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

Changing patterns of morbidity and mortality in HIV disease

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ABSTRACT

In patients with HIV infection, highly active antiretroviral therapy is improving survival, but at the price of a variety of metabolic side effects. Patterns of morbidity and mortality are changing: the leading cause of death is now kidney or liver failure instead of opportunistic infections.

AGGRESSIVE TREATMENT with highly active antiretroviral therapy (HAART) is extending the life expectancy of HIV-infected patients by decades[1]—and also creating new challenges in the primary care of such patients. The powerful HAART drugs have profound metabolic complications, principally lipodystrophy, lactic acidosis, and osteopenia, causing some to question whether to begin HAART therapy early in all cases of HIV disease. Furthermore, the aggressive use of HAART has shifted the main cause of death in HIV patients from opportunistic infections to end-organ failure.

This paper describes the metabolic complications observed in HAART-treated patients, the possible rationale for delaying therapy in patients without symptoms with low plasma viral levels and preserved CD4 cell counts, and the appropriateness of considering HIV patients for organ transplantation.

*The author has indicated that he has a relationship which, in the context of his presentation, could be perceived as a potential conflict of interest; ie, he serves as a consultant for the Immunex, Amgen, SmithKline, Searle, and Schering-Plough corporations.

HIV LIPODYSTROPHY: A CAUSE OF CORONARY DISEASE?

HIV lipodystrophy is a misnomer. It is actually a consequence of treatment for HIV, observed in patients who respond to antiretroviral therapy.

In its fully developed form, HIV lipodystrophy is a heterogeneous syndrome that consists of three components: carbohydrate intolerance, dyslipidemia, and body fat redistribution. Its clinical significance is not yet fully understood, although data strongly suggest that it leads to premature cardiovascular disease.

Carbohydrate intolerance

In 1997, the Food and Drug Administration warned of an unexpectedly high rate of new-onset diabetes mellitus in patients taking protease inhibitors as a component of HAART. Fasting hyperinsulinemia and insulin resistance are common in patients who take protease inhibitors as part of their HAART regimen. The prevalence of clinical diabetes in HIV-infected patients under longitudinal care at the Cleveland Clinic is 8%, most cases of which have occurred since the advent of HAART. Carbohydrate intolerance typically occurs in patients whose HIV is well controlled.

In treating HIV, success brings new problems

Lipid disorders

In the HAART/protease inhibitor era, dyslipidemia has become common, most likely related to treatment with protease inhibitors. Dyslipidemia occurs shortly after initiation of HAART and is independent of the increased fasting insulin levels that may also develop. In one study, normal controls who were given protease inhibitors developed hypercholesterolemia and hypertriglyceridemia within 2 weeks.[2]

Preliminary, unpublished data from 90 HAART-treated patients at the Cleveland Clinic indicate that 50% had levels of low-density lipoprotein (LDL) cholesterol greater than 130 mg/dL and 60% had total cholesterol levels greater than 200 mg/dL—many in excess of 280 mg/dL (Calabrese LH, unpublished data). In addition, nearly one third had HDL cholesterol levels less than 35 mg/dL, and well over half had HDL levels less than 44 mg/dL. More than 60% had triglyceride levels greater than 200 mg/dL, and triglyceride levels greater than 1,000 mg/dL were common.

Body fat changes

Body fat changes associated with HAART occur in two forms: a fat accumulation syndrome and peripheral wasting. These two forms frequently occur together but may also occur independently. Prospective studies show that 50% of HAART recipients demonstrate lipodystrophy by 10 months of therapy.[3] The factors that contribute to body fat changes are still under investigation.

Fat accumulation tends to occur as abdominal obesity: HIV lipodystrophy has been referred to as protease paunch, Crix belly, and pseudo-Cushing's syndrome. The body fat accumulation in HIV lipodystrophy is not only topical but visceral as well.

Significant peripheral wasting is more common than fat accumulation in our practice and is a clear sign that patients are being treated aggressively. It occurs most often in the arms and legs.

One assessment of HIV lipodystrophy in patients with HIV RNA levels of 13,000 to 710,000 copies/mL found fat depletion in 57% of men and 22% of women, abdominal fat accumulation in 70% of men and 100% of women, and gynecomastia in 31% of men and 74% of women.[4]

Factors that appear to correlate with the development of lipodystrophy are age older than 40 years at the time of evaluation, a longer duration of infection, and the time from the CD4 nadir.

Clinical implications of lipodystrophy

The rate of unexplained cardiovascular events has increased in HAART recipients who otherwise had no other cardiovascular risk factors. Because the use of these powerful drugs has been routine for only 3 to 4 years, epidemiologic and case-control studies have yet to show an increasing pattern of stroke or myocardial infarction with HAART. Several studies in which carotid intima-media thickness or brachial artery reactivity were measured, however, have shown conflicting evidence of premature vascular disease.[5–7] In a small study, we used electron beam computed tomography to look for calcification of the coronary arteries in 17 patients who had been receiving HAART for at least 1 year and who had clinical hyperlipidemia. Of these, 13 (76%) had evidence of calcification, and one third had coronary calcium scores greater than the scores of matched controls (Acevedo M, Sprecher D, Calabrese LM, unpublished data).

