>254 mg/dL and an earlier time to an adverse event [5]. The multiple biases that affect the report by Schewe et al. [1] may have led to an underestimation of the potential of tenofovir, compared with stavudine, to be associated with a better lipid profile. This result can be easily observed when homogeneous populations are prospectively enrolled in controlled trials (as opposed to open-label studies), when antiretroviral-naive patients are enrolled, when subjects who have received prior or concurrent antilipidemic therapy are excluded, and when open-label switches to regimens that include a protease inhibitor, boosted protease inhibitor, or efavirenz are prohibited [2–5]. The residual statistical significance emphasized by Schewe and colleagues probably represents tenofovir’s value over stavudine in patients with HAART-related dyslipidemia.

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Reply to Manfredi

To the Editor—We agree with Manfredi [1] that our study may have underestimated some of the beneficial effects on lipid levels associated with switching from stavudine to tenofovir. His remarks concerning the validity and the potential of bias in observational cohort data are correct; however, these issues are generally inherent to the design of cohort studies. Our study included a selected group of patients with advanced disease who had a long treatment history and complications of antiretroviral therapy. If we had allowed concomitant changes in antiretroviral therapy (ART), such as switching from a protease inhibitor to a nevirapine-containing regimen, that would have invalidated our results.

Manfredi’s [1] major criticism concerns the possible influence of changes in concomitant antiretroviral medications or lipid-lowering agents on lipid levels. As stated in the Methods section of our article [2], only patients with no other concomitant changes in ART or lipid-lowering therapy were included. The values were monitored and included in the study only until any change in ART or lipid-lowering therapy occurred. Manfredi may have missed that this major source of bias was excluded.

In our study, 5 patients were receiving statins, and 5 were receiving fibrates. To provide the SD or the statistical mean for the median duration of lipid-lowering therapy received before treatment would be inappropriate because of the low number of cases (n = 10). Manfredi’s [1] criticism of the long duration of pretreatment lipid-lowering therapy (4–47 months) is not warranted. Usually, 1 month after initiation of or after a change in lipid-lowering therapy, new levels of cholesterol and triglycerides are reached. Thus, the lower limit of the range observed allows for a steady state in lipids.

Median times of previous antiretroviral therapy were given, because the values did not fit a normal distribution curve; therefore, it would be inappropriate to calculate means and standard deviations. In clinical trials, the steepest increase in lipid levels is seen within the first 8 weeks after initiation of antiretroviral therapy [3, 4]. We believe that the duration of stavudine therapy was sufficiently long to see significant effects on lipid levels, although it is true that lipid levels during receipt of stavudine therapy continue to increase over time.

Manfredi [1] questioned the reasons for the switch, as well as the definition of hyperlipidemia, which was any elevation in the cholesterol or triglyceride level (or both). In clinical practice, many factors contribute to the decision to change an antiretroviral regimen, and in fact, lipodystrophy associated with stavudine treatment—and not hyperlipidemia—was the driving force for a switch in most patients. Although the extent of the reduction in the cholesterol level after 3–18 months does not compare with that for high–dose statin therapy, any reduction in cholesterol levels is clinically relevant and is associated with a reduced risk of cardiovascular diseases, for which HIV-infected patients are at increased risk.

Manfredi [1] reproaches us for not having cited 4 important articles on the effects of tenofovir on lipid levels. However, 2 of these articles (Gallant et al. [5] and Domingo et al. [6]) were discussed and cited. The 2 other articles, which were by Latham et al. [7] and Jones et al. [8], had not yet been published at the time that
our manuscript was submitted to *Clinical Infectious Diseases*.

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