# Factors Influencing Time to Sputum Conversion Among Patients with Smear-Positive Pulmonary Tuberculosis

**Edward E. Telzak, Barkat A. Fazal, Cathy L. Pollard, Glenn S. Turett, Jessica E. Justman, and Steve Blum**

*From the Division of Infectious Diseases, Bronx Lebanon Hospital Center, and the Department of Medicine and Department of Epidemiology and Social Medicine, Albert Einstein College of Medicine, Bronx, New York*

**For hospitalized patients with smear-positive pulmonary or laryngeal tuberculosis, the Centers for Disease Control and Prevention recommends that three consecutive sputum samples be negative for acid-fast bacilli (AFB) before respiratory isolation is discontinued. Limited data are available to predict the length of time to obtain three negative sputum smears and cultures and to determine factors associated with a prolonged interval before sputum smear and culture conversion, especially among patients infected with human immunodeficiency virus (HIV). For 100 consecutive patients with smear-positive pulmonary tuberculosis, the mean and median numbers of days from the initiation of appropriate therapy to the first of three consecutive negative smears were calculated, and associated risk factors were determined. The mean number of days before the first of three consecutive negative sputum smears was 33 days; the median was 23 days. On stepwise multiple regression analysis, cavitary disease, numerous AFB on the initial smear, and no prior history of tuberculosis were the factors independently associated with an increased number of days for both smear and culture conversion. HIV does not prolong the period of infectiousness.**

Tuberculosis, caused by *Mycobacterium tuberculosis,* is spread primarily by the airborne route. Therefore, it is usually only patients with pulmonary tuberculosis who are infectious. Numerous studies and reviews have highlighted the various factors associated with infectivity [1]. These factors include the bacillary load; the severity of coughing and other forced expiratory maneuvers such as sneezing, yelling, and singing; and the type and duration of antituberculous chemotherapy [2–5].

Guidelines have been established by the Centers for Disease Control and Prevention (CDC) to limit nosocomially transmitted pulmonary or laryngeal tuberculosis [6]. These guidelines recommend placing patients suspected of having or known to have tuberculosis in acid-fast bacilli (AFB) isolation rooms. Isolation rooms should have negative pressure with at least six total air exchanges per hour, including at least two outside exchanges, with germicidal ultraviolet lamps considered as a supplement to ventilation.

See editorial response by Iseman on pages 671–2.

Available data suggest that once patients with tuberculosis begin receiving effective chemotherapy, they rapidly become less infectious [5, 7, 8]. The CDC, however, recommends that isolation be discontinued only when patients are receiving effective chemotherapy, their conditions are improving clinically, and when three consecutive sputum samples, collected on different days, are AFB-smear-negative [6].

Our hospital has adhered to these CDC recommendations, given the high rate of HIV infection among household contacts and hospitalized patients, the high rate of drug-resistant (including multidrug-resistant) tuberculosis seen at our institution [9, 10], and the possibility that severely immunosuppressed HIV-infected patients with tuberculosis might be more infectious than HIV-uninfected patients with tuberculosis. This last concern was prompted by the numerous outbreaks of both drug-susceptible and multidrug-resistant tuberculosis that were seen among HIV-infected patients [11–16].

Data are currently limited to predict the length of time to obtain three negative sputum smears and cultures after an initial positive sputum smear and to determine factors associated with prolonged time to sputum smear and culture conversion. The current study was undertaken to obtain this information. With such information, the use of respiratory isolation rooms could be anticipated more accurately. In addition, we sought to determine whether respiratory isolation could reasonably be discontinued for certain patients with fewer than three consecutive negative sputum specimens.

## Methods

Bronx-Lebanon Hospital Center (BLHC) is a 565-bed acute-care facility located in the South Bronx, New York City. The average daily inpatient census includes >125 patients with AIDS. To effectively manage the large number of patients

Received 6 December 1996; revised 17 March 1997.

Presented in part at the Lancet Conference on Tuberculosis (Washington, D.C.), held in September 1995.

