

Criteria for assessing cutaneous anergy in women with or at risk for HIV infection

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Background: Controversy exists about both the clinical utility of anergy testing and the optimal criteria for defining anergy. **Objective:** We sought to assess various definitions of cutaneous anergy for ability to distinguish HIV status, level of immunodeficiency, and ability to mount a tuberculin reaction among women with or at risk for HIV infection.

Methods: HIV-seropositive (n = 721) and HIV-seronegative (n = 358) at-risk women at academic medical centers in Baltimore, Detroit, New York, and Providence had cutaneous testing with mumps, *Candida*, tetanus toxoid, and tuberculin antigens. Associations with HIV status and CD4⁺ lymphocyte levels were analyzed.

Results: *Candida*, mumps, and tetanus antigens alone or in combination elicited reactions significantly less often in HIV-seropositive than in HIV-seronegative women and less often in seropositive women with lower CD4⁺ counts, regardless of induration cutpoint chosen to define a positive reaction. The best antigen combinations for distinguishing groups included tetanus and mumps. Some women nonreactive to the 3 antigens ("anergic") had positive tuberculin reactions among both seropositive subjects (range, 1.1% to 2.9% depending on induration cutpoint for defining anergy) and seronegative subjects (range, 8.9% to 14%).

Conclusion: Absence of reactions to *Candida*, mumps, and tetanus antigens alone or in combination and at any induration cutpoint is associated with HIV status and with CD4⁺ level. Combinations, including tetanus and mumps antigens with an induration cutpoint of less than 2 mm, may be the best for defining anergy. (J Allergy Clin Immunol 1999;103:93-8.)

Key words: Anergy, cellular immunity, delayed hypersensitivity, skin tests

Abbreviations used

CDC:	Centers for Disease Control and Prevention
CI:	Confidence interval
DTH:	Delayed-type hypersensitivity
HERS:	HIV Epidemiology Research Study
OR:	Odds ratio
PPD:	Purified protein derivative

The hallmark of advanced HIV infection and AIDS is a severe defect in cell-mediated immunity.^{1,2} In addition to marked depletion of the CD4⁺ subset of T lymphocytes, advanced HIV infection is often accompanied by cutaneous anergy, which is defined as the inability to mount a delayed-type hypersensitivity (DTH) response to intradermal injection of recall antigens.³⁻¹⁰ The determination of cutaneous anergy in persons with HIV infection may be important for 2 reasons. First, cutaneous anergy has been reported to be an independent predictor of HIV disease progression, even when controlling for CD4 lymphocyte level.^{7,9,11} Although it is not known whether this remains true when HIV viral load is taken into account, it is likely that DTH testing will continue to be used for evaluating the immune function of patients with or at risk for HIV infection, especially in areas of the world where viral load measurements and even lymphocyte subset assays may be unavailable or unaffordable (eg, Africa).¹² Second, evaluation for cutaneous anergy may be helpful in certain settings for interpretation of a negative response to tuberculin testing.^{13,14}

However, the literature relating to this issue is confusing, and the utility of anergy testing is controversial. In 1991, the Centers for Disease Control and Prevention (CDC) issued guidelines for anergy testing in persons with or at risk for infection.¹³ Investigators have reported that DTH testing in such persons may be clinically useful.^{5-7,10,15} However, several subsequent studies demonstrated that anergy measured by DTH testing is not stable in individuals with HIV infection over time,^{16,17} raising doubts about the clinical utility of this procedure. In 1997, the CDC revised its recommendations so that anergy testing in conjunction with tuberculin testing is no longer routinely recommended for screening programs for *Mycobacterium tuberculosis* in HIV-infected persons, although it may be useful in selected situations.¹⁸

Factors possibly contributing to the uncertainty about

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TABLE I. Selected characteristics of study subjects

