Most people living with HIV will face making decisions about treating their HIV disease at some point. Over time, some will change their regimens for various reasons, and likely change them several times. This can lead to being in a position where there are few options for adding new HIV drugs when it’s necessary.

Having extensive experience with various regimens is one reason you may face choosing third line therapy. Another reason could be that your HIV has become resistant to at least one drug in each of the three major classes: protease inhibitors, NRTIs and NNRTIs. A third reason includes treatment failure on at least two other regimens. The specific reasons why you switched from specific medicines determine if or how these drugs might be used again in another regimen.

Sometimes, people refer to third line therapy as salvage or rescue therapy. True or “deep” salvage therapy is when a person literally has no treatment options with resistance and/or intolerance to virtually all HIV drugs. Most people with some treatment failure do not need true salvage therapy. It’s often possible to create a viable, if not ideal, regimen for people even if you believe you’ve run out of options.

This publication sheds light on issues to consider when you’re confronted with making decisions for third line therapy. It also helps guide people who face true salvage therapy.
Why a regimen fails

In general, a regimen has failed when your HIV level:

- does not drop by at least 90% within the first six months on a new regimen, and/or
- becomes and stays (on at least two tests in a row) detectable again after being undetectable.

Discovering the reasons why your current regimen is failing (and past regimens if possible) is key to creating a new one. The main reason that some people switch individual drugs or their entire regimens is because their current combination no longer keeps their HIV levels undetectable. For others, HIV levels may be only one factor among others that contributes to a failing regimen. These can include:

- developing drug-resistant virus,
- difficulty with staying on a regimen,
- not having high enough blood level of drugs, and
- side effects.

Drug resistance

Drug resistance occurs when HIV can reproduce in the presence of drugs. Cross resistance occurs when HIV that reproduces in the presence of a particular drug can also reproduce in the presence of other drugs in the same class. For instance, HIV that's resistant to Sustiva (efavirenz) is usually cross resistant to both Viramune (nevirapine) and Rescriptor (delavirdine). When a person develops drug resistance or cross resistance, it can severely limit effective the options of HIV drugs.

Two kinds of tests help determine if your HIV has become resistant. Both require that your HIV level be at least 1,000 for best results. The genotype test finds out which drugs your HIV has become resistant to. The phenotype test is used to find out the degree of resistance. However, both can fail to detect resistance because drug-resistant HIV may not be present in the blood sample, or may be present at too low a level for detection.

It's important to emphasize two points. The first is that resistance tests give the most meaningful results when they're done while you're on HIV therapy. This way, the results are likely most relevant to the drugs you're taking. The other is that the results are only part of the story when considering other drugs. Considering your history and experiences with other regimens is critical to choosing the best drugs to use for your next regimen.

adherence

One factor that can lead to drug resistance is not taking your meds exactly as prescribed. People are far more likely to get and maintain undetectable HIV when they take more than 95% of their doses as prescribed. Even when adherence is nearly perfect, however, treatment failure can occur. More than one study found that drug-resistant HIV could be found even in people who adhered to their regimens most of the time. Identifying why adherence is challenging for you and doing something about it is important. (Project Inform’s publication, Adherence: Keeping Up with Your Meds, has helpful tips.)
Treatment failure due to side effects

Unfortunately, side effects can go hand-in-hand with the getting benefits of being on HIV therapy. Some may moderately impact your quality of life or they may only last a short time. Before you switch your HIV drugs, it can help rule out their possible causes or consider ways to manage them. (Project Inform’s publication, Dealing with Drug Side Effects, offers helpful tips.)

Deciding what to do about other side effects, like elevated cholesterol and triglycerides, insulin resistance and fat redistribution, can be more challenging. Since many people have limited treatment options, switching from the offending drugs simply isn’t an option. In this case, the choice may be to switch to a regimen which includes drugs they’ve used before that carry fewer risks for these side effects until other drugs become available.

If you’ve had side effects with a drug or regimen in the past, it does not necessarily mean you can’t use it again. Some people find that a drug that had caused them unacceptable side effects before actually causes them no side effects whatsoever when they used it again.

