AIDS: Where Are We Now?

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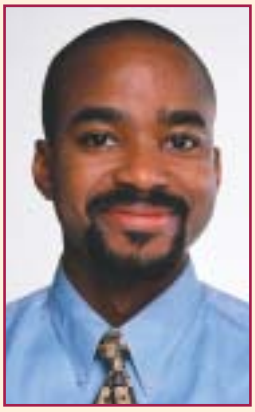
When the AIDS epidemic emerged at the beginning of the 80s, it was the number one cause of death among people aged 20 to 40 until the mid-1990s. Highly active antiretroviral therapy (HAART) has significantly improved HIV-related mortality and morbidity since its introduction in 1996. Prophylaxis guidelines against opportunistic infections were modified since HAART's success, however, limitations of anti-HIV drugs have since emerged, relating to:

- drug-specific resistance,
- toxic side-effects,
- drug interactions, and
- high pill burden.

Moreover, increases in CD4 levels do not always represent a complete reconstitution of immunity and are sometimes accompanied by an inflammatory syndrome known as immune reconstitution syndrome.

Markus' Cocktail



Markus, 40, first presented in 1991 with *Pneumocystis carinii* pneumonia (PCP), associated with the diagnosis of HIV infection. The CD4 cell count was 10/mm^3. The patient was treated with cotrimoxazole and responded; this same therapy was continued as prophylaxis for PCP. He also initially received zidovudine (ZDV), 500 mg/day, followed by didanosine (ddI), 500 mg/day. In addition, prophylaxis was prescribed for Mycobacterium avium complex (MAC).

In January 1996, Markus complained about blurred vision. A subsequent fundoscopy revealed signs consistent with *Cytomegalovirus* (CMV) retinitis. The patient was treated by gancyclovir intravenous (IV), followed by maintenance therapy.

In February 1996, Markus began antiretroviral therapy, which included ZDV, lamivudine, and indinavir. The number of CD4 cells gradually rose to 200/mm^3 and the viral load (VL) went down to an undetectable limit.

Two years after starting this regimen, when the CD4 level was 300/mm^3, all maintenance and prophylaxis therapies were stopped.

By 2001, VL increased to 7,000 copies/mL and the CD4 count diminished to 200 /mm^3. Antiretroviral therapy was changed based on viral resistance testing to amprenavir boosted by ritonavir, abacavir and ddI. The CD4 count then increased to 400/mm^3 and VL again diminished to undetectable levels.

Antiretroviral therapy

Since the introduction of antiretroviral therapy (ART), modifications have been made based on time of initiation, the type of regimen to be used, and strategy taken after the initial failure of therapy. These modifications are related to the occurrence of drug resistance, drug toxicity, the advent of new drugs, and new laboratory assays to monitor outcome. There are currently 19 anti-

Table 1

Currently available antiretroviral drugs

NRTIs	NNRTIs	PIs	HIV-entry inhibitor
Zidovudine (ZDV	Efavirenz (EFV)	Indinavir (IDV)	Enfuvirtide (T-20)
Stavudine (d4T)	Nevirapine (NVP)	Ritonavir (RTV)	
Didanosine (ddI)	Delavirdine (DLV)	Saquinavir (SQV)	
Zalcitabine (ddC)		Nelfinavir (NFV)	
Abacavir (ABC)		Amprenavir (APV)	
Lamivudine (3TC)		Atazanavir (ATV)*	
Emtricitabine (FTC)*		Lopinavir/Ritonavir (LPV/RTV)	
Tenofovir** (TDF)			

* Soon to be approved in Canada
** Nucleotide analogue

NRTI: Nucleoside reverse transcriptase inhibitor
NNRTI: Non-nucleoside reverse transcriptase inhibitor
PI: Protease inhibitor

retroviral drugs approved, or soon to be approved, in Canada for treatment of HIV infection (Table 1).

What's the first step?

The decision of when to initiate ART is guided by clinical and laboratory factors. While symptomatic patients, or those with CD4 count of < 200/mm^3, should be started on HAART (which must include at least three drugs), the optimal time at which to initiate therapy in asymptomatic patients is less obvious. Therefore, in these cases, a recommendation for therapy must be balanced by the readiness of the patient for treatment, a consideration of the prognosis for disease-free survival, and an assessment of the risks and potential benefits associated with initiating ART. Observational studies have found the risk of progression in the absence of ART is increased. Therefore, different approaches, both aggressive and less aggressive, may be considered in asymptomatic patients with CD4 counts above 200/mm^3.

How do I start?

Recommended antiretroviral regimens for first-line therapy include non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI)-based regimens, combined with a small amount of ritonavir (RTV) that acts to boost plasma levels of PIs.

Once-daily therapy is considered to be important for patient convenience and adherence. The following drugs are approved by the U.S. Food and Drug Administration (FDA) for once daily use:

- efavirenz (EFV),
- didanosine (ddI),
- tenofovir (TDF),
- lamivudine (3TC),
- stavudine (extended release),
- emtricitabine (FTC),
- atazanavir, and
- amprenavir/ritonavir (APV/RTV).