Preventing and treating HIV lipodystrophy: Should HAART ever be deferred?

Multiple studies indicate that switching from a protease inhibitor-based regimen to a non-protease inhibitor-based regimen leads to improvement in dyslipidemia. The adverse changes in the lipid profiles of patients on HAART would qualify many of them for treatment of dyslipidemia under the guidelines established by the National Cholesterol Education Program. The use of lipid-lowering agents can improve lipid profiles of patients with HIV lipodystrophy, but these agents have no effect on fat redistribution or carbohydrate intolerance. Recommendations for treatment have recently been published.[8]

The rate of cardiovascular events has increased in HAART recipients

Although removing protease inhibitors from the regimen does not reverse diabetes once it appears, withdrawing them at an early stage of carbohydrate intolerance may help prevent the development of diabetes. Oral hypoglycemic agents, particularly the thiazolidinediones, help reverse peripheral insulin resistance but have not been shown to be potent in small, early studies in this disease.[9]

Maintaining CD4 cell counts may delay development of lipodystrophy. A newer strategy gaining popularity is to withhold antiretroviral therapy in asymptomatic patients until their viral load exceeds 30,000, regardless of CD4 cell counts. In the absence of high viral load, we often delay initiation of

HAART until CD4 levels fall below 350 cells/mm^3.

BONE COMPLICATIONS

Recent studies demonstrate a dramatic increase in the incidence of osteoporosis in HAART-treated HIV-positive patients. As with HIV lipodystrophy, osteoporosis appears to be associated with the use of protease inhibitors. In one study,[10] HAART-treated patients receiving protease inhibitors had a relative risk of 2.2 for osteopenia compared with controls. At this time it appears prudent to recommend calcium and vitamin D supplements to all HIV-infected patients, particularly those on therapy.

Another bone complication recently recognized is avascular necrosis of bone. A recent case-control study has demonstrated HIV-infected patients to be at significant risk for aseptic necrosis of bone, particularly when combined with other risk factors (ie, hyperlipidemia, excessive alcohol intake).[11] Clinical septic necrosis of bone has been found in about 1% of our HIV population over the past decade.

HIV may not absolutely preclude a transplant

END-ORGAN FAILURE

In the past 2 years, the leading cause of death in HIV-infected patients has been end-organ failure. End-stage renal disease and end-stage liver disease are two increasingly important causes of morbidity and mortality in HIV-infected patients.

Renal disease

End-stage renal disease in the HIV population occurs primarily in African-Americans. HIV-associated renal disease manifests as a sclerosing, collapsing, glomerulonephropathy of uncertain etiology.

Liver disease

The increased incidence of end-stage liver disease due to hepatitis C virus (HCV) infection is an even larger cause of death in the HIV-infected population. Coinfection with HCV is common in HIV-positive patients: 300,000 of the 900,000 patients infected with HIV in this country are also infected with HCV. In the presence of HIV, HCV progresses to end-stage liver disease nearly 100 times faster than in patients not infected with HIV.[12] The treatment of HCV has improved with combinations of alpha interferon and ribavirin, with long-term viral response rates approaching 50% with combination therapy. In HIV-infected patients with CD4 counts of at least 200 cells/mm^3, the response rate with interferon and ribavirin is not much different than the response rate in populations not infected with HIV.

Transplantation

Only a few years ago, HIV disease was considered an absolute contraindication to solid organ transplantation because of shortened life expectancy and adverse effects of adjuvant immunosuppression in already immunosuppressed patients. Recently, the possibility of solid organ transplantation in HIV-infected patients has been proposed. A multicenter consortium under the auspices of the National Institutes of Health is studying transplantation of kidneys and livers in HIV-infected individuals with CD4 counts of at least 200 cells/mm^3 and nondetectable viral loads for prolonged periods. Several kidney recipients with HIV disease have survived up to 8 years with adjuvant immunosuppression.[13] A recently completed multicenter randomized, placebo-controlled trial showed no clinically adverse effects from cyclosporine immunosuppression in patients with HIV disease.[14]

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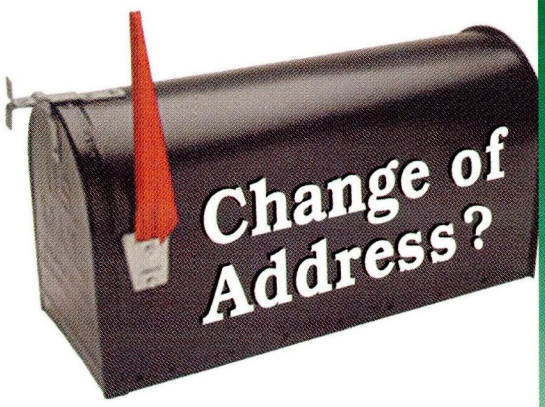

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CME ANSWERS

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