New developments in long-term treatment of HIV: The honeymoon is over

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ABSTRACT

New recommendations advise starting highly active antiretroviral therapy (HAART) slightly later in the course of HIV disease compared with earlier guidelines. HAART has prolonged life in HIV patients, altering the spectrum of problems being treated. As the immune system recovers, long-term prophylaxis against some secondary infections can be discontinued. The problem, however, is that HAART also has serious long-term side effects such as lactic acidosis, lipodystrophy, and the promotion of drug-resistant strains of HIV.

When CD4 counts rise, some prophylaxis can be stopped

WHEN PROTEASE INHIBITORS came into common use in 1996, mortality from HIV markedly decreased. This decrease initially led to a period of great optimism about HIV, but in the past 2 to 3 years, this honeymoon has ended. We now recognize that we won't be able to stem the epidemic any time soon. We also recognize that as patients live longer, they are presenting new types of problems to the outpatient clinic.

This article discusses issues in the long-term treatment of the HIV outpatient, including:

- Prophylaxis during immune system reconstitution
- Identifying drug resistance
- Predicting outcome in patients with unusual ("discordant") responses to HAART
- Monitoring drug toxicities
- Deciding when to begin therapy.

PROPHYLAXIS DURING IMMUNE SYSTEM RECONSTITUTION

During HAART treatment, the immune system is able to reconstitute itself after being depleted by HIV. The reconstituted immune system differs somewhat from before the infection, but nevertheless, the strengthened immunity means that long-term prophylaxis against many secondary infections can be discontinued.

Immune reconstitution occurs in two unequal phases. In the first, the number of memory CD4 cells rises rapidly, reconstituting the immunologic repertoire of the patient before HAART was started. However, in the second phase, naive cells of thymic origin are replenished, and these "untrained" cells soon make up the vast majority of the patient's CD4 cell population.

When can prophylaxis be discontinued?

HIV-infected patients with failing immune systems are generally started on prophylaxis against *Pneumocystis carinii* pneumonia (PCP) when their CD4 count falls below 200×10^6 cells/L. A nonrandomized, multicenter cohort study[1] suggests that it is appropriate to discontinue PCP prophylaxis when the CD4 count rises to above 200×10^6 cells/L and remains above that threshold. This study followed 146 patients with rising CD4 counts who discontinued PCP prophylaxis and 345 similar patients who continued prophylaxis with trimethoprim-sulfamethoxazole. Over more than a year of follow-up, no cases of PCP occurred in either group. Other observational studies, one retrospective review, and one prospective trial support this.

A second study[2] suggests that prophylaxis against *Mycobacterium avium* complex (MAC)

infection can also be safely discontinued in HAART-treated patients with a sustained elevation of CD4 counts above 100×10^6 cells/L. In this randomized trial, 520 patients on HAART with CD4 counts that rose to more than 100×10^6 cells/L were assigned to either azithromycin or placebo. Over a median follow-up of 12 months, no cases of MAC occurred in either group. Bacterial pneumonia was also rare, occurring in 1.2% of the azithromycin group and 1.9% of the placebo group. Similar findings were reported almost simultaneously by Currier et al.[3]

The US Public Health Service now recommends discontinuing primary PCP prophylaxis at a threshold of 200×10^6 cells/L if the increase in CD4 cells is sustained 3 to 6 months, and discontinuing primary MAC prophylaxis at a threshold of 100×10^6 cells/L.[4] The guidelines do not yet recommend discontinuing primary prophylaxis against toxoplasmosis, but recent data indicate that discontinuation may be safe.[4]

These guidelines do not mention primary prophylaxis against *cryptococcus*, which is not generally recommended for HIV patients.

IDENTIFYING DRUG RESISTANCE

Between 30% and 60% of patients treated with HAART experience treatment failure and rising viral loads. As a result, drug-resistance HIV assays, though somewhat costly, are becoming routine in many HIV clinics.

Testing HIV for resistance to antiretroviral agents

Last year, two studies confirmed that these genotype assays can lead to better patient outcomes. The Genotypic Antiretroviral Resistance Testing (GART)[5] study looked at more than 150 patients who were experiencing rapidly dropping CD4 counts and rising viral load while on a three-drug HAART regimen. In these patients, viral load fell more rapidly when therapeutic decisions were made in light of the results of the genotype assay than when they were made after a careful history and physical alone. Similar results were reported in the Viradapt study.[6]

These two studies also showed that the treatment failure could be the result of resistance to one, two, or all three drugs in the three-drug HAART combination, and that the genotype assay could identify which of the drugs was the key. Previously, it had been assumed that all three drugs had to be changed when patients did not respond to HAART.