Similarly, it can be difficult to know which drug in your regimen was the culprit for a given side effect. If you’re taking four drugs, you might be able to use two or even three of them again with no ill effects.

It’s also sometimes very difficult to sort out drug side effects from the symptoms of HIV disease. Did a drug cause your diarrhea or was it caused by HIV or something else altogether? As long as the drug can be used safely again, it might still stay in your toolbox of options. It might take some mental preparation and planning in case the side effect re-emerges. But in general, having stopped a drug because of side effects doesn’t always rule it out for future use.

Research shows that people with lower CD4 counts are more likely to experience side effects, and they tend to be more severe. Therefore, if you started a drug regimen in the past when your CD4 count was lower than now, you may be less likely to experience trouble.

Expert guidance

When forming a new regimen, it’s especially important to have expert guidance when making these complex decisions. People who see an HIV experienced doctor are less likely to face disease progression than those who see doctors with less experience.

For those who can’t see an experienced doctor, a regional AIDS Education and Training Center (AETC) site may help provide expert guidance to your doctor. You can reach these centers at www.aids-ed.org or by having your doctor call 1-800-933-3413 (not available to patients). Lastly, the American Academy of HIV Medicine at www.aahivm.org can guide doctors and patients to other doctors who the Academy certifies as HIV specialists.
Creating your next regimen
The most ideal regimen contains at least two potent drugs to which you have no resistant HIV, preferably ones you’ve never used before. Many studies show that people who start a regimen with at least two new, fully active drugs are likely to have better treatment outcomes.

For some people, the recently approved drugs — Intelence (etravirine), Isentress (raltegravir) and Selzentry (maraviroc) — are enough to make a regimen with two new drugs. For others, these might only offer one. Some people will depend on expanded access programs, third line therapy studies, or a mix of these to access other new drugs.

The pace of drug development
Developing new drugs is an uneven and unpredictable process. For example, from late 2006 to early 2008, four new drugs were approved, including two new classes. This allowed many people with limited treatment options to construct new potent, fully active regimens — often for the first time in many years. Unfortunately, no new drugs are expected until sometime in 2010. If you’re heavily treatment experienced, with resistance to many of the older HIV drugs, this new crop represents a great chance to create an effective and durable regimen.
It’s possible to find a successful regimen even when you can’t construct a new one with two new drugs. The success of these strategies may not equal that of a completely new regimen, but they have produced favorable results in at least some people in studies to date. These strategies often need expert guidance and monitoring. They may also come with other risks of side effects and disease progression.

Staying on your “failing” regimen, with stable CD4s

Sometimes, when HIV changes and becomes resistant to some drugs, it may not reproduce as well. This is particularly true with protease inhibitors and some NRTIs — Emtriva (emtricitabine/FTC) and Epivir (lamivudine/3TC) — that cause HIV to develop the M184V mutation.

When HIV doesn't reproduce as well on its own, for example with the M184V mutation, this is called a reduction in its viral fitness or replication capacity. So, when HIV has poorer viral fitness in people whose CD4 counts remain high and stable, it may allow them to stay on their “failing” regimens, with some benefit, as they wait for new treatments to become available.

A major risk when staying on a failing therapy is having HIV that develops several mutations, which increases your chance for both resistance and cross resistance. Another risk is that as HIV levels climb above 100,000 in treatment experienced people, it may lower their chances that their next regimens will work as well. Although staying on a failing regimen is far from ideal, it may be useful for some people awaiting new drugs.

Creating a new regimen, with expert guidance, with five or more drugs

Several studies have looked at the possible benefits of using multiple drug combinations after treatment failure. This is sometimes called megaHAART or gigaHAART. Although one study looked at a regimen with two NNRTIs (Sustiva and Viramune), most of them included using two and possibly three protease inhibitors along with NRTIs. Up to four NRTIs were sometimes used. The challenges of such a strategy are obvious. The more drugs a person uses, the higher their risk for side effects and the greater the possible impact on their quality of life.

