

Rescue me

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What are the options when you're running out of options?

The word alone is unnerving enough. 'Salvage' conjures up images of desperation, a last-ditch attempt to make the best of a bad situation. But while it's true that 'salvage therapy' (also known, just as alarmingly, as 'rescue therapy') is a fact of life for people at the sharp end of HIV/AIDS, there's no real need for desperation.

While finding effective treatments for people with significant immune impairment and multiple drug resistance is far from straightforward, the prospects for success have never been better.

Salvage therapy can mean different things in different contexts, ranging from the last-ditch scenario the name suggests to devising second and third-line regimens in people with relatively good immune function and only limited drug resistance.

The reality is that the distinction between first-line therapy and salvage is not black and white, but instead they refer to different regions on the spectrum of treatment approaches. Because of this, many of the principles that guide salvage therapy also apply across that whole spectrum: choosing the best available treatments for the individual concerned, careful monitoring and attention to adherence, and support to help manage side effects and deal with other health issues.

There is also an important maxim here which bears repeating: the best way to ensure effective salvage is to do whatever is possible to avoid getting to the stage where salvage is necessary. For us, that means making the most of those first and second line regimens through rigorous adherence and monitoring; for the pharmaceutical industry it means developing better, less toxic, antiretrovirals which are less likely to lead to [resistant](#) [1]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. virus.

But regardless of how hard we try to make treatments work, people are still human and the treatments we have are still far from perfect. So some of us will have to deal with the scenario of multiple drug resistance and treatment failure, and salvage will continue to be necessary. When that happens, making the right treatment choices becomes more important — and more complex — than ever.

First things first

An important first step is to try to understand the reasons why previous treatments failed. Both you and your doctor will be better armed to make decisions if you understand the impact of things such as poor adherence, or low blood concentrations due to individual metabolic or dietary characteristics. This can be beneficial in developing a plan of attack for salvage.

If low blood concentrations are suspected, your doctor may want to investigate using therapeutic drug monitoring to ensure the dose of your new combination is right. If your adherence has been poor in the past, what will you do differently to ensure you get the best possible mileage from your new treatments? There may be support services you can access to assist in this.

A second important issue is defining the expectations you and your doctor have for your salvage regimen. While the 'standard' treatment goals — undetectable [viral load](#) [2]A measurement of the quantity of HIV RNA in the

blood. Viral load blood test results are expressed as the number of copies (of HIV) per milliliter of blood plasma, and increased CD4s — still apply, for people with multiple drug resistance these goals may be more difficult to achieve.

A small study conducted in 2000 demonstrated that the chances of getting to undetectable decline the more treatments you've taken.[1] After one year, 60 percent of people on their third regimen had undetectable viral load. For those on their fourth regimen, the rate was 36 percent. No-one in this study on their fifth or sixth regimen was undetectable after one year.

While the prospects of achieving undetectable viral load may be limited, there is substantial evidence that even modest reductions in viral load are helpful, and can lead to increased CD4 counts over time (see the December-January edition of PL).

Setting realistic, achievable goals at the outset, and focusing those goals on the most important issue — staying alive — is an important step. You don't have to abandon hope of getting to undetectable — a substantial minority of people with triple-class resistance have been able to do so, especially since the arrival of T-20 (of which more in a moment).

What are the odds?

By shifting the goalposts slightly from 'achieving undetectable viral load' to 'staying alive and as healthy as possible', the prospects of success are excellent.

A large Canadian study published in 2003 showed that people on salvage therapy have much the same medium-term prospects for survival as those who are starting treatment for the first time.[2] The investigators compared 341 people with multiple previous treatment failures who started mega-HAART [3] Highly Active Antiretroviral Therapy ??? aggressive treatment of HIV infection using several different drugs together. regimens (more on these below) with 1047 people starting HIV treatment for the first time.

The patients in the first group had all failed at least two HAART regimens and had taken, on average, seven different antiretrovirals before starting this study. More than one-third had developed resistance to all three major [4] A group of anti-HIV drugs with the same target of action. Anti-HIV drug classes include *nucleoside analogue reverse transcriptase inhibitors*, *protease inhibitors* and *non-nucleoside analogue reverse transcriptase inhibitors*, as well as several others. Combining drugs from three or more classes is the basis of Highly Active Antiretroviral Therapy (HAART)..

