Dideoxynucleoside Analogues Should Be Used Cautiously in Patients with Hepatic Steatosis

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(See article by McGovern et al. on pages 365–72)

Hepatic steatosis, defined as abnormal lipid accumulation in hepatocytes, is found in almost one-third of the United States population. As a result of increases in the prevalences of obesity, insulin resistance, and hyperlipidemia, the number of people with hepatic steatosis continues to expand [1–3]. Because the condition will not progress in the vast majority of steatotic patients, hepatic steatosis was previously considered a benign condition. More recently, steatosis has been recognized as the first step in a pathway that may lead to steatohepatitis, stellate cell activation, fibrosis, and eventually cirrhosis [4]. Furthermore, in patients with coexisting liver diseases, such as hepatitis C virus (HCV) infection, the presence of steatosis can accelerate disease progression.

Because patients with hepatic steatosis are frequently asymptomatic, the diagnosis of steatosis should be considered in patients with associated risk factors, such as obesity, diabetes mellitus, hyperlipidemia, or the use of specific medications [5].

Steatosis is frequently identified when elevated transaminases are noted incidentally during routine laboratory evaluation. Unenhanced hepatic CT is the optimal imaging study for the detection of hepatic steatosis, although it can also be detected by ultrasonography and MRI [6]. However, liver biopsy continues to play a central role in the evaluation of steatosis, because of its ability to detect inflammation, fibrosis, and other associated hepatocyte changes indicative of advanced liver disease.

Hepatic steatosis is found in 40% to >80% of HCV-infected patients [7–9]. In HCV infection, both viral and metabolic factors can lead to steatosis. In patients infected with HCV genotype 3, steatosis is predominantly virus mediated. In these patients, the prevalence and severity of steatosis are elevated (compared with patients who are infected with other HCV genotypes) and correlate with serum and liver HCV RNA levels, and steatosis largely resolves in patients who are successfully treated [10–13]. In patients with HCV genotype 1 infection, host factors, such as excessive alcohol intake, age, central obesity, and hyperlipidemia, are predominant causes of hepatic steatosis. In these patients, steatosis is increasingly recognized as a component of the metabolic syndrome, a condition generally associated with insulin resistance. Hepatic steatosis is also common in HIV-infected patients [14–16]. However, whether HIV directly induces steatosis or whether it occurs secondary to antiretroviral therapy, alcohol use, obesity, or other factors has yet to be determined.

The combination of 2 potentially steatogenic viruses, HIV and HCV, in the same individual may have important pathogenic consequences on the outcome of disease. Six studies—including the study by McGovern et al. [17] in this issue of Clinical Infectious Diseases—have evaluated hepatic steatosis in HIV-HCV–coinfected individuals and have reported a prevalence of 40%–72% [18–22]. However, findings regarding the prevalence of steatosis, factors associated with steatosis, and whether antiretroviral therapy affects steatosis vary greatly between studies (table 1). In 2 studies that included both HCV-monoinfected patients and HIV-HCV–coinfected patients, the prevalence of steatosis was reported to be both higher [22] and lower [19] in HIV-HCV–coinfected patients than in HCV-monoinfected patients. Most studies reported that metabolic factors, such as elevated body mass index (calculated as weight in kilograms divided by the square of height in meters), lipid abnormalities, and age, are also associated with steatosis in HIV-HCV–coinfected patients.

In this issue of Clinical Infectious Diseases, McGovern et al. [17] performed a
<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Steatosis prevalence, %</th>
<th>Steatosis-associated factor(s)a OR (95% CI)</th>
<th>Steatosis-associated ART factor(s)b OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[22]</td>
<td>554</td>
<td>52</td>
<td>Hypertriglyceridemia 6.69 (1.94–23.14) ART use for ≥4 years 1.35 (1.18–1.55)</td>
<td></td>
</tr>
<tr>
<td>[17]</td>
<td>NA</td>
<td>NA</td>
<td>None</td>
<td>ART use for ≥4 years 1.35 (1.18–1.55)</td>
</tr>
<tr>
<td>[18]</td>
<td>NA</td>
<td>NA</td>
<td>White race 11.2 (1.6–79.2) Stavudine exposure 5.1 (1.1–22.9)</td>
<td></td>
</tr>
<tr>
<td>[20]</td>
<td>NA</td>
<td>NA</td>
<td>Increased body mass index 1.30 (1.13–1.49) None</td>
<td></td>
</tr>
<tr>
<td>[21]</td>
<td>NA</td>
<td>NA</td>
<td>HCV genotype 3 infection 3.02 (1.91–4.79) None</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** ART, antiretroviral therapy; NA, not available; NRTI, nucleoside reverse-transcriptase inhibitors; HDL, high-density lipoprotein.

