

High Rates of Clinical and Subclinical Tuberculosis among HIV-Infected Ambulatory Subjects in Tanzania

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(See the editorial commentary by Cohn on pages 1508–10)

Background. We sought to determine the prevalence of active tuberculosis among ambulatory HIV-infected persons in Tanzania with CD4 cell counts of ≥ 200 cells/mm³ and a bacille Calmette-Guérin vaccination scar.

Methods. Subjects who volunteered for a tuberculosis booster vaccine trial were screened for active tuberculosis by obtainment of a history, physical examination, chest radiography, sputum culture and acid fast bacillus (AFB) stain, and blood culture. All subjects underwent a tuberculin skin test (TST) and lymphocyte proliferation assays (LPAs) for detection of responses to mycobacterial antigens.

Results. Active tuberculosis was identified at baseline in 14 (15%) of the first 93 subjects who were enrolled: 10 (71%) had clinical tuberculosis (symptoms or chest radiograph findings), and 4 (29%) had subclinical tuberculosis (positive sputum AFB stain or culture results but no symptoms or chest radiograph findings). An additional 6 subjects with subclinical tuberculosis were identified subsequently. The 10 subjects with subclinical tuberculosis included 3 with positive sputum AFB stains results and 7 who were only identified by a positive sputum culture result. Compared with subjects who did not have tuberculosis, the 10 subjects with subclinical tuberculosis were more likely to have peripheral lymphadenopathy, positive TST results, and elevated LPA responses to early secreted antigenic target-6 (ESAT). Eight of 10 patients had received isoniazid because of a positive TST result before active tuberculosis was recognized.

Conclusions. Clinical and subclinical tuberculosis are common among ambulatory HIV-infected persons, and some cases can only be identified by sputum culture. World Health Organization guidelines for screening for latent tuberculosis before treatment do not recommend sputum culture and, therefore, may fail to identify a substantial number of HIV-infected persons with subclinical, active tuberculosis.

Tuberculosis is the leading cause of death among persons with HIV infection in the developing world [1–4]. Reduction in morbidity and mortality due to HIV-associated tuberculosis depends on the identification of both latent tuberculosis infection and active tubercu-

losis disease and on the application of distinct treatment strategies for each [5, 6]. Tuberculin skin tests (TSTs) are used for detection of latent infection, and preventive therapy is administered with isoniazid [7–9]. To exclude patients with active tuberculosis from receiving inappropriate single-drug preventive therapy, the World Health Organization recommends performing chest radiography [10]. In addition, because it is assumed that most HIV-infected persons with active tuberculosis will be symptomatic, it is recommended that patients who have had cough for >3 weeks have 3 sputum samples obtained for acid-fast bacillus (AFB) smear. The sensitivity of this approach for detection of active tuberculosis has not been tested in practice. Furthermore, chest radiographs and smears may not always be avail-

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able in resource-poor settings. Finally, tuberculosis often has an extrapulmonary presentation in patients with HIV infection [11]. Collectively, these factors highlight the potential difficulties in separating latent infection from active disease in HIV infection.

While screening HIV-positive subjects for an ongoing tuberculosis booster vaccine trial in Tanzania, we found that previously undiagnosed active tuberculosis was common and that it was often difficult to distinguish latent infection from active disease at a single evaluation, despite the availability of chest radiography and sputum AFB smears. The use of mycobacterial cultures and longitudinal follow-up allowed us to identify cases of subclinical tuberculosis with no clinical or radiologic manifestations but with baseline sputum culture results that were reported to be positive several weeks later. This appears to be an early and subtle form of active tuberculosis in HIV infection. Delayed recognition of subclinical tuberculosis led to administration of several weeks of initial, preventive, single-drug isoniazid therapy for these subjects.