Treatments were chosen on the basis of the patient's previous history, preference and resistance test results, and the two groups were followed for up to three years. The investigators found that the rate of death was much the same for the two groups, despite the salvage group having somewhat lower CD4 counts and higher viral loads than the previously untreated group. Despite the fact that the salvage group were on an average of six antiretrovirals each, levels of adherence were good and side effects and toxicities were said to be manageable. The overall risk of death from HIV was only 1.17 times higher for those on salvage compared with those taking treatments for the first time.

Mega-HAART

The treatment strategy used in the Canadian study is called 'mega-HAART' or 'giga-HAART'. Mega-HAART regimens typically contain six, seven or more antiretrovirals taken together. It's a controversial approach, calling for an even greater commitment to treatment than is required for standard HAART, a much higher pill burden, and the likelihood of a wider range and increased severity of side effects.

Mega-HAART is far from ideal and not all [clinical](#) [5] Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. studies have had favourable results, however many clinicians are now prescribing these regimens to patients.

It's important to make a distinction between developing an effective mega-HAART strategy and simply adding more drugs to an already failing regimen. Clinicians need to be as careful as ever in selecting treatments which have the best chances of success and which are appropriate to be used in combination. This can be challenging

enough when designing a three-drug regimen; getting the right combination of six or more drugs is much more complex.

Recycling

A core guideline for effective anti-HIV treatment is to avoid reusing drugs which have been taken previously, or drugs which are cross-resistant to those taken before. But for people who have already taken several HAART combinations, this can prove difficult — while there numerous drugs now available, there are limited ways in which they can be combined to form a viable HAART regimen. For people looking at mega-HAART, there is even greater likelihood that at least some of the drugs in the combination will be recycled.

Although it's far from the ideal, there are two reasons why recycling might be an option.

Firstly, we know that drug-resistant virus tends to be less able to reproduce than non-drug-resistant virus. This means that when the drug which produced the resistance is withdrawn, the virus naturally reverts to 'wild type' over time. But some resistant virus always remains, and this means that even years after stopping a drug, resistance is often quick to re-emerge if that drug is used again.

Secondly, total drug resistance is rare — in most cases drugs remain at least partially effective against HIV. This is the argument behind mega-HAART: if the drugs are only likely to be partially effective, using more drugs in combination may help offset that loss of efficacy.

Unfortunately, there isn't a lot of hard data on the [effectiveness](#) [6](Of a drug or treatment). The maximum ability of a drug or treatment to produce a result regardless of dosage. A drug passes efficacy trials if it is effective at the dose tested and against the illness for which it is prescribed. In the standard procedure, Phase II clinical trials gauge efficacy, and Phase III trials confirm it. of recycling, but it may be an effective stop-gap measure until new treatments arrive.

Resistance testing

Resistance tests — blood tests which identify the medications your HIV has become resistant to — are still not routinely available in Australia, and are not funded (yet) by Medicare. But they are available through some hospitals, clinics and state health departments, and can be very useful when designing a salvage regimen.

The goal is to assemble a combination of drugs which have the best possible chances of success and the least likelihood of resistance, and resistance testing can provide a guide to which choices are most likely to work. But they aren't foolproof and, even without resistance testing, it's often possible to rule drugs in or out based on your own treatment history and the known patterns of cross resistance.

New drugs

Ideally, every new HIV treatment combination should use drugs (and drug classes) to which you've not previously been exposed.

In the past, clinicians sometimes added promising new drugs to existing regimens, especially if the patient was in danger of disease progression or if the new drug seemed especially promising. We now know this is not an ideal approach, as the risk of treatment failure — and the exhaustion of another promising new treatment option — is considerable.

Fortunately, the number of treatments available has increased substantially in recent years. Some key developments have been the arrival of T-20 and the emergence on the treatments horizon of tipranavir and TMC 114.

T-20 (enfuvirtide or Fuzeon) has been available on the [PBS](#) [7][Pharmaceutical Benefits Scheme] The federal government program which subsidises medication costs in Australia. Anti-HIV drugs are part of a special part of the PBS called Section 100 (S100) which is used for expensive, highly specialised drugs. since December. As the first approved HIV drug from an entirely new class for some years, T-20 has been a major step forward.

