POPULATIONS AT RISK

Validity of a Self-reported History of a Positive Tuberculin Skin Test

A Prospective Study of Drug Users

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OBJECTIVE: **To define the prevalence of and factors associated with having a negative purified protein derivative (PPD) among persons who self-report a prior positive PPD and to define the safety of repeat testing in such persons.**

DESIGN: **Observational cohort study.**

SETTING: **Methadone maintenance program with onsite primary care.**

PATIENTS/PARTICIPANTS: **Current or former drug users enrolled in methadone maintenance treatment.**

INTERVENTIONS: **Structured interview, tuberculin skin testing regardless of self-reported PPD status, and anergy testing.**

MEASUREMENTS AND MAIN RESULTS: **Nearly one third (31%) of participants who self-reported a prior positive PPD had a negative measured PPD, despite receipt of a "booster" PPD. A single participant (0.5%) blistered in response to the PPD without lasting ill effect. Participants with PPD results discordant from their history were more likely to be HIV-seropositive and nonreactive to the anergy panel. The discordance rate among HIV-infected participants was 43%, and was largely attributable to immune dysfunction. Among HIV-seronegative participants, the discordance rate was 27%. Recent crack-cocaine use was independently associated with discordance in the absence of HIV infection.**

CONCLUSIONS: **We confirmed that planting a PPD in patients who self-report a positive PPD history confers minimal risk. Substantial rates of discordance exist between self-reported history of a positive PPD and measured PPD status. Further research is needed to define the optimal management of PPD-negative patients who self-report a prior positive PPD and who have not received prior treatment for latent tuberculosis.**

KEY WORDS: **tuberculin skin testing; PPD; tuberculosis screening; drug users.**
J GEN INTERN MED 2004;19:1039–1044.

Received from the Albert Einstein College of Medicine (HVK, AAH, RSK, JHA, AHL, EES); and Montefiore Medical Center (HVK, AAH, RSK, JHA, AHL, EES), Bronx, NY; and the New York University School of Medicine (MNG), New York, NY.

An earlier version of this paper was presented as an abstract at the Society of General Internal Medicine 26th annual meeting, May 2003.

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Targeted screening and treatment of latent tuberculosis infection is a key component of the national plan to eliminate tuberculosis in the United States by the year 2010.[1] High rates of latent tuberculosis among illicit drug users, and high rates of progression to active disease among those coinfected with HIV, justify targeted screening and treatment for such high-risk patients.[2] Substance users who report prior screening for tuberculosis without formal documentation of the result present a dilemma for clinicians, who must decide whether to replant the PPD or rely on the patient's self-report of the prior positive result.

The optimal approach to managing patients who report a prior positive PPD but who have not been treated for latent tuberculosis is unknown. Because drug users with HIV infection have an increased risk of both active tuberculosis and of cutaneous anergy, and because retesting tuberculin-positive persons may pose risk of adverse reactions, clinicians may opt to offer treatment to persons reporting a positive PPD without a current documented positive result.[3] However, the potential for adverse isoniazid-associated consequences, such as hepatoxicity, may disuade some physicians from treating based on self-reported history alone.[4]

Scant evidence exists to help clinicians decide whether self-reported PPD status predicts the measured PPD status, and if so, what factors are associated with this relationship. We sought to determine the safety of repeat PPD testing in participants with self-reported prior positive results, the relationship between self-reported and measured PPD status, and factors associated with discordance between these two measures.

METHODS

Study Cohort

Subjects were recruited from among participants in the Bronx HIV Epidemiologic Research on Outcomes

(HERO) study, a longitudinal investigation of HIV infection among current and former drug users. Participants in the HERO study were recruited beginning in 1985 from the methadone maintenance treatment program at Montefiore Medical Center, Bronx, NY, as previously reported.[5] Individuals underwent standardized interview and phlebotomy semiannually, whether or not they remained enrolled in the substance abuse treatment program. Data collected included information about drug use behaviors, medical history, HIV testing, and T-cell lymphocyte studies.

