

# New approaches to antiretroviral therapy

Looking back at a decade of progress

By Dr. Marianne Harris



The year 1996 marked the beginning of the highly active antiretroviral therapy (HAART) era, where three-drug combinations became the standard for HIV treatment. A decade of using, testing and improving the drugs used in these combinations has led to regimens that are more effective and easier to take. Here, we'll look back at what we've learned and what's changed in the past 10 years.

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## What drugs were used in 1996?

The nucleosides (NRTIs) available in 1996 were AZT, ddC, ddI, d4T, and 3TC. The only protease inhibitors (PIs) at that time were saquinavir, indinavir, and zalcitabine. In 1997, a fourth PI, nelfinavir, appeared. The third class of drugs, non-nucleoside reverse transcriptase inhibitors (NNRTIs), didn't

become available until 1998; of these, delavirdine was the first to be approved in Canada, followed later by nevirapine and efavirenz.

So 10 years ago, common starting regimens involved taking 10 to 20 pills a day, in two or three separate doses. (See the sidebar on pages 5 and 6 for a complete listing of approved antiretroviral

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drugs). Some drugs, notably ddI and indinavir, had to be taken on an empty stomach, and indinavir users required an additional 1.5 litres of water/day to prevent **kidney stones**. Common side effects included nausea and vomiting (common with AZT, ddI and PIs), diarrhea (common with AZT, ddI and PIs, especially nelfinavir), and peripheral neuropathy (common with d4T, ddC and ddI). It's little wonder that people found it difficult to stay on these regimens for any length of time.

### Improvements over the decade

A number of advances over the years have led to more streamlined, and at the same time, more effective, treatment regimens.

### Ritonavir boosting

The PI ritonavir was difficult to tolerate. At the required doses of 600 mg twice daily, the drug tasted bad and caused many side effects, including numbness around the mouth and nausea, vomiting and diarrhea. However, it was discovered that small doses of ritonavir, usually 100 mg, slowed down the metabolism of other PIs, allowing the second PI to reach higher levels in the blood and stay at effective levels in the body for a longer time. The practice of combining ritonavir with another PI is called "ritonavir boosting." In these regimens, ritonavir is not used for its own antiviral effect but rather to boost the levels of the second PI. This allows you take a lower dose of the second PI, hence fewer pills and fewer doses per day. Most modern PIs are used with ritonavir boosting, allowing them to be taken once daily as part of a first-line HAART regimen. (These include atazanavir, fosamprenavir and lopinavir [co-formulated with ritonavir as Kaletra®]).

### Once-daily dosing

Another important discovery was that some NRTIs could be taken once a day without losing their effectiveness. NRTIs that were originally prescribed twice daily, and have been shown to work just as well taken once a day, include ddI, 3TC, and abacavir. The newest drugs in this class, tenofovir and FTC, are also used once daily. So now you can have a two-drug NRTI regimen, such as abacavir/3TC or tenofovir/FTC, that only needs

to be taken once a day. Some NRTIs, such as AZT and d4T, still need to be taken twice a day.

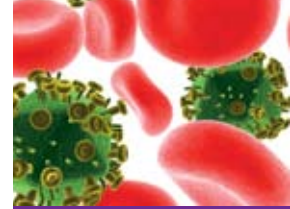
### Fixed-dose combinations

These formulations combine two or more anti-retroviral (ARV) drugs in the same pill. The main advantage is that you have to take fewer pills to get the same amount of medication. For example, instead of taking one capsule of AZT and one tablet of 3TC twice a day, you can take one Combivir® pill twice a day, which contains the same total amount of AZT and 3TC. Kaletra® contains lopinavir and ritonavir, so you don't have to take ritonavir separately. The most commonly used NRTI fixed-dose combinations are Truvada® (tenofovir + FTC) and Kivexa® (abacavir + 3TC), which both provide a one-pill, once-a-day NRTI "backbone."

There are presently two combinations which contain full doses of three ARV drugs. Trizivir® contains the NRTIs AZT, 3TC, and abacavir, and for a while was used as a simple first-line regimen (one pill twice daily). However, this all-NRTI regimen was found to be less effective than treatments containing two NRTIs plus either a PI or an NNRTI, so Trizivir® is now seldom used alone as a first-line treatment. The newest three-drug combination is Atripla™, containing tenofovir, FTC and efavirenz. This allows an effective combination of two NRTIs and an NNRTI in a single tablet that can be given once daily. While this treatment may not be appropriate for everyone, it represents a significant advance from the days when a first treatment for HIV meant taking 10–20 pills per day on a two- or three-times-a-day schedule.

