made solely on the basis of the deformities of the limbs observed [2]. More recently, the Queen of Punt syndrome, clinically described as a rugged face, gluteal femoral obesity, hyperlordosis, and symmetrical deposits of fat on the trunk, limbs, and thighs, seems to be a more unifying explanation for the graphic representation of the Queen [3]. This syndrome appears to be a single phenotype grouping several dermatological pathologies (Launois Ben-saude lipomatosis, Dercum disease, neur-olfibromatosis, congenital lipodystrophy, achondroplasia, familial obesity, Proteus syndrome, and X-linked dominant hypophosphatemic rickets) [4–6]. Clearly, in the absence of any genetic or bioanthropo-logical evidence of a mummy, the clinical diagnosis that should be ascribed to the Queen of Punt still remains elusive after 34 centuries.

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References


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Reply to Bodi et al.

To the Editor—We congratulate Dr. Bodi and colleagues for their recent article [1], which demonstrates a significant as-sociation between the use of guideline-concordant antibiotics and mortality for patients with community-acquired pneu-monia who require hospitalization in an intensive care unit. However, we wish to correct an error in their article regarding our recent article [2] in the American Jour-nal of Medicine. In the discussion, the au-thors state that “the effects of other factors such as age, presence of comorbidities, and complications associated with pneumonia (e.g., septic shock and receipt of mechanical ventilation) were not analyzed” [1, p. 1714]. This is incorrect. Comorbid conditions and age are part of the pneumonia severity index developed by Fine et al. [3], which was included in our multivariable models. The pneumonia severity index is a validated prediction rule for 30-day mortality for patients with community-acquired pneumonia. This rule is based on 3 demographic characteristics, 5 comorbid illnesses, 5 physical examination findings, and 7 laboratory results and radiographic findings obtained at the time of presen-tation. Age, chronic renal disease, liver dis-ease, congestive heart failure, prior stroke, and neoplasia are all components of the pneumonia severity index.

Regarding adjusting for complications associated with pneumonia, although we did not adjust for these 2 factors directly, we included a dichotomized variable for the need of hospitalization in an intensive care unit as one of the factors in our mul-tivariable analyses. We found that need for hospitalization in an intensive care unit was a much stronger predictor of mor-tality than was either septic shock or me-chanical ventilation as individual vari-ables. In addition, we were unable to put all of these factors in the same multivari-

Improvement of Dyslipidemia during Different HAART Regimens: Tenofovir- versus Stavudine-Containing Antiretroviral Combinations

To the Editor—Schewe et al. [1] recently analyzed the switch from antiretroviral regimens that contain stavudine to those
that contain tenofovir, but their conclusions about dyslipidemia are hampered by the study’s limitations, which probably did not allow them to obtain the same degree of evidence that has been obtained else-where [2–5]. The study by Schewe and colleagues was conducted retrospectively with only 66 patients from a treatment center that cares for 1860 patients. How is 3.5% of the cohort representative of the entire population? Patient selection and follow-up were conducted on an open-label basis, so that the only characteristic they were ensured of sharing was the “switch from stavudine to tenofovir without additional changes to either their antiretroviral regimen or their concomitant lipid-lowering therapy” [1, p. 145], whereas the authors did not control for a number of relevant variables that could have weakened the study. The authors claim that no changes were allowed in lipid-lowering treatment ≤1 month before the stavudine-tenofovir switch, and prior stavudine treatment was considered to be “stable” when it had been received for at least 1 month [1]. Other than the confounding role of the lipid-lowering therapy, the authors do not specify whether statins, fibrates, polyunsaturated omega-3 fatty acids, niacin, or other drugs or drug combinations were used; this omission is important, because a very different action against cholesterol triglycerides is expected with these agents. Unspecified lipid-lowering therapy was received before the switch to tenofovir by 15.2% of the 66 patients for a median duration of 18 months; the range of the treatment duration was very extensive (4–47 months), and no SD or SE values were given. The lack of a change in the unspecified lipid-lowering drugs received in the last month before enrollment may have generated unpredictable effects on serum lipid values, as may have the very variable prior stavudine exposure.