METHODS

Protocol. Subject data are derived from the DARDAR Study of the epidemiology and vaccine-based prevention of HIV-associated tuberculosis [12], which is being conducted in Dar es Salaam, Tanzania. Eligible subjects are ambulatory, HIV-positive adults with a CD4 cell count of ≥ 200 cells/mm³, a bacille Calmette-Guérin (BCG) vaccination scar present, and no evidence of active tuberculosis. At baseline, all potential subjects undergo a physical examination and standardized interview that includes questions about weight loss in the past 3 months and about the presence and duration of any cough or fever. HIV ELISAs and TSTs (RT-23; State Serum Institute) are performed, and CD4 cell counts and HIV loads are determined. Enrolled subjects are randomized to receive a 5-dose series of an investigational inactivated mycobacterial vaccine [13] or placebo over 1 year and are subsequently observed for a median duration of 3 years. The research protocol was approved by the Ethics Committee of the Muhimbili University College of Health Sciences (Dar es Salaam) and the Dartmouth Committee for the Protection of Human Subjects (Lebanon, NH).

Screening for tuberculosis. Screening for active tuberculosis among enrolled subjects includes the following studies: 3 expectorated sputum samples for AFB stain and mycobacterial culture, mycobacterial blood culture, in vitro immunologic studies, and posterior-anterior chest radiography. Enrolled subjects with evidence of active pulmonary tuberculosis are deferred from immunization and referred to the National Tuberculosis and Leprosy Program (NTLP) for treatment. Enrolled subjects with TST reactions of ≥ 5 mm, no evidence of active tuberculosis, and no history of prior treatment for tuberculosis are given isoniazid (300 mg q.d. for 6 months). After a high rate

of unsuspected active tuberculosis was found among the first 93 enrolled patients, the screening protocol was changed to require completion of all tuberculosis screening tests before enrollment; subjects with even minimal suspicion of active tuberculosis were referred to the NTLP before enrollment and were not followed further in the study.

Tuberculosis treatment. Subjects are referred to the NTLP for treatment of active tuberculosis by study clinicians on the basis of clinical signs and symptoms, findings of chest radiographs or of other imaging studies, and results of laboratory tests. For subjects without clinical features of tuberculosis, treatment may be delayed until the organisms yielded on cultures are definitively identified as *Mycobacterium tuberculosis* by DNA probe or until clinical features develop. Follow-up data on the treatment outcomes of enrolled subjects were obtained by interview, examination, and testing at months 2, 5, and 8 of treatment.

Laboratory studies. Sputum samples were processed at the National Tuberculosis Reference Laboratory at Muhimbili National Hospital in Dar es Salaam, Tanzania. A separate laboratory was established for the study, and only study specimens were processed in this laboratory. AFB smears were performed directly on clinical specimens with use of the auramine-rhodamine method, with confirmation of positive results by Ziehl-Neelsen staining. AFB-negative smears of samples with subsequent mycobacterial growth on culture were reexamined by a second technologist. Mycobacterial sputum cultures were processed daily as they were received and were first decontaminated in 2% NaOH, concentrated by centrifugation, and then plated on Löwenstein-Jensen slants and incubated in air at 37°C for 10 weeks. Positive growth was quantitated as the total number of colony-forming units (cfu). Blood cultures were shipped to Dartmouth-Hitchcock Medical Center (Lebanon, NH) for processing with an automated system (MB/BacT 240; bioMérieux) [14]. Mycobacterial isolates were tested at Dartmouth-Hitchcock Medical Center for the presence of the *M. tuberculosis* complex with use of DNA probes (Accuprobe; GenProbe). IS6110 typing was performed on all isolates at the Public Health Research Institute (New Jersey) using standard methods [15]. Lymphocyte proliferation assays were performed with freshly isolated PBMCs using a standard ³H-thymidine incorporation method with media alone, 2 µg/mL *Mycobacterium vaccae* sonicate, 1 µg/mL *M. tuberculosis* Ag85, 2 µg/mL *M. tuberculosis* early secreted antigenic target-6 (ESAT-6), or 1 µg/mL *M. tuberculosis* whole-cell lysate. Results were expressed as a proliferation index (counts per min [cpm] of antigen-stimulated cells divided by cpm of unstimulated cells), and a proliferation index ≥ 3 was considered to be a positive result.

