Switching HIV Treatment

Let's face it. No one drug, or combination of drugs, is going to work for everyone—or forever. While some people, especially those who start treatment with modern antiretrovirals, can stay on one regimen for a long time, others are unable to keep their viral load down and their CD4 cells up or to tolerate the side effects of their first regimen.

Others are looking for simpler regimens that have a lower pill burden, require less frequent dosing or contain fewer drugs. Maintenance treatment, which aims to maintain existing viral suppression, using just two drugs is now a switch option for some people who have achieved a stable undetectable viral load on a standard three-drug regimen.

The good news is that treatment options have greatly expanded and improved in recent years. With a better understanding of drug resistance and the development of new drugs to treat drug-resistant virus, most people with HIV are able to keep the virus under control over the long term.

Why do people with HIV switch medications?

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

- Viral load is not fully suppressed. Inability to achieve or maintain an undetectable viral load, known as treatment failure, is less common with modern antiretrovirals. However, some people are still taking older drugs, using combinations that are less potent or find it hard to stick to their treatment.
- Incomplete CD4 cell recovery. Some people who adhere well to treatment and have fully suppressed viral load still may not see their CD4 counts increase to normal levels, which could leave them vulnerable to opportunistic illnesses.
- Difficulty taking meds regularly. Some people have trouble maintaining good adherence to their HIV 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

(STRs), meaning a single pill taken once a day. Long-term injectable options are currently being studied.

- Short-term and long-term side effects. If side effects are negatively affecting quality of life, it may be possible to switch to medications that are better tolerated. Short-term side effects include diarrhea, skin rash or difficulty sleeping; examples of longer-term effects are increased cholesterol or glucose in the blood or signs of liver damage, kidney damage or bone loss.
- Drug-drug interactions. Some antiretrovirals can interact with medications for other conditions. People living with HIV may have other chronic infections, such as hepatitis B or C. As people age, they are more likely to develop conditions such as hypertension or diabetes that also need treatment. Interactions are most likely when a regimen includes the booster drugs ritonavir or cobicistat. Some newer HIV meds, in particular integrase inhibitors, are less likely to interact with other medications.
- Swallowing, food or fluid needs. Trying to swallow larger pills can be a problem for some people. 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.
- Some HIV medications have been better studied than others for use during pregnancy. Pregnancy can also alter blood levels of certain antiretrovirals. An appropriate regimen should be planned before conception and monitored throughout pregnancy to protect the health of both the mother and child and to reduce transmission risk.
- Health care costs. Some HIV meds cost less than others, and older drugs are increasingly available in less expensive generic versions. Some people with HIV may face insurance restrictions that limit their choice of medications.

What is treatment failure?

Simply put, treatment failure means that one or more HIV medications are not doing what they should. Virological failure means a regimen is not keeping the virus fully suppressed. In many cases, this happens because the virus has mutated, or changed at the genetic level, enough to avoid the effects of a medication.

If your viral load does not fall to an undetectable level while on treatment—or if it does not stay down while taking the drugs—you are at risk for disease progression. Having a detectable viral

load also means that transmission of the virus is still possible.

Usually, CD4 counts will rise as viral load falls because HIV is no longer killing these cells. However, some people do not regain normal CD4 cell levels despite having a stable undetectable viral load. This is known as immunological failure. If your CD4 count stays below 200, 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 directly measure the amount of HIV in the blood. This is known as the viral load, or HIV RNA level.

In regular HIV care, undetectable viral load generally means that the number of copies of HIV in a small drop of blood is below 50. However, some highly sensitive tests used for research can measure much lower levels. Conversely, “detectable” viral load simply means above 50 copies. The lower the viral load, the less risk for disease progression. Studies show that people with a viral load below 200 do not transmit HIV through sex.

It is important to check your viral load after you first start treatment or switch to a new regimen to determine if the new meds are working. The Department of Health and Human Services (DHHS) HIV 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 two years or more can cut back to testing every six months.

How do I know if my treatment is not working?

If any of the following occurs, your drugs might not be working:

- Viral load does not begin to fall soon after starting treatment: If the new meds are working well, most people will see a substantial drop in viral load within the first few months after starting therapy.
- Viral load is not below 50 copies at 48 weeks after starting treatment. It’s reasonable to expect today’s medications to bring viral load to an undetectable level well before 48 weeks. However, some people may take up to a year to get there.
- An undetectable viral load becomes detectable again. A rise in viral load after being undetectable could mean that treatment has stopped working. However, it is important to consider trends over time rather than a specific measurement. A single detectable viral load could simply be the result of a lab error or a temporary “blip.” Such blips may occur, for

example, if you have the flu or recently received a vaccine. A blip of less than 400 copies that occurs only once is usually nothing to worry about. But if a second test confirms the first—and especially if viral load is rising—it might be time to change your regimen.

- CD4 count does not increase while on treatment. CD4 counts usually rise by 50 to 200 cells, on average, during the first year on treatment. However, some people who started with a very low CD4 count, as well as older people, may take more than a year to see this level of improvement. If your CD4 count does not rise by at least 25 to 50 cells during the first year—and especially if it falls—changing medications might help.

What causes treatment failure?

