CME CREDIT

TAKE-HOME POINTS FROM LECTURES BY CLEVELAND CLINIC AND VISITING FACULTY

HIV update 2002: Delaying treatment to curb rising resistance

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ABSTRACT

The recommendation for HIV antiretroviral therapy is changing from "treat early, treat hard" to "treat a little later, treat hard" as more toxicities of the drugs are recognized. Drug-resistant HIV is becoming a serious problem, even in treatment-naive patients. For HIV patients with organ failure, transplantation is increasingly an option.

AMONG THE MOST controversial topics in HIV management today is when to start antiretroviral therapy for patients with asymptomatic HIV infection. Recommendations on therapy initiation have shifted several times in the last 3 years, and are likely to do so again.

These recommendations are so changeable because of the competing needs to optimize patients' immunologic and virologic outcomes while reducing the toxicity of antiretroviral regimens and the development of drug-resistant HIV strains. This article reviews current thinking on antiretroviral therapy initiation and other recent developments in HIV management, including:

- The growing problem of HIV resistance
- Long-term toxicities of therapy
- The increase in organ failure and cancer among HIV-infected patients as AIDS deaths decrease
- The increasing use of transplantation in HIV-infected patients with organ failure
- Evolving views on when to stop prophylaxis against opportunistic infections
- New approaches to antiretroviral therapy and the status of HIV vaccines.

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WHEN TO START HAART

From its beginnings in the second half of the 1990s, highly active antiretroviral therapy (HAART) for HIV infection involved "treating early and treating hard."

While "treating hard" continues to be integral to HAART, the wisdom of early treatment for HIV-infected patients without symptoms is being questioned. This is a new development: as recently as 2000, recommendations called for initiating antiretroviral drugs in an HIV-infected patient when the CD4 cell count fell below 500 cells/μL or the HIV viral load exceeded 20,000 copies/mL.[1]

The pendulum is swinging toward starting HAART later to minimize drug exposure

Awareness of the toxicity of antiretroviral regimens and the development of drug-resistant HIV strains led to more conservative recommendations in 2001.[2] These called for delaying antiretroviral therapy until the CD4 count dropped below 350 cells/μL or the viral load was greater than 55,000 copies/mL.

Today many experts favor placing greater emphasis on CD4 cell counts rather than on HIV viral load when deciding when to start antiretroviral therapy. All agree that HAART should be initiated before CD4 counts fall below 200 cells/μL, but the optimal time to start therapy for those with CD4 counts between 200 and 350 cells/μL remains controversial. Patients with high viral loads require more frequent monitoring of their CD4 counts.[3]

The pendulum is clearly swinging toward starting antiretroviral therapy later, in order to reduce drug toxicity and viral resistance. Earlier treatment, however, may improve immunologic and virologic outcomes, so the pendulum may swing back toward a more aggressive treatment approach in the future.

RESISTANCE INCREASING AMONG THE TREATED AND UNTREATED

The development of drug-resistant strains of HIV is one worrisome problem prompting a reevaluation of when to start therapy. Although genotypic and phenotypic resistance assays can help guide specific antiretroviral therapy, HIV resistance patterns are not fully understood.

Furthermore, cross-resistance within a class of antiretrovirals is common, meaning that the loss of one drug in a class to viral resistance may lead to the loss of that entire class of antiretrovirals, be they protease inhibitors, nucleoside reverse transcriptase inhibitors, or non-nucleoside reverse transcriptase inhibitors. As a result, patients may develop resistance to virtually all medications despite being exposed to very few.

The chance of treatment success is halved with each successive HAART regimen used

Getting HAART right the first time is key

For that reason, the best chance for successful viral suppression is with the first antiretroviral combination regimen used. New data from the large multicenter HIV Outpatient Study[4] show that the chance of treatment success is approximately halved with each successive HAART regimen used, after accounting for adherence and other confounding factors:

- First regimen, 49.0% chance of success
- Second regimen, 29.6% chance of success
- Third regimen, 14.9% chance of success.

Resistance rises in the treatment-naive

Drug-resistant HIV is also a problem in patients who are antiretroviral-naive. Little et al[5] recently reported results of a retrospective longitudinal analysis of newly infected, antiretroviral-naive patients with HIV in 10 North American cities. They found that the frequency of high-level resistance to one or more antiretrovirals rose from 3.4% in 1995–1998 to 12.4% in 1999–2000.

These findings suggest that antiretroviral-treated patients infected with resistant strains of HIV are increasingly transmitting these strains to others. As this trend continues, the response rate to the first HAART regimen will decline further, making treatment of antiretroviral-naive patients more challenging.