	HIV+ (n = 721)	HIV- (n = 358)	P value
Median age (y)	36	36	NS
Race (%)			
Black	58.9	53.1	
White	20.0	29.1	
Hispanic	16.6	15.4	
Other	4.3	2.3	.004
Education (% less than high school)	45.5	37.7	.009
Median annual household income	\$9000	\$9000	NS
Employed (%)	16.3	25.8	.002
Injection drug use since 1985 (%)	52.6	49.2	NS
CD4+ cell count/mm ³ (%)			
<200	23.1	0	
200-499	48.1	1.7	
≥500	28.9	98.3	<.001

the usefulness of DTH testing include the facts that the antigens used for anergy testing vary among reported studies in number, type, concentration, and manufacturer^{6-8,10,11,16,19} and that the reported criteria used for interpreting each reaction as positive or negative vary as well.^{3,5,8-10,16,19,20}

In this study we sought to assess the effect of varying the number of antigens and the induration cutoff considered reactive for defining cutaneous anergy and to determine the relative values of various definitions in distinguishing HIV status, level of immunodeficiency, and ability to respond to tuberculin skin testing. To this end we studied at-risk women with and without HIV infection participating in a large multicentered study of the natural history of HIV infection in women, the HIV Epidemiology Research Study (HERS).

METHODS

The HERS is a collaborative study of 871 HIV-seropositive and 439 HIV-seronegative at-risk women in New York, Providence, Baltimore, and Detroit.²¹ Women at risk for HIV infection through injection drug use (since 1985) or sex (with an at-risk male, in exchange for drugs or money, or with more than 5 partners within 5 years) were enrolled and scheduled to be evaluated every 6 months. The design of the HERS and the characteristics of participants have been reported previously.²¹

In brief, evaluations consisted of an interview regarding sociodemographics; general medical and health history; obstetric, gynecologic, and contraceptive history; drug use and sexual behaviors; health care use; and psychosocial measures. General physical and pelvic examinations were performed; blood specimens were obtained for HIV antibody testing (enzyme immunoassay with confirmation by Western blot), T lymphocyte subsets, and other tests; and testing for cutaneous DTH and tuberculin reactivity were done.

Intradermal injection of 0.1 mL of the following antigens were used for testing: (1) Mumps Skin Test Antigen USP (Connaught Laboratories Inc, Swiftwater, Pa); (2) dermatophytin "O" (*Candida*) 1:100 (Miles Inc, Elkhart, Ind); (3) tetanus toxoid SP diluted 1:10 (Connaught Laboratories Inc); and (4) tuberculin purified protein derivative (PPD, Mantoux) 5 tuberculin units (Connaught Labora-

tories Inc). Individuals with a history of positive PPD reactions were not excluded from participation. Skin tests were performed, and results were read at 48 to 72 hours by trained research personnel. The transverse diameter was recorded in millimeters of induration. Study personnel were aware of the subjects' HIV status but not the CD4+ cell count at the time of evaluation. Data from the first visit, at which results were available for all *Candida*, mumps, and tetanus skin tests, were included in this analysis.

Categorical variables were analyzed by using chi-square or Fisher's exact test as appropriate; continuous variables were analyzed by using ANOVA or the Kruskal-Wallis test. Findings were considered statistically significant at *P* values of .05 or less. All tests were 2-tailed. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.

All participants provided written informed consent, and the study was approved by the Institutional Review Boards for the Protection of Human Subjects at each of the participating medical centers.

RESULTS

Of the 1310 HERS participants, 1079 (82.4%) had results of DTH testing with *Candida*, tetanus, and mumps antigen performed at the same visit. Selected characteristics of the 721 HIV-seropositive and 358 HIV-seronegative women included in this analysis are shown in Table I. Women had a median age of 36 years; African American, Latina, and white women were well represented, with few women of other racial or ethnic backgrounds; and women generally were poor, with median annual household incomes of \$9000. HIV-seropositive women were less likely to be white, to have completed high school, and to be employed. Women were similar to all HERS participants.²¹

The prevalence of DTH reactions by HIV status for *Candida*, mumps, and tetanus antigens and the effect of varying the cutpoint for reaction sizes considered positive are shown in Table II. All antigens were significantly more likely to result in negative reactions among HIV-seropositive women, regardless of the induration cutpoint chosen. Of the 3 antigens tested, tetanus best distinguished the HIV-seropositive and HIV-seronegative groups, with the highest ORs for negative reactions in seropositive subjects compared with seronegative subjects. Although induration cutpoint did not have a major effect on the ORs for comparisons by HIV status for any of the antigens, increasing the cutpoint affected the proportion of women considered nonreactive. For example, increasing the cutpoint from less than 1 mm to less than 5 mm increased the proportion of seronegative women considered nonreactive by 54.3% for mumps antigen (from 28.2% to 43.3%), by 23.1% for *Candida* antigen, and by 16.5% for tetanus antigen.

