meds, herbs and supplements and street drugs.
- Drug resistance. Certain changes, or mutations, in HIV's genes can make the virus less responsive to antiretrovirals. This is one of the most common reasons for treatment failure.
 Some people acquire HIV strains that are already resistant to certain drugs. In other cases, resistance develops over time; this is most likely if meds are not taken as directed.
- Poor adherence. HIV medications work only if you take them consistently. Adherence refers to how well you follow your provider's instructions about how to take your meds. Factors that can interfere with adherence include side effects, inconvenient regimens, forgetfulness, a hectic or unpredictable schedule, unstable housing and interrupted access to treatment due to cost or other reasons. Missing doses allows the virus to resume its multiplication, which can lead to disease progression and the development of drug resistance that limits future treatment options. Tell your provider or pharmacist if you do not understand how to take your meds or are having trouble taking them as directed. They may be able to help you find another regimen that is easier to take.

What should I switch to?

Which new regimen to use depends on your treatment history and why you are switching. People

who already have an undetectable viral load and wish to switch for other reasons—for example, to lessen side effects or improve convenience—are likely to have more options.

In many cases, people who have been taking more than one pill once a day can switch to a singletablet regimen. Traditionally, standard HIV regimens have included two nucleoside/nucleotide reverse transcriptase inhibitors plus a nonnucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor or integrase inhibitor. But people who have already achieved an undetectable viral load and have no history of treatment failure and no resistance mutations may be able to switch to a two-drug maintenance regimen, such as Juluca (dolutegravir/rilpivirine) or Dovato (dolutegravir/lamivudine) pills. Another option is <u>Cabenuva</u> (injectable cabotegravir and rilpivirine), long-acting injections administered once monthly or every other month.

When switching regimens because of virological failure, it's important to have a discussion with your doctor about adherence, side effects, drug interactions and other factors that may prevent your meds from working as they should. Resistance tests can show which drugs in your regimen are not working due to viral mutations and which alternative antiretrovirals are likely to work best. However, it can be hard to get accurate results if your viral load is detectable but low.

If there's no evidence of drug resistance, it may be possible to switch to a simpler regimen that promotes better adherence—for example, a combination that requires fewer pills or is taken less often. If side effects are a problem, it's often possible to manage them (for example, with antinausea meds) or switch to better tolerated antiretrovirals.

Switching treatment is more challenging for people who have been living with HIV for a long time, have used many older drugs (in some cases one at a time or in suboptimal combinations) and whose virus has developed resistance to multiple medications (known as multidrug-resistant HIV). Although these individuals have fewer switch options, many can still construct an effective new regimen that enables them to achieve and maintain viral suppression.

Ideally, a new regimen should contain at least two, preferably three, fully active drugs, but this is not always possible. Adding a single drug to a failing regimen raises the risk of resistance. Some people may be able to use a so-called salvage regimen containing four, five or more partially active drugs. Others may be able to add newer antiretrovirals that work in different ways—such as the monoclonal antibody entry inhibitor <u>Trogarzo</u> (ibalizumab) or the twice-yearly injectable capsid inhibitor <u>Sunlenca</u> (lenacapavir)—to an optimized background regimen of the most active drugs according to resistance testing. Another option is to join a <u>clinical trial</u> to access experimental antiretrovirals, but currently there are few investigational antiretrovirals in the development pipeline.

The bottom line

If your current HIV treatment is not working or you find it difficult to take consistently, switching one or more medications may be an option. Modern antiretrovirals are more potent, less likely to lead to drug resistance, better tolerated and more convenient than older HIV meds. Many people can take single-tablet regimens that require just one pill a day. Using the newest drugs, even people who have been living with HIV for years and have highly resistant virus can usually find a treatment approach that keeps their HIV in check.

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