Definitions and data analysis. Subjects treated for tuberculosis were divided into those with clinical tuberculosis (i.e., clinical features were present) and those with subclinical tuberculosis (i.e., clinical features were absent, but sputum cul-

tures were positive for *M. tuberculosis*). When treatment for tuberculosis was complete, cases were categorized as definite, probable, or possible tuberculosis with use of study case definitions (table 1). The Mann-Whitney *U* test was used to compare factors measured on a continuous scale (e.g., lymphocyte proliferation indices, age, CD4 cell count, and weight). Fisher's exact test was used to compare differences in categorical outcomes between subject groups (e.g., sex and history of tuberculosis). A 2-sided *P* value of <.05 was considered to be statistically significant. Analyses were performed using SAS (SAS Institute) and Stata (Stata) statistical software.

RESULTS

Subjects. Study subjects were residents of Dar es Salaam who had been referred by HIV testing centers after recent confirmation of HIV infection or by word of mouth from other study subjects. Among 161 subjects who were screened during the period October 2001 through February 2003, a total of 93 (58%) had CD4 cell counts of ≥ 200 cells/mm³ and had a BCG scar present and were enrolled in the study. A diagnosis of active tuberculosis at baseline was made for 14 (15%) of 93 enrolled subjects, including 10 subjects (71%) with clinical tuberculosis and 4 (29%) with subclinical tuberculosis. In the subsequent phase of the study—when subjects with even minimal suspicion of tuberculosis were deferred before enrollment (and for whom no microbiologic or clinical follow-up data are available)—407 subjects were found to be eligible, and 6 were later determined to have subclinical tuberculosis at baseline on the basis of positive sputum culture results. Data for these 6 patients and for the prior 4 patients were combined for additional analysis of subclinical tuberculosis.

Clinical tuberculosis. Of the 10 subjects with clinical tuberculosis, 7 (70%) had chest radiograph findings suggestive of active tuberculosis, and 5 (50%) had either a duration of cough of ≥ 2 weeks (4 subjects) or a duration of fever of ≥ 2 weeks (1 subject). Only 2 patients (20%) had both symptoms of tuberculosis (cough or fever) plus abnormal radiographic findings. TST reaction sizes ranged from 0 mm to 21 mm (mean size, 10.7 mm). All subjects had negative AFB stain results, and 2 (20%) had sputum cultures that were positive for *M. tuberculosis*. Treatment of tuberculosis was started 1–20 weeks after enrollment (mean, 7 weeks). For 5 patients, the diagnosis was not established until >2 months of follow-up, when symptoms or chest radiograph findings persisted without an alternate diagnosis. Final categorization of the 10 clinical cases was as follows: definite tuberculosis, 1 patient; probable tuberculosis, 6 patients; and possible tuberculosis, 3 patients (2 subjects with possible tuberculosis had no follow-up data, preventing potential classification of their cases as probable tuberculosis). Follow-up data were available for 7 subjects, 4 (57%) of whom died 11–30

Table 1. Study definitions of active tuberculosis.

Category, criteria
Definite
Isolation of <i>Mycobacterium tuberculosis</i> from 2 sputum samples or isolation of ≥ 10 cfu of <i>M. tuberculosis</i> from 1 sputum sample
Probable
Any isolation of <i>M. tuberculosis</i> from a sputum sample plus symptoms or positive chest radiograph findings
Symptoms, positive chest radiograph findings, and response to treatment
Possible
Symptoms and positive chest radiograph findings
Positive chest radiograph findings and response to treatment
Symptom, sign, or positive chest radiograph finding and loss to follow-up

NOTE. Positive chest radiograph findings were defined as presence of ≥ 1 of the following: infiltrate (with or without cavitation), pleural effusion, adenopathy, or cavity. Signs included ≥ 1 of the following: rales, dullness, or consolidation on chest examination; lymphadenopathy (size, ≥ 1 cm) at ≥ 2 sites; or hepatosplenomegaly. Symptoms included ≥ 1 of the following: cough or fever of ≥ 2 weeks' duration, night sweats, or weight loss of ≥ 5 kg/year. Response to treatment was defined as ≥ 2 of the following findings: clearance of fever; 50% improvement in cough, adenopathy, or chest radiographic findings; and weight gain of 3 kg. cfu, Colony-forming units.

months after presentation, and 3 (43%) were alive a median of 22 months after presentation (range, 11–30 months).