Table III shows the number of HIV-seropositive women by CD4+ cell level with negative reactions to each antigen for each induration cutpoint. For all 3 antigens, the proportion of seropositive women who were reactors differed significantly by CD4+ cell level, regardless of the induration cutpoint used. Differences in reaction rates by CD4+ cell level were greatest for tetanus antigen; among seropositive women with CD4+ cell counts of 500/mm³ or greater, at every induration cut-

TABLE II. Effect of varying induration cutpoint on DTH testing among 721 HIV-seropositive and 358 HIV-seronegative at-risk women

Induration cutpoint*	Number of women (%) nonreactive to each antigen								
	<i>Candida</i>			Tetanus			Mumps		
	HIV–	HIV+	OR (95%CI)	HIV–	HIV+	OR (95%CI)	HIV–	HIV+	OR (95%CI)
<1 mm	181 (50.6)	497 (68.9)	2.2 (1.7-2.8)	78 (21.8)	444 (61.6)	5.8 (4.3-7.7)	101 (28.2)	483 (67.0)	5.2 (3.9-6.8)
<2 mm	182 (50.8)	498 (69.1)	2.2 (1.7-2.8)	78 (21.8)	447 (62.0)	5.9 (4.4-7.8)	102 (28.5)	484 (67.1)	5.1 (3.9-6.8)
<3 mm	190 (53.1)	522 (72.4)	2.3 (1.8-3.0)	81 (22.6)	466 (64.6)	6.2 (4.7-8.4)	112 (31.3)	498 (69.1)	4.9 (3.7-6.4)
<4 mm	209 (58.4)	539 (74.8)	2.1 (1.6-2.8)	85 (23.7)	482 (66.9)	6.5 (4.9-8.6)	128 (35.8)	527 (73.1)	4.9 (3.7-6.4)
<5 mm	223 (62.3)	575 (79.8)	2.4 (1.8-3.2)	91 (25.4)	501 (69.5)	6.7 (5.0-8.9)	155 (43.3)	564 (78.2)	4.7 (3.6-6.2)

*Reaction size defining lack of DTH response.

TABLE III. Difference by CD4 level in reactivity rates to DTH testing among 693 HIV-seropositive women*: Effect of varying induration cutpoint

Induration cutpoint†	Number of women (%) nonreactive to each antigen											
	<i>Candida</i>				Tetanus				Mumps			
	(CD4+ cells/mm ³)				(CD4+ cells/mm ³)				(CD4+ cells/mm ³)			
	<200	200-499	≥500	P value	<200	200-499	≥500	P value	<200	200-499	≥500	P value
<1 mm	132 (82.5)	220 (66.1)	126 (63.0)	.0001	141 (88.1)	195 (58.6)	87 (43.5)	<.0001	133 (83.1)	223 (67.0)	107 (53.5)	.0001
<2 mm	133 (83.1)	220 (66.1)	126 (63.0)	.0001	142 (88.8)	197 (59.2)	87 (43.5)	<.0001	133 (83.1)	224 (67.3)	107 (53.5)	.0002
<3 mm	136 (85.0)	232 (69.7)	135 (67.5)	.0002	146 (91.3)	206 (61.9)	93 (46.5)	<.0001	134 (83.8)	232 (69.7)	112 (56.0)	.0006
<4 mm	137 (85.6)	239 (71.8)	144 (72.0)	.0005	149 (93.1)	212 (63.7)	99 (49.5)	<.0001	141 (88.1)	243 (73.0)	122 (61.0)	.0001
<5 mm	144 (90.0)	255 (76.6)	156 (78.0)	.0003	153 (95.6)	223 (67.0)	103 (51.5)	<.0001	147 (91.9)	259 (77.8)	137 (68.5)	.0001

*One hundred sixty women had a CD4+ count less than 200/mm³, 333 had a CD4+ count of 200 to 500/mm³, and 200 had a CD4+ count greater than 500/mm³.

