

# Rescue therapy

What are your options after multiple treatment failures?

by Dr. Marianne Harris and Dr. Julio Montaner

**Rescue or salvage therapy is generally used to describe the stage in treatment when options are limited because previous anti-retroviral (ARV) regimens have failed to work. Most doctors use the term when you've been exposed to at least one drug from each of the three drug classes initially available (i.e. NRTIs, NNRTIs and PIs) and those treatments haven't succeeded in keeping your viral load at undetectable levels.**

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Often at this point tests will show that the HIV in your body has developed resistance to drugs from each of these classes, so the potential effectiveness of available treatments has really been compromised. Your doctor might be able to design a treatment combination that will get your viral load down to undetectable levels and keep it there, but chances are the treatment will not be as simple to take as standard first-line three-drug combinations.

## Reasons for treatment failure

The first things to consider when faced with the prospect of salvage therapy are the reasons why previous treatments failed. Were you taking your therapy and if so, how well were you able to

stick to the med schedule? If you weren't able to take your meds regularly due to aspects of your lifestyle or drug side effects, these issues need to be dealt with so they won't happen again when you're faced with a more complicated drug regimen.

Secondly, were the drugs getting into your bloodstream in high enough levels to be effective? Drug levels can be reduced by factors such as poor absorption from the GI tract (for example, due to diarrhea) and interactions between the antiretrovirals and other drugs (including some herbal remedies and nutritional supplements). These problems will need to be fixed to make sure your new regimen will work as well as possible.

Third, has the virus developed resistance to some of the antiretroviral drugs, making them less able to decrease the viral load? Your HIV may be resistant to a drug that you've never taken, because it's resistant to a similar drug that you did take. Your doctor will probably want to do a number of resistance tests on blood samples taken during your current and previous treatments, in order to assess the amount of

drug resistance that's present and select the drugs most likely to be effective.

### Salvage treatment with T20

Once a number of treatment regimens have failed and your virus has become resistant to several drugs, what are your options? The best option is a new regimen containing at least two fully effective drugs, that is, drugs which your HIV has never seen and to which it remains vulnerable. The first approved drug from a new drug class, the fusion inhibitor T20 (Fuzeon® or enfuvirtide) may be one such option. Unlike NRTIs, NNRTIs, and PIs, this drug works by preventing HIV from getting into your cells. Even HIV that's resistant to the other three classes of drugs will still be susceptible to T20, because it's from a different drug class and there's no cross-resistance with the other classes. T20 is also different from other antiretrovirals because it must be given twice daily by subcutaneous injection (like insulin). Some people find this scary, but once they've been taught to give themselves the injections (or have a friend or family member do it), they get used to it and usually do quite well. For people who absolutely cannot deal with needles, T20 may also be given using a needle-free, gas-powered injection system.

### New drugs

Although T20 is very effective in salvage therapy, if it's started as the only new drug, the virus

can quickly develop resistance to it. To retain its effectiveness, T20 needs to be given with at least one other active drug (i.e. one to which your HIV is not resistant). If your virus is very resistant to available NRTIs, NNRTIs, and PIs, the only option for another fully effective agent might be a new experimental drug. For example, the newly approved PI TPV and the experimental PI TMC114 have been shown to be very effective against HIV that's resistant to the available PIs (both of these drugs need to be boosted with ritonavir in order to work). There are also experimental NNRTIs, such as TMC125, that work against NNRTI-resistant HIV. TMC114 and TMC125 are not available by prescription in Canada, but they may be available to you through clinical trials or expanded access programs. Because experimental drugs haven't been approved by Health Canada as being safe and effective, you'll need to read and sign an informed consent form before getting access to them.

