Reply to Tattevin et al.

Sir—Dr. Tattevin et al. [1] pose two questions regarding the patient (an illegal immigrant) from case study 6 in our article [2] about patients treated with posaconazole. They asked, “(1) what was done to prevent this patient's expulsion from the United States, given the knowledge that it was likely a death sentence, and (2) did the pharmaceutical company that manufactures this precious investigational drug try to deliver it to the patient after he had been returned to Mexico?” [1, p. 1212].

In answer to the first question, the patient was enrolled in the trial and received medical care regardless of his nationality (he was a Mexican citizen living illegally in the United States) and was treated at University Health System, a public institution in the United States. He received medications for HIV infection from the state of Texas. However, federal immigration authorities abruptly sent the patient back to Mexico. This happened before any of the physicians involved in his care could intercede on his behalf. We are also uncertain whether any condition that is not immediately life-threatening would prevent deportation of an illegal immigrant. Furthermore, it is unfortunate that the patient himself was poorly compliant with antiretroviral therapy and never achieved either HIV suppression or immune reconstitution. Because of this, he was at high risk for death due to AIDS, regardless of whether or not he remained in the United States.

In regard to the second question, the pharmaceutical company enrolled this patient in the trial without asking questions about his residency status. However, once a patient in a clinical trial is unable to obtain follow-up care, for whatever reason, it would be unethical to continue administration of an experimental drug that might have unforeseen adverse effects. At the time of this study [2], it was unknown whether the drug was lifesaving. This clinical trial was not being conducted in Mexico, and because there could not have been appropriate follow-up, it was not possible for the company to supply the drug. This patient’s situation illustrates an unfortunate reality: we live in a have or have-not world in terms of the distribution of medical (and other resources) and lines on a map sometimes count for more than human suffering.

Acknowledgments


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References


The Importance of Culture for Diagnosing Tuberculosis

Sir—We read with interest the article by Munyati et al. [1] elucidating causes of chronic cough in 544 primary health care attendees with a high prevalence of HIV infection. For this study, tuberculosis diagnosis was attempted using both acid-fast bacillus smear and solid-media mycobacterial culture. A total of 83% of the study population was HIV-infected, making this an ideal population to address what role culture should play in the diagnosis of tuberculosis in areas where HIV is epidemic. Of the 544 clinic attendees with a chronic cough, 184 (34%) had microbiologically confirmed tuberculosis (by positive smear and/or culture results), and 19 (10%) of these 184 had tuberculosis confirmed by culture alone. Of the 162 HIV-infected patients with tuberculosis diagnosed on the basis of bacteriological test results, 17 (10%) had the diagnosis microbiologically confirmed by culture results alone. In addition, 17 (27%) of 62 HIV-infected patients diagnosed with tuberculosis who had negative smear results had cultures positive for Mycobacterium tuberculosis. We therefore strongly disagree with the authors’ conclusions that “the findings of TB culture added relatively little to the findings of fluorescent microscopy of concentrated sputum specimens” [1, p. 1818].

Since 1996, the World Health Organization has promoted tuberculosis case detection through sputum acid-fast bacillus smear microscopy [2]. Although simple and inexpensive, this method is less sensitive than mycobacterial sputum culture [3, 4], particularly among HIV-infected patients. Emerging data demonstrate the significant benefit of sputum culture for detection of tuberculosis in HIV-infected patients. Recently, our research group has shown that as many as one-third of asymptomatic HIV-infected patients with CD4 cell counts ≥200 cells/mm³ have subclinical tuberculosis that can only be detected using sputum culture [5]. Follow-up data on this small group of HIV-infected patients indicated that 90% were still alive at 2 years, raising the possibility that detection by sputum culture and early treatment may improve the outcome of HIV-associated tuberculosis. Mycobacterial sputum culture is generally considered too impractical and too
expensive for routine use in resource-poor areas. At an estimated $2 per culture, the cost for each additional tuberculosis case identified in HIV-infected persons in the Munyati study [1] would range from $53 to $163 (depending on the number of cultures per patient, which is usually 1–3). The cost of not using culture (e.g., increased transmission and higher mortality rates) would certainly be greater.

We believe that the use of mycobacterial culture to identify tuberculosis in resource-poor areas should be revisited. The work by Munyati et al. [1] adds to the growing evidence that culture can contribute significantly to the diagnosis of tuberculosis, a disease that remains the leading cause of death in HIV-infected persons.

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References


Reply to Talbot et al.

Sir—We thank Talbot et al. [1] for their interest, and we fully agree that management of smear-negative cases of tuberculosis in Africa needs review. One of the main aims of our study [2], which was undertaken at the primary health care level, was to determine the burden of smear-negative, culture-positive tuberculosis among patients with chronic cough in Harare. We were surprised by the low numbers. Smear-negative, culture-positive tuberculosis was diagnosed in only 17 (8%) of 207 HIV-positive patients with tuberculosis and 2 (7%) of 27 HIV-negative patients with tuberculosis [2]. In terms of clinical usefulness the contribution was even lower, with positive culture results preceding decision to treat tuberculosis in only a handful of patients.

Our experience was that the recommended approach in Africa—the use of serial smears, radiologic imaging, and trial of antibiotics, followed by response to treatment for tuberculosis—contributed more information in a more timely fashion than did use of culture. Culture may have been more useful had we been using either a rapid-liquid culture system or a less sensitive smear protocol (we performed multiple serial smears that were examined under fluorescence after concentration).

The findings reported by Mtei et al. [3] are interesting, but also demonstrate the limitations of culture: only 2 of their 10 patients with clinical tuberculosis had culture results that were positive, and 8 of the 10 patients with culture-positive subclinical tuberculosis received the test results too late to prevent commencement of isoniazid preventive therapy. Culture-positive subclinical tuberculosis is well described from the days before treatment for tuberculosis was available, particularly in children [4]. We have specifically looked for cases of subclinical tuberculosis using systemic cross-sectional population-based prevalence surveys. The point prevalence of asymptomatic tuberculosis with positive culture results was <3% in HIV-positive South African gold miners [5] and <0.5% in HIV-positive Harare factory workers (E.L.C., unpublished data). Because of this, we are not convinced that the very high burdens reported by Mtei et al. [3] are representative of HIV-infected adults in the general community. A number of large, ongoing studies of the prevalence of coinfection with HIV and Mycobacterium tuberculosis in Zambia, South Africa, and Zimbabwe should provide a definitive answer in the coming year.

The barriers to being able to use culture for diagnosis at the primary health care level in Africa are considerably greater than the reagent costs. Strengthening health systems so that patients with tuberculosis can and do present early, improving follow-up so that positive culture results can be reacted to in a timely fashion, expanding laboratory facilities and personnel to the extent needed—each of these would require a considerable investment. A recent technical statement from the International Union Against Tuberculosis and Lung Disease concurs with our suggestion [2] that increasing the sensitivity of sputum-smear microscopy should be the higher priority in resource-poor areas, and concludes, “Culture is much more difficult to set up and is usually impossible to decentralise….The technique should only be used as a preliminary to drug susceptibility testing” [6, p. 355]. We agree that the use of culture needs to be revisited, particularly to support active case-finding among known HIV-positive persons; however, there are competing priorities. For example, in 2004 our study clinics had minimal capacity to test for HIV infection, and they still do not offer long-term care for HIV-infected persons.