Reprints or correspondence: Dr. Edward E. Telzak, Chief, Division of Infectious Diseases, Bronx-Lebanon Hospital Center, 1650 Grand Concourse, Bronx, New York 10457.

**Clinical Infectious Diseases 1997; 25:666–70**

1058–4838/97/2503–0017$03.00

with suspected or diagnosed tuberculosis at our hospital, a designated tuberculosis team and a directly observed therapy (DOT) program for tuberculosis have been established [9, 17]. Once a patient's smear is positive, sputum is collected on a weekly basis until the patient becomes smear-negative.

All cases of culture-confirmed tuberculosis from 1 April 1993 to 31 March 1995 were identified through a review of the microbiology logs. For patients with sputum smear–positive tuberculosis, data on demographic and clinical characteristics, treatment, and outcome were gathered by a review of records from the hospital, the outpatient tuberculosis clinic, and the DOT program. Microbiology data, including the results of smears, cultures, and susceptibility tests, were obtained from the mycobacteriology laboratory records.

### Laboratory Methods

All expectorated and induced sputum specimens obtained by the microbiology laboratory for AFB smear and culture were decontaminated with sodium hydroxide in combination with N-acetyl-L-cysteine and processed in a standard manner [18]. The Ziehl-Neelsen stain was used throughout the study. All smear-positive sputum specimens were placed into BACTEC (Becton Dickinson, Sparks, MD) liquid medium and Löwenstein-Jensen solid medium [19]. Mycobacterial species were identified with nucleic acid probes [20]. Testing for susceptibility to first-line drugs was performed with the BACTEC system.

### Statistical Analysis

Analyses focused on risk factors associated with times to AFB smear and culture conversion. Candidate independent variables included previous history of tuberculosis; HIV status; CD4 cell count (for HIV-infected patients); drug susceptibility pattern, including multidrug resistance (to at least isoniazid and rifampin), full susceptibility (to isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin), and other; the presenting chest roentgenogram pattern (cavitary, normal, other); and quantification of organisms on sputum smear (numerous, $>1$ organism/field; few, $>10$ organisms/slide; and rare, $1–9$ organisms/slide).

The outcomes of interest included the time from the initiation of appropriate therapy (with $\geq 2$ drugs with in vitro activity against the isolate) to the first of three consecutive negative sputum smears and the first of 3 consecutive negative sputum cultures. Median and mean times (in days) are presented along with $\pm 2$ standard errors of the mean, which is equivalent to the 95% confidence interval, and the means are compared with either analysis of variance for normally distributed data or the Kruskal-Wallis statistic for non-normally distributed data. Stepwise multiple regression analyses were performed to identify which of all the above potential predictors were independently associated with time to the first of three consecutive negative smears and the first of three consecutive negative sputum cultures.

## Results

From 1 April 1993 through 31 March 1995, 199 cases of culture-positive tuberculosis were diagnosed at BLHC. Of these patients, 150 (75%) had pulmonary disease alone, 4 (2%) had pulmonary and pleural disease, 27 (14%) had pulmonary and extrapulmonary tuberculosis, 5 (3%) had only pleural disease, and 13 (7%) had extrapulmonary disease alone. Of the 181 patients with pulmonary tuberculosis, 117 (65%) were AFB smear–positive.

For 100 (85%) of the sputum smear–positive patients, complete information was obtained, and all of them ultimately had three consecutive negative smears. Of the remaining 17 patients, 12 died before a third negative sputum was obtained and 3 left the facility against medical advice and were lost to follow-up; for 2 patients, the starting date of appropriate treatment could not be determined. The 100 patients had a median of four smears performed prior to the first of three consecutive negative smears.

Table 1 shows the relationship between different variables and the mean and median number of days before the first of three consecutive negative smears and the first of three consecutive negative cultures. The mean number of days before the first of three consecutive negative sputum smears for this group was 33 days; the median was 23 days. On bivariate analyses, HIV-negativity, no prior history of tuberculosis, presence of numerous AFB on sputum smear, and cavitary disease were associated with increased time to sputum smear conversion. Gender, race/ethnicity, and pattern of antimicrobial susceptibility did not influence the time to sputum conversion.

