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## Reply to Remtulla and Decker

TO THE EDITOR—We appreciate the correspondence by Remtulla and Decker [1] in response to our recent article in *Clinical Infectious Diseases* [2]. Remtulla and Decker profile 2 white, male, nonobese patients whose cases of nonalcoholic steatohepatitis (NASH) progressed to hepatic cirrhosis over a multiple-year period, during which time they received antiretroviral therapy regimens that included dideoxynucleoside analogues (stavudine or didanosine) and that suppressed HIV infection. In patient 2, liver biopsy findings were compatible with drug-induced liver disease.

We agree with Remtulla and Decker [1] that, as previously demonstrated by Herman and Easterbrook [3] and Nunez and Soriano [4], exposure to nucleoside analogues (such as zalcitabine, stavudine, zidovudine, and didanosine) is associated with liver mitochondrial toxicity resulting in microvesicular steatosis, lactic acidosis, and mitochondrial DNA depletion. These changes can evolve to fibrosis and macrovesicular steatosis with focal necrosis.

In our analysis, the patients' cumulative median durations of exposure to stavudine and didanosine were just 51 and 31 months, respectively, and nearly one-half of patients had never been exposed to those drugs. Our own data clearly suggest

an etiologic role for prolonged NRTI exposure in the development of nonalcoholic fatty liver disease (NAFLD), but we did not discern progression to NASH or overt cirrhosis, because we did not perform consecutive liver biopsies. We surmise that it is possible that some patients with such drug exposure can indeed experience progression to hepatic cirrhosis.

Several issues are worthy of consideration:

1. The modalities used to monitor the progression from NAFLD to NASH—modalities that increasingly include non-invasive techniques, such as liver elastometry and fibroscan assessments—are diagnostic interventions in evolution that are commonly compared to liver biopsy. Liver biopsy remains a gold standard, although sampling error is a concern [5], especially if differential involvement with NAFLD or NASH occurs in various anatomic liver regions. Given the improved prognosis of HIV infection and the differential histologic pattern of metabolic (macrovesicular) and toxic (microvesicular) liver injury, it would be advisable to perform liver biopsies for patients more often than is done now [6].

2. The determinants of progression of metabolic fatty liver disease in HIV-infected individuals are poorly characterized. Although long-term NRTI treatment is likely a factor, pathophysiologic processes other than mitochondrial toxicity are likely involved. Experience with HIV-uninfected patients who have NAFLD suggests that insulin resistance may be a major determinant of disease progression [7]. However, whether this also occurs in HIV-infected persons remains to be ascertained.

3. Although our findings are consonant with observations made in the general population that persons with NAFLD experience low rates of progression to NASH and cirrhosis [8], we acknowledge that the “full story” of the continuum of liver disease among NRTI-treated patients, its causes, its patterns of progression, and

the optimal modalities for ongoing disease assessment remain to be fully elucidated.

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## Smartphone Utilities for Infectious Diseases Specialists

TO THE EDITOR—I read with interest the