

Randomized Trial of Isoniazid as Secondary Prophylaxis for Prevention of Recurrent Pulmonary Tuberculosis in HIV-positive Patients After One Episode of Tuberculosis

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A. Study Purpose and Rationale

a. Study Purpose

The purpose of this study is to determine whether administration of isoniazid will decrease the rates of recurrence of pulmonary tuberculosis in patients with HIV after curative treatment for a first episode of pulmonary tuberculosis. The study also aims to evaluate whether CD4 counts at the beginning of treatment are a predictor for relapse of tuberculosis.

b. Background and Rationale

One third of the world's population is infected with tuberculosis. Of those, around 8 million people become sick with active tuberculosis each year, and 2 million die from tuberculosis each year. With the rise in HIV infection worldwide, the global epidemic of tuberculosis is growing. HIV-infected persons are at markedly increased risk for primary or reactivation tuberculosis, as well as re-infection from exogenous sources. Among persons with a positive PPD test, HIV-positive persons have a 5 to 10 percent probability of developing active tuberculosis each year compared with 0.01 percent probability in HIV-negative persons. In the US, the incidence of tuberculosis peaked in 1992, and the resurgence was attributed to HIV infection. The rates of tuberculosis in the US have decