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Anergy Skin Testing and Preventive Therapy for HIV-Infected Persons: Revised Recommendations

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Anergy Skin Testing and Preventive Therapy for HIV-Infected Persons: Revised Recommendations

Summary

*This report updates and supersedes previous recommendations (*MMWR *1991;40[No. RR–5]:27–33) for the use of anergy skin testing in conjunction with purified protein derivative (PPD)-tuberculin skin testing of persons infected with human immunodeficiency virus (HIV). In February 1997, CDC convened a meeting of consultants to discuss current information regarding anergy skin testing, PPD skin testing, and tuberculosis (TB) preventive therapy for HIV-infected persons. In formulating these recommendations, CDC considered the results of this meeting, as well as a review of published studies pertaining to PPD and anergy skin testing of persons who are infected with HIV.*

Isoniazid preventive therapy is effective in reducing the incidence of active TB among persons who have HIV infection and latent TB. Because of the complications associated with TB disease in HIV-infected persons, these persons must be screened for tuberculin infection. HIV-infected persons who have positive reactions to skin testing with PPD tuberculin should be evaluated to exclude active TB and offered preventive therapy with isoniazid if indicated. However, HIV-infected persons may have compromised ability to react to PPD-tuberculin skin testing, because HIV infection is associated with an elevated risk for cutaneous anergy.

Anergy testing is a diagnostic procedure used to obtain information regarding the competence of the cellular immune system. When a clinician elects to use anergy testing as part of a multifactorial assessment of a person's risk for TB, the two Food and Drug Administration-approved Mantoux-method tests (mumps and Candida), *used together, with cut-off diameters of 5 mm of induration, are recommended. Efforts to apply the results of anergy testing to preventive therapy decisions must be supplemented with information concerning the person's risk for infection with* Mycobacterium tuberculosis.

Factors limiting the usefulness of anergy skin testing include problems with standardization and reproducibility, the low risk for TB associated with a diagnosis of anergy, and the lack of apparent benefit of preventive therapy for groups of anergic HIV-infected persons. Therefore, the use of anergy testing in conjunction with PPD testing is no longer recommended routinely for screening programs for M. tuberculosis *infection conducted among HIV-infected persons in the United States.*

INTRODUCTION

Persons infected with human immunodeficiency virus (HIV) are at risk for having active tuberculosis (TB) disease (*1–3*) because of either reactivation of latent infection with *Mycobacterium tuberculosis* (*4*) or rapid progression of newly acquired infection (*5*). Active TB, in turn, may hasten the evolution of HIV-related disease, possibly through mechanisms involving increased cytokine production and accelerated HIV

replication (*6,7*). Isoniazid preventive therapy administered to persons who have positive reactions to purified protein derivative (PPD) tuberculin is important in preventing active TB in the United States. However, HIV-infected persons may have compromised ability to react to PPD-tuberculin skin testing, because HIV infection is associated with an elevated risk for cutaneous anergy (*8,9*).

In 1991, CDC published guidelines recommending that anergy skin testing be performed in conjunction with PPD-tuberculin skin testing for HIV-infected persons who are being evaluated for latent infection with *M. tuberculosis* (*10*). Demonstration of anergy in an HIV-infected, PPD-negative person at high risk for infection with *M. tuberculosis* was recommended as an indication for isoniazid preventive therapy. Since the publication of these guidelines, several studies have been conducted to examine the results of anergy and PPD skin testing in HIV-infected persons and the effect of isoniazid for the prevention of TB in anergic HIV-infected persons. In February 1997, CDC convened a meeting of consultants to discuss these recent publications and other available data. CDC has used both the results of discussions at this meeting and a review of published literature to prepare this updated report, which provides recommendations concerning the use of anergy testing for HIV-infected persons in the United States.

BACKGROUND

Anergy in HIV Disease and Risk for Active TB in HIV-Infected Persons

Anergy skin testing assesses the responses to skin-test antigens to which a cell-mediated, delayed-type hypersensitivity (DTH) response is expected. Anergy or DTH tests placed by using the Mantoux method of intradermal injection have conventionally been classified as positive if an induration measuring ≥5 mm is observed at the injection site within 48–72 hours. Persons who have positive skin tests are considered to have relatively intact cell-mediated immunity. Persons who do not mount a DTH response are considered to be anergic and to be at elevated risk for complications of deficient cell-mediated immunity. PPD-tuberculin skin testing itself elicits a DTH reaction, so persons who have positive PPD responses are not anergic. Responsiveness to DTH antigens may be decreased in HIV-infected persons, and the 1991 guidelines (*10*) recommended the use of companion or "control" antigens in conjunction with PPD testing to provide additional information about a person's ability to mount a DTH response.

Impaired DTH response, which is directly related to decreasing CD4+ T-lymphocyte count, is a predictive factor for progression of acquired immunodeficiency syndrome and mortality in HIV-infected persons (*11–14*). In some studies, after the data were stratified by CD4+ count, anergy skin-test results have provided additional prognostic information about HIV-related complications and death (*11–14*). The results of several studies have suggested that HIV-infected persons diagnosed as anergic have a greater risk for active TB than do nonanergic, PPD-negative, HIV-infected persons from the same population (*15–19*). In addition, among HIV-infected persons who have positive PPD-tuberculin skin-test results, data from one study demonstrated that those who

did not respond to testing with a control antigen had a higher risk for active TB than did PPD-positive persons who reacted to such testing (*19*). Although CD4+ counts in HIV-infected persons have been reported as inversely related to their risk for active TB, being anergic has in itself been associated with an elevated risk for TB, even after the data were stratified by CD4+ count (*16,19*). Two studies suggest that mortality may be increased in HIV-infected persons who have active TB and who do not respond to testing with PPD compared with patients who have TB and HIV infection from the same population who respond to PPD testing (*20,21*).

Anergy and Interpretation of PPD-Tuberculin Skin Tests

The results from supplemental anergy testing, in conjunction with PPD-tuberculin skin testing, have been interpreted in two ways (*10*). A positive DTH response to anergy testing, in conjunction with a negative PPD skin-test result, has been interpreted as evidence that the negative PPD test result is a true negative and the person tested is not infected with *M. tuberculosis*. Lack of DTH response to anergy skin testing, in conjunction with a negative PPD skin-test result, has been interpreted as evidence that the person is unable to mount a positive response to PPD even if infected with *M. tuberculosis.*

Certain issues, however, compromise the validity of both of these interpretations. Selective nonreactivity to PPD is a recognized phenomenon in some patients with active culture-positive TB (*22,23*). The observations that mumps reactivity may remain after loss of PPD reactivity (*24*) and that PPD boosting can occur in persons who have an initial positive reaction to control antigens (*25–27*) suggest the possibility that DTH response to other antigens may be preserved after loss of PPD reactivity. Therefore, a DTH response is not proof that a negative PPD applied at the same time indicates absence of infection with *M. tuberculosis*. Lack of response to one or more control antigens, however, does not always mean inability to respond to PPD. In populations in which the prevalence of tuberculin reactivity is high, the percentage of persons who react to PPD may be higher than the percentage reacting to several other antigens (*28,29*). Even in populations in which the prevalence of PPD positivity is low, some persons respond to PPD testing despite lack of response to a companion antigen (*19*). Furthermore, a valid demonstration of anergy does not predict infection with *M. tuberculosis*; instead, it indicates that, for the anergic person, the PPD test results may not be useful in judging the likelihood of infection with *M. tuberculosis* and the need for TB preventive therapy.

ANERGY SKIN TESTING AND DECISIONS REGARDING TB PREVENTIVE THERAPY

Because of the complications associated with active TB in HIV-infected persons, these persons must be screened for latent TB infection and receive complete preventive treatment with isoniazid if indicated. Several factors limit the usefulness of anergy skin testing for making decisions regarding TB preventive therapy for HIV-infected persons in the United States. These factors include problems with the standardization and reproducibility of anergy skin-testing methods, the variable risk for TB associated with a diagnosis of anergy, and the lack of documented benefit of anergy skin testing

as part of screening programs for *M. tuberculosis* infection among HIV-infected persons.

Difficulties in Interpreting Anergy Skin-Testing Results

The decision of whether to perform anergy testing cannot be separated from determining how to perform it. Lack of standardization and lack of outcome data based on uniform antigens and tests are among the greatest obstacles to evaluating the effectiveness of anergy testing and making decisions concerning TB preventive therapy. Studies have been based on a variety of control antigen preparations and skin-test administration and methods for reading test results. Studies involving multiple-DTH antigen panels have demonstrated that several antigens may be necessary to maximize the likelihood that all persons able to respond are identified (*29,30*). DTH responses may vary in different populations of immunocompetent groups (*31*). DTH reactions of <5 mm of induration have been reported in young children (*32*), who might not be expected to have fully developed cellular immunity, and reactions of <5 mm of induration also have been noted in response to diluent without antigen (*33–35*).

The variability in test readings noted for the PPD-tuberculin skin test (*36,37*) is likely to be associated with other DTH tests. Data from one study of variation between duplicate PPD tests (*37*), indicated that more than half of the discordant readings occurred in persons with one test measured as zero and the other as 1–4 mm of induration. Serial anergy testing among HIV-infected persons has shown unpredictable differences over time (*24,38*). This variation may result from changes in host immune competence or from characteristics of the tests themselves. Furthermore, the choice and number of companion antigens and the criteria used for the interpretation of results of anergy testing may lead to false classification of a) persons with intact cell-mediated immunity as anergic or b) anergic persons as nonanergic.

The applicability of skin-testing methods to pediatric populations is uncertain. Children who have HIV infection have had DTH responses, and lack of response has been associated with the stage of HIV-related disease (*39,40*). However, no clear utility of anergy testing for the evaluation for TB among children has been established (*41*). Skin testing for DTH reactions is an important tool in diagnosing a variety of primary immunodeficiency diseases (i.e., non-HIV–related immunodeficiency diseases). Therefore, any recommendations regarding anergy testing should take into account its value in patients who have primary immunodeficiency diseases.

Anergy and Risk for Active TB

In studies conducted both in the United States and elsewhere, no definite association has been determined between anergy and the risk for active TB in HIV-infected persons; the results of these studies indicated that the magnitude of the risk is variable and the reason for the variation uncertain. Rates of TB in groups defined as anergic have ranged from zero to >12 per 100 person-years. The risk for active TB in anergic HIV-infected persons may be associated with ongoing risk for *M. tuberculosis* transmission (i.e., residence in areas of high TB case rates), rather than with a high probability of latent *M. tuberculosis* infection alone (*15–19,42–45*). This finding implies that any effect of isoniazid preventive therapy might be attributable not only to

prevention of reactivation of latent infection, but also (or instead) to primary prophylaxis against new acquisition of infection.

Effect of TB Preventive Therapy in Anergic Persons

Two recent studies of 6 months of isoniazid preventive therapy among anergic persons at risk for infection with *M. tuberculosis* have been conducted. One study involving HIV-positive anergic patients in the United States demonstrated no statistically significant effect of therapy, despite a 56% reduction in rates of TB from 0.9 per 100 person-years in placebo recipients to 0.4 per 100 person-years in isoniazid recipients (*42*). The failure to find statistical significance with a 56% point estimate for protection may result from a lower-than-expected TB case rate in placebo recipients. Researchers concluded that, because the TB rate in the untreated group was low (0.9%), preventive therapy would have minimal impact in reducing the number of incident TB cases among HIV-positive anergic persons but would result in a substantial number of uninfected persons being treated with isoniazid. The other study, involving HIV-positive anergic patients in Kampala, Uganda, demonstrated a high TB case rate (three per 100 person-years) in placebo recipients, but only a statistically insignificant (17%) reduction in isoniazid recipients (*43*). In summary, even if anergic HIV-infected persons are assumed to be at high risk for active TB and are administered isoniazid preventive therapy, the effectiveness of this intervention has not been established for this population.