Subclinical tuberculosis. The 10 subjects with subclinical tuberculosis had no signs, symptoms, or abnormal chest radiographic findings suggestive of active tuberculosis but had baseline sputum cultures later reported to be positive for *M. tuberculosis* (table 2). Subjects were aged 20–39 years, and 8 patients (80%) were female. None reported a duration of fever of ≥ 2 weeks or a duration of cough of ≥ 2 weeks (2 patients reported a duration of cough of <1 week). Baseline temperatures were normal in all subjects. Five subjects had lymphadenopathy ≥ 1 cm at ≥ 2 anatomical sites, but the nodes were not considered to be sufficiently abnormal to obtain aspirations or biopsy specimens. TST reaction sizes of ≥ 5 mm were present in 8 (80%) of 10 subjects. Chest radiographic findings were normal in 9 subjects and showed lower-zone scarring in 1 subject. AFB smear results were considered to have been negative at baseline for 9 of 10 subjects and to have been positive for 1 subject. Sputum culture results were positive for 2 samples in 3 subjects, positive for 1 sample (≥ 10 cfu) in 4 subjects, and positive for 1 sample (1–2 cfu) in 3 subjects. After detection of positive culture results, stored sputum smears were restained, and the results were positive for a single sample in 2 additional subjects (for a total of 3 subjects with positive AFB smears). One (10%) of 10 subjects died 5 months after enrollment, and 9 (90%) were alive at a median of 22 months after enrollment (range, 17–31 months).

IS6110 patterns were unique for all 10 subjects with sub-

Table 2. Characteristics of 10 HIV-infected subjects with subclinical tuberculosis (TB).

Patient	CD4 cell count, cells/mm ³	Symptom	Sign(s)	TST reaction size, mm	ESAT-6 proliferation index ^a	Chest radiograph findings	AFB stain result			TB culture result, no. of cfu			Duration of INH therapy, days	Time until TB treatment, days	TB definition
							First	Second	Third	First	Second	Third			
1	525	None	None	16	NA	Normal	-	-	-	0	0	>10	85	89	Definite
2	880	None	L (CAI)	12	2.20	Normal	-	-	-	1	0	0	66	120	Probable
3	538	None	None	0	NA	Normal	-	-	-	0	0	>10	0	112	Definite
4	362	None	None	0	NA	Normal	-	-	-	0	0	1	0	81	Probable
5	386	None	None	20	0.49	Normal	-	+	-	>20	>20	0	28	59	Definite
6	324	None	L (CAI)	15	1.20	Normal	-	-	-	0	0	2	4	175	Probable
7	261	None	None	14	23.49	Cardiac enlargement	-	-	-	>20	0	0	48	162	Definite
8	630	None	L (CA)	38	29.86	Scarring of left lower lobe	+	-	-	>20	0	0	49	129	Definite
9	445	None	L (CAI)	17	38.21	Normal	-	-	-	0	>20	9	45	53	Definite
10	365	None	L (CAI)	20	7.07	Normal	-	+	-	5	>20	0	28	41	Definite

NOTE. Symptoms were defined as cough of >2 weeks' duration, fever of >2 weeks' duration, or weight loss in past year; patients 5 and 10 had a duration of cough of <1 week. AFB, acid-fast bacilli; ESAT-6, early secreted antigenic target-6; INH, isoniazid; L (CA), cervical and axillary lymphadenopathy; L (CAI), cervical, axillary, and inguinal lymphadenopathy; NA, not available; TST, tuberculin skin test; +, positive; -, negative.

^a Positive result, ≥ 3.0 .