At best, these strategies have provided only modest benefits in most cases and often increase side effects and greatly complicate managing drug interactions. The trend now is to try and reduce the number of drugs a person is on, when that can be done safely. In fact, the Federal Guidelines just added language on how and when to safely reduce the number of drugs a treatment experienced person is taking.

Interrupting therapy before starting a new regimen

Some studies have used a structured treatment interruption (STI) before switching to a new or recycled regimen. It was hoped that drug-resistant virus would fade into the background during the interruption. In theory, this would allow wild-type HIV (virus that’s sensitive to the HIV drugs) to take over, giving people a more beneficial response to the new regimen.

The results from these studies are mixed. One shows some benefit to taking an STI before starting a new regimen while others show none. In each, those who interrupted therapy had significant increases in their HIV levels and steep drops in their CD4 counts. The main danger of using STIs in third line therapy is the risk for serious disease progression. In all studies, people who tried STIs typically lost at least half of their CD4 counts. People who have low CD4 counts at any time are at the greatest risk from STIs.

There’s a growing body of evidence suggesting that STIs are risky. By far the most important study in this regard was the SMART study, which compared continuous HIV treatment to intermittent treatment guided by CD4 counts in about 6,000 people worldwide. As reported here, www.projectinform.org/news/08_croi/020408d.shtml, SMART was stopped early when higher rates of illness and death were seen among people in the intermittent group. Other studies, including PART, DART and TRIVICAN have found similar risks for STIs. For more information, read Project Inform’s publication, Structured Treatment Interruptions.
Checking the blood levels of drugs

Some researchers believe that variations in how a person's body breaks down (metabolizes) drugs may be largely responsible for treatment failure when a person adheres to their regimen. HIV drugs are generally developed to produce the largest drops in HIV with the fewest side effects in most people. However, some people will accumulate levels of drug that are higher than average, perhaps leading to more side effects. Others won't maintain enough drug, perhaps leading to resistance. So even though some people may take all their prescribed doses, there may be times when there's too little or too much drug in their systems.

For this reason, several European nations routinely check the blood levels of HIV therapy after starting a person on a new regimen. When problems are found, they adjust the dose to ensure that a person is getting an adequate dose of drug. This process is commonly called Therapeutic Drug Monitoring (TDM), and it has been used for quite some time in other diseases.

A few studies that have used TDM in treating HIV have shown a better response in people whose levels of drugs are consistently at ideal levels. These and other studies have also shown greater side effects in people whose drug levels were consistently too high.

However, there are two problems with using TDM for HIV. First, the level of drug in a person's body can vary somewhat from day to day. This can be especially true for women during their periods or pregnancy. Second, most HIV drugs work inside cells, and TDM tests generally measure the amount of drug in blood plasma, or outside cells.

While it's logical to assume there's a strong relationship between the amount of drug found outside and inside cells, the limited amount of this research has produced conflicting results. In the US, standard TDM lab kits are not available for HIV drugs. It's now being studied in the US and may have more of a role in the future. Outside these studies, there's no way for most people to use TDM to guide their treatment decisions.

A final word on third line therapy

The first step in developing a strategy for third line therapy is to understand why your current regimen is no longer working and why earlier ones have "failed". This helps make clearer what options truly are available to you. Resistance test results are necessary to guide these decisions.

Ideally, creating a regimen with at least two drugs that are active against HIV is often possible by using resistance test results, expert guidance and new treatments. When it's not possible, getting into expanded access programs and clinical studies may offer other options for you.

Some people may continue to benefit from their current regimens even as their HIV levels increase. Therefore, those who can safely wait for new drugs to become available in order to build a new regimen with two active drugs may wish to do so. However, waiting until your HIV level climbs above 100,000 may further limit your treatment options down the road.

Over the past 10 years, most new HIV drugs have been studied first in people with extensive treatment experience. Some of the newer generation of drugs have shown the best-ever results in these people. While many have been helped by these new drugs, Project Inform continues to push for new options for heavily treatment experienced people.