Interviews

From May 1995 to December 1998, HERO participants were offered enrollment in a companion study of *M. tuberculosis* infection in drug users, with study visits coinciding with HERO semiannual visits. Participants completed a supplemental standardized interview that elicited detailed information regarding prior PPD status, and treatment of active or latent tuberculosis infection, and were screened for at-risk ethanol use by the CAGE questionnaire.[6]

Prior PPD status was assessed by asking whether subjects had ever been tested for tuberculosis, and the result of their prior tests. Prior treatment of latent tuberculosis was assessed by asking whether participants had been offered treatment to prevent active tuberculosis, and whether they had taken the medication.

PPD Testing

All participants who did not report a prior severe local reaction to tuberculin skin testing underwent 2-step tuberculin testing, regardless of prior tuberculin test results. A dose of 0.1 ml of 5-tuberculin unit purified protein derivative (PPD; tubersol; Connaught Laboratories, Toronto, Canada) was injected intradermally in the volar aspect of the participants' forearms with a 26-gauge beveled syringe. Delayed-type hypersensitivity testing was performed concomitantly with the Multitest CMI device (Merieux Institute, Miami, Fla), which delivered 7 antigens and 1 control percutaneously to the contralateral forearm.

The diameter of induration of the PPD test and each of the Multitest antigens and control was measured 48 to 72 hours after placement using the ballpoint pen technique.[7] Research assistants who measured the induration had each completed a course in skin testing technique taught by the New York City Department of Health Bureau of Tuberculosis Control.

All participants with a negative baseline PPD test were eligible to receive a second (booster) PPD 1 week later. Tuberculin positivity for HIV-infected participants was defined as ≥5 mm induration, to either the baseline or booster PPD, and for HIV-uninfected participants as ≥10 mm induration.[2] React-ivity to the Multitest device was defined as a reaction to any of the active antigens of at least 2 mm more than that produced by the control prong of the device. All participants with a positive PPD result were referred to a medical provider for further evaluation.

Participants received monetary compensation for each research study visit. The study protocol was approved by the institutional review board of Montefiore Medical Center, and all participants provided written informed consent.

Statistical Analysis

We were primarily interested in the relationship between self-reported positive PPD history and measured PPD status. Our main analysis was therefore conducted with participants who self-reported prior positive PPD results and completed 2-step tuberculin testing. Because all subjects in the main analysis reported prior positive PPD results, those with a negative measured PPD were classified as PPD-discordant and those with a positive measured PPD were classified as PPD-concordant. The main outcome variable was PPD discordance. Associations between this outcome and sociodemographic characteristics, drug and alcohol use, HIV status, CD4+ lymphocyte count (for HIV-seropositive participants), and reactivity to the Multitest device were determined using *t* tests (for continuous variables) or χ^2 or Fisher's exact tests (for categorical variables). Multivariate logistic regression analysis was performed to assess independent predictors of discordant PPD status among participants with a self-reported positive PPD history. Separate models were used for HIV-infected and HIV-uninfected participants. Odds ratios and 95% confidence intervals were computed using SPSS software version 10.0 (SPSS, Inc., Chicago, Ill).

RESULTS

Participants

Nine hundred and eleven participants in the HERO cohort were offered enrollment in the tuberculosis companion study. Of these, 25 persons declined to participate, citing such reasons as work schedule and fear of anergy testing. An additional 59 persons agreed to participate, but did not complete the required baseline protocol. Thus, 827 persons completed the interview and underwent tuberculin and HIV testing. Of the 648 participants with an initial negative PPD (<5 mm for HIV-infected participants, and <10 mm for HIV-uninfected participants), 471 (73%) completed the second (booster) tuberculin test. Thus, 650 participants either had a positive reaction to the initial PPD ($N = 179$) or completed booster testing ($N = 471$). Participants with negative tuberculin results at baseline who did not return for boosting were excluded from further analysis, because we were unable to exclude the possibility that they might be tuberculin positive with booster testing. Excluded individuals did not differ from the study sample with respect to age, race, or education. Of participants with negative PPDs at baseline, a greater proportion of HIV-seronegative

