In her case report, Crum-Cianflone describes an HIV-infected patient receiving antiretroviral therapy with no history of significant alcohol use and an undetectable HIV-1 RNA level who presented with a recurrent, mildly elevated alanine aminotransferase level. The patient underwent an extensive biochemical workup for chronic liver disease, the findings of which were unrevealing. Ultrasonographic findings were consistent with hepatic steatosis. Ultimately, a liver biopsy demonstrated moderate hepatic steatosis and minimal intra-acinar inflammation—features consistent with nonalcoholic fatty liver disease (NAFLD).

This sequence of events should by now be familiar to most hepatologists, infectious disease specialists, and HIV care experts. Fatty liver disease in this setting need not necessarily be causally related to HIV disease and its treatment. Indeed, as pointed out by Crum-Cianflone, NAFLD is a common condition, and many of the persons affected, not surprisingly, will be HIV-infected. The prevalence of NAFLD appears to be increasing, driven largely by the obesity epidemic in this country, which is by no means sparing HIV-infected persons. The present paradigm is that insulin resistance is the underlying pathophysiological disturbance leading to NAFLD. This has led many investigators to describe NAFLD as the hepatic manifestation of the metabolic syndrome. The patient described in this case report was lean, euglycemic, and not reported to be hypertensive. His waist circumference was not reported; however, he did have a low high-density lipoprotein cholesterol level and hypertriglyceridemia. As such, he had at least 2 of 5 diagnostic components of the metabolic syndrome; at least 3 must be present for that diagnosis to be made.

Clues to a possible underlying cause of NAFLD may be derived from the patient’s medication record. His current medications included zidovudine, and he had a history of other NRTI exposure (didanosine and stavudine), which had led to the development of neuropathy. The "d-drugs" (stavudine [d4T], didanosine [ddI], and zalcitabine [ddC]) are well known to have a strong capacity to deplete mitochondrial DNA through an interaction with DNA polymerase γ, and they specifically have been shown to deplete hepatic mitochondrial DNA in persons coinfected with HIV and hepatitis C virus (HCV) as compared with those not receiving a d-drug–containing regimen where no significant mitochondrial DNA depletion was observed. The role of d-drug NRTIs in disrupting the mitochondrial respiratory chain is also well established.

Mitochondrial toxicity has now been implicated in the pathogenesis of NAFLD in a number of settings, including the metabolic syndrome. Mechanisms proposed include respiratory chain disruption and a compensatory response to increased free fatty acid delivery to the liver by an increase in mitochondrial β-oxidation, leading to the generation of cytotoxic, reactive oxygen species. The description of megamitochondria seen with electron micrography in nonalcoholic steatohepatitis further illustrates this point.

Indeed, the histological hallmark of a seemingly divergent array of liver diseases that are associated with mitochondrial toxicity, such as acute fatty liver of pregnancy, Wilson disease, and alcoholic liver disease, is hepatic steatosis. It is therefore not surprising that recent clinical evidence has linked hepatic steatosis with the use of NRTIs in a cohort of HCV/HIV-coinfected patients, in addition to the established risk factors for hepatic steatosis, such as the viral cytopathic effect of HCV genotype 3 infection and hepatic fibrosis. But is there more to the story than this? We do not know whether the patient in this case had any features of lipoatrophy or lipohypertrophy. The evidence for an association between these entities and hepatic steatosis, although circumstantially present, is blurred by the almost universal coexistence of "the usual suspects": the
metabolic syndrome; exposure to antiretroviral drugs, namely NRTIs with affinity to DNA polymerase γ; and the recurring theme of mitochondrial toxicity. But does it really matter?

It would be interesting to observe the prevalence of NAFLD in HIV-infected persons over the next few years, since as current practice is geared toward avoiding the use of d-drugs and thymidine NRTIs and using more mitochondrial-friendly NRTIs, such as abacavir or tenofovir. To that effect, one study has found the use of abacavir to be protective against the development of NAFLD in a group of HIV/HCV-coinfected patients.

The author nicely summarizes currently investigated therapies and the lack of any established treatments for NAFLD. We would like to think that with the accumulation of additional knowledge about the mechanisms of hepatic steatosis, biochemical and imaging tools might become available in the near future to pinpoint a more specific etiological agent in the pathophysiology of NAFLD, resulting in better, targeted treatments for this liver disease.

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