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## ASHM 2006: Strategies for coping with multiple drug resistance

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Finding effective treatment options for people who have taken many treatments and have multiple resistance mutations continues to be a significant challenge for HIV clinicians, and their patients. At the 2006 [ASHM](#) [1] Australasian Society for HIV Medicine. The peak Australasian organisation representing the medical and health sector in HIV/AIDS and related areas. Conference, Alice Pau from the National Institutes of Health in the US presented a roundup of current thinking about how to deal with this troublesome situation<sup>1</sup>.

In recent years there has been a clear shift in direction in HIV drug development, away from developing first-line therapies and towards drugs for treatment-experienced patients. This makes sense as people with HIV live longer on treatment and second-line and [salvage](#) [2][salvage therapy] A treatment strategy for managing HIV in people who have developed resistance to existing therapies. regimens become more important, but Pau questioned whether the loss of emphasis on improved first-line therapies was helpful.

“For some reason the pharmaceutical companies are satisfied with [efficacy](#) [3](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. that is really less than desirable,” she said. In clinical trials, [antiretrovirals](#) [4]A medication or other substance which is active against retroviruses such as HIV. intended for first-line use are typically able to get [viral load](#) [5]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. down to undetectable in about 60-70 percent of patients after 48 weeks on treatment. “What about the others?” asked Pau. “Will they develop multiple drug resistance?” Clearly this is a problem which will be with us for some time.

Multiple drug resistance is fairly common – an American study published in 1998 found that 13 percent of patients with detectable viral loads had triple class resistance, meaning they were [resistant](#) [6]HIV which has mutated and is less susceptible to the effects of one or more anti-HIV drugs is said to be resistant. to at least one drug in each of the three main treatment classes<sup>2</sup>. Drug resistance is an issue for people who have never taken treatments, too: an Australian study (also presented at ASHM) found that in Victoria, 14 percent of newly-diagnosed people already had resistance to at least one drug, and 2.7 percent had multiple drug resistance at diagnosis<sup>3</sup>.

Multiple drug resistance can be a self-fulfilling process: people with resistant [virus](#) [7]A small infective organism which is incapable of reproducing outside a host cell. are likely to have detectable virus, and this in turn leads to the development of new resistance mutations, which blunt the response to treatment, increase the viral load and so on. The end-point of such a scenario is disease progression and the evolution of a very difficult-to-treat virus in that individual – a nightmare scenario.

### Constructing a viable treatment regimen

Pau says the first step should be identifying the drugs to which you're resistant. This can be done by looking at your treatment history, and increasingly through resistance testing. The availability of resistance testing in Australia varies (it's not covered by Medicare) and so the use of these tests depends on local funding and they are far from routine.

Once your doctor has a picture of which drugs you're resistant to, the next step is to try to put together an 'optimised background regimen' of at least two existing drugs, before deciding whether to add any of the newer therapies.

The fusion inhibitor **T-20** (enfuvirtide, Fuzeon) is one option that should be considered. T-20 is available on the [PBS](#) [8][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. and has proven a powerful tool, producing sustained reductions in viral load

and CD4 count increases. Much has been made of T-20's inconvenient administration (self-injection twice daily) but in practice most people find they are able to manage the drug's routine. T-20 appears to have a synergistic effect with tipranavir, darunavir and integrase inhibitors, Pau said.

The newest protease inhibitors, **tipranavir** (Aptivus) and **darunavir** (Prezista), are available in Australia under special access schemes. Both of these drugs have been developed with resistant virus in mind, and have been the subject of extensive [clinical](#) [9] Pertaining to or founded on observation and treatment of participants, as distinguished from theoretical or basic science. trials in pre-treated patients.

Tipranavir has been around a bit longer than darunavir, and has been used in a larger number of patients worldwide. Pau noted some of the factors associated with a better response to tipranavir, including lower viral load at the time treatment is started, and co-administration with T-20.

Side effects have become a significant concern with tipranavir, and may be more serious than those experienced by people taking darunavir. [Liver](#) [10] A large organ, located in the upper right abdomen, which assists in digestion by metabolising carbohydrates, fats and proteins, stores vitamins and minerals, produces amino acids, bile and cholesterol, and removes toxins from the blood. toxicity and serious bleeding in the brain have both been associated with this drug.

Darunavir is designed to be effective against HIV with resistance to other PIs, but Pau said "not all patients will respond to darunavir, and resistance can develop." Darunavir and tipranavir do have a limited amount of cross-resistance.

The newest non-[nucleoside drug](#) [11] A type of anti-HIV drug that works by inhibiting a stage of the HIV life cycle called reverse transcription. Non-nucleosides work in a similar way, but are chemically different., **etravirine**, is also a new possibility for people with limited options. It remains active against viral strains which have become resistant to the other non-nucleosides, and in clinical trials about one-third of heavily pre-treated patients had a significant viral load response.

Coming from a whole new class, **MK-0518** is the first integrase inhibitor to be available outside clinical trials. It has performed extremely well in clinical trials, with about 80 percent of patients achieving substantial viral load reductions.

You can read more about etravirine and MK-0518 on page 7 of this issue of PL.

Looking further into the future, another new group of drugs which could expand the options for those with multi-drug resistance are the CCR5 antagonists, **vicriviroc** and **maraviroc**. While there are questions about whether these drugs will be suitable for everybody, they show promise. An [expanded access](#) [12] Before a drug has been approved, manufacturers often provide the drug free of charge to people who cannot participate in a clinical trial and who meet certain criteria under a Special Access Scheme (SAS). program for maraviroc has been announced in Europe, but these drugs are not yet available in Australia except in clinical trials.

In summary, Pau said the number of options available for treating people with multiple drug resistance is improving. "Maximal viral suppression [undetectable viral load] may be possible in some patients," she said, but the durability of this is unknown. We don't know enough about the possible development of resistance in the future, and we need better, more "user-friendly" regimens.

In the meantime, she said, avoiding the development of multi-class resistance remains the best approach: "Adherence is the key."

<sup>1</sup> Pau A, 2006. "Challenges in Management of Treatment-Experienced virologically non-suppressed patients with multiple [HIV-1](#) [13] One of two distinct HIV species, HIV-1 is the predominant type in Australia and around the world.

<sup>2</sup> Richman D et al, 2004. "The prevalence of antiretroviral drug resistance in the United States". AIDS 18:1393-1401.

<sup>3</sup> Morris J et al, 2006. "Transmitted Antiretroviral Drug Resistance: A 10-year Analysis of Victorian Patients from 1996 to 2005". ASHM 2006.

- [adherence](#)
- [darunavir](#)
- [drug resistance](#)
- [enfuvirtide \(T-20\)](#)
- [etravirine \(TMC-125\)](#)
- [maraviroc](#)
- [salvage therapy](#)
- [tipranavir](#)
- [vicriviroc](#)

**Links:**

- [1] <http://www.napwa.org.au/glossary/term/382>
- [2] <http://www.napwa.org.au/glossary/term/111>
- [3] <http://www.napwa.org.au/glossary/term/486>
- [4] <http://www.napwa.org.au/glossary/term/122>
- [5] <http://www.napwa.org.au/glossary/term/416>
- [6] <http://www.napwa.org.au/glossary/term/109>
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