†Reaction size defining lack of DTH response.

point a smaller proportion of women were nonreactors to tetanus than to the other 2 antigens tested.

The number of women defined as “anergic” (nonreactors) with regard to the 3 antigens in various combinations is shown in Table IV for each induration cutpoint. The difference in reaction rates by HIV status was greatest for the combination of tetanus and mumps (ORs for nonreactivity in HIV-seropositive women ranged from 6.6 to 7.9 depending on induration cutpoint chosen) compared with either of the other 2 antigen combinations. For seropositive women compared with seronegative women, the ORs with the combination of tetanus and mumps exceeded that for any of the single antigens and equaled or exceeded the difference by HIV status with use of all 3 antigens, regardless of induration cutpoint chosen.

Table V shows that among HIV-seropositive women, reaction rates by CD4+ cell level differed significantly ($P < .0001$) for all combinations of 2 or more antigens with any induration cutpoint.

Results of PPD testing performed at the same visit were available for 1025 (95.0%) women. Using definitions for PPD positivity of 10 mm or greater induration for seronegative women and 5 mm or greater for seropositive women, we compared the numbers of women with positive PPD reactions among those considered anergic and those considered nonanergic on the basis of DTH testing with various combinations of *Candida*, mumps, and tetanus antigens and with different induration cut-

points. Among HIV-seronegative women, depending on the criteria chosen to define anergy, from 8.9% to 14% of anergic subjects had PPD reactions of 10 mm or greater; there were no significant differences in rates of positive PPD reactions between women who did and those who did not react to any combination of the 3 other antigens, regardless of induration cutpoint used to define anergy (data not shown). However, among HIV-seropositive women, the proportions with positive PPD reactions were significantly lower among women defined as anergic for all antigen combinations and induration cutpoints, with a single exception (Table VI). Only for women nonreactive to *Candida* and mumps antigens at an induration cutpoint of less than 5 mm did differences fail to achieve significance ($P = .06$).

DISCUSSION

The ability to mount a cutaneous DTH reaction to the combination of tetanus and mumps antigens, with or without *Candida* antigen, best differentiated women by HIV status. An induration cutpoint of less than 2 mm seems most reasonable for determining whether a person reacts to an antigen. The choice of induration cutpoint considered nonreactive had little effect on ability to discriminate groups by level of immunodeficiency, whichever combination of antigens was included, but larger cutpoints increased the proportion of persons considered nonreactive. Therefore it may be appropriate to consider any induration at 48 to 72 hours as evidence of at least

TABLE IV. Rates of cutaneous anergy by HIV status: Effect of varying number of antigens and induration cutpoint*

Antigens tested	Number (%) of nonreactive women		
	HIV- (n = 358)	HIV+ (n = 721)	OR (95%CI)
Anergy defined as <1 mm to:			
<i>Candida</i> and tetanus	50 (14.0)	335 (46.5)	5.4 (3.8-7.6)
<i>Candida</i> and mumps	70 (19.6)	372 (51.6)	4.4 (3.2-6.0)
Tetanus and mumps	46 (12.8)	355 (49.2)	6.6 (4.6-9.4)
<i>Candida</i> , tetanus, and mumps	34 (9.5)	293 (40.6)	6.5 (4.4-9.8)
Anergy defined as <2 mm to:			
<i>Candida</i> and tetanus	50 (14.0)	339 (47.0)	5.5 (3.9-7.8)
<i>Candida</i> and mumps	70 (19.6)	374 (51.9)	4.4 (3.2-6.1)
Tetanus and mumps	46 (12.8)	358 (49.7)	6.7 (4.7-9.6)
<i>Candida</i> , tetanus, and mumps	34 (9.5)	297 (41.2)	6.7 (4.5-10.0)
Anergy defined as <3 mm to:			
<i>Candida</i> and tetanus	52 (14.5)	359 (49.8)	5.8 (4.1-8.3)
<i>Candida</i> and mumps	77 (21.5)	393 (54.5)	4.4 (3.2-5.9)
Tetanus and mumps	49 (13.7)	384 (53.3)	7.2 (5.1-10.2)
<i>Candida</i> , tetanus, and mumps	36 (10.1)	317 (44.0)	7.0 (4.7-10.4)
Anergy defined as <4 mm to:			
<i>Candida</i> and tetanus	60 (16.8)	381 (52.8)	5.6 (4.0-7.7)
<i>Candida</i> and mumps	96 (26.8)	422 (58.5)	3.9 (2.9-5.2)
Tetanus and mumps	55 (15.4)	413 (57.3)	7.4 (5.3-10.4)
<i>Candida</i> , tetanus, and mumps	42 (11.7)	343 (47.6)	6.8 (4.7-9.9)
Anergy defined as <5 mm to:			
<i>Candida</i> and tetanus	65 (18.2)	417 (57.8)	6.2 (4.5-8.5)
<i>Candida</i> and mumps	116 (32.4)	471 (65.2)	3.9 (3.0-5.2)
Tetanus and mumps	60 (16.8)	443 (61.4)	7.9 (5.7-11.0)
<i>Candida</i> , tetanus, and mumps	47 (13.1)	380 (52.7)	7.4 (5.2-10.6)