METHODS AND USES FOR ANERGY SKIN TESTING

Mumps and *Candida* antigens have been approved by the Food and Drug Administration (FDA) for intradermal DTH testing to assess cell-mediated immunity. Mumps skin-test antigen has been available for a longer time; lack of response to mumps antigen in HIV-infected persons has been associated with risk for TB (*19*), but some patients who have lost PPD reactivity with progression of HIV disease may still react to mumps (*24*). *Candida* DTH skin-test antigen was approved more recently. Data linking DTH response to this *Candida* antigen and risk for TB are limited, and published studies describing *Candida* skin-test responses have used different products marketed as allergenic extracts.

Both mumps and *Candida* antigens are applied by using the Mantoux method. The number of control antigens and the method of reading may affect the usefulness of Mantoux-method skin tests. More than two control antigens may be needed to avoid misclassifying immunocompetent persons as anergic (*29,30*). Limited information is available regarding the sensitivity and specificity of the two FDA-approved DTH tests used together. Other antigens (e.g., fluid tetanus toxoid and *Candida* extracts marketed for allergy testing) frequently are used for anergy testing, but with differing preparations, dosages, and dilutions.

The conventional cut-off measurement of induration diameter for interpreting a Mantoux-method skin-test result as positive is 5 mm of induration. In recent years, attempts have been made to detect DTH in HIV-infected patients by using smaller cut-off diameters (3 mm, 2 mm, 1 mm, or "any induration"). In addition to the validity concerns already noted, the use of smaller cut-offs is subject to technical

difficulties (*46*) and has not improved predictive value. A multiple-puncture test battery (MULTITEST CMI®), which includes seven antigens and a diluent control, has been approved by the FDA for DTH testing. Results have been associated with clinical outcomes in several studies of HIV-infected persons (*12,15–17*). The use of this product, however, is likely to be limited by cost and availability.

Because several studies suggest a relationship between anergy and risk for TB, health-care providers may find the results of anergy testing useful in individual situations, despite the lack of consensus on how to perform anergy skin testing. Efforts to apply the results of anergy testing to evaluation of latent TB infection and preventive therapy decisions should be supplemented by information concerning the person's risk for exposure to and infection with *M. tuberculosis*. Used in this way, anergy tests, in conjunction with PPD testing, may assist in estimating TB risk for selected HIV-infected patients in specific situations. If a decision is made to perform anergy testing, technical expertise, feasibility, and cost may be important factors in choosing which test(s) to employ. The purpose of anergy testing also may be a factor: if the primary concern is to avoid misclassifying anergic persons as nonanergic, the use of two Mantoux-method tests with a 5-mm of induration cut-off may be appropriate. Use of more antigens may be indicated, however, if the primary concern is to avoid misclassifying immunocompetent persons as anergic. The expertise of the health-care provider and a clear understanding of the limitations of anergy testing are critical to appropriate use.

ROLE OF ANERGY SKIN TESTING IN TB PREVENTION AND CONTROL PROGRAMS

Isoniazid preventive therapy administered to HIV-positive persons who have positive reactions to PPD tuberculin is important both as a personal health intervention and as part of efforts to prevent active TB disease in the United States. The prevalence of *M. tuberculosis* infection and active TB disease differs among different groups of the U.S. population infected with HIV. To reach a community's groups at high risk for TB, CDC has recommended that the design of tuberculin screening programs be based on local data regarding the prevalence and incidence of *M. tuberculosis* infection and the sociodemographic characteristics of patients with TB and *M. tuberculosis* infection (*47*).

In studies conducted in the United States in which preventive therapy was administered principally to PPD-positive persons (*44,45*), no cases of TB were observed in anergic persons. (In one of these reports, selected anergic persons also received isoniazid [*45*].) In a multicenter study (*19*), the effect of area of residence on risk for TB was much greater than that of anergy. The precise risk for TB in HIV-positive anergic persons in the United States cannot be determined; however, the overall risk seems to be low. In addition, there are no simple skin-testing protocols that can reliably identify persons as either anergic or nonanergic and that have been proven to be feasible for application in public health tuberculosis screening programs. In the United States, the public health impact of finding and treating patients who have infectious TB to prevent further transmission and of providing preventive therapy to PPD-positive, HIV-infected persons to prevent additional infectious TB cases should be greater than the effect of preventive therapy for HIV-positive anergic persons.

