

State of the art

HIV therapy in 2006

by Dr. Alex Klein



It's gratifying to see the large and growing array of treatment options now available for HIV. Equally important are the efforts to design and continually update treatment guidelines to incorporate newer agents and seek to maximize the benefits and minimize the risks associated with all HIV drugs. We can now look forward to drug regimens that are easier to take, have fewer side effects and provide increasing options for those who have developed resistance.

Treatment approaches are changing to respond to three distinct but interrelated challenges:

- **Treatment simplification:** This has been a goal for some time and in recent years we've seen progressive reductions in both the number of pills and number of daily doses. For one regimen, we have now reached the "holy grail" of treatment with one pill a day, though this simplest regimen will only be appropriate for a limited number of individuals.
- **Toxicities (side effects):** Improved understanding of the potential toxicities of HIV medications has resulted in the use of "safer" medications wherever possible. With life expectancy now much longer, it's essential that the drugs can be taken safely for many years. Long-term follow-up of medication effectiveness and side effects is now the norm. With a greater number of options available, it's increasingly possible to avoid using more potentially toxic drugs.
- **Resistance:** New medications, which are powerful enough to overcome even highly resistant viruses, offer hope to individuals previously deemed to have run out of options.

(tenofovir + FTC®). These foundation combos offer excellent side-effect profiles with one-pill convenience. A genetic test can now predict hypersensitivity (allergy) to abacavir, which is the main side effect of this drug*. A third agent from either the non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) class completes the regimen, and many are now available in once-daily doses of between one and three pills.

New studies have demonstrated that the PI and NNRTI classes offer equal viral load suppression and recovery of CD4 cells. PIs had slightly higher failure rates in some studies due to their

*The test is available through the manufacturer of abacavir, GlaxoSmithKline, in Vancouver, Toronto and Montreal.

Starting regimens

For patients taking therapy for the first time, there are now a variety of possible regimens. The backbone of a starting regimen has long included the nucleoside reverse transcriptase inhibitors (NRTIs) d4T and AZT, which produce fat wasting (lipoatrophy), as well as other problems, in a number of people. Now, the preferred NRTIs are abacavir and tenofovir, which are both available coformulated with either 3TC® or its class cousin FTC® in the once-daily pills Kivexa® (abacavir + 3TC) or Truvada®

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STARTING TREATMENT

ANTIRETROVIRALS SHOULD BE STARTED WITH:

- Any history of AIDS-defining illness
- HIV symptoms
- Less than 200 CD4 T cells/ μ L
- Less than 350 CD4 T cells/ μ L if recommended by physician

DRUG RESISTANCE (GENOTYPE) TESTING SHOULD TAKE PLACE BEFORE STARTING TREATMENT: YOU CAN BE INFECTED WITH VIRUS THAT IS ALREADY RESISTANT TO DRUGS YOU HAVE NEVER TAKEN.

First-time combos* PREFERRED COMBOS

	ANTIRETROVIRALS	NUMBER OF PILLS/DAY
1 NNRTI +	efavirenz (Sustiva®) +	2-3
2 NRTIs	lamivudine (3TC®) or emtricitabine (FTC®) + zidovudine (AZT) or tenofovir (Viread®)	
1-2 PIs +	lopinavir/ritonavir (Kaletra®) +	6-7
2 NRTIs	lamivudine (3TC®) or emtricitabine (FTC®) + zidovudine (AZT) or tenofovir (Viread®)	

*As per US Department of Health and Human Services (DHHS) guidelines, May 2006

side effects, but these should be much less of a problem with reformulated PIs that have fewer effects on lipids (increasing fats such as cholesterol in the blood) and the gastrointestinal system (e.g. nausea, diarrhea) as well as fewer pills and convenient dosing. The main drawback with the NNRTI class is the higher risk of viral load rebound and virologic failure when doses are missed. If you're likely to be less than perfect with pill-taking, you might want to discuss with your doctor if this is the best option for you.

