extreme immunosuppression with very low CD + cell counts.

What we believe, on the basis of these data, is that a possible phenomenon of higher infectiousness of HIV-infected patients with tuberculosis probably is limited to the minority of such patients who develop active disease at an advanced stage of HIV infection, so that on a large scale this should not be considered as a constant feature of tuberculosis/HIV association. In any case, we agree with Drs. Castro and Dooley that those involved in the care of these patients should be aware of such possibility and adequate infection control practices must be ensured in the care centers hosting these patients. Future investigational efforts probably will provide definitive answers to this question.

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REFERENCES

1. Di Perri G, Cadeo GP, Castelli F, et al. Transmission of HIV-associated tuberculosis to healthcare workers. *Infect Control Hosp Epidemiol* 1993;14:67-72.
2. Di Perri G, Cazzadori A, Concia E, Bassetti D. Transmission of HIV associated tuberculosis to health-care workers. *Lancet* 1992;340:1412.
3. Breslow NE, Day NE. *Statistical Methods in* Cancer *Research, 2. The Design* and *Analysis of Cohort Studies.* Lyons, France: IARC Scientific Publications; 1987.
4. Elliott A, Halwindi B, Luo B, et al. The human immunodeficiency virus on tuberculosis in Zambia: infectivity. Presented at the Seventh International Conference on AIDS; June 1621, 1991; Florence, Italy.
5. Cauthen GM, Dooley S, Bigler W, Burr J, Ihlo W. Tuberculosis (TB) transmission by HIV-associated TB cases. Presented at the Seventh International Conference on AIDS; June 1621, 1991; Florence, Italy.
6. Manoff SB, Cauthen GM, Stoneburner RL, et al. TB patients with AIDS: are they more likely to spread TB? Presented at the Fourth International Conference on AIDS; June 16-21, 1988; Stockholm, Sweden.
7. Standaert B, Niragira F, Kadende P, Piot P. The association of tuberculosis and HIV infection in Burundi. *AIDS Res Hum Retroviruses* 1989;5:247-251.
8. Brodt HR, Schultze-Werninghaus G, Helm EB. Tuberkulose gefahrdung despflage personals durch AIDS-patienten. 1. Deutscher Kongress fur Infektions und Tropenmedizin; March 21-23. 1991: Berlin. Germanv. Abstract 122.
9. Franchini D, Hewlett D, Alfalla D, et al. Tuberculin skin test conversions among 64 employees at an urban hospital assoicated with an inoatient AIDS unit. Presented at the 32nd Interscience Conference on Antimicrobial Agents and Chemotheraov; October 11-14. 1992: Anaheim, California. Abstract 1197.
10. Prego V, Glatt AE, Roy V, et al. Comparative yield of blood culture for fungi and mycobacteria, liver biopsy, and bone marrow biopsy in the diagnosis of fever of undetermined origin in human immunodeficiency virus-infected patients. *Arch Intern Med* 1990;150:333-336.
11. Shriner KA, Mathisen GE, Goetz MB. Comparison of mycobacterial adenitis among persons infected with human immunodeficiency virus and seronegative controls. *Clin Infect Dis* 1992:15:601-605.
12. Kennedy DJ, Lewis WP, Barnes PE Yield of bronchoscopy for the diagnosis of tuberculosis in patients with human immunodeficiency virus infection. *Chest* 1992;101:1040-1044.
13. Miro AM, Gibilara E, Powell S, Kamhola SL. The role of fiberoptic bronchoscopy for diagnosis of pulmonary tuberculosis in patients at risk for AIDS. *Chest* 1992;101:1211-1214.
14. Manson-Bahr PEC, Bell DR. Leprosy. In: Manson-Bahr PEC, Bell DR, eds. *Manson's Tropical Diseases,* 19th ed. Philadelphia, PA: Bailliere Tindall; 1987:757-785.
15. Jones B, Kramer F, Barnes I? CD4 count and presentation of tuberculosis (TB) in patients with human immunodeficiency virus (HIV) infection. *Am Rev Respir Dis* 1992;145:A186.

The authors reply:

We appreciate the comments of Dr. Di Perri and colleagues, and we would like to respond to some of the points they raise. First, we would like to correct a typographical error that appeared in our editorial.[1] The editorial reads, "When the rate of active tuberculosis is calculated based on the total number of healthcare workers among those caring for HIV-infected patients (7/135) versus non-HIV infected patients (2/186), the difference is not statistically significant (relative risk, 2.75; 95% confidence interval, 0.58 to 12.96)." This should read "'..versus non-HIV infected patients (2/106)..." The relative risk and confidence interval are correct.