*Reaction size defining lack of DTH response.

partially intact DTH because even small induration sizes correlate with positive lymphoproliferative responses and show the histologic findings of DTH.²⁰ However, reaction sizes of 1 mm are difficult to measure reliably, and only 7 (0.2%) of 3237 reactions to *Candida*, mumps, and tetanus antigens were recorded as 1 mm induration. By using the cutpoint of less than 2 mm, more than 90% of HIV-seronegative women were reactive to 1 or more of the antigens tested.

The literature on cutaneous anergy testing in persons with HIV infection has been complicated both by the considerable variation in number, type, concentration, and manufacturer of antigens used^{6-8,10,11,16,19} and by the different criteria used for interpreting reactions as positive or negative.^{3,5,8-10,16,19,20,22-25} Many of these antigens have not been standardized or approved by the Food and Drug Administration for use by the Mantoux procedure for testing DTH.^{13,26,27} Others represent antigens that are restricted geographically, and therefore absence of reaction may reflect lack of exposure rather than

TABLE V. Nonreactivity to DTH testing by CD4+ cell count among HIV-seropositive women: Effect of varying number of antigens

Antigens tested	Number (%) of nonreactive women* CD4+ cells/mm ³		
	<200 (n = 160)	200-499 (n = 333)	≥500 (n = 200)
Nonreactivity defined as <1 mm			
<i>Candida</i> and tetanus	118 (73.8)	144 (43.2)	58 (29.0)
<i>Candida</i> and mumps	116 (72.5)	163 (48.9)	79 (39.5)
Tetanus and mumps	121 (75.6)	159 (47.7)	58 (29.0)
<i>Candida</i> , tetanus, and mumps	108 (67.5)	125 (37.5)	47 (23.5)
Nonreactivity defined as <2 mm			
<i>Candida</i> and tetanus	120 (75.0)	146 (43.8)	58 (29.0)
<i>Candida</i> and mumps	117 (73.1)	164 (49.2)	79 (39.5)
Tetanus and mumps	122 (76.3)	161 (48.3)	58 (29.0)
<i>Candida</i> , tetanus, and mumps	110 (68.8)	127 (38.1)	47 (23.5)
Nonreactivity defined as <3 mm			
<i>Candida</i> and tetanus	124 (77.5)	158 (47.4)	62 (31.0)
<i>Candida</i> and mumps	118 (73.8)	176 (52.9)	85 (42.5)
Tetanus and mumps	126 (78.8)	176 (52.9)	65 (32.5)
<i>Candida</i> , tetanus, and mumps	112 (70.0)	141 (42.3)	51 (25.5)
Nonreactivity defined as <4 mm			
<i>Candida</i> and tetanus	128 (80.0)	167 (50.2)	70 (35.0)
<i>Candida</i> and mumps	126 (78.8)	186 (55.9)	95 (47.5)
Tetanus and mumps	133 (83.1)	185 (55.6)	77 (38.5)
<i>Candida</i> , tetanus, and mumps	120 (75.0)	149 (44.7)	60 (30.0)
Nonreactivity defined as <5 mm			
<i>Candida</i> and tetanus	138 (86.3)	184 (55.3)	79 (39.5)
<i>Candida</i> and mumps	133 (83.1)	210 (63.1)	111 (55.5)
Tetanus and mumps	142 (88.8)	199 (59.8)	84 (42.0)
<i>Candida</i> , tetanus, and mumps	129 (80.6)	168 (50.5)	69 (34.5)