### Improved side effect profiles

Decreasing the number of pills and the number of daily doses has doubtless made a big impact, but the greatest improvement in quality of life for people on HIV treatment has come from the improved side effect profiles of newer agents. Once researchers and drug companies identified agents with potent anti-HIV effects and were able to combine them in effective three-drug regimens, they started to develop drugs based not only on their potency but also their side effect profile.







## Antiretrovirals approved in Canada up to 2008

In chronological order of approval within each class





### NRTIs

- zidovudine (ZDV, AZT) Retrovir® 
- didanosine (ddI) Videx®, Videx EC® 
- zalcitabine (ddC) Hivid® (no longer available) 
- stavudine (d4T) Zerit® 
- lamivudine (3TC) 3TC® 
- abacavir (ABC) Ziagen® 
- tenofovir (TDF) Viread® 
- emtricitabine (FTC) Emtriva® 

### NNRTIs

- delavirdine (DLV) Rescriptor® 
- nevirapine (NVP) Viramune® 
- efavirenz (EFV, EFZ) Sustiva® 
- etravirine (TMC125, ETV) Intelence™ 

### PIs

- saquinavir (SQV) Invirase®, Fortovase® 
- ritonavir (RTV) Norvir® 
- indinavir (IDV) Crixivan® 
- nelfinavir (NFV) Viracept® 



## PIs cont'd

amprenavir (APV)  
Agenerase  
(no longer available)



lopinavir/ritonavir (LPV/r)  
Kaletra®



atazanavir (ATZ)  
Reyataz®



fosamprenavir (FPV)  
Telzir®



tipranavir (TPV)  
Aptivus®



darunavir (TMC114, DRV)  
Prezista®



## Entry inhibitors

enfuvirtide (T20)  
Fuzeon®



maraviroc (MVC)  
Celsentri™



## Integrase inhibitors

raltegravir (RAL)  
Isentress™



## Fixed-dose formulations

AZT/3TC  
Combivir®



AZT/3TC/ABC  
Trizivir®



ABC/3TC  
Kivexa®



TDF/FTC  
Truvada®



TDF/FTC/EFV  
Atripla™



These efforts were encouraged by the realization, in the last 10 years, that the effectiveness of treatment depended on very strict adherence to ARV therapy. People who experience unpleasant side effects from their drugs are less likely to take them perfectly on schedule, and are more likely to develop **viral rebound** (when the viral load in the blood becomes detectable again after being undetectable), and drug resistance (when HIV becomes less sus-

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ceptible to antiretroviral drugs). So the most effective regimens are the ones that cause the fewest side effects. Also, since HAART is more effective than previous single- and double-drug treatments, people with HIV are living longer and need to worry about long-term side effects from their drugs. Issues like lipodystrophy (fat redistribution) and risk of heart disease become more important.

The older NRTIs such as AZT and d4T had significant side effects such as fatigue, nausea, headache (for AZT) and peripheral neuropathy (for d4T). They have also recently been shown, particularly d4T, to be major contributors to lipoatrophy (fat loss). The NRTIs commonly used today, Kivexa® (abacavir/3TC) and Truvada® (tenofovir/FTC) are usually better tolerated and don't seem to cause fat loss. In fact, in one study, switching from an AZT- or d4T-based regimen to one that includes abacavir or tenofovir, halted and even reversed fat loss.

The earliest PIs (indinavir, saquinavir, ritonavir, and nelfinavir) commonly caused serious problems with the gastrointestinal (GI) system, including nausea, vomiting and diarrhea, as well as other side effects. Indinavir and ritonavir in particular were important causes of lipodystrophy, especially the gain in abdominal fat (hence the term "Crix belly," for the trade name of indinavir which is Crixivan®). Some PIs were also found to cause increases in cholesterol and triglycerides, factors associated with an increased risk of heart attacks and strokes. Researchers and drug companies now study new drugs very closely during clinical trials for their effect on lipids. The PI atazanavir, which is often used today in first-line therapy, doesn't cause GI problems for most people and doesn't increase the cholesterol and triglycerides as much as most

other PIs. We don't yet know whether this will translate into a lower occurrence of heart disease.

## Better results

Advances in the last decade have simplified first-line treatments for HIV. Newer agents and combinations are often easier to take, not only because they involve fewer pills but also because they produce fewer side effects. The enhanced adherence has translated into real benefits in

effectiveness. In British Columbia in 2000, 65% of people on ARV drugs had a viral load <50 copies/mL, the target for effective ARV therapy. This has increased steadily over the years, so that in 2007 the proportion of treated people reaching this target was 86%. This clearly shows that simpler and more tolerable ARV regimens are easier to take over the long term and translate into more effective treatment for HIV. **R**