US Public Health Service guidelines for genotype assays

As a result of these studies, the US Public Health Service issued new guidelines in 2001 recommending that these expensive genotype assays be used when the viral load rises or fails to come under control on HAART.[7] Interestingly, the new guidelines also recommend that genotype assays should be considered in patients who have just acquired HIV and are displaying the characteristic fever and adenopathy of acute infection; this is because of repeated reports of patients contracting multidrug-resistant HIV directly from other patients.

However, genotypic assays are not recommended in patients who have already discontinued HAART, because these patients usually have mixed populations of viruses; drug-resistant strains may persist even after the population appears to revert to the wild type. Genotype assays are also not recommended when the viral load is very low.

Test for HIV drug resistance to improve treatment decisions

PREDICTING OUTCOME IN PATIENTS WITH DISCORDANT RESPONSES TO HAART

For most patients, the CD4 count and the viral load are inversely related; that is, as one rises, the other falls. However, some patients on HAART experience so-called discordant responses; either the CD4 count or the viral load responds to treatment, but not both. The result is that the CD4 count and viral load either both increase or both decrease. Discordant responses have been the focus of intense study, and a recent report shows that in these patients, the immunologic response is more important in predicting outcome than the virologic response.[8]

In this multicenter study of more than 2,000 patients, about half were complete responders, 16% were complete nonresponders, and 36% were discordant responders (19% had only an immunologic response, and 17% had only a virologic response).

The complete nonresponders and those with only a virologic response had a significantly higher risk for clinical progression at 6 months than did the complete responders. However, the difference between the complete responders and the immunologic responders was not significant. The authors concluded that patients exhibiting an immunologic response at 6 months were at a lower risk of disease progression regardless of virologic response. Thus, a CD4 count rise trumps a viral load decline.

For the clinician, a patient with a low viral load but falling CD4 count on HAART should be monitored closely and a change in the HAART regimen considered.

MONITORING DRUG TOXICITIES

As survival improves in HIV, clinics are seeing more long-term complications of HAART. Women, obese patients, and those on prolonged nucleoside reverse transcriptase inhibitor (NRTI) therapy are at higher risk, but these complications may also occur in patients with none of these risk factors.

Lipodystrophy and lactic acidosis are long-term complications of HAART

Mitochondrial toxicity

Mitochondrial toxicity is thought to arise when the NRTIs inhibit mitochondrial DNA polymerase, impairing the mitochondrial respiratory chain and pyruvate metabolism, which promotes lactic acid production and gluconeogenesis. The result is lactic acidosis and secondary diabetes. In addition, acetyl-coenzyme A is overproduced, which is a substrate for fatty metabolism; the result may be severe hepatic steatosis. Other effects of mitochondrial toxicity include peripheral neuropathy, pancreatitis, myopathy, and cardiomyopathy.

The clinical manifestations of mitochondrial toxicity are, unfortunately, nonspecific gastrointestinal symptoms such as fatigue, nausea, vomiting, diarrhea, abdominal pain, bloating, weight loss, and hepatomegaly.

The diagnostic laboratory finding is an unexplained anion gap higher than 16 mmol/L. Lactate levels are generally above 3 mmol/L, and patients display ketoacidosis, secondary diabetes, and an enlarged fatty liver visible on ultrasound or computed tomography.

HIV lipodystrophy

HIV lipodystrophy is usually considered a complication of protease inhibitors (PI), but it may also be associated with NRTIs, and in addition has on rare occasions been described in HIV patients who have not received HAART. It may manifest in any of three ways; hyperglycemia (or frank diabetes), hyperlipidemia, or fat redistribution.

The fat redistribution is generally gradual, producing abdominal fat accumulation and wasting in the arms and legs. Other effects may include a so-called "buffalo hump" of fat below the nape of the neck, breast enlargement, and facial wasting. The prevalence among HAART-treated patients has been reported to be as low as 6% and as high as 80%, depending on the case definition.

The mechanism of this lipodystrophy is unclear. The changes occur without evidence of hypercortisolism, and hyperlipidemia is often but not always associated with hyperinsulinemia. No firm data are available on treatment, although exercise and switching antiviral class have been attempted.