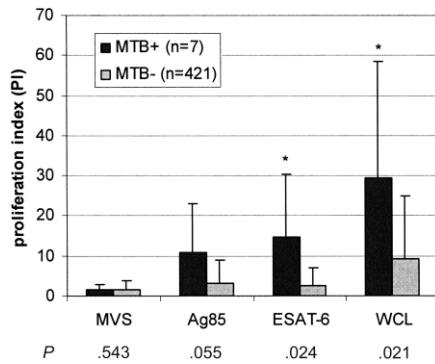


Figure 1. Lymphocyte proliferation indices to mycobacterial antigens in subjects with subclinical tuberculosis (MTB+) and subjects without tuberculosis (MTB-). *Statistically significant (i.e., 2-sided P value of $<.05$). Ag85, *Mycobacterium tuberculosis* antigen 85 complex; ESAT-6, *M. tuberculosis* early secreted antigen 6; MVS, *Mycobacterium vaccae* sonicate; WCL, *M. tuberculosis* whole-cell lysate.

clinical tuberculosis. In 2 cases, no other sputum samples were processed on the same day. In 8 cases, >1 additional sputum sample was processed on the same day (none of the samples from 8 subclinical cases were processed on the same day as each other): in 6 cases, the IS6110 patterns were distinct from those of other samples tested on the same day; in 1 case, the

other isolate could not be tested because of bacterial overgrowth; and in 1 case (in patient 10), the 2 other isolates from the same day were identical to the isolate from the patient with the subclinical case. The patient with subclinical tuberculosis had 2 positive culture results and 1 positive sputum smear result. Blood culture results were negative for all subjects. Final categorizations for the 10 subjects with subclinical tuberculosis were as follows: definite tuberculosis, 7 patients; and probable tuberculosis, 3 patients. (Among the subset of 4 patients from the first phase of the study, 2 had definite tuberculosis, and 2 had probable tuberculosis).

Lymphocyte proliferation indices to mycobacterial antigens are shown for 7 subjects with subclinical tuberculosis and 421 subjects without tuberculosis in figure 1. Subjects with subclinical tuberculosis had elevated indices to all 3 *M. tuberculosis* antigens but not to the nontuberculous vaccine antigen. In subjects with tuberculosis, indices to *M. tuberculosis* ESAT-6 and whole-cell lysate were significantly elevated, compared with indices in subjects without tuberculosis.

Characteristics of enrolled subjects with subclinical tuberculosis, clinical tuberculosis, and no tuberculosis are compared in table 3. The combination of peripheral lymphadenopathy at ≥ 2 sites and a TST reaction size of ≥ 10 mm yielded the following test values for the detection of subclinical tuberculosis:

Table 3. Comparison of data for subjects without a diagnosis of tuberculosis (TB), subjects with clinical TB, and subjects with subclinical TB.

Characteristic	Subjects without TB (n = 478)	Subjects with clinical TB (n = 10)	P^a	Subjects with subclinical TB (n = 10)	P^b
Age, median years	34	41	.012	30	.24
Male sex	119 (25)	1 (10)	.46	2 (20)	1.0
CD4 cell count, median cells/mm ³	416	315	.099	416	.69
History of TB	46 (10)	3 (30)	.069	1 (10)	1.0
TST reaction size, mm ^c					
<5	268 (58)	4 (40)	.33	2 (20)	.021
≥ 5	192 (42)	6 (60)	.33	8 (80)	.021
≥ 10	175 (38)	6 (60)	.18	8 (80)	.016
≥ 15	114 (25)	5 (50)	.13	6 (60)	.021
Duration of cough of ≥ 2 weeks	11 (2)	3 (30)	.002	0 (0)	1.0
Duration of fever of ≥ 2 weeks	2 (0)	1 (10)	.060	0 (0)	1.0
Weight, median kg	62.3	60.8	.51	62.0	.68
Weight loss in past 3 months	49 (10)	3 (30)	.08	0 (0)	.61
Lymphadenopathy					
At ≥ 2 sites	123 (26)	2 (20)	1.0	6 (60)	.025
TST reaction of ≥ 10 mm	45 (9)	1 (10)	1.0	6 (60)	.0001
TST reaction of ≥ 15 mm	34 (7)	1 (10)	.528	4 (40)	.005
ESAT LPA index of >3 , n/N (%)	80/412 (19)	2/10 (10)	1.0	4/7 (57)	.032

