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Hepatic Steatosis in HIV/HCV–Coinfected Patients: Time to Reevaluate!

See "Incidence and risk factors for steatosis progression in adults coinfected with HIV and hepatitis C virus," by Woreta TA, Sutcliffe CG, Mehta SH, et al, on page 809.

In patients with hepatitis C virus (HCV) infection, hepatic steatosis results in accelerated progression of liver disease. Risk factors include HCV genotype 3 and host-related factors, including visceral adiposity, hyperlipidemia, and peripheral insulin resistance (IR).[1,2] Some studies have suggested that hepatic steatosis is more common and severe in HCV/HIV-coinfected patients than in those with HCV alone.[3,4] It is important to understand the modifiable risk factors that may contribute to these observations because liver-related disease remains an important cause of death among HIV-infected patients (Figure 1).

Is Antiretroviral Therapy the Culprit?

Since the first description of HIV-associated lipodystrophy in 1998, there has been concern regarding the role antiretroviral therapy (ART) may play in the development of the morphologic and metabolic abnormalities observed during treatment. The lipid changes induced by HIV itself were exacerbated further by the addition of the early generation protease inhibitors (PIs; ritonavir, nelfinavir, lopinavir), as well as nucleoside reverse transcriptase inhibitors (zidovudine, stavudine), which mediate fasting lipolysis. Certain PIs (eg, indinavir and full-dose ritonavir) are implicated in the development of IR through inhibition of the glucose transporter GLUT-4; there are conflicting data regarding the effect of lopinavir.[5,6] Zidovudine and stavudine may also mediate IR, although the mechanism remains unclear.[7,8]

The dideoxynucleosides (eg, didanosine and stavudine) are tied strongly to mitochondrial toxicity, sometimes with fatal outcomes. In one cross-sectional study where stavudine and didanosine use was highly prevalent, microvesicular steatosis was identified in approximately half of the liver biopsies.[9] In fact, with increasing recognition of ART-associated toxicities, interest in conservation of therapy took center stage, spawning a randomized trial examining the impact of intermittent versus continuous ART.[10] However, ART interruption had negative clinical consequences on AIDS and non-AIDS events—namely cardiovascular, cancer, and liver-related outcomes—which may have been mediated by the unleashing of proinflammatory mediators (eg, interleukin-6) as viremia rebounded.[11]

Seeing ART in a New Light

Thus, the first natural history study of steatosis in HIV/HCV-coinfected patients presents welcome and informative data, which help to clarify the effects of ART on liver disease in a new era. Over a 15-year span (1993–2008), Woreta et al[12] assembled a cohort of 222 HIV/HCV-coinfected patients who had ≥2 liver biopsies.[12] All 345 biopsy pairs were evaluated by a single pathologist for trivial or significant steatosis. Predictors of regression or progression of fat were analyzed over time in this mainly African American cohort with HCV genotype-1 infection.

Woreta confirmed that steatosis was associated with fibrosis, which corroborates results of other cross-sectional studies.[9,13] However, the "good news" side of the story is that HIV suppression and immunologic recovery