RECOMMENDATIONS

Programmatic Use of Anergy Testing

Since the publication of guidelines in 1991, additional information has documented limitations in the usefulness of anergy testing in public health tuberculosis screening programs. These limiting factors include the variability in the available anergy testing methods, their lack of reproducibility, the variation in absolute risk for TB among different anergic groups, and the lack of demonstrated efficacy of a preventive therapy program in anergic HIV-infected groups. Therefore, anergy testing in conjunction with PPD-tuberculin testing is no longer routinely recommended for inclusion in screening programs for *M. tuberculosis* infection among HIV-infected persons. However, DTH evaluation may assist in guiding individual decisions regarding preventive therapy in selected situations.

TB Preventive Therapy Among HIV-Positive, PPD-Positive Persons

Unless specifically contraindicated, HIV-positive persons a) who have positive reactions to PPD tuberculin (≥5 mm of induration), b) who have not already been treated for TB infection, and c) whose test results exclude active TB should be considered for 12 months of preventive therapy with isoniazid (*48*). This preventive therapy is indicated even if the date of PPD skin-test conversion cannot be determined.

TB Preventive Therapy Among HIV-Positive, PPD-Negative Persons

When assessing HIV-infected persons who have negative PPD-tuberculin skin-test results or who are known to be anergic, the most important factors in considering TB preventive therapy are the likelihood of exposure to transmissible active TB and the likelihood of latent *M. tuberculosis* infection. Preventive therapy should be considered for HIV-infected persons who do not have a documented positive PPD-tuberculin response but who have had recent contact with patients who have infectious pulmonary TB. Repeat PPD testing of initially PPD-negative contacts 3 months after cessation of contact with infectious TB is sometimes used to assist in decisions about duration of preventive therapy (*49*). However, most of these patients should complete a full 12-month course of isoniazid preventive therapy.

In certain cases, preventive therapy with isoniazid for persons who are not PPD positive also may be considered. Such therapy may be beneficial for a) children who are born to HIV-infected women and are close contacts of a person who has infectious TB and b) HIV-infected adults who reside or work in institutions and are continually and unavoidably exposed to patients who have infectious TB. Some experts recommend continuing isoniazid preventive therapy indefinitely for HIV-infected persons who have an ongoing high risk for exposure to *M. tuberculosis* (e.g., inmates of prisons in which the prevalence of TB is high). In these situations, the results of anergy testing may be useful for deciding which persons should be offered prolonged preventive therapy in settings in which a) exposure is likely but PPD conversion has not

occurred, b) the consideration of primary prophylaxis may arise, and c) the most vulnerable persons in immunologic terms may have high priority for preventive therapy.

Future Programmatic Directions

For formulating future recommendations regarding programmatic uses of anergy testing, results from systematic studies of the two FDA-approved Mantoux-method tests used together with a cut-off diameter of 5-mm of induration would be useful, as would comparisons between results with this combination and with the seven-antigen multipuncture battery. Ultimately, development of a simpler standard skin test or of another method for measuring the same components of immune responses more reliably is desirable.

CONCLUSIONS

Recent studies suggest that impaired DTH is related to risk for active TB in some HIV-infected populations, despite variability in anergy skin-testing procedures. When a clinician elects to use anergy testing as part of a multifactorial assessment of a person's risk for TB, the two FDA-approved Mantoux-method tests (mumps and *Candida*), used together and with cut-off diameters of 5 mm of induration, are recommended. Studies based on these approaches may result in data useful for formulating guidelines regarding future programmatic uses of anergy testing. Improvements in TB screening and preventive therapy practices in HIV-infected persons require better standardization of anergy testing methods and validation of their predictive value or development of an adequate alternative measure of cellular immunity or of an alternative test for the detection of latent TB infection.

In selected situations, anergy testing may assist in guiding individual decisions regarding individual therapy. However, results of currently available anergy-testing methods in U.S. populations have not been demonstrated to make a useful contribution to most decisions about isoniazid preventive therapy. Therefore, anergy testing is no longer recommended as a routine component of TB screening among HIV-infected persons in the United States.

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