Eighty-five patients had both 3 negative smears and 3 negative cultures; 15 who had 3 negative smears never had 3 negative cultures. Of these 15, 8 had no additional specimens obtained, 2 could not produce sputum, 3 were lost to follow-up, and 2 died.

Factors associated with the time to sputum culture conversion are also detailed in table 1. The mean number of days until the first of three consecutive negative sputum cultures was 32 days; the median was 26 days. On bivariate analyses, the same factors associated with prolonged time to smear conversion were also associated with prolonged time to culture conversion: HIV-negativity, no prior history of tuberculosis, numerous AFB on smear, and cavitary disease. There was no relationship between age and time to the first of three negative sputum smears or cultures.

Table 2 details the variables that in stepwise multiple regression analyses were significantly and independently associated with an increased number of days until three consecutive negative sputum smears and cultures. These variables were numerous AFB on initial smear, cavitary disease, and no prior history of tuberculosis.

**Table 1.** Potential predictors of time to the first of three consecutive negative smears and cultures among patients with sputum smear–positive tuberculosis.

| | Smears ($n$ = 100) | | | | Cultures ($n$ = 85) | | | |
|---|---|---|---|---|---|---|---|---|
| Factor | No. of patients | Mean (d) ± 2 SE | Median (d) | $P$ value | No. of patients | Mean (d) ± 2 SE | Median (d) | $P$ value |
| Gender | | | | | | | | |
| Male | 61 | 33 ± 8.2 | 23 | NS | 52 | 34 ± 6.6 | 26 | NS |
| Female | 39 | 33 ± 11.8 | 22 | | 33 | 30 ± 8.7 | 25 | |
| Race/ethnicity | | | | | | | | |
| Black | 65 | 34 ± 9.0 | 23 | NS | 57 | 31 ± 6.7 | 24 | NS |
| Hispanic | 30 | 30 ± 7.9 | 24 | | 24 | 36 ± 8.9 | 38 | |
| White | 5 | 41 ± 37.1 | 17 | | 4 | 28 ± 21.0 | 20 | |
| HIV status | | | | | | | | |
| Positive | 59 | 26 ± 7.8 | 19 | .05 | 51 | 25 ± 5.7 | 17 | <.001 |
| Negative | 15 | 43 ± 14.5 | 48 | | 14 | 39 ± 10.9 | 39 | |
| Unknown | 26 | 42 ± 15.0 | 34 | | 20 | 47 ± 12.9 | 45 | |
| History of tuberculosis | | | | | | | | |
| No | 80 | 37 ± 7.6 | 25 | .0006 | 67 | 35 ± 5.9 | 27 | .04 |
| Yes | 20 | 15 ± 7.4 | 13 | | 18 | 22 ± 10.6 | 16 | |
| No. of AFB on smear | | | | | | | | |
| Numerous | 28 | 44 ± 10.0 | 39 | <.001 | 47 | 43 ± 7.1 | 43 | <.001 |
| Few | 57 | 21 ± 5.2 | 21 | | 25 | 20 ± 4.9 | 17 | |
| Rare | 15 | 11 ± 5.8 | 12 | | 13 | 17 ± 12.9 | 15 | |
| Chest roentgenogram | | | | | | | | |
| Cavitary | 23 | 51 ± 17.2 | 48 | <.01 | 22 | 48 ± 12.5 | 49 | .001 |
| Normal | 8 | 23 ± 10.8 | 20 | | 7 | 17 ± 9.6 | 12 | |
| Other | 69 | 28 ± 6.9 | 22 | | 56 | 28 ± 5.3 | 26 | |
| Susceptibility pattern | | | | | | | | |
| MDR | 11 | 17 ± 14.8 | 11 | NS | 9 | 22 ± 8.0 | 20 | NS |
| Susceptible | 77 | 33 ± 6.2 | 24 | | 65 | 32 ± 14.0 | 25 | |
| Other | 12 | 48 ± 34.3 | 19 | | 11 | 40 ± 5.9 | 26 | |

NOTE. AFB = acid-fast bacilli; MDR = multidrug resistance; ±2 SE = ±2 standard errors of the mean.