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Table 2

Three types of treatment failure

- **Virologic failure:** Incomplete viral response (not achieving VL < 400 copies/mL by 24 weeks or < 50 copies/mL by 48 weeks in treatment-naïve patients initiating ART).
- **Immunologic failure:** An increase of < 25 to 50 cells/mm^3 above the baseline CD4 cell count after the first year of therapy, or a decline to below the base line CD4 cell count while on therapy.
- **Clinical failure:** An HIV-related event after at least 3 months on ART, excluding the occurrence of immune reconstitution syndrome.

VL: Viral load
ART: Antiretroviral therapy

Treatment failure

Treatment failure may be related to virologic, immunologic, and/or clinical failure (Table 2).

After excluding adherence, tolerance, and drug interactions, therapy should be modified according to the history of ART and viral resistance testing (performed while the patient is still on the failing regimen). For patients with limited prior treatment, the goal is to re-suppress the viral load (VL) to an undetectable limit by changing the entire regimen or one or two drugs, based on the results of resistance testing.

For patients with extensive prior treatment, viral suppression is usually difficult to achieve. The goal for such patients is to preserve the level of CD4 cells and to prevent clinical progression. In patients with CD4 > 200/mm^3, and in whom therapeutic options are limited, it may be appropriate to observe the patient while on the same regimen.

However, a change in therapy is critical in patients with CD4 < 200 mm^3. Two recent controlled trials have shown the benefit of adding enfuvirtide, a new drug that prevents the entry of HIV-1 into target cells, in patients who failed ART.[1,2] All patients in both studies were treated with a regimen chosen on the basis of their treatment history and viral-resistance patterns. At 24 weeks, patients showed decreases in VL and a higher CD4 cell count. However, it should be kept in mind that adding a single active drug to a failing treatment regimen may rapidly select for resistance to the newly added drug.

Resistance testing

Testing for HIV resistance to antiretroviral drugs may be a useful tool for guiding ART. Different studies have reported a strong association between the presence of drug resistance and a failure of drugs to suppress HIV replication in the short term.[3,4]

Adding a single active drug to a failing treatment regimen may rapidly select for resistance to the newly added drug.

Therapeutic drug monitoring (TDM)

Concentrations among different drugs may vary among patients who take the same dose. This may be due to differences in absorption from patient to patient, or different drug-drug or drug-food interactions. It can result in sub-optimal blood levels of some drugs, or toxicity caused by higher levels of concentration.

Take-home message

- Introducing or changing a therapy inappropriately may lead to more rapid failure of a new regimen.
- Optimal therapy is key to success, and the general practitioner should be aware of drug interactions between various antiretroviral drugs, as well as interaction between antiretroviral compounds and other drugs that patients may be taking simultaneously.

Concentration-response data exist for PIs and NNRTIs. A limiting factor with regard to implementation of TDM, aside from the cost, is a lack of prospective studies that demonstrate improvement of clinical outcome.

HAART-associated adverse events

Any drug component of a HAART regimen may be associated with serious adverse events. Some NRTIs are associated with mitochondrial toxicity, which can rarely lead to severe decompensated lactic acidosis. All drugs can be associated with hepatic toxicity.

Among the NNRTIs, nevirapine (NVP) has the greatest potential for causing clinical hepatitis, especially during the first weeks of treatment.

PIs are often associated with metabolic abnormalities, such as hyperlipidemia and hyperglycemia.

Since other toxicities are widely reported for different drugs, it is strongly recommend physicians check drug-related toxicities and drug interactions whenever a patient is treated.

Immune therapy

Immune therapy is still a matter of ongoing research. The most well-studied compound in this regard is interleukin-2, which has resulted in increased CD4 cell counts and some clinical benefit, when combined with HAART. However, despite increases in CD4 levels, the issue of whether immune responsiveness is enhanced in this circumstance is still a matter of debate, as is the question of durability of effect.

What you need to remember

Antiretroviral therapy for HIV patients is complex and constantly changing based on:

- new data regarding pathogenesis,
- ongoing studies on ART,
- generation of new drugs from existing classes,
- development of new drug classes, and
- the availability of newer diagnostic assays. CME

References

1. Lalezari JP, Henry K, O'Hearn M, et al: Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003; 348(22):2175-85.
2. Lazzarin A, Clotet B, Cooper D, et al: Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. N Engl J Med 2003; 348(22):2186-95.
3. Cingolani A, Antinori A, Rizzo MG, et al: Usefulness of monitoring HIV drug resistance and adherence in individuals failing highly active antiretroviral therapy: a randomized study (ARGENTA). AIDS 2002; 16(3):369-79.
4. Durant J, Clevenbergh P, Halfon P, et al: Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. Lancet 1999; 353(9171):2195-9.