*Nonreactivity rates differ significantly ($P < .0001$) by CD4 level for all combinations tested.

inability to respond.^{22,24,27,28} The reported criteria for interpreting a DTH response as reactive have included any induration,^{8,13,19} 2 mm or greater induration,^{3,5} 3 mm or greater induration,^{10,16} 5 mm or greater induration,^{22,23,29} or 5 × 5 mm induration.^{7,11,25} It is possible that the large proportion of HIV-seronegative individuals reported as being anergic in some studies may be caused, at least in part, by the choice of antigens tested or by an inappropriately high induration cutpoint.

In persons with HIV infection, cutaneous anergy testing has generally been used for 2 purposes, as a measure of immunologic status and to assist in assessing risk for tuberculosis. Anergy has been associated with decreasing immunocompetence and has been reported to be a predictor of HIV disease progression, even when controlling for CD4+ count.^{7,9,11} With the recent availability of HIV viral load assays, the best measure of HIV disease progression,³⁰⁻³³ it is unclear whether anergy testing will still add information regarding prognosis. However, in much of the less-industrialized world, where measures

TABLE VI. PPD reactions in 683 HIV-seropositive anergic and nonanergic women: Effect of varying definition of anergy

	Number (%) of women with positive PPD*		
	Anergic	Nonanergic	OR (95% CI)
Anergy defined as <1 mm to:			
<i>Candida</i> and tetanus	4/322 (1.2)	23/361 (6.4)	5.4 (1.9-15.8)
<i>Candida</i> and mumps	6/356 (1.7)	21/327 (6.4)	4.0 (1.6-10.0)
Tetanus and mumps	4/342 (1.2)	23/341 (6.7)	6.1 (2.1-17.9)
<i>Candida</i> , tetanus, and mumps	4/282 (1.4)	23/401 (5.7)	4.2 (1.4-12.4)
Anergy defined as <2 mm to:			
<i>Candida</i> and tetanus	4/326 (1.2)	23/357 (6.4)	5.5 (1.9-16.2)
<i>Candida</i> and mumps	6/358 (1.7)	21/325 (6.5)	4.1 (1.6-10.2)
Tetanus and mumps	4/345 (1.2)	23/338 (6.8)	6.2 (2.1-18.2)
<i>Candida</i> , tetanus, and mumps	4/286 (1.4)	23/397 (5.8)	4.3 (1.5-12.7)
Anergy defined as <3 mm to:			
<i>Candida</i> and tetanus	5/345 (1.4)	22/338 (6.5)	4.7 (1.8-12.7)
<i>Candida</i> and mumps	6/375 (1.6)	21/308 (6.8)	4.5 (1.8-11.3)
Tetanus and mumps	4/370 (1.1)	23/313 (7.3)	7.3 (2.5-21.2)
<i>Candida</i> , tetanus, and mumps	4/305 (1.3)	23/378 (6.1)	4.9 (1.7-14.3)
Anergy defined as <4 mm to:			
<i>Candida</i> and tetanus	6/365 (1.6)	21/318 (6.6)	4.2 (1.7-10.6)
<i>Candida</i> and mumps	10/402 (2.5)	17/281 (6.0)	2.5 (1.1-5.6)
Tetanus and mumps	5/396 (1.3)	22/287 (7.7)	6.5 (2.4-17.4)
<i>Candida</i> , tetanus, and mumps	5/329 (1.5)	22/354 (6.2)	4.3 (1.6-11.5)
Anergy defined as <5 mm to:			
<i>Candida</i> and tetanus	6/398 (1.5)	21/285 (7.4)	5.2 (2.1-13.0)
<i>Candida</i> and mumps	13/448 (2.9)	14/235 (6.0)	2.1 (0.98-4.6)
Tetanus and mumps	6/424 (1.4)	21/259 (8.1)	6.1 (2.5-15.4)
<i>Candida</i> , tetanus, and mumps	6/364 (1.6)	21/319 (6.6)	4.2 (1.7-10.6)

*Positive PPD defined as 5 mm or greater in HIV+ women.

for viral load and T-lymphocyte subset assays may be unavailable or prohibitively expensive, DTH testing may still be useful for evaluation of current immunologic status and prognosis.