Dr. Di Perri raises questions about the appropriate denominator to use in calculating the risk to healthcare workers. In our editorial, we suggested that it would be appropriate to use the number of exposed healthcare workers as the denominator. Dr. Di Perri notes that this approach ignores the difference in the cumulative number of human immunodeficiency virus (HIV)-seropositive and HIV-seronegative tuberculosis patients to which the healthcare workers potentially were exposed. In fact, it would be preferable to use a denominator that takes into account both of these factors. However, in calculating the number of potential source cases to be used in the denominator, it is important to recognize that the infectiousness of patients with tuberculosis is quite variable. It depends on a number of factors, including the site of disease, the presence of cough, the presence of pulmonary cavitation, the presence and the number of acid-fast bacilli on a sputum smear, and the effectiveness and the duration of therapy. Even among patients with similar clinical characteristics, there can be considerable variation in the proportion of contacts who become infected following exposure. This indicates that other factors related to the source patient, the environment, and the person being exposed play an important role in modulating the risk of transmission.

In the nosocomial tuberculosis outbreaks reported during the past two decades, transmission gen-

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erally has been associated with patients who had unrecognized tuberculosis and who were not yet receiving effective therapy.[2-9] Transmission also has been associated with procedures that induce the aerosolization of respiratory secretions, such as bronchoscopy, endotracheal intubation, sputum induction, and the administration of aerosolized medications. This experience has been borne out in recent nosocomial outbreaks of multidrug-resistant tuberculosis, in which factors contributing to the outbreaks included the delayed diagnosis of tuberculosis, the delayed recognition of drug resistance, the delayed initiation of effective therapy, and prolonged infectiousness among patients with multidrug-resistant disease.[10-16]

For these reasons, it is difficult to evaluate the risk of tuberculosis transmission from patients to healthcare workers as a simple function of the number of patients to which the workers are exposed or as a function of the number of days of exposure. Other critical factors must be considered: whether the patient was known to have or suspected of having tuberculosis at the time of admission, how long the diagnosis was delayed, how long the patient was hospitalized before treatment was initiated, whether any cough-inducing procedures (eg, diagnostic bronchoscopy or sputum induction) were performed on the patient before treatment was initiated and whether workers were exposed during these procedures, whether the treatment prescribed was adequate to eliminate infectiousness, and how long the interval was between the initiation of therapy and the clinical and bacteriologic response.

For example, in an outbreak previously reported by Di Perri et al, the presumed source patient was hospitalized for 28 days before tuberculosis was recognized and treatment initiated.[17] A case of active tuberculosis in a healthcare worker who was exposed to tuberculosis in this outbreak is included among the healthcare worker cases described in the current report of Di Perri et al.[18] However, any transmission that resulted from the source patient in this outbreak should not be ascribed to the patient being more infectious, but rather simply to the fact that while in the hospital for 28 days, the patient had tuberculosis that was undiagnosed, untreated, and presumably infectious. Furthermore, the three healthcare workers who developed tuberculosis at the Mantova General Hospital were all apparently infected by one patient.[18] This does not suggest a higher level of infectiousness among HIV-infected tuberculosis patients in general. Rather, it suggests that there was something about this individual patient that resulted in a high level of infectiousness. It would be very instructive to know more about this particular patient and the circumstances under which transmission occurred.

The sort of information described above can be used to identify specific factors that contribute to transmission, as well as to estimate the number of infectious person-days (rather than the number of total person-days) of exposure for use in calculating risk. The importance of this approach is demonstrated in a recent nosocomial outbreak of multidrug-resistant tuberculosis, in which 25 patients with multidrug-resistant disease were hospitalized for a total of 860 person-days and were sputum-smear-positive on 375 (44%) of those person-days.[14] During the same time interval, 62 patients with drug-susceptible disease were hospitalized a total of 1445 person-days but were sputum-smear-positive on only 197 (14%) of those person-days ($P<0.001$). There were fewer patients with drug-resistant tuberculosis, and these patients had fewer total person-days of hospitalization; yet they actually exposed healthcare workers to a significantly greater number of infectious person-days than did the patients with drug-susceptible disease.

In their letter, Dr. Di Perri and colleagues cite three references as providing evidence for the increased infectiousness of tuberculosis patients who are coinfected with HIV We have not reviewed the abstract by Brodt. The paper by Standaert does note that more new cases of tuberculosis were found among household members of HIV-seropositive patients with tuberculosis than among HIV-seronegative patients with tuberculosis; however, this difference was not statistically significant.[19] The abstract by Franchini does not provide enough information to determine what the causes of transmission might have been; thus, it cannot be used as evidence of the increased infectiousness of HIV-seropositive patients with tuberculosis.[20]

Finally, issues related to the environment must be considered in trying to understand factors involved in tuberculosis transmission. For example, the outbreak reported previously by Di Perri et al[17] occurred in a setting where most of the beds are grouped in rooms of four, a bathroom is shared by two rooms, and the recirculated air is not filtered. This type of setting is highly conducive to the transmission of airborne pathogens. The multidrug-resistant outbreaks recently investigated by the Centers for Disease Control and Prevention (CDC) also have been characterized by significant problems with ventilation. These problems contributed to transmission, but often they were not evident until detailed

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evaluations of the air-handling systems were conducted.