NOTE. Data are no. (%) of patients, unless otherwise indicated. ESAT LPA, early secreted antigenic target-6 lymphocyte proliferation assay; TST, tuberculin skin test.

^a For patients with clinical TB vs. patients without TB.

^b For patients with subclinical TB vs. patients without TB.

^c Data are for 460 patients.

positive predictive value, 12% (6 of 51 cases); negative predictive value, 99% (433 of 437); sensitivity, 60% (6 of 10); and specificity, 91% (433 of 478).

Isoniazid administration. Eight subjects with subclinical tuberculosis had received isoniazid for 4–85 days because of a positive TST result before the suspicion or confirmation of active tuberculosis. Among the 7 subjects who received isoniazid for ≥ 28 days before institution of 4-drug therapy for active tuberculosis, additional evaluation revealed new symptoms (cough duration of ≥ 2 weeks or fever duration of ≥ 2 weeks) or chest radiographic findings in 3 subjects. At the time of the additional evaluation, isoniazid therapy had already been discontinued for 114, 80, and 17 days. None of the 8 subjects for whom an additional sputum culture was performed at the time of reevaluation had positive culture results. Data on response to treatment for tuberculosis were available for 8 subjects: 6 had weight gain of >3 kg, and 2 additional subjects had clearing of chronic cough or fever.

DISCUSSION

While screening HIV-positive ambulatory subjects with CD4 cell counts of ≥ 200 cells/mm³ from an area where tuberculosis was endemic, we found that previously undiagnosed active tuberculosis was common, often asymptomatic, and difficult to detect on the basis of a single evaluation. Cases were identified only after longitudinal follow-up or because a baseline sputum culture grew *M. tuberculosis*. Patients with subclinical tuberculosis had no clinical features of pulmonary tuberculosis at baseline, and their cases were detected only by sputum stains or culture. These patients had a better prognosis than did those with clinical tuberculosis. Clinical tuberculosis was difficult to distinguish from latent tuberculosis, and patients with subclinical tuberculosis had often been treated with isoniazid before active tuberculosis was recognized.

The 15% rate of previously unrecognized active tuberculosis that we detected in the present study is higher than has been reported in other studies that were based on a single evaluation. A community-based, cross-sectional study from Haiti that used culture and radiography identified active tuberculosis among 5.8% of HIV-positive persons [16]. In a study from Baragwanath Hospital in Soweto, South Africa, active tuberculosis was detected in 3% of HIV-positive pregnant women [17]. The highest reported prevalence was from a study from Thailand that used examination and sputum culture; overall, 53 (12%) of 441 HIV-positive patients were identified with active tuberculosis, and sputum culture results were positive for 41 of these patients [18].

Previous reports have emphasized atypical presentations of active tuberculosis in patients with advanced HIV infection who have CD4 cell counts of <200 cells/mm³ and have concluded that clinical features are more typical in those with CD4 cell

counts of ≥ 200 cells/mm³ [3, 19, 20]. In this study, we identified a syndrome of subclinical tuberculosis in subjects with CD4 cell counts of ≥ 200 cells/mm³ that was detected only by ≥ 1 positive result of sputum AFB stain or culture. Most of these cases met a rigorous study definition for tuberculosis. We were unable to identify clinical predictors of subclinical tuberculosis, but a TST reaction size of <10 mm, combined with the absence of peripheral lymphadenopathy, had a high negative predictive value.