The most important principle to remember is that new drugs should never be added one at a time to a failing regimen

### Multiple drug therapy

If experimental drugs are not an option for you, drug recycling might work. The idea is that two or three drugs which are partially effective (due to some degree of drug resistance) may equal one that's fully effective. This is because for some drugs, resistance is not an "all-or-nothing" thing. So a combination including drugs you've taken before, or drugs from the same class, may also work, especially if combined with a new drug such as T20. Unfortunately this may result in the need for very complicated, multiple-drug regimens, also known as Multiple Drug Rescue Therapy (MDRT), mega-HAART, or giga-HAART. These complex regimens may be quite effective in suppressing the viral load to undetectable levels, but are usually hard to take over long periods of time, particularly due to drug side effects. However, MDRT may be a temporary option while you're waiting for newer drugs to become available. The most important principle to remember is that new drugs should never be added one at a time to a failing regimen, because this will inevitably result in more resistance and further treatment failure.

## Why did treatment fail?

**Adherence:** Before you start salvage therapy, resolve issues that led to non-adherence

**Absorption:** Whether caused by GI problems or interactions between antiretrovirals and other drugs, herbal remedies or supplements, absorption problems need to be fixed before salvage therapy can work.

**Resistance:** The next choice of drug will aim to get around resistance your HIV has developed to one drug or class of drugs. Resistance tests may be needed to figure out what's most likely to work.





### Partially suppressive therapy

What if there are no new drugs available to you right now and you can't tolerate MDRT? Some people have had success with "minimal therapy", regimens with a few tolerable drugs that keep your viral load down a bit but do not suppress it completely. The reason that this works may be that it keeps drug-resistant viruses around, and those viruses are often less able to reproduce and multiply than wild-type (non-drug-resistant) HIV. Therefore your viral load stays relatively low. The danger of taking a partially suppressive regimen for a long time is that

susceptible to drugs, would come back, making the next treatment more effective. This strategy has been looked at in a number of large studies and unfortunately it doesn't work. This is because the drug-resistant viruses never really go away (they just decrease in number so that they're sometimes not picked up on standard resistance tests). Once treatment is restarted, they come back and the treatment fails. Even worse, during an STI your CD4 cell counts can drop to dangerous levels and AIDS-related infections are more likely to happen. So taking an STI before you start salvage therapy isn't currently recommended as a means of improving the response to treatment. However, if you need to take a drug holiday for other reasons, such as drug toxicities, this may be all right for a minority of patients as long as you get regular blood tests under your doctor's supervision.

Taking a strategic treatment interruption before you start salvage therapy isn't currently recommended as a means of improving the response to treatment

it may lead to more and more resistant virus. However, minimal therapy may work as a stop-gap measure to preserve your CD4 cell counts until newer and more effective treatments become available.

### Strategic treatment interruptions

A few years ago there was a lot of interest in strategic treatment interruptions (STIs), where you take a break from antiretroviral therapy after it fails in order to make the salvage therapy more effective. The theory was that during the time off therapy, the drug-resistant HIV would go away and the wild-type virus, which is more

### Hope for tomorrow

If you've been on a number of different antiretroviral combinations in the past and these have stopped working, you'll need to work with your doctor to figure out why those treatments failed and what you can do next. Even though your options may be limited, effective salvage treatments can usually be designed using T20 together with older drugs and new or experimental drugs. Chances are that salvage treatment will be a bit more complex than your earlier regimens and will require even more dedication from you. But keep in mind that researchers all over the world are busy trying to find new HIV drugs that will work after others fail. **R**

## Rescue treatment options

Fusion inhibitor T20: Prevents HIV from getting into your cells; must be injected under the skin; must be given with another active drug

Experimental PIs: The newly approved TPV and experimental TMC114 appear effective against HIV resistant to other PIs; available only through clinical trials or expanded access programs

Experimental NNRTIs: TMC125 works against NNRTI-resistant HIV; available only through clinical trials or expanded access programs

Partially suppressive or minimal regimens: Keep resistant HIV, which is weaker than wild-type HIV, around. May lead to more resistant virus in the long run

Treatment interruptions: Allow wild-type virus which will be more susceptible to drugs, to re-emerge while drug-resistant virus remains but may not show up on resistance testing. May cause dangerous drops in CD4 and greater likelihood of infections