The durations of prior HAART and stavudine use were highly variable (duration antiretroviral therapy, 1–13.5 years; duration of stavudine therapy, 1–95 months).

The leading reason for the switch from stavudine to tenofovir (for 79% of patients) was “some degree of physician-defined lipodystrophy,” but “hyperlipidemia” (which is not better defined) was reported for only 16.7% of patients, whereas 15.2% of subjects switched from stavudine because of virological failure, which is a profoundly different situation. Although some details are provided regarding novel HAART combinations (which included drugs associated with an elevated risk of dyslipidemia, such as lopinavir-ritonavir and efavirenz), the prior regimens that were not mentioned were probably represented by multiple different combinations that affect the lipid profile differently.

During the course of the study (4–36 months), the mean cholesterol level “decreased significantly (mean decrease, 18 mg/dL) within 3 months (P = .003) and remained significantly lower than baseline values during the 18 months of follow-up (mean decrease, 36 mg/dL; P = .002)” [1, p. 146]. Once again, SD and SE values are not reported. Although statistically significant, a mean decrease in the cholesterol level of 18 mg/dL for patients who had a mean baseline value of 227 mg/dL does not appear to be clinically significant. Although Schewe et al. [1] report that 67% of patients had baseline cholesterol levels >200 mg/dL, the follow-up values are not provided, although figure 2 in the article reveals that a sustained percentage of subjects had cholesterol levels that remained greater than this threshold value during the 18-month period [1]. The trend in triglyceride values is not evaluable in these experimental conditions, because the prior HAART regimens are not reported, and a relevant number of patients had their regimens switched to include a protease inhibitor (25.8% of enrolled subjects) or efavirenz (40.9%) [1]. Because these latter compounds can cause hypertriglyceridemia [6, 7], all data regarding triglyceridemia cannot be accurately interpreted.

Of the 7 pertinent references, 4 are conference abstracts, but relevant literature findings are poorly or not discussed [2–5]. A prospective, randomized, double-blind study assessed 602 antiretroviral-naive patients who received tenofovir or stavudine, in combination with lamivudine and efavirenz, and who were observed for 144 weeks [2]; clear-cut increases in both fasting cholesterol and triglyceride levels were observed in the stavudine group [2]. A significant increase in the triglyceride level was observed among stavudine-treated patients (P < .001) [2], although the role played by efavirenz cannot be ignored [6, 7].

Another prospective study of regimen switches observed patients for whom stavudine was switched to tenofovir; hypertriglyceridemia and hypercholesterolemia occurred in 271 and 193 subjects, respectively [3]. Neither substitution of other drugs nor receipt of antilipidemic compounds was allowed concomitantly with the introduction of tenofovir, and the duration of previous stavudine treatment was 2–5 years. At the week 12 analysis [3], a strongly significant (P < .001) decrease in triglyceride and cholesterol levels was observed (mean decrease in the cholesterol level, 34.8 mg/dL), which differs from the observations of Schewe et al. [1].

Latham et al. [4] showed that adherence to coformulated zidovudine, lamivudine, abacavir, and tenofovir in a simplified salvage regimen was associated with a decreased cholesterol level among heavily pretreated individuals who maintained virological suppression. Jones et al. [5] examined 1664 patients with baseline cholesterol levels <215 mg/dL who started receiving their first HAART regimen (57.1% received 2 nucleoside analogues and a nonnucleoside reverse-transcriptase inhibitor, 38.4% received 2 nucleosides and a protease inhibitor, and 4.4% received 2 nucleosides plus a boosted protease inhibitor). Regimens that contained stavudine or a protease inhibitor were associated with a significantly higher risk of development of the established end point of hypercholesterolemia (cholesterol level,
>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 significance emphasized by Schewe and colleagues probably represents tenofovir’s significance emphasized by Schewe et al. [1] may have led to a possible influence of changes in concomitant 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...