For 87 patients, once two consecutive negative smears were obtained, the third negative smear immediately followed. Among the 13 patients for whom this did not occur, nine had a single positive smear after the second consecutive negative smear, followed immediately by three consecutive negatives.

## Discussion

The HIV epidemic has had a profound impact on the epidemiology of tuberculosis. An analysis of a tuberculosis outbreak in a residential facility for HIV-infected persons documented that early progression of new tuberculosis infection may occur in almost 40% of persons within 4 months, compared with 2%–5% of historical controls in the first 2 years [12]. Among persons infected with tuberculosis who become infected with HIV, active tuberculosis develops at an annual rate of 7%–10%, compared with a lifetime risk of reactivation of 5%–10% [21].

**Table 2.** Stepwise multiple regression analyses for factors independently associated with an increased number of days to first of three consecutive negative sputum smears and cultures.

| | $P$ value | |
|---|---|---|
| Factor | Smears ($n$ = 100) | Cultures ($n$ = 85) |
| Numerous AFB on smear | .0001 | .003 |
| Cavitary disease | .014 | .012 |
| No previous history of tuberculosis | .001 | .022 |

NOTE. $n$ = number of patients.

Since the beginning of the resurgence of tuberculosis, there has been concern that HIV-infected patients with tuberculosis are more infectious and are infectious for a longer period of time than patients with tuberculosis who are not HIV-infected. Several studies have refuted this hypothesis. Rates of tuberculosis infection among household contacts of HIV-infected and HIV-uninfected patients with sputum smear–positive tuberculosis were compared in Kinshasa, Zaire, and no differences were found [22]. Authors of other studies, by investigating contacts, have also concluded that HIV-associated pulmonary tuberculosis is not more infectious than tuberculosis alone [23–25].

Brindle et al. [26] studied the duration of infectivity in HIV-positive patients. They found that the majority of a group of Kenyan patients treated for pulmonary tuberculosis with streptomycin, thiacetazone, and isoniazid remained culture-positive

after 4 weeks of treatment, although the proportion becoming culture-negative was greater in the HIV-infected group than in the HIV-uninfected group [26]. Nevertheless, given the severely immunosuppressed state of our hospitalized HIV-infected patients with tuberculosis (median CD4 counts, $<100/mm^3$), we initially hypothesized that the sputum of patients who were HIV-infected, because of their immunocompromised condition, would take longer to convert to smear- and culture-negative. This hypothesis was incorrect.

As AFB sputum smear and culture specimens were obtained on an almost-weekly basis for most patients while they were smear-positive, we were able to determine with a high degree of accuracy the mean and median number of days until patients became both smear- and culture-negative and to determine factors associated with increased time to conversion to smear- and culture-negativity. We have found that among patients who have both smear- and culture-positive pulmonary tuberculosis, HIV infection is not associated with a longer time to clearance of sputum smears or cultures. In fact, in bivariate analysis it was more likely that the sputum smears and cultures of HIV-infected patients would convert more rapidly than the smears and cultures of HIV-uninfected patients.

The smears of the 59 patients who were HIV-infected converted in a mean of 26 days, compared with 43 days for the 15 patients who tested HIV-negative. It became apparent on multivariate analysis, however, that HIV was not an independent predictor. Instead, cavitary disease evident on a chest roentgenogram, a large number of organisms on the AFB smear, and no prior history of tuberculosis were independent predictors of a longer time to sputum smear and culture conversion.

The fact that HIV-infected patients' sputum smears convert more rapidly is not surprising when it is recalled that HIV-infected patients are less likely to have cavitary disease and often even have normal chest roentgenograms on admission [27, 28]. In addition, they have been shown in some studies to have higher rates of smear-negativity than HIV-uninfected patients and fewer AFB in their sputum [29]. We also found that HIV-infected individuals were more likely to have few organisms on AFB smear and were less likely to have cavitary disease, which is the reason HIV status did not attain statistical significance in the multivariate analysis.