Table 1. Demographic and Clinical Characteristics of 214 Participants with a Positive PPD History by Self-report*

	HIV-seropositive *N* = 58 (27%)	HIV-seronegative *N* = 156 (73%)	Total *N* = 214 (100%)
Mean age, y (SD)	46.3 (6.1)	46.7 (7.5)	
Gender			
Female	20 (35)	59 (38)	79 (37)
Male	38 (65)	97 (62)	135 (63)
Race/ethnicity			
Hispanic	40 (70)	95 (61)	135 (63)
African American	15 (26)	36 (23)	51 (24)
White	2 (3)	24 (15)	26 (12)
Other	1 (2)	1 (1)	2 (1)
Mean education, y† (SD)	11.0 (2.5)	10.5 (2.6)	10.9 (2.5)
Enrolled in methadone maintenance (MMTP)	51 (88)	148 (95)	199 (93)
Substance use history			
Any illicit drug use within 6 months of PPD	26 (45)	83 (53)	109 (51)
Injection drug use within 6 months of PPD	8 (14)	20 (13)	28 (13)
Crack-cocaine use within 6 months of PPD†	7 (12)	27 (17)	34 (16)
≥2 positive answers to CAGE screening for alcoholism	23 (40)	62 (40)	85 (40)
Absent response to Multitest antigen panel†	13 (22)	5 (3)	18 (8)‡
Offered treatment for latent tuberculosis?†			
Yes	54 (93)	126 (82)	180 (85)§
No	4 (7)	28 (18)	32 (15)
Took treatment (among those offered)?†			
Yes	52 (96)	115 (92)	167 (93)
No	2 (4)	10 (8)	12 (7)

* *Data are presented as numbers (percents) unless otherwise noted.*
† *Data were missing for education (n = 2), crack-cocaine (n = 1), absent response to the Multitest (n = 1), offered treatment (n = 1), and took treatment (n = 1).*
‡ P < *.001.*
§ P = *.04.*
PPD, purified protein derivative; SD, standard deviation.

participants than HIV-seropositive participants completed boosting (76% vs 67%; $P = .01$).

Characteristics of Participants with Self-reported Positive PPDs

Among the 650 participants, 214 (33%) reported a prior positive PPD (Table 1). Only 1 participant (0.5%) had an adverse (blistering) response to tuberculin testing, which resolved with topical treatment. Reactivity to the Multitest device was greater among HIV-negative participants ($P < .001$). A higher proportion of HIV-infected participants than HIV-uninfected participants reported having been offered prophylaxis for tuberculosis ($P = .04$). Among those offered treatment for latent tuberculosis, the proportion reporting adherence with treatment did not differ by HIV status.

Discordance: Positive PPD History and Negative Measured PPD

Among the 214 participants who reported a prior positive PPD, 67 (31%) had a negative (discordant) PPD when tested. Discordant results were more common among HIV-infected participants than uninfected participants (43% vs 27%; $P = .02$) and among participants who were not responsive to the Multitest (89% vs 26%; $P < .001$). In addition, 46% of recent injection drug users had discordant PPD results compared to 29% of former or nonusers of injection drugs ($P = .06$). Report of other drug use, including recent use of crack-cocaine, or lifetime heavy alcohol use (as measured by ≥2 affirmative answers to CAGE questions), was not associated with discordance, nor were any other sociodemographic characteristics. A self-reported history of having taken isoniazid for treatment of latent tuberculosis had no association with discordance.