A high standard for adherence: Even small lapses lead to resistance

What's more, anything short of virtually perfect patient adherence to antiretroviral regimens further exacerbates HIV resistance. An observational study by Paterson et al[6] showed that even small lapses in adherence lead to dramatic rises in virologic failure. While only 19% of patients with greater than 95% adherence had virologic failure over a median follow-up of 6 months, this proportion shot up to 36% among patients with 90% to 95% adherence and to 50% among those with 80% to 90% adherence. Unfortunately, it is in these patients who take most but not all of their antiretroviral medications that resistance develops most rapidly.[7]

LONG-TERM TOXICITIES

The other aim of minimizing drug exposure through delayed treatment initiation is to reduce the many toxicities associated with HAART. In addition to the well-recognized acute side effects of antiretroviral drugs, the problems of mitochondrial toxicity and metabolic disorders have emerged in patients taking long-term HAART. These toxicities have been widely reviewed and will not be discussed in detail here. The manifestations, however, are varied.

Mitochondrial toxicity, caused primarily by the nucleoside reverse transcriptase inhibitors, can lead to myopathy, neuropathy, pancreatitis, cardiomyopathy, bone marrow suppression, nephrotoxicity, and the potentially fatal syndrome of lactic acidosis with hepatic steatosis. The susceptibility to these complications appears to depend on both host factors and the inciting agent.[8]

The metabolic disorders associated with long-term HAART include osteonecrosis and osteoporosis, hyperglycemia, hyperlipidemia, and lipodystrophy (abnormal fat distribution).[9,10] Lipodystrophy includes lipoatrophy,

or loss of fat in the face and extremities, as well as fat accumulation manifesting as central obesity and the development of a "buffalo hump" or dorsocervical fat pad. The toxicities can lead to significant disability and can be treatment-limiting.

FEWER AIDS DEATHS, MORE ORGAN FAILURE AND CANCER

As the HAART era has brought new types of toxicities, it also has brought significantly changed patterns of morbidity and mortality in HIV-infected patients. Most fundamentally, it has slashed mortality due to HIV, as the number of deaths attributable to HIV infection among US adults 25 to 44 years old plummeted from about 40 per 100,000 population in 1995 to about 10 per 100,000 population in 2000.[11]

HIV-infected patients also are experiencing a different kind of death, one that's more likely to be due to organ failure or cancer and less likely to be due to opportunistic infection or "end-stage AIDS" (AIDS without recognized infection or malignancy).

Rodriguez and colleagues recently presented data that illustrate some of these trends.[12] The percentage of HIV-infected patients treated at Case Western Reserve University in Cleveland who died from AIDS or its complications declined from 89% in 1995 to 46% in 2001. Over the same period, the proportion of deaths due to infection decreased from 43% to 17% while the proportion due to neoplastic disease rose from 9% to 29%.

The fall in deaths from opportunistic infections corresponds with a steep decline in the incidence of these infections, which results from the immune system reconstitution that HAART makes possible.

Organs at risk

Two forms of organ failure are most commonly encountered in HIV-infected patients: end-stage renal disease and end-stage liver disease.

Renal disease in HIV-infected patients is multifactorial. The most common cause is HIV-associated nephropathy, a rapidly progressive form of nephropathy that is seen predominantly in black men. It is now the third leading cause of end-stage renal disease in black men 20 to 64 years old.[13]

No known treatments exist for HIV-associated nephropathy other than supportive care. Dialysis is merely a stopgap measure, and HIV-infected patients on dialysis have shorter survivals than do other patients on dialysis.

End-stage liver disease is even more prevalent and of greater concern than renal disease in HIV-infected patients. Any number of factors can cause liver disease in this population, including hepatitis C, hepatitis B, and hepatitis D.

Hepatitis C is by far the leading cause of morbidity from liver disease in HIV-infected patients. Of the estimated 900,000 HIV-infected patients in the United States, about one third are coinfected with hepatitis C virus.[14]

Several studies[14] have shown that coinfection with hepatitis C virus is associated with more rapid progression of HIV infection and with less tolerance of HAART and a lower response rate to it.

Likewise, hepatitis C, which is generally chronic and slowly progressive, is greatly accelerated with HIV infection. Hepatitis C patients who are coinfected with HIV are more likely to develop cirrhosis and are more apt to die from its complications once it develops. Owing to this acceleration of its natural history, hepatitis C is considered an opportunistic infection in the setting of HIV infection.

Coinfection with hepatitis C worsens the response to HAART

Advances in hepatitis C therapy, including combination therapy with interferon and ribavirin, have led to sustained virologic remissions in up to 50% of patients. The availability of long-acting pegylated forms of interferon have raised response rates even further. Unfortunately, hepatitis C patients who are coinfected with HIV do not tolerate these therapies well. In these patients, toxicities such as anemia and, less commonly, lactic acidosis often lead to poor adherence to hepatitis C treatment regimens. Moreover, the virologic response to these regimens is far less robust in patients with CD4 cell depletion (< 500 cells/μL).

Transplantation now an option

Before 1995, transplantation centers were reluctant to provide solid organ transplants to HIV-infected patients. They were concerned about the adverse effects of antirejection therapy and about the ethics of possibly "wasting" scarce organs on a population with uncertain

life expectancies.