Cavitary disease and numerous AFB on smear are well-recognized risk factors for lengthening of the time to sputum smear and culture conversion. In addition, we found that for patients who had a prior history of tuberculosis, sputum smears and cultures converted more rapidly than for those who did not have a prior history of tuberculosis. This association may be explained in part by the fact that patients with a prior history of tuberculosis have T cells previously sensitized to mycobacterial antigens [30]. These patients have a greater number of immunologically specific T cells that can accumulate in infected regions more rapidly, producing lymphokines that can accelerate macrophage accumulation and activation that, in turn, more rapidly destroy the bacilli.

Animal models have also suggested that a first tuberculosis infection provides partial protection from subsequent infection. Guinea pigs challenged with *M. tuberculosis* after a first infection with tuberculosis have fewer organisms recovered in necropsy studies than do those who have not had a prior infection [31]. However, Nardell et al. found that among alcoholic residents of a homeless shelter, those with exogenous reinfection were more likely to have destructive disease, with numerous AFB on sputum smears and cavitation [32]. Clearly, additional and larger studies will be required to substantiate our observation.

Of the 100 smear-positive patients who ultimately had three consecutive negative smears, only 13 did not have their third negative smear immediately after the first series of two negative smears. However, nine of these 13 had a single positive smear immediately followed by three consecutive negatives. If this single positive smear can be considered an anomaly, then there appears to be reasonably convincing evidence that the overwhelming majority of patients may be removed from isolation after only two consecutive negative smears, especially in situations where isolation rooms are in demand.

In conclusion, we have defined the time course and factors associated with sputum smear and culture conversion among HIV-infected and HIV-uninfected patients with smear-positive pulmonary tuberculosis. Even among a population where severe immunosuppression as a result of HIV infection is common, cavitary disease, a large number of organisms on the initial AFB smear, and no prior history of tuberculosis are the major risk factors for prolonged sputum positivity. HIV infection does not prolong the period of infectiousness of patients with smear-positive pulmonary tuberculosis. Finally, consideration should be given to discontinuing AFB respiratory isolation after two consecutive negative AFB smears.

**References**


1. Hopewell PC. Factors influencing the transmission and infectivity of *Mycobacterium tuberculosis:* implications for clinical and public health management. In: Sande MA, Hudson LD, Root RK. Respiratory infections. New York: Churchill Livingstone, **1986:**191–216.
2. Loudon RG, Roberts RM. Singing and the dissemination of tuberculosis. Am Rev Respir Dis **1968**;98:297–300.
3. Gunnels JJ, Bates JH, Swindoll H. Infectivity of sputum-positive tuberculous patients on chemotherapy. Am Rev Respir Dis **1974**;109:323–30.
4. Noble RL. Infectiousness of pulmonary tuberculosis after starting chemotherapy. Am J Infect Control **1981**;9:6–10.
5. Mitchison DA. Infectivity of patients with pulmonary tuberculosis during chemotherapy [editorial]. Eur Respir J **1990**;3:385–6.
6. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. MMWR Morb Mortal Wkly Rep **1994**;43(suppl RR-13):1–132.
7. Brooks SM, Lassiter NL, Young EC. A pilot study concerning the infection risk of sputum positive tuberculous patients on chemotherapy. Am Rev Respir Dis **1973**;108:799–804.
8. Jindani A, Aber VR, Edwards EA, Mitchison DA. The early bactericidal activity of drugs in patients with pulmonary tuberculosis. Am Rev Respir Dis **1980**;121:939–49.