Among HIV-seronegative participants, factors associated with discordance included recent injection drug use, recent crack-cocaine use, and an absent response to the Multitest (Table 2). Among HIV-infected participants, factors associated with discordant PPD status included Hispanic ethnicity, absent response to the Multitest, and low CD4 lymphocyte counts. The rate of discordance among HIV-infected participants varied inversely with CD4+ lymphocyte count. Among participants with the lowest CD4+ lymphocyte counts (≤200 cells/mm^3), 64% had discordant PPDs; among participants with CD4+ lymphocyte counts between 200 and 499, 53% had discordant PPDs, but among those with the highest counts (>500 cells/mm^3), only 11% had discordant PPD results. In contrast to the HIV-seronegative participants, recent crack-cocaine use among HIV-seropositive participants was associated with a

Table 2. Factors Associated with Current PPD Status Among 214 Participants with a Positive PPD History Stratified by HIV Infection Status*

Characteristic	HIV-positive Participants			HIV-negative Participants		
	Discordant PPD Status *N* = 25	Concordant PPD Status *N* = 33	*P* Value	Discordant PPD Status *N* = 42	Concordant PPD Status *N* = 114	*P* Value
Mean age, y (SD)	45.2 (5.8)	47.2 (6.3)	.23	45.2 (7.8)	47.2 (7.4)	.15
Gender						
Female	8 (32)	12 (36)	.68	17 (40)	42 (37)	.73
Male	17 (68)	21 (64)		25 (60)	72 (63)	
Years school completed†						
<12 years	18 (72)	20 (61)	.37	18 (44)	62 (55)	.23
≥12 years	7 (28)	13 (39)		23 (56)	51 (45)	
Race/ethnicity†						
Latino	21 (84)	19 (59)	<.001	21 (50)	74 (66)	.21
African American	2 (8)	13 (41)		13 (31)	23 (20)	
White	2 (8)	0 (0)		8 (19)	16 (14)	
Current methadone treatment	21 (84)	30 (91)	.45	41 (98)	107 (94)	.68
Substance use history						
Any illicit use within 6 months of PPD	10 (40)	16 (48)	.52	25 (60)	58 (51)	.34
Injection use within 6 months of PPD	4 (16)	4 (12)	.48	9 (21)	11 (10)	.05
Crack-cocaine use within 6 months of PPD†	0 (0)	7 (21)	.02	12 (29)	15 (13)	.02
≥2 positive answers to CAGE screening	7 (28)	16 (48)	.11	18 (43)	44 (39)	.63
Absent response to Multitest antigen panel†	12 (48)	1 (3)	<.001	4 (10)	1 (1)	.02
CD4+ lymphocytecount (cells/mm^3)†						
<200	9 (43)	5 (17)				
200 to 499	10 (48)	9 (30)	.004			
≥500	2 (9)	16 (53)				
Offered treatment for latent tuberculosis?†	24 (96)	30 (91)	.63	32 (78)	94 (83)	.46
Took treatment (among those offered)?†	23 (96)	29 (97)	.70	30 (94)	85 (91)	.5

* *Data are presented as numbers (percents) unless otherwise noted.*
† *Data were missing for the following variables: education (n = 2), crack-cocaine (n = 2), absent response to the Multitest antigen panel (n = 1), CD4+ lymphocyte count (n = 7), history of being offered treatment (n = 2), and history of taking treatment (n = 1).*
PPD, purified protein derivative; SD, standard deviation.

Table 3. Multivariate Logistic Regression Models of Factors Associated with PPD Reactivity Discordance in HIV-seronegative and HIV-seropositive Drug Users

Variable	Adjusted OR (95% CI)	*P* Value
HIV-seronegative participants		
Absent reactivity to Multitest antigen panel	15.4 (1.6 to 146.5)	.02
Crack-cocaine use within 6 months	3.0 (1.2 to 7.3)	.02
Injection drug use within 6 months	2.5 (0.9 to 6.8)	.08
HIV-seropositive participants*		
CD4+ lymphocyte count, cells/mm^3		
≤200	20.0 (1.4 to 287.6)	.03
201 to 500	6.7 (0.60 to 74.5)	.12
>500	1.0	reference

* *Model adjusted for race and reactivity to Multitest antigen panel.*
PPD, purified protein derivative; OR, odds ratio; CI, confidence interval.

positive PPD test result—that is, a result concordant with history.

