Hope for the treatment-experienced

New meds allow better combos for multi-drug-resistant HIV

By Dr. Ken Kasper

The goal of HIV treatment is to reduce the viral load to undetectable levels (less than 50 copies per mL). In 2007, this goal is becoming a reality for more people with HIV thanks to two entirely new classes of drug (integrase inhibitors and CCR5 inhibitors) as well as drugs designed specifically for multi-drug-resistant HIV like tipranavir (Aptivus®), darunavir (Prezista®) and TMC-125 (etravirine).

Most people achieve undetectable viral loads on their first treatment combination. However, if HIV is already resistant to certain antiretroviral drugs (ARVs) when you contract it, or if it develops resistance to one of the drugs in your starting regimen over time, your viral load can increase and your CD4 cell count can decline, putting you at risk for opportunistic infections. At this stage, your doctor will suggest a change in one or more of the drugs you're taking in hopes of once again achieving an undetectable viral load and restoring or preserving your immune system.

Challenges in salvage therapy

"Salvage therapy" or "rescue therapy" are terms used to describe the stage in treatment when previous drug combinations have failed to work and your virus has developed resistance mutations to at least one drug in each of the three main drug classes: protease inhibitors (PI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and nucleoside reverse transcriptase inhibitors (NRTI). As these mutations accumulate, it becomes more difficult to design a treatment regimen that will be well tolerated and bring viral load back down to undetectable levels.

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For a regimen to be successful, it should include at least two fully effective drugs. They must either come from a new class of medications that your virus hasn't seen before (e.g. T-20 [enfuvirtide, Fuzeon®] or integrase inhibitors) or be more potent, newer drugs that can overcome the resistance your virus has developed to other drugs in the same class (e.g. darunavir or tipranavir).

Running out of acceptable options has been a significant fear for people living with HIV. The new drugs and drug classes coming to the Canadian market will help to overcome some of the challenges posed by drug resistance.

New HIV drugs

Class	Drug
Protease inhibitors	Tipranavir (Aptivus®) Darunavir (Prezista®)
NNRTIs	TMC-125 (etravirine)
Integrase inhibitors	MK-0518 (raltegravir)
CCR5 inhibitors	maraviroc

Switch only when necessary

Newer drugs have distinct advantages for treating resistant HIV, but if your current regimen is still working, switching is not recommended. These new medications may not be effective in everyone and may have long-term side effects that have not yet become apparent. For example, when D4T (stavudine, Zerit®) came to market, it caused much excitement for its ability to control the HIV virus, but its role in lipoatrophy only became clear much later. Some drugs may not live up to their initial potential. The new drugs available this year appear safe and potent but we don't yet have the long-term data that's available for current regimens.

New drugs in existing classes

Some of the drugs now available for resistant HIV are new additions to existing drug classes.

Protease inhibitors (PIs)

Two new PIs have hit the Canadian market in the past two years: tipranavir (Aptivus®) and darunavir (Prezista®). Both need to be taken with ritonavir (Norvir®) in order to achieve effective levels of the medication in the blood. Darunavir is the most recent and its Expanded Access program is just winding down as it comes to market. The main clinical trial testing darunavir's efficacy, the POWER trial, involved people with multi-drug-resistant HIV taking darunavir alongside the best available background drug combination. Approximately 40% of study participants who received darunavir achieved an undetectable viral load. Tipranavir showed similar efficacy in the RESIST trial. Both sets of trials found that the more fully active drugs people had in their background regimen, the better the chance of success with these new PIs.

The choice between tipranavir and darunavir in salvage therapy is based on a number of individual factors. The presence of specific resistance mutations may make one or the other a better choice. Doctors may prefer darunavir because it's less likely to increase bad cholesterol levels and may have fewer liver side effects. People who don't tolerate darunavir, or develop resistance to it, may still find tipranavir effective.

A number of patients (30%) taking these drugs in studies had acquired enough protease inhibitor mutations to prevent them from achieving undetectable viral loads with the new PIs, even with the best optimized background treatment (other drugs chosen for the best chances of success). It's possible, though, that combining the new PIs with the new classes of ARV described on page 6 will provide enough fully active agents to enable them to achieve undetectable viral loads.

The new NNRTI: TMC-125 (etravirine)

In the past, when your HIV developed resistance to a NNRTI-based regimen (e.g. efavirenz [Sustiva®], nevirapine [Viramune®]), it generally ruled out the entire class of medications for salvage therapy. TMC-125 was developed to provide a NNRTI option that remains effective even after some class resistance develops. It's currently available through Expanded Access programs in Canada, is given in doses of two pills twice a day and requires food for best absorption.

TMC-125 can generally be considered one of the two "fully active" agents needed to make salvage therapy successful, but the presence of mutations to NNRTIs reduces its effect: the more mutations your virus has accumulated from previous NNRTI-based regimens, the less effective TMC-125 will be.

The effectiveness of combining TMC-125 and darunavir is being studied in the DUET trial, for which results will be available soon. Tipranavir and TMC-125 cannot be combined because of an unfavourable drug interaction.

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Classes of 2007

Two exciting new classes of medication will also be available through Expanded Access in Canada in 2007. These will offer even more new options for creating salvage therapy regimens as they offer people a type of medication that their HIV hasn't seen before.

With the addition of new medications, 2007 promises more options for people with multi-drug-resistant HIV

Integrase inhibitors

The integrase inhibitor that will probably come to market first is MK-0518 (raltegravir). At the recent HIV conference in Los Angeles, data from two clinical trials known as BENCHMARK showed that adding 400 mg of raltegravir twice a day to an optimized background regimen allowed up to 60% of patients with triple class-resistant HIV to achieve undetectable viral loads at 16 weeks. The integrase inhibitor was very well tolerated and no major laboratory abnormalities were noted.

CCR5 inhibitors

The CCR5 inhibitor maraviroc was studied in two trials called MOTIVATE 1 and 2, and results were also presented in Los Angeles this year. Added to an optimized background regimen, maraviroc allowed up to 50% of triple class-experienced patients to reach an undetectable viral load. The hitch with this medication is that patients need to have a "tropism" assay done first to be sure that their virus uses the CCR5 receptor (see In Brief: Why CCR5s won't work for everyone, p. 7). If it doesn't, the drug won't be effective. In the MOTIVATE trial, 45% of those screened for the CCR5 inhibitor didn't use this receptor exclusively and were unlikely to achieve significant viral load suppression.

Experience treatment success

With the addition of the medications mentioned above, 2007 promises more options in developing optimized treatment regimens for people with multi-drug-resistant HIV. As a result, many more treatment-experienced people will achieve the goal of a viral load less than 50 copies/mL. The new drugs may not work for all patients and you certainly need to discuss your medication history and history of side effects carefully with your doctor to help you make the right choices.

If your current salvage regimen has reduced your viral load to less than 50 copies/mL and you're tolerating your medications well, you should probably continue on this regimen: if it fails in the future, you can be sure that other options will be available.

If you're on a salvage regimen and have reached an undetectable viral load but aren't tolerating the medications well, then switching to one of the newer agents may be a possibility for you. The risk of changing a working regimen is that the next one may not work as well or may produce different side effects.

It's an exciting year for HIV management as these new agents become available in Canada. But as always, it will take a few more years of observation in clinical use and data accumulation to know where they will fit into future guidelines.

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