In conclusion, as we noted in our editorial, a number of factors related to the source patient, the environment, and the exposed host can lead to markedly variable rates of transmission. All of these factors must be examined carefully before an apparent increased risk of transmission can be ascribed to a patient's HIV serostatus. We would like to reemphasize that tuberculosis transmission in healthcare facilities is a significant risk, both to healthcare workers and to patients, regardless of whether the patients with tuberculosis are coinfected with HIV. The challenge remains for healthcare providers to identify rapidly infectious tuberculosis, initiate effective acid-fast bacillus isolation precautions promptly, and initiate effective antituberculosis therapy rapidly.

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REFERENCES

1. Castro KG, Dooley SW. *Mycobacterium tuberculosis* transmission in healthcare settings: is it influenced by coinfection with human immunodeftciency virus? *Infect Control Hosp Epidemiol* 1993;14:65-66.
2. Brennen C, Muder RR, Muraca PW. Occult endemic tuberculosis in a chronic care facility. *Infect Control Hosp Epidemiol* 1988;9:548-552.
3. Catanzaro A Nosocomial tuberculosis. *Am Rev Respir Dis* 1982;125:559-562.
4. Ehrenkranz NJ, Kicklighter JL. Tuberculosis outbreak in a general hospital: Evidence of airborne spread of infection. *Ann Intern Med* 1972;77:377-382.
5. Haley CE, McDonald RC, Rossi L, et al. Tuberculosis epidemic among hospital personnel. *Infect Control Hosp Epidemiol* 1989;10:204-210.
6. Hutton MD, Stead WW, Cauthen GM, et al. Nosocomial transmission of tuberculosis associated with a draining tuberculous abscess. *J Infect Dis* 1990;161:286-295.
7. Kantor HS, Poblete R, Pusateri SL. Nosocomial transmission of tuberculosis from unsuspected disease. *Am J Med* 1988;84:833-838.
8. Lundgren R, Norrman E, Asberg I. Tuberculous infection transmitted at autopsy. *Tubercle* 1987;68:147-150.
9. Centers for Disease Control. *Mycobacterium tuberculosis* transmission in a health clinic-Florida, 1988. *MMWR* 1989;38:256-264.
10. Centers for Disease Control. Nosocomial transmission of multidrug-resistant TB to health-care workers and HIV-infected patients in an urban hospital-Florida. *MMWR* 1990;39:718-722.
11. Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons-Florida and New York. 19881991. *MMWR* 1991:40:585-591.
12. Edlin BR. Tokars JI, Grieco MH, et al. An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. N *Engl J Med* 1992;326:1514-1521.
13. Pearson ML, Jereb JA, Frieden TR, et al. Nosocomial transmission of multidrug-resistant *Mycobacterium tuberculosis.* A risk to patients and healthcare workers. *Ann Intern Med* 1992;117:191-196.
14. Beck-Sague C, Dooley SW, Hutton MD, et al. Outbreak of multidrug-resistant *Mycobacterium tuberculosis* infections in a hospital: transmission to patients with HIV infection and staff. *JAMA* 1992;268:1280-1286.
15. Fischl MA, Uttamchandani RB, Daikos GL, et al. An outbreak of tuberculosis caused by multiple-drug-resistant tubercle bacilli among patients with HIV infection. *Ann Intern Med* 1992;117:177-183.
16. Dooley SW, Jarvis WR, Martone WJ, Snider DE Jr. Multidrug-resistant tuberculosis. *Ann Intern Med* 1992;117:257-258. Editorial.
17. Di Pert-i G, Cruciani M, Danzi MC, et al. Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet* 1989;2:1502-1504.
18. Di Perri G, Cadeo GP, Castelli F, et al. Transmission of HIV-associated tuberculosis to healthcare workers. *Infect Control Hosp Epidemiol* 1993;14:67-72.
19. Standaert B, Niragira F, Kadende P, Piot I? The association of tuberculosis and HIV infection in Burundi. *AIDS Res Hum Retroviruses* 1989;5:247-251.
20. Franchini D, Hewlett D, Alfalla D, et al. Tuberculin skin test conversions among 64 employees at an urban hospital associated with an inpatient AIDS unit. Presented at the 32nd Interscience Conference on Antimicrobial Agents and Chemotherapy; October 11-14, 1992; Anaheim, California. Abstract 1197.

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