drome” as the immediate cause of death when chart review clearly showed that the patient died of the complications of end-stage liver disease. The inaccuracy of death certificates has been reported in the literature [18–20].

We wish to emphasize that our statement that hepatotoxicity is a limiting factor for the use of highly active antiretroviral therapy in the 1998 cohort is not meant to discourage initiation of antiretroviral therapy for patients with HIV/HCV coinfection. We report that the ability of clinicians to treat HIV infection was restricted by the underlying liver disease, and we advise that close laboratory monitoring be done during highly active antiretroviral therapy, as recommended by the US Public Health Service and the Infectious Diseases Society of America [15].

The burden of disease among HIV-seronegative patients with hepatitis C infection is expected to increase during the next 2 decades—the number of deaths related to liver disease is expected to triple. We fully expect that this dismal picture will be even more accentuated among our HIV-infected patients, whose rates of fibrosis progression are accelerated [21]. Cainelli and colleagues suggest that we may be overestimating the need for IFN-ribavirin treatment of chronic hepatitis C [2]. We disagree, and we suggest that an approach that embraces aggressive treatment of HIV infection without careful evaluation for possible underlying chronic active hepatitis may come back to haunt us in the decades to come.

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References

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Tuberculosis Recurrence after Directly Observed Therapy

Sr.—The analysis of tuberculosis recurrence by Narita et al. [1] addresses the interesting question of why tuberculosis is not always cured by directly observed therapy (DOT). Their report reempha-
sizes the well-known contribution of nonadherence to acquired drug resistance but leaves many questions unanswered. Was DOT administered on both an outpatient and an inpatient basis? What was the patient’s actual adherence to therapy? What were the methods, duration, and completeness of posttreatment surveillance? The availability of data on serum drug levels for a relatively large sample (“approximately half” of 193 patients) is a potential contribution of the study, yet the authors elected not to present these data.

The recurrence rate (13%), which is remarkably high for patients who have received DOT, requires explanation. The negative results regarding risk factors for recurrence carry little weight, since the likelihood of type II error is high in the statistical analyses (note the wide confidence intervals). Were any clinical features of the tuberculous disease associated with later recurrence? Were any patients at unusual risk for exogenous reinfection because of their place of residence or exposure history (and/or immunodeficiency)? In summary, while the authors may be correct in their final views on the risk factors analyzed, no reliable conclusions are possible on the basis of their brief and sketchy report. Their approach to elucidating tuberculosis recurrence, although commendable in principle, would require data for a larger number of such patients to be statistically valid—a difficult goal for any single treatment center to realize.

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Reply
Sir—We appreciate the thoughtful comments by Dr. Hill [1] concerning our article [2]. As we stated in the article, the patients in the study were those admitted to A. G. Holley State Hospital, a tertiary referral facility, which treats patients with tuberculosis (TB) who are unable to complete TB therapy on an outpatient basis. Thirteen percent of those admitted had a recurrence of TB that previously had been “adequately” treated. Most had received their previous TB treatment as traditional outpatient directly observed therapy. “TB recurrence” was defined as TB disease in persons who had been free of disease, as determined by microbiologic criteria, for at least 3 months after they had received 6 months of directly observed therapy (as documented by medical records).

For posttherapy surveillance, the patients had a follow-up evaluation every 6 months. TB recurrence, when seen, occurred an average of 2.1 years after the end of therapy. In population-based, prospective studies, the risk of TB recurrence has been reported to be 3%–5% [3, 4]. The high recurrence rate of 13% that we found among the patients in our series was due, in part, to the type of patients admitted to A. G. Holley State Hospital. Although we could not distinguish exogenous reinfection from true relapse due to the unavailability of specimens for molecular analysis, no specific clinical features of TB disease appeared to be associated with recurrence among HIV-positive or HIV-negative patients.

We are particularly encouraged that many clinicians and investigators are increasingly interested in the relationship between serum drug levels and the risk of TB recurrence. Although data presented in our brief report were preliminary, we plan to publish the results of a collaborative effort to analyze pharmacokinetic data further.

We acknowledge that our study had limited statistical power, a point that we discussed in the article. It is important to note that, although the lack of statistical power, as reflected by wide confidence intervals, results in less precision, it does not necessarily threaten the validity of the point estimate.

Dr. Hill’s comments on our article raise important issues concerning the need for further clinical research on patients with TB. We agree that prospective studies involving large numbers of patients at multiple centers are needed to answer many important clinical questions regarding TB recurrence.

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