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## Reply

In the absence of postexposure prophylaxis for hepatitis C virus (HCV) infection, the current recommendations for postexposure management of health care professionals in the United States [1] are intended to reduce the risk of chronic disease by identifying infected persons early and thereby allowing those individuals to receive appropriate medical management, including antiviral therapy, if appropriate. The ideal timing, frequency, and type of follow-up testing are controversial, as are the timing and regimen of antiviral therapy to prevent chronic infection and disease.

The main reason for the controversy is a lack of data. For example, we recommend that the source of the exposure be tested for antibody to HCV and that all positive results of screening tests be confirmed by a supplemental antibody assay (i.e., recombinant immunoblot testing) [1]. Others might recommend that the source be tested for HCV RNA. However, there are insufficient data to support determination of the need for follow-up solely on the basis of the results of testing for HCV RNA; virtually all studies of the risk of HCV transmission following an occupational exposure have been based on anti-HCV testing. There are also insufficient data on which to base a recommendation for treatment of acute HCV infection because there are no data on the effect of treating patients with acute infection who have no evidence of disease [1, 2]. Treatment begun early in the course of chronic infection might be just as effective and would eliminate the need to treat per-

sons whose infections spontaneously resolve. Even if we considered treating only those who had positive HCV RNA test results 3–4 months after exposure, the appropriate treatment regimen is unknown [3]. Finally, we do not know the frequency of HCV RNA testing or the specific length of HCV RNA testing follow-up that is adequate to document a lack of HCV transmission after exposure to an HCV-positive source.

Determining the ideal approach to the management of health care workers who have been exposed to HCV is particularly problematic because most persons exposed do not become infected, and, of those who do become infected, most are asymptomatic. Developing broad (e.g., nationwide) recommendations for screening in such a situation requires taking into account both practical and scientific considerations [1]. As De Carli et al. [4] indicate, routine HCV RNA testing of every health-care worker exposed to an HCV-positive source would be extremely costly and of low yield. In contrast, HCV RNA testing for the purposes of clinical diagnosis in a person with symptoms of acute hepatitis C, as described by Garcia et al. [5], would usually be considered part of a standard medical evaluation. However, this does not mean that such testing should be performed “soon after receipt of [every] needlestick” [5, pg. 1634]. In the limited studies available, antiviral treatment of persons with symptomatic acute hepatitis C >12 weeks after exposure to HCV resulted in high sustained-response rates [6].

Balanced against all of these issues are the psychological needs of the exposed persons and the knowledge and preferences of the medical professionals who are caring for them. Some health care professionals are so anxious after an exposure that they want to be tested for HCV RNA every week; others do not want to be tested at all. Some physicians offer treatment to exposed persons as soon as their HCV infection is detected; others recommend waiting to determine if the infection will

naturally resolve. Thus, until additional data are available on which a consensus can be reached, recommendations for follow-up after exposure to HCV should be flexible.

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## Rifampin and Recurrence of Tuberculosis among Patients Infected with HIV

SIR—Korenromp et al. [1] have performed an impressive meta-analysis on the subject of tuberculosis recurrence among patients infected with human immunodeficiency virus (HIV), but we feel their conclusions should be more nuanced, given that their analysis has several methodological limitations, some of which have been addressed by the authors and others of which have not.

First, some studies that meet the inclusion criteria given for this systematic literature review seem to be missing, including randomized controlled clinical trials (RCT) and/or studies reporting on a high number of patients [2–7]; the group of such articles cited in our reference list is nonexhaustive. More importantly, the heterogeneity between studies—an important issue in meta-analysis [8]—is nowhere discussed in their article, and it is not clear whether their meta-analysis tested for heterogeneity or investigated the sources of any heterogeneity. Understanding variations of effect (or outcome) between studies can be highly relevant, both clinically and scientifically, as was demonstrated, for instance, by the controversy around bacillus Calmette-Guerin, the vaccine against tuberculosis [9]. Eyeballing of the results across the studies included by Korenromp et al. [1] suggests heterogeneity. Apart from numerous variations between study methods, a probable source of heterogeneity between studies that report on TB recurrences might be the respective contribution of relapse and reinfection. Most tuberculosis recurrences usually occur in the first 6 months after therapy [10]; in the review by Korenromp et al. [1], this fact was confirmed for HIV-negative patients only. This is probably because true relapse, which reflects insufficient treatment of the first TB episode, is more likely to occur soon after this first episode, whereas the risk of recurrence following reinfection is more likely to be constant over time. Therefore, studies with a short duration of follow-up will report a higher recurrence rate than will studies with a longer duration of follow-up. Early and late recurrences could be best analyzed separately, because their causes and determinants are likely to be different. In such circumstances, computing pooled estimates (such as in table 2 of Korenromp et al. [1]) will produce results that, though they might be mathematically correct, are clinically and epidemiologically less meaningful. Moreover, the 2 causes of recurrence—namely, relapse and reinfection—

being independent from each other (i.e., more instances of one does not imply fewer instances of the other), a summary measure of their respective proportions across the few studies that document both of them is even more misleading, as we have argued in our recent review on the subject [11].

It is highly plausible that the risk of TB recurrence increases with an increase in background TB incidence, but computing an estimate of this increase would probably produce results too imprecise to be useful. As for the possibility that a higher risk of recurrence caused by reinfection is found among HIV-positive patients than among HIV-negative patients, this is also highly plausible and has been documented [12]); however, we believe the evidence is not sufficient to draw conclusions regarding a decrease in the risk of true relapse with an increase in the duration of rifampin therapy administered as part of a rifampin-containing treatment regimen.

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## Reply

SIR—We thank Lambert et al. [1] for comparing and contrasting their recent analysis of tuberculosis (TB) recurrences and concurrent HIV infection [2] with our own [3]. It is true that our meta-analysis did not include every study of TB recurrences in which HIV was not a consideration. We included a total of 41 studies of HIV-uninfected patients and found that the relative risks of recurrence associated with HIV-positivity and with the duration of rifampin treatment did not change with the addition of the last few studies of HIV-uninfected patients that we identified. Rather, the results were determined by the more-limited set of data on HIV-positive patients, consisting of 21 studies.

Of the additional studies suggested by