Multivariate logistic regression analyses were conducted to identify factors independently associated with a negative (discordant) PPD (Table 3). Among HIV-seronegative participants, absent reactivity to the Multitest and recent crack-cocaine use were independently associated with PPD discordance adjusting for recent injection drug use. Crack users were 3 times as likely to have PPD results discordant with their self-reported tuberculin positivity as non-crack users (adjusted odds ratio [OR], 3.0; 95% confidence interval [CI], 1.2 to 7.3), and participants not reactive to the Multitest were 15 times more likely to have discordant results (adjusted OR, 15.4; 95% CI, 1.6 to 146.5).

Among HIV-seropositive participants, having a CD4+ lymphocyte count ≤200 cells/mm^3 was independently associated with having a negative PPD reaction (discordance) after controlling for race and absent reactivity to the Multitest. Because all HIV-seropositive participants who had recently used crack-cocaine had concordant PPDs, we could not further evaluate this relationship in the multivariate model.

DISCUSSION

Nearly one third of participants who self-reported a prior positive PPD had a negative measured PPD, a result discordant with their history, despite receipt of a "booster" PPD. In addition, we confirmed that planting a PPD in an individual with a self-reported positive PPD history conveys minimal risk: only a single participant had a blistering response, which resolved with topical treatment. Participants with measured PPD results that were negative and therefore discordant from their history were more likely to be HIV-seropositive and nonreactive to the Multitest antigen panel.

The 43% discordance rate among HIV-infected participants was accounted for in large part by immune dysfunction; among HIV-infected individuals, only a low CD4+ lymphocyte count (<200 cells/mm^3) was independently associated with discordance, and 92% of those with negative tuberculin testing were also nonreactive to Multitest. The discordance rate of 27% among HIV-seronegative participants was surprising. Despite the statistical association between discordance and nonreactivity to the Multitest, only 4 of the 42 HIV-seronegative participants with discordance failed to react to the Multitest. This suggests that cutaneous anergy is not the principal explanation for the 27% discordance rate observed in HIV-uninfected participants.

Other investigations have also documented significant rates of PPD discordance among individuals with self-reported positive PPDs. Prior to the era of HIV, in a similar investigation to ours, Reichman and O'Day found a PPD discordance rate higher than the 27% we found among HIV-negative participants: 58% of New York City Board of Education employees had a negative PPD despite reporting a positive PPD history.[8] In their study of risk factors for a positive tuberculin test among active drug users, Salomon et al. found that, among nonanergic HIV-seropositive and -seronegative participants, self-reported history of PPD positivity or of TB therapy was the strongest predictor of having a measured positive PPD.[9] In absolute terms, however, the 48% rate of discordance among participants in that study was higher than both the 27% we found among HIV-seronegative participants and the 43% we found among HIV-seropositive participants.

The discordance we observed between measured PPD and self-reported positive history may represent PPD reversions or may reflect erroneous self-report of prior positive PPD status. Reversion of PPD results among immunocompetent individuals has been well documented.[10,11] In addition, an extensive literature has documented the association between immune status and tuberculin reactivity. In particular, advanced HIV disease has been associated with decreased reactivity to tuberculin as well as to other intradermally applied antigens.[12] Among HIV-seronegative patients, the proportion of patients that are reported to lose reactivity to PPD over time has varied. At the lower end, one investigation found that 7% of children with PPD reaction sizes ≥10 mm had reverted their PPD (to <10 mm) at 1 year.[13] Other studies have documented higher proportions of reversions, such as 25% among nursing home patients,[14] and 41% in developmentally delayed children.[15] In a prospective multicenter study of women with or at-risk for HIV infection, the proportion of HIV-seronegative and -seropositive women who reverted their PPD status was 44% and 46%, respectively.[16] Thus, the discordance rate we observed may be consistent with the phenomenon of reversion.