First-line regimens can and should remain effective for a long time. The biggest threat to their effectiveness is the acquisition of drug-resistant HIV strains at the time of initial infection or, occasionally, by superinfection. Infection with a resistant bug will limit your treatment options. Resistance is present in 10-14% of new infections in Europe and America and at least 7% in Canada. It's most significant for NNRTI medications where one mutation currently eliminates the entire class. Because of this, it's now standard to have genotype (resistance) testing done before starting treatment to ensure the right drugs are selected.

Second-line regimens

Second-line treatments are rarely as easy as first-line, but have become reasonably simple, with several pills twice daily now the norm. The exact regimen will be chosen according to what caused the failure and the results of a genotype test. But a caution: the fact that your regimen has only failed once doesn't guarantee an easy second round. Bad resistance to all agents in the initial trio of meds could potentially eliminate two classes of drugs. What's most important is to detect virologic failure early: this can prevent resistance development to preserve the widest possible range of options.

As the number of available replacement agents expands, the trend is to take people off failing regimens more quickly.

More options, later

The biggest developments this year were the new options available to those whose regimens have failed more than once. Tipranavir and then darunavir were added to the list of approved PIs. These agents along with Fuzeon® (enfuvirtide or T20, the first member of a 4th drug class: fusion inhibitors) offer the possibility of optimal response — an undetectable viral load and rising CD4 cell count, though Fuzeon® requires injections (which can now be needle-less) twice a day. Pill burden remains low, with side effects generally comparable to earlier second-line regimens. For many, the newest regimens are dramatically easier, with far fewer pills, toxicities and side effects than previous “salvage” strategies.

Waiting in the wings

Clinical trials are very advanced for TMC 125 (etravirine) and it will be available on a compassionate basis very soon. This is the first of a second generation in the NNRTI class and can overcome the known resistance mutations to this class. More of these second-generation NNRTIs are in development.

Two entirely new classes of drugs are also waiting in the wings: the entry inhibitor maraviroc blocks CCR5 receptors, which are used by viruses to gain entry into CD4 cells and are most often seen in less advanced disease. Maraviroc will likely be used as an alternative first-line agent but its optimal position in the treatment sequence has yet to be established.

The big star on the horizon is the now rapidly emerging class of integrase inhibitors. After more than a decade spent pursuing such agents, several (each with different mechanisms of action) are at varying stages of development. Recent clinical trials data on the first of these compounds, MK 0518, was presented at the 16th International AIDS Conference in Toronto. Results look comparable to gold-standard treatment with a faster rate of viral load decline. No serious side effects have emerged. Unlike the entry inhibitors, these agents will be active against all virus types and will likely be used initially against drug-resistant viruses.

Earlier start to treatment

As safety and tolerability of treatment regimens improve, we'll likely see a gradual shift back to starting therapy earlier. Two important benefits of this strategy are the potential for more complete recovery of the immune system (not just the CD4 cells) and the possibility of reducing new infections by decreasing the infectivity of people with HIV. Studies have confirmed both of these outcomes.

There's no cure yet, and vaccines still look a decade away, but overall, the landscape's optimistic for reaching a stalemate with the virus. **R**

EASIER DOSING



NEW FORMULATIONS

atazanavir (Reyataz®) + ritonavir
lopinavir/ritonavir (Kaletra tablet®)

DOSE

Once-daily dosing (3 pills)
No food restrictions/
no refrigeration
(4 pills once daily
or 2 pills twice daily)

CO-FORMULATED NRTI COMBINATIONS

zidovudine/lamivudine (AZT/3TC®)	Combivir®
abacavir/lamivudine (Ziagen®/3TC®)	Kivexa®
tenofovir/emtricitabine (Viread®/FTC®)†	Truvada®
zidovudine/lamivudine/abacavir (AZT/3TC®/Ziagen®)	Trizivir®

CO-FORMULATED MULTI-CLASS COMBINATIONS

Efavirenz/tenofovir/emtricitabine (efavirenz/tenofovir/FTC®)†	Atripla®
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†not yet available in Canada