Hyperlipidema

HAART-associated hyperlipidemia involves elevated triglycerides and cholesterol. It may or may not be associated with fat redistribution or hyperglycemia. Hyperlipidemia is most strongly associated with protease inhibitors, and ritonavir is the most heavily implicated drug. The onset of hyperlipidemia may occur within 1 month of initiating therapy. The mechanism is unclear, but it is possible that the protease inhibitors interfere with the normal cellular proteins involved in lipid metabolism.

The implications of HAART-related hyperlipidemia are unclear. No case-control study has shown a definitive increased risk of cardiovascular events on HAART, but in part this may merely reflect the need for longer follow-up with these relatively new drugs. There have been case reports of young HIV patients experiencing premature myocardial infarction or stroke which may be related to hyperlipidemia.[9] Studies of brachial artery reactivity have had contradictory results, but in some screening studies of large populations, over half of the HIV patients had significant hypercholesterolemia.[7]

Many of our patients meet the National Cholesterol Education Program guidelines for the use of cholesterol-lowering agents, and a recent guideline paper recommended that HIV patients with elevated lipids be given the same dietary and drug interventions as patients without HIV.[10] However, the effectiveness of lifestyle modifications and medications has not been studied in this patient population.

Taking patients off protease inhibitors may also improve lipids. Some have recommended testing lipids every 3 to 4 months in all patients on protease inhibitors, and more frequently in patients with underlying cholesterol problems. Care should be taken when mixing protease inhibitors with some of the statins because of drug interactions. Treatment options include use of lipid-lowering agents such as gemfibrozil, niacin, and the HMG coenzyme A reductase inhibitors (statins).[7,11] All of the statins except pravastatin potentially interact with protease inhibitors.

WHEN TO START THERAPY: HIT HARD, BUT NOT SO EARLY

Lipodystrophy and other serious side effects of HAART, our inability to eradicate the virus, and the emergence of multidrug resistant HIV strains have raised our awareness of the problems with HAART and have made our treatment approach somewhat more conservative. In 1996–1997, we were urged to "treat early and treat hard." Today, we are more likely to "treat hard, but not so early."

Symptomatic patients are still treated aggressively with HAART, as are asymptomatic patients with CD4 counts of lower than 200×10^6 cells/L. Asymptomatic patients with CD4 counts as high as 350×10^6 cells/L are also generally treated. Most would also begin HAART in patients with CD4 counts higher than 350×10^6 cells/L but viral loads of more than 55,000 copies/mL. However, asymptomatic patients with higher CD4 counts and viral loads below 55,000 copies might today be observed in order to postpone the beginning of HAART treatment.

REFERENCES

1. **Yangco BG, Von Bargen JC, Moorman AC, Holmberg SD.** Discontinuation of chemoprophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection. HIV Outpatient Study (HOPS) Investigators. Ann Intern Med 2000; 132:201–205.
2. **El-Sadr WM, Burman WJ, Grant LB, et al.** Discontinuation of prophylaxis for *Mycobacterium avium* complex disease in HIV-infected patients who have a response to antiretroviral therapy. Terry Beirn Community Programs for Clinical Research on AIDS. N Engl J Med 2000; 342:1085–1092.
3. **Currier JS, Williams PL, Koletar SL, et al.** Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count. A randomized, double-blind, placebo-controlled trial. AIDS Clinical Trials Group 362 Study Team. Ann Intern Med 2000; 133:493–503.
4. **U.S. Public Health Service and Infectious Diseases Society of America.** 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons with human immunodeficiency virus. MMWR 1999; 48(Aug 20): No. RR-10.
5. **Baxter JD, Mayers DL, Wentworth DN, et al.** A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. AIDS 2000; 14:F83–F93.
6. **Durant J, Clevenbergh P, Halfon P, et al.** Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. Lancet. 1999 Jun 26; 353:2195–2199.
7. **Department of Health and Human Services and the Henry J. Kaiser Family Foundation.** Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. http://www.hivatis.org. Accessed April 23, 2001.
8. **Grabar S, Le Moing V, Goujard C, et al.** Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy. Ann Intern Med 2000; 133:401–410.
9. **Flynn TE, Bricker LA.** Myocardial infarction in HIV-infected men receiving protease inhibitors. Ann Intern Med 1999; 131:1548.
10. **Dubé MP, Sprecher D, Henry WK, et al.** Preliminary guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving antiretroviral therapy: recommendations of the adult ACTG Cardiovascular Disease Focus Group. Clin Infect Dis 2000; 31:1216–1224.
11. **Falusi OM, Abery JA.** HIV and cardiovascular risk factors. AIDS Reader 2001; 11(5):253.

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