HIV-seropositive women nonreactive to DTH testing with *Candida*, mumps, and tetanus antigens were significantly less likely than women reactive to those antigens to have a positive PPD reaction. The combination of DTH antigens that best distinguished women able to mount a positive PPD response from those not able to do so again included tetanus and mumps. Persons with negative PPD reactions include both individuals who are not infected with *M tuberculosis* and those who are infected but unable to mount a normal DTH response to tuberculin. It would be expected that anergic subjects in populations exposed to tuberculosis would be at increased risk for latent *M tuberculosis* infection compared with nonanergic persons with negative tuberculin reactions who presumably are not infected. In addition, to the extent that anergy reflects immunodeficiency, infected anergic individuals would be expected to have an increased risk of reactivating latent tuberculosis. Available data support an increased risk for tuberculosis in anergic

HIV-infected persons relative to nonanergic individuals with negative tuberculin reactions.³⁴⁻³⁵ However, reports on the instability of anergy, the occurrence of "false-negative" tuberculin reactions in nonanergic persons, and data interpreted as showing no benefit from tuberculosis prophylaxis in anergic individuals (all among HIV-infected persons), recently led the CDC to suggest that anergy testing for persons with HIV infection need no longer be done routinely but should be reserved for selected settings.¹⁸ It is important to note that because even among HIV-seropositive women considered anergic a PPD reaction of 5 mm or greater induration occasionally occurred, tuberculin testing should not be omitted in such individuals if otherwise indicated.

Prior studies of cutaneous anergy in persons with HIV infection have included no or a small percentage of women,^{7-9,11,19} have been restricted to a single geographic area,^{3,5,16,19,36} or have included individuals with a single HIV risk behavior.^{5,16,19,36} A strength of this study is that it includes the largest number of women with HIV infection assessed for cutaneous anergy reported to date, women from 4 different metropolitan areas, and women at risk for HIV infection by both injecting drug use and sexual behaviors.

Several limitations to the study should be noted. We used the 3 antigens that the CDC recommended in 1991 for DTH anergy testing.¹³ The *Candida* antigen was that most commonly used at the time, but it since has been discontinued by the manufacturer; other *Candida* preparations may give different results. More than 97% of women were born in the United States or Puerto Rico and attended school, and therefore it seems likely that most had been immunized against tetanus and mumps; these antigens may prove less useful in parts of the world where immunization rates are low. We have no data on the use of other antigens for DTH testing. In addition, other causes of immune deficiency, such as malnutrition, may confound the associations of skin test results with HIV status and CD4+ lymphocyte count. Finally, our study included only women, and therefore caution may be warranted in generalizing the findings to men. However, we are not aware of any data suggesting that gender is likely to independently affect DTH response.

In conclusion, cutaneous DTH testing with mumps and tetanus toxoid antigens, with or without *Candida* antigen and with a cut-point of less than 2 mm induration for defining anergy, is effective in distinguishing groups of women with and without immunodeficiency and those able to mount a positive tuberculin reaction from those less able to do so. Tuberculin testing may still provide valuable information in persons nonreactive to other antigens and when indicated should not be omitted because of apparent cutaneous anergy. This study did not directly assess the clinical utility of DTH testing in individuals with or at risk for HIV infection. Further study will be necessary to resolve the controversy surrounding the use of this procedure for clinical decisions regarding individual patients. However, clinical protocols and programmatic policies must often be based on epidemiologic

considerations of overall risk by group, rather than on knowledge of exact individual risk. When used in groups of individuals with or at risk for HIV infection, anergy testing can still provide valuable information.

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