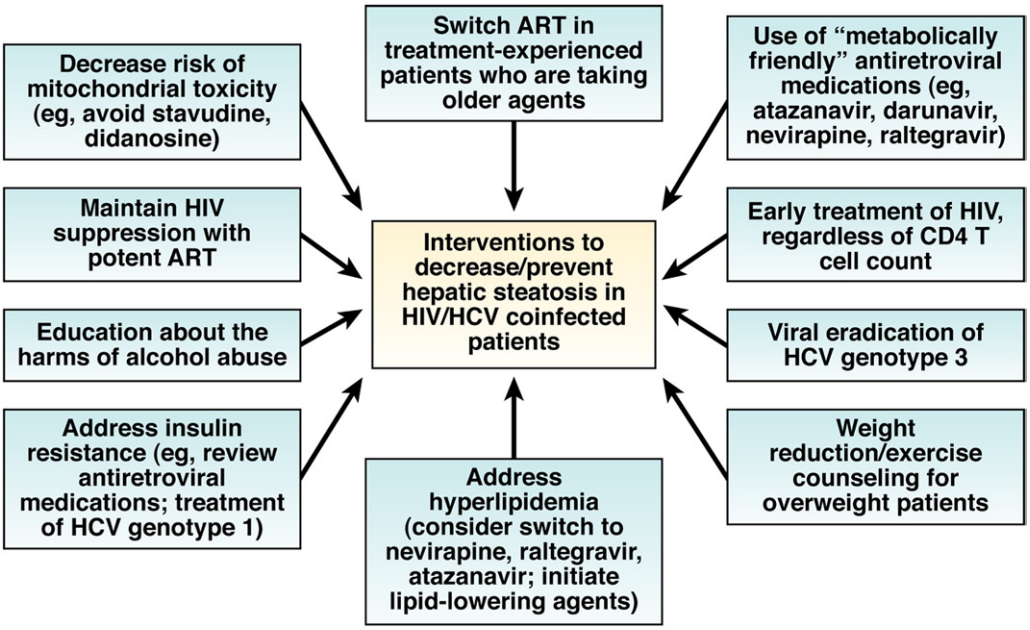

Figure 1. Potentially modifiable factors that contribute to hepatic steatosis in HIV-infected patients.

were associated with reduced steatosis progression. This raises several points for discussion. First, current nucleoside reverse transcriptase inhibitors are safer than earlier agents (eg, stavudine and didanosine). Tenofovir, emtricitabine, and abacavir have a lower affinity for mitochondrial DNA polymerase, rendering them unlikely to cause mitochondrial toxicity. In addition, contemporary PIs, such as atazanavir and darunavir, are more "metabolically friendly" than their predecessors.

This study also adds to a growing literature that suggests that HIV suppression is beneficial to overall liver health.[14,15] With the availability of later-generation antiretroviral agents that are more potent and less toxic, we are finally able to separate out the beneficial effects of HIV suppression from the liver-related toxicities of older drugs that induced steatosis, IR, and hyperlipidemia. In fact, several studies show that fibrosis progression rates in HIV/HCV coinfected patients are similar to HCV-monoinfected patients when HIV suppression is achieved.[15] Recently, a trial of maintenance interferon in coinfected patients was terminated early owing to futility, because progression rates in the control arm (ART alone) were slower than expected.[16] These and other indirect data have led to major shifts in HIV treatment guidelines, which recommend ART in HIV/HCV co-infected patients, regardless of $CD4^+$ T-cell count.

HIV and Transmicrobial Location: Liver-Related Implications

This paradigm shift from drug conservation to earlier HIV treatment acknowledges groundbreaking breakthroughs in HIV pathogenesis, which have direct implications for liver disease progression. Several studies have demonstrated that the virus makes a punishing attack against the $CD4^+$ T-cell population of the gut-associated lymphoid tissue, leaving behind a disrupted mucosal barrier, which can no longer contain microbial products of the gut from entering the peripheral circulation. Evidence of microbial translocation is suggested by high lipopolysaccharide (LPS) levels in plasma of untreated patients.[17] The inflammatory characteristics of LPS may be at the heart of chronic immune activation, which drives HIV disease progression. Interestingly, LPS directly stimulates Kupffer cells and a cascade of events downstream (via Toll-like receptor 4), which eventually leads to the upregulation of proinflammatory and fibrogenic cytokines (eg, tumor necrosis factor-α and interleukin-6). In one study, elevated LPS levels were associated strongly with cirrhosis in HIV-infected patients with HCV who were followed before and after HIV seroconversion.[18] In a similar vein, it is biologically plausible that these same proinflammatory molecules may also "fuel the fire" of lipid peroxidation, thereby leading to stellate cell activation, collagen deposition, and fibrosis progression.

The Hidden Problem of Alcoholism

The relative homogeneity of the Johns Hopkins patient population, and the scarcity of HCV genotype-3 infection, allows us a glimpse into potentially modifiable host factors that confer an increased risk of steatosis.[12] In a multivariate analysis, overweight/obesity and a history of alcoholism were independent predictors of steatosis. Interestingly, although almost half of the patients had a

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