Receipt of treatment with isoniazid has been found to increase the prevalence of reversion. Several prior investigations have found that patients treated with isoniazid soon after PPD conversion are more likely to lose their reactivity to tuberculin than patients untreated or treated after an indeterminate time of being tuberculin positive.[17,18] Although we were not able to determine the time between conversion to tuberculin positivity and treatment for latent tuberculosis, there was no association between discordance and receipt of isoniazid among participants in our study.

An alternative explanation for the discordance may be that medical history recall among drug users is inaccurate. There is limited information on the accuracy of self-reported tuberculin reactivity by drug users specifically, but one retrospective study of injection drug users using medical record review found that 90% of PPD-positive and -negative participants correctly self-reported their PPD results.[19] In addition, positive predictive value of self-report by drug users for other medical conditions has been found to be high. In one study, 98% of those reporting seropositivity to hepatitis C virus were found to be seropositive[20]; in another, 89% of individuals self-reporting HIV infection tested seropositive for HIV.[21] Erroneous self-report of PPD status is therefore less likely to be a major factor accounting for our results.

Of the types and routes of drug use we examined, only recent crack-cocaine use was independently associated with PPD discordance in the absence of HIV infection. Previously reported data from this cohort demonstrated that any (lifetime) use of crack-cocaine was predictive of PPD positivity among HIV-seronegative participants.[22] Our finding of PPD discordance among HIV-seronegative recent crack users may be a function of crack-cocaine's adverse effects on immune functioning,[23] causing partial anergy.[24]

We documented the safety of placing a PPD on both immunocompetent and immunocompromised participants with self-reported prior positive PPDs and without prior adverse reactions to tuberculin testing. Our finding is consistent with previous investigations that have shown that skin testing itself does not induce delayed-type hypersensitivity, and that repeat testing of documented tuberculin reactors is safe.[8,9,25] Thus, clinicians need not be concerned about adverse reactions to PPD testing in patients who report prior tuberculin reactivity without blistering or other severe reactions.

Based on our findings, among HIV-seronegative individuals who report a prior positive PPD but who have not

been treated for latent tuberculosis, we believe there is insufficient evidence to recommend for or against treatment of latent disease without retesting. Even if the discordance rate of 27% among HIV-seronegative individuals represents false-negative reactions in persons with true latent tuberculosis, the risk of subsequent active disease is much lower than in HIV-seropositive individuals. Because our data demonstrate that retesting such individuals is safe, we recommend retesting HIV-seronegative individuals who have a positive PPD history.

In HIV-infected drug users, on the other hand, given the very high risk of activation and progression of tuberculosis, there is a great imperative to treat latent disease. Treating all HIV-seropositive individuals with a positive PPD history would ensure that all individuals with latent tuberculosis who may have subsequently lost their tuberculin reactivity would receive treatment. Unneeded treatment, however, would likely expose some patients unnecessarily to potentially serious hepatoxicity. We therefore recommend replanting PPDs in HIV-seropositive individuals with a history but not current documentation of positive PPD, in order to focus treatment efforts. If the measured PPD is positive, the indication for treatment is clear, and the patient does not incur harm by the retesting process. If the measured PPD is negative, as it was in 43% of participants in our sample, the clinician should attempt to obtain documentation of prior test results, and the reason treatment was not prescribed if the test was positive. If prior results are not available, the clinician should individualize treatment decisions based on epidemiological risk, particularly in those patients who are anergic or who have low CD4 lymphocyte counts. Further research is needed to define the optimal management of PPD-negative patients who self-report a prior positive PPD and who have not received treatment for latent tuberculosis.

Dr. Kunins is supported by National Institutes on Drug Abuse grant DA-R25-DA14551. Drs. Klein and Gourevitch were supported in part by National Institutes on Drug Abuse grant RO1-DA09521. Dr. Arnsten was supported by the National Institute on Drug Abuse grant R01-DA11869, and by a Robert Wood Johnson Generalist Physician Faculty Scholar Award. Drs. Arnsten, Gourevitch, and Klein were supported in part by National Institute of Allergy and Infectious Diseases Centers for AIDS research grant AI-051519.

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