9. Fazal BA, Telzak EE, Blum S, et al. Impact of a coordinated tuberculosis team in an inner-city hospital in New York City. Infect Control Hosp Epidemiol **1995**;16:340–3.
10. Turett GS, Telzak EE, Torian LV, et al. Improved outcomes for patients with multidrug-resistant tuberculosis. Clin Infect Dis **1995**;21: 1238–44.
11. Torres R, Mani S, Altholz J, Brickner P. Human immunodeficiency virus infection among homeless men in a New York City shelter: association with *Mycobacterium tuberculosis* infection. Arch Intern Med **1990**;150: 2030–6.
12. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus: an analysis using restriction-fragment-length polymorphisms. N Engl J Med **1992**;326:231–5.
13. Di Perri G, Cruciani M, Danzi MC, et al. Nosocomial epidemic of active tuberculosis among HIV-infected patients. Lancet **1989**;2:1502–4.
14. 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**;326:1514–21.
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**;117:177–83.
16. Centers for Disease Control and Prevention. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons—Florida and New York, 1988–1991. MMWR Morb Mortal Wkly Rep **1991**;40: 585–91.
17. Turett GS, Marshall CJ, Belinken L, et al. Directly observed therapy (DOT) for tuberculosis (TB) at Bronx-Lebanon Hospital Center (BLHC), an inner-city hospital [abstract 148]. Clin Infect Dis **1996**;23:887.
18. Nolte FS, Metchock B. *Mycobacterium.* In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of clinical microbiology. 6th ed. Washington, DC: ASM Press, **1995:**400–17.
19. Roberts GD, Goodman NL, Heifets L, et al. Evaluation of the BACTEC radiometric method for recovery of mycobacteria and drug susceptibility testing of *Mycobacterium tuberculosis* from acid-fast smear-positive specimens. J Clin Microbiol **1983**;18:689–96.
20. Gonzales R, Hanna BA. Evaluation of Gen-Probe DNA hybridization systems for the identification of *Mycobacterium tuberculosis* and *Mycobacterium avium–intracellulare.* Diagn Microbiol Infect Dis **1987**;8: 69–77.
21. Selwyn PA, Hartel D, Lewis VA, et al. A prospective study of the risk of tuberculosis among intravenous drug users with human immunodeficiency virus infection. N Engl J Med **1989**;320:545–50.
22. Klausner JD, Ryder RW, Baende E, et al. *Mycobacterium tuberculosis* in household contacts of human immunodeficiency virus type 1–seropositive patients with active pulmonary tuberculosis in Kinshasa, Zaire. J Infect Dis **1993**;168:106–11.
23. Elliott AM, Hayes RJ, Halwiindi B, et al. The impact of HIV on infectiousness of pulmonary tuberculosis: a community study in Zambia. AIDS **1993**;7:981–7.
24. Nunn P, Mungai M, Nyamwaya J, et al. The effect of human immunodeficiency virus type-1 on the infectiousness of tuberculosis. Tubercle and Lung Disease **1994**;75:25–32.
25. Cauthen GM, Dooley SW, Onorato IM, et al. Transmission of *Mycobacterium tuberculosis* from tuberculosis patients with HIV infection or AIDS. Am J Epidemiol **1996**;144:69–77.
26. Brindle RJ, Nunn PP, Githui W, Allen BW, Gathua S, Waiyaki P. Quantitative bacillary response to treatment in HIV-associated pulmonary tuberculosis. Am Rev Respir Dis **1993**;147:958–61.
27. Pitchenik A, Rubinson HA. The radiographic appearance of tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. Am Rev Respir Dis **1985**;131:393–6.
28. Perlman DC, El-Sadr W, Nelson E, et al. Radiographic presentations of HIV-related tuberculosis vary by CD4+ count [abstract 455]. Clin Infect Dis **1995**;21:795.
29. Klein NC, Duncanson FP, Lenox TH III, Pitta A, Cohen SC, Wormser GP. Use of mycobacterial smears in the diagnosis of pulmonary tuberculosis in AIDS/ARC patients. Chest **1989**;95:1190–2.
30. Molloy A, Kaplan G. Cell-mediated immune response. In: Rom WN, Garay S, eds. Tuberculosis. Boston: Little, Brown and Company, **1993:** 305–14.
31. Dannenberg AM Jr. Pathogenesis and immunology: basic aspects. In: Sclossberg D, ed. Tuberculosis. 3rd ed. New York: Springer-Verlag, **1994:**17–39.
32. Ziegler JE, Edwards ML, Smith DW. Exogenous reinfection in experimental airborne tuberculosis. Tubercle **1985**;66:121–8.