Since 1995, the argument that HIV infection greatly shortens life expectancy is no longer valid. Additionally, a recent controlled trial[15] has shown that antirejection drugs such as cyclosporin A can be safe in the setting of HIV infection and may even confer benefits, such as suppression of immune activation and possibly a direct antiviral effect.

Over the years a number of organ transplants in the setting of HIV have taken place serendipitously, in cases involving unrecognized HIV infection in the organ recipient or in the donated organ or blood products. While many of these transplant patients fared poorly, some showed long-term graft responses and fared quite well.

Earlier this year these mixed historical results were supplemented by promising preliminary data from a prospective National Institutes of Health trial.[16] To date, 23 HIV-infected subjects have received liver (n = 10) or kidney (n = 13) transplants. At enrollment, all patients had CD4 counts in the range of 375 to 475 cells/μL and nondetectable plasma viral loads. At a median post-transplant follow-up of 307 days (range 8–1,462), only 2 of the 23 patients had died (1 from an opportunistic infection). Rejection occurred in 30% of patients; grafts in all other patients survived through the follow-up period and all but 4 patients maintained undetectable viral loads.

The ethical argument against transplants in HIV patients has been turned on its head

Findings like these have turned the earlier ethical argument against transplantation in HIV-infected patients on its head. Halpern et al[17] have argued compellingly that withholding organ transplantation from HIV-infected patients is unethical, given current data on transplantation in HIV disease. They cite our ability to identify patients at low risk for HIV progression, growing evidence that patients can tolerate antirejection therapies, and early experience suggesting that many HIV-infected transplant recipients will overcome end-organ failure.

SUPPORT FOR STOPPING PROPHYLAXIS

The big drop in the incidence of opportunistic infections in the HAART era has translated into changes in the strategies for chemoprophylaxis against opportunistic infections.

In 2000 and 2001, data emerged in support of stopping primary prophylaxis against opportunistic infections in HIV-infected patients with increased CD4 counts.[18,19] More recent data suggest that, in selected patients, secondary prophylaxis (maintenance therapy) can be discontinued with a low risk of infection recurrence. For instance, Kirk et al[20] recently reported only five episodes of recurrent infections after stopping secondary prophylaxis among 358 HIV-infected patients in Europe who had experienced 379 episodes of cytomegalovirus disease, *Mycobacterium avium* complex infection, toxoplasmic encephalitis, or extrapulmonary cryptococcosis.

These findings suggest that reconstitution of the immune response to many recall antigens is clinically significant. Unfortunately, the immune response against HIV itself does not improve with therapy, and data suggest that despite significant improvement in CD4 counts, responses to many antigens are still incomplete.[21]

NEW APPROACHES TO TREATMENT AND PREVENTION

Current efforts to improve the treatment of HIV are focused on developing antiretrovirals and antiretroviral regimens with less toxicity and a lower pill burden. For example, selected patients are maintained on a three-drug HAART regimen consisting of only two pills per day. In addition, once-daily regimens are being studied to enhance treatment adherence and quality of life.

Structured intermittent therapy

One therapeutic approach under study is structured intermittent therapy. This approach alternates intervals of HAART with drug holidays. Initially investigators hoped that this strategy would facilitate the development of HIV-specific immune responses by allowing the viral load to rise, re-exposing the immune system to HIV.

Results in chronically infected patients have not been promising, but limited studies in patients treated at the time of their primary HIV infection are more hopeful.[22] Alternately, very short-cycle treatment interruptions that do not lead to increased viral replication may

reduce drug toxicity by reducing exposure to the antiretroviral agents.[23]

All intermittent treatment regimens are investigational, however, and should be pursued only in the context of a study.

Vaccines

Much work has gone toward the development of a vaccine against HIV, with little payoff to date. Obstacles to the development of an HIV vaccine are many and include the high genetic diversity of HIV, its ability to escape immune control, its high rate of mutation, and its complex structure.

Whereas most vaccines are truly prophylactic, HIV researchers are trying primarily to initially develop a vaccine that is therapeutic or perhaps an immune therapy, designed to help the body fight HIV infection more than to prevent infection.

One of the more promising vaccine candidates is the adenovirus vaccine (Adhu 5), which is a replicative defective adenovirus. Unlike prior vaccines against HIV, it has shown a durable response, extending to 2 years so far. It also shows cross-clade activity and thus has a broader response than prior vaccines.

Unfortunately, because adenovirus is a common virus in humans, previous exposure may result in a muted response to the vaccine. Moreover, the adenovirus vaccine can cause positive serology, with the resulting risk of false-positive HIV tests.

TWO WORLDS OF HIV: THE DEVELOPING WORLD GOES UNTREATED

No update on HIV therapy in the developed world is complete without mention of the starkly different reality for HIV-infected patients in the world's developing nations, particularly in sub-Saharan Africa. Less than 3% of the world's HIV-infected population has access to the antiretroviral therapies discussed here. As these infected millions remain without therapy, they remain without hope.

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