a Factors significantly associated with steatosis on multivariate analysis (P < .05).
b The prevalence of steatosis was not reported, but the mean steatosis scores (± SD) for HCV-monoinfected patients and HIV-HCV–coinfected patients were 0.70 ± 0.69 and 0.50 ± 0.55, respectively.
retrospective analysis to identify factors associated with hepatic steatosis. The study included 183 HIV-HCV–coinfected patients, making it the largest such study, to our knowledge, performed to date in the United States. The principal finding of the study was an association between steatosis and the use of nucleoside reverse transcriptase inhibitors (NRTIs). An even stronger association was observed between steatosis and an NRTI subclass, the di-deoxynucleoside analogues, which are also known as “D drugs” (i.e., stavudine [d4T], didanosine [ddl], and zalcitabine [ddC]).

Similar conclusions were made in 2 other studies. Gaslightwala and Bini [22] reported an association between the use of any antiretroviral agent for at least 4 years and steatosis, whereas Sulkowski et al. [18] found that stavudine exposure was an independent predictor of hepatic steatosis.

Although multivariate analysis revealed that an association between antiretroviral therapy and steatosis in HIV-HCV–coinfected patients has not been a universal finding among the studies that have been performed to date, a connection between antiretroviral therapy and steatosis is becoming increasingly apparent. In these studies, multiple authors have reported weaker relationships between steatosis and antiretroviral therapy, as determined using univariate analysis. For example, undetectable HIV load [17, 19], the use of NRTI-based treatment [21], and cumulative HIV protease inhibitor (PI) exposure [18] were associated with steatosis.

Exposure to certain PIs has been closely linked to metabolic abnormalities, including hyperlipidemia, hyperglycemia, insulin resistance, and diabetes mellitus [23–25], all of which are well-recognized causes of hepatic steatosis. Unlike PIs, which have been linked indirectly to steatosis, the association between NRTIs and steatosis appears to be more direct. Although the mechanism of NRTI-induced steatosis remains obscure, mitochondrial toxicity is likely responsible for their harmful effects [26–29]. D drugs, which were shown by McGovern et al. [17] to be strongly associated with steatosis, are the antiretroviral therapy agents with the strongest capacity to deplete mtDNA through the interaction with DNA polymerase-γ [30]. The connection between mtDNA depletion and steatosis, however, remains to be elucidated. Besides direct effects of NRTIs on steatosis development, indirect effects may also play a role, because thymidine analogues—in particular, stavudine—have been linked to lipoatrophy, insulin resistance, and hyperlipidemia [29].

Another clue to the mechanism of NRTI-induced steatosis may accrue from a more precise histopathologic analysis of hepatic lipid accumulation on biopsies from steatotic patients. Fat is distributed in the hepatocyte in two distinct patterns. In macrovesicular steatosis, frequently associated with alcohol intake, obesity, hyperlipidemia, and type 2 diabetes mellitus, a single large fat droplet displaces the hepatocyte nucleus. Microvesicular steatosis, which is associated with mitochondrial toxicity, is characterized by multiple intracellular droplets within the hepatocyte [31]. HIV-HCV–coinfected and HCV-monoinfected patients may differ in the histologic appearance of steatosis (i.e., macrovesicular versus microvesicular steatosis). Three studies detected microvesicular steatosis in HIV-HCV–coinfected patients [17, 20, 22]. One study also showed an increased prevalence of macrovesicular steatosis among HIV-HCV–coinfected patients than among HCV-monoinfected patients and a higher prevalence of microvesicular steatosis among coinfected patients receiving antiretroviral therapy or NRTIs than among those who were not receiving therapy [22]. Because both microvesicular steatosis and use of NRTIs are implicated in mitochondrial toxicity, these observations support the role of NRTIs in the development of hepatic steatosis.

In HIV-HCV–coinfected patients, multiple processes contribute to the progression of liver disease. HCV pathogenesis is altered in HIV-infected patients, leading to accelerated fibrosis progression [32]. Steatosis has recently been recognized as a cofactor in fibrosis progression in HIV-HCV–coinfected patients. Suspicion of hepatic steatosis should be an additional indication for obtaining a liver biopsy specimen from HIV-HCV–coinfected patients who are initiating an antiretroviral therapy regimen that contains an NRTI.

In this issue of Clinical Infectious Diseases, McGovern et al. [17] have strengthened the connection between NRTI use and steatosis. In the clinical treatment of HCV-HIV–coinfected patients, and especially for those with steatosis, the D drugs should be used cautiously.

Acknowledgments


References