- Weak drug combinations. Certain HIV drugs or combinations are not as potent as others. Most recommended antiretroviral regimens can keep HIV under control in most people. However, people with a very high viral load (above 500,000 copies) may need to start treatment with stronger drugs. In some cases, it’s possible to switch to less potent drugs after viral load becomes undetectable; this is known as maintenance treatment.
- Poor absorption. Absorption refers to the amount of drug that is taken up into the bloodstream and distributed to cells. 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 (such as antacids) around the same time as HIV drugs can affect absorption. Vomiting or diarrhea after taking your meds can also lead to poor absorption.
- Drug-drug interactions. Some HIV drugs are broken down in the body by a liver enzyme called P450. This enzyme also metabolizes many other common medications. P450 can either increase or decrease the level of antiretrovirals in the blood. The booster drug ritonavir is especially likely to cause drug interactions. Make sure you tell your provider about all the medications you are taking, including prescription drugs, over-the-counter meds, 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 to happen if meds are not taken consistently. If your treatment is not effective, resistance testing can show which drugs in your regimen are not working and which alternative meds are most likely to work better.

- 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 good adherence include inconvenient regimens, side effects, unstable housing and interrupted access to treatment due to cost or other reasons. Missing doses can allow the virus to flourish, and it may also lead to 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?

This depends on your treatment history and the results of drug resistance testing.

People who have an undetectable viral load on their current regimen and want 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 single-tablet regimen.

Traditionally, standard HIV regimens have included two nucleoside/nucleotide reverse transcriptase inhibitors plus either a nonnucleoside reverse transcriptase inhibitor, a protease inhibitor or an integrase inhibitor.

But today, two-drug combinations are an option for some people. HIV treatment guidelines list Juluca (dolutegravir/rilpivirine) and Dovato (dolutegravir/lamivudine) as successful strategies for switching from a three-drug regimen to a two-drug combo when viral load is suppressed (below 50) and there is no known resistance to the component drugs.

People who have been living with HIV for a long time and have tried many older drugs may have virus that is resistant to multiple medications (known as multidrug-resistant HIV). Although they have fewer switch options, more potent modern antiretrovirals and newly approved medications that work in different ways may be able to suppress their virus.

Here are a few general rules from the DHHS guidelines about when and how to switch treatment regimens.

- Viral load between 50 and 200 copies: People with low-level viral load increases, including one-time blips, usually do not need to change treatment. The risk of developing drug resistance is relatively low in this situation. The guidelines say that such people should stay on their current regimen and have their viral load measured at least every three months to see whether they need future treatment changes. This is an opportunity to discuss adherence and get additional support if needed.
- Viral load between 200 and 1,000 copies: People with viral loads in this range—especially when they're above 500—are at higher risk of developing drug resistance. Resistance testing should be done, although it can be hard to get accurate results if the viral load is below 500. If resistance testing cannot be done, switching should be done on a case-by-case basis, taking into account whether a new regimen that is expected to fully suppress the virus can be constructed using available drugs.
- Viral load above 1,000 copies with no known drug resistance: This situation is usually due to adherence issues. It is important to identify and address the underlying reasons for missing doses and get additional support. If a current regimen is well tolerated with no drug or food interactions, it's reasonable to stay on the same combination. In some cases, it may be possible to switch to a simpler regimen with fewer pills, less frequent dosing and no food requirements. If side effects are a problem, it may be possible to manage them with medications (for example, anti-nausea meds) or switch to better tolerated antiretrovirals. A viral load test should be done soon afterward to see whether the virus is undetectable. If not, resistance testing should be done to see if a new resistant HIV strain has emerged.
- Viral load above 1,000 copies with identified drug resistance: In this case, treatment should be changed as soon as possible to prevent the emergence of more resistance mutations. Studies show that switching treatment is most likely to be successful while viral load is lower and CD4 counts are higher. The availability of newer antiretrovirals, including some that work in different ways, makes it possible to achieve viral suppression in most cases.
- Extensive prior treatment with drug resistance: Given the most recently approved new drugs, many people with extensive treatment experience and multidrug-resistant HIV can still build an

effective new regimen. Ideally, a new regimen should contain at least two, preferably three, fully active drugs. Despite resistance, some drugs may retain partial activity. For some people, a modern boosted protease inhibitor combined with other meds may do the trick, even if the other drugs are only partially active. For those with more extensive resistance, the entry inhibitor Trogarzo (ibalizumab) may be an option.

- People without two new active drugs: Some people have such extensive drug resistance that they do not have two new active drugs to try. In such cases, it's reasonable to stay on a failing regimen if there are few or no other options. Even a partially effective regimen may offer some benefit. However, the benefits of partial suppression should be weighed against the risk of developing new resistance mutations. Starting a single new active drug is not recommended because resistance can develop rapidly. It's preferable to save such new medications until another active drug becomes available and they can be started together.

I've already tried most of HIV medications—what now?

You and your provider should review your entire medical history to find any possible treatment opportunities. Genotypic and phenotypic resistance tests can show which drugs still have some activity against your specific virus.

One approach is trying a drug that targets HIV at a different step in its life cycle. If you've never tried a CCR5 inhibitor, such as Selzentry (maraviroc), for example, that could be a possible option. Trogarzo, a monoclonal antibody that attaches to CD4 receptors and prevents HIV from entering cells, works differently than other HIV meds.

Another option might be to use a so-called salvage regimen that contains four, five or more partially active drugs. Even if this approach does not fully suppress HIV, it could keep viral load lower than it would be without treatment and may help maintain your CD4 count and protect against opportunistic illnesses. However, the main problem with taking so many drugs, aside from inconvenience, is the potential for multiple side effects and drug interactions.

What about experimental drugs?

In some cases, it may be possible to join a clinical trial of a new experimental drug or treatment strategy. Other options for accessing experimental medications include expanded access programs or single-patient access arranged on a case-by-case basis through a pharmaceutical company and the Food and Drug Administration. However, at this time, there are few experimental HIV meds 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 once a day. Using the newest drugs, even people who have been living with HIV for a long time and have highly resistant virus can usually find a treatment approach that keeps their HIV under control.

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