Although as many as 8% of HIV-infected patients may have normal chest radiographic findings [21], the pattern that we describe here of sputum culture–positive subclinical tuberculosis in HIV-infected patients, with neither clinical nor radiologic features of tuberculosis, has, to our knowledge, not been described previously. Positive sputum culture results for patients without symptoms or radiologic features of tuberculosis have been reported from the pre-HIV era and were thought to have represented primary infection with *M. tuberculosis* [22]. Asymptomatic pulmonary tuberculosis has also been reported in pregnant women [23]. The pathophysiology of subclinical tuberculosis in our HIV-infected patients is unclear. Transient colonization seems unlikely, given the later development of symptoms in some subjects, the in vitro responses to ESAT, and the response to treatment for tuberculosis in most subjects. The presence of cervical lymphadenopathy in some subjects is consistent with extrapulmonary disease. Disease did not appear to be systemic, and subjects were not bacteremic. Early respiratory tract disease, perhaps with initial involvement of the tonsils or other lymphoid respiratory tissue, is another possibility.

Subjects with subclinical tuberculosis had significantly elevated cellular immune responses to the *M. tuberculosis* protein ESAT-6. Responses to ESAT, typically measured by levels of IFN- γ or of cells positive for IFN- γ , have been noted in other patients with active tuberculosis but not previously in patients with HIV coinfection [24]. These responses indicate that there is an active host immune response to the organism and substantiate the conclusion that the positive culture results for these subjects were associated with invasive infection rather than with transient colonization. The positive responses in subjects with subclinical tuberculosis are also in accord with the finding that strong recognition of ESAT in household contacts correlates with the subsequent development of active tuberculosis during a 2-year period [25]. Collectively, these findings raise the possibility of an immunodiagnostic approach to early diagnosis of subclinical tuberculosis.

An important finding in our study was the fact that most subjects with subclinical tuberculosis had received single-drug isoniazid treatment for latent tuberculosis for >4 weeks before therapy was changed to multiple-drug treatment for active tuberculosis. Cough is recommended as the marker to screen for active tuberculosis, and chest radiography is also recommended,

although this appears to have limited utility in asymptomatic patients [10, 26]. Our study demonstrates that neither cough nor chest radiography findings would have identified the 10 subjects with subclinical tuberculosis.

The development of drug resistance might be expected after receipt of single-drug treatment for active tuberculosis. All of the subjects with active tuberculosis in our study had negative sputum culture results after receipt of isoniazid, but symptoms had progressed during or after isoniazid monotherapy in some subjects. Furthermore, subjects generally had therapies switched to 4-drug treatment for active tuberculosis before they received a full course of isoniazid preventive therapy, thereby preventing the emergence of drug resistance. Early studies of isoniazid monotherapy showed success rates in the 70% range, which is comparable to the rate for the combination of streptomycin and para-aminosalicylic acid [27], and isoniazid may not be harmful in patients with subclinical tuberculosis if organism burdens are less than those associated with intrinsic drug resistance. This issue deserves additional study, because delays in treatment of active tuberculosis not only have the potential to induce drug resistance, but they may permit acceleration of the course of HIV infection [28].

Our study is subject to several limitations. We cannot exclude the possibility that some HIV-positive subjects may have been reluctant to describe symptoms, because the diagnosis of tuberculosis is still associated with a significant stigma in sub-Saharan Africa. However, the objective measurement of temperature was normal in all subjects, and 7 of 10 subjects with subclinical tuberculosis had cases that met rigorous case definitions for definite tuberculosis. Laboratory cross-contamination was excluded in 8 patients on the basis of IS6110 typing findings.

In summary, culture-based longitudinal evaluation of HIV-positive subjects with CD4 cell counts of ≥ 200 cells/mm³ who live in an area where tuberculosis is endemic indicate that active tuberculosis is common and is difficult to identify on the basis of a single evaluation. A substantial proportion of subjects with active tuberculosis have a syndrome of HIV-associated subclinical tuberculosis in which typical features of active disease are absent at a time when the sputum culture results are positive and a cellular immune response to *M. tuberculosis* is already evident. This might tentatively be considered a form of incipient tuberculosis, and it appears to have a good prognosis.

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