Reply to Sartin et al.

Sir—we appreciate the comments by Sartin et al. [1] on our article [2] encouraging routine HIV testing. For HIV testing to become a routine part of medical care, procedural barriers, including signed informed consent and pretest counseling, need to be reexamined.

The policy of obtaining signed informed consent prior to HIV testing was created to protect the privacy of patients at a time when therapy for HIV infection was minimal or nonexistent. Pretesting requirements have not changed in concordance with the development of HAART. Now, with widespread availability of potent antiretrovirals, pretest requirements need to be minimized to increase the number of individuals being offered HIV tests. As noted by Sartin et al. [1], there are already new federal policies in effect to protect patients’ private health information.

Pretest counseling also needs to be simplified. As recommended recently by the Centers for Disease Control and Prevention [3], pretest counseling should not be a barrier to testing. Rather than providing information through lengthy counseling, which many healthcare providers might view as overly burdensome, information regarding HIV infection and treatment can be provided in a more succinct form and a more time-efficient manner.

Routine HIV testing will not necessarily cause a significant increase in paperwork and testing-associated bureaucracy, if pretest requirements can be modified. HIV testing can be incorporated into other healthcare activities, such as annual examinations. It can also be performed routinely with other routine blood testing unless patients “opt out.” Pretest counseling can be replaced by the provision of information about HIV infection via an appropriate written pamphlet. Further counseling will be necessary only for patients who test positive or those who identify themselves as being at high risk.

We advocate, in concert with Sartin et al. [1], a reevaluation of HIV testing policies and procedures in order to eliminate barriers and obstacles to routine HIV testing. The only way to reduce the number of individuals who are unaware of their HIV-infection status is to increase the number of HIV tests being offered. It is time our testing policies catch up with our ability to treat HIV infection.

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Systemic Steroid Treatment of Paradoxical Upgrading Reaction in Patients with Lymph Node Tuberculosis

Sir—we read with interest the article by Hawkey et al. [1]. They report that paradoxical upgrading reactions (PUR) to antituberculous treatment occurred in 23% of non–HIV-infected patients. This is the highest percentage ever reported in an immunocompetent population, in whom PUR is usually <5% [2, 3]. A plausible explanation is that the authors’ definition of PUR includes worsening of tuberculosis in patients treated for only 10 days, and the presence of a discharging sinus and persistent lymphadenopathy. We think that a minimum of 4 weeks should elapse between the start of antituberculous therapy and the development of PUR because, by definition, an initial clinical improvement should take place before worsening [2–4]. Also, because a discharging sinus was a well-known complication of benign tuberculous lymph node disease in the preantibiotic era, it is difficult to justify as a defining symptom of PUR.

These considerations are important in the analysis of the effect of corticosteroids in the treatment of PUR. In contrast with previous studies [2–5], Hawkey et al. [1] did not find any evidence of a beneficial effect and questioned the effectiveness of corticosteroids to treat PUR. We think that their analysis could be biased by their definition of PUR, by the different use of steroids depending upon the severity of disease, and by the difficulties involved in the follow-up of the evolution of PUR by means of medical charts. In our experience with patients with severe PUR to antituberculous treatment after exposure to infliximab, anti-inflammatory treatment played an important role [4]. In our cohort study, surgery to control PUR was required in all patients that did not receive anti-inflammatory agents. Conversely, no patient treated with anti-inflammatory drugs required surgery. Our results, and the well-known beneficial effects of corticosteroid therapy in reducing edema in intracranial tuberculomas [5–7], would suggest that severe PUR must be treated with steroids. Dosing and duration of treatment have not been defined; our limited experience would indicate that 4–6 weeks of oral steroids is adequate.

Hawkey et al. [1] made the interesting observation that high peripheral blood monocyte counts at baseline were associated with greater risk of developing PUR. Elevation of the TNF-α level, stimulated by lipoarabinomannan and other lipopolysaccharides present in the Mycobacterium tuberculosis cell wall, has been postulated as an initial step in the pathogenesis of PUR [8, 9]. TNF-α is secreted by macrophages and monocytes, and the
observations of Hawkey et al. [1] give support to the hypothesis that increased production of this cytokine and its proinflammatory activity play a central role in the development of PUR. Better understanding of PUR as an inflammatory disease is important to understanding the beneficial effect of steroid treatment in these patients.

In conclusion, the optimal management for PUR is unknown. However, because the beneficial effect of steroids in patients with severe PUR has been well documented, early recognition and treatment should result in a more favorable outcome. Nevertheless, the role of anti-inflammatory therapy deserves further study.

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Reply to Garcia Vidal and Garau

Sir—We thank Drs. Garcia Vidal and Garau [1] for their interest in our article [2]. We agree with their opinion that paradoxical upgrading reactions (PUR) in tuberculosis arise as a consequence of immune dysregulation. We also agree with the statement in their final paragraph that the optimal management is unknown; this needs to be defined by clinical trial. Two questions were raised regarding the incidence of PUR and its treatment with steroids. With respect to incidence, our data do not suggest that some PURs were identified in lymph nodes that were enlarging before treatment, nor that an arbitrary cut-off time could distinguish PURs from “normal” enlargement of lymph nodes before treatment had begun to have an effect (figure 1). The onset of PUR occurred 10–406 days after the start of therapy. The median time to onset was 46 days after the start of therapy, and the lower quartile was 25.5 days. The geometric mean was 58 days, and there was no evidence that the time to onset, when log-transformed, was not from a normal distribution (Shapiro-Wilk test for normality). In patients with sinus formation, it was a complication of new or enlarging lymph nodes. The clinical course of these patients supports the statistical evidence that early paradoxical reactions can occur. Several patients who developed PUR within the first month of treatment went on to experience complex reactions, with further new symptoms occurring after 28 days. An arbitrary cut-off time at 28 days would clearly fail to describe these early but prolonged reactions adequately.

Of course, it is entirely possible that incidence varies according to geographic location. Although we documented no significant association, there was a trend in our analysis toward a greater likelihood of vitamin D deficiency among those who subsequently developed a PUR [2].

Figure 1. Histogram of time of onset of paradoxical reactions. TB, tuberculosis.