Much has been made of the inconvenience of T-20's twice-daily injections, but both research studies and clinical experience have demonstrated that many people are able to accommodate this drug into their lives, often with excellent clinical results. (For more information about T-20, see the October-November 2004 edition of PL.)

Another drug which promises to be a valuable option for salvage is the protease inhibitor **tipranavir**. It's not yet available on the PBS, but an emergency access program is in place for people who need it and meet eligibility criteria including having a CD4 count below 100. NAPWA is negotiating with the manufacturer to have the eligibility criteria widened.

Tipranavir's novel chemical structure means it remains effective against HIV which has become resistant to other drugs in the protease inhibitor class. The two major studies of tipranavir, RESIST-1 and RESIST-2, have both focused on its potential in heavily pre-treated people with multiple resistance, with good results.[3][4]

Another protease inhibitor which is being keenly anticipated for its promise as a key salvage drug is **TMC 114**. Like tipranavir, TMC 114 appears to be active against protease inhibitor-resistant virus.

In a study presented at the Retrovirus conference in February (see [John Daye's report](#) [8]), TMC 114 produced significant viral load reductions (averaging 1.85 logs) at the highest of three doses studied, and was even effective in five of 13 people in whom resistance testing had failed to identify any active antiretrovirals.[5]

A [phase 3](#) [9]A large clinical trial designed to establish whether a drug is effective and safe enough for widespread use. Phase III studies include expanded controlled and uncontrolled trials after preliminary evidence suggesting effectiveness of the drug has been obtained, and are intended to gather additional information to evaluate the overall benefit-risk relationship of the drug and provide an adequate basis for physician labeling. Study of TMC 114 is now underway in several countries, including Australia.

Life preserver

The name may carry unfortunate connotations, but our understanding of salvage therapy is more advanced than ever.

The basic rules of effective HIV treatment still apply: use multiple drugs from different classes in combination, avoid reusing previously-failed treatments, and pay careful attention to adherence and monitoring. Sometimes these rules need to be bent to adapt to the circumstances of salvage, however, through approaches such as mega-HAART and drug recycling, until newer, better, treatments come along.

References

¹ Fessell WJ et al. *Salvage therapy and formulation of highly active antiretroviral therapy*. Journal of AIDS 24(2):194-195, 2000

² Lee N et al. *Rates of Disease Progression among Human Immunodeficiency Virus-Infected Persons Initiating Multiple-Drug Rescue Therapy*. Journal of Infectious Diseases;188:137-141, 2003

³ Hicks C et al. *RESIST-1: a phase 3, randomized, controlled, [open label](#) [10]A clinical trial in which doctors and participants know which drug or vaccine is being administered., multicenter trial comparing tipranavir/ritonavir (TPV/r) to an optimized comparator protease inhibitor/r (CPI/r) regimen in antiretroviral ([ARV](#) [11]A medication or other substance which is active against retroviruses such as HIV.) experienced patients: 24 week data*. 44th Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, abstract H-1137a, 2004.

⁴ Cahn P et al. *24-week data from RESIST-2: phase 3 study of the efficacy and safety of either tipranavir/ritonavir (TPV/r) or an optimized ritonavir (RTV)-boosted standard-of-care (SOC) comparator PI (CPI) in a large randomized multicenter trial in treatment-experienced HIV+ patients*. Seventh International Congress on Drug Therapy in HIV Infection, Glasgow, abstract PL14.3, 2004.

⁵ Katlama C et al. *Efficacy of TMC114/r in 3-class experienced patients with limited treating options: 24-week*

planned interim analysis of 2 96-week multinational dose-finding trials. Twelfth Conference on Retroviruses and Opportunistic Infections, Boston, abstract 164LB, 2005.

- [adherence](#)
- [darunavir](#)
- [drug resistance](#)
- [enfuvirtide \(T-20\)](#)
- [HIV treatments](#)
- [resistance tests](#)
- [salvage therapy](#)
- [tipranavir](#)

Links:

- [1] <http://www.napwa.org.au/glossary/term/109>
- [2] <http://www.napwa.org.au/glossary/term/416>
- [3] <http://www.napwa.org.au/glossary/term/96>
- [4] <http://www.napwa.org.au/glossary/term/124>
- [5] <http://www.napwa.org.au/glossary/term/475>
- [6] <http://www.napwa.org.au/glossary/term/486>
- [7] <http://www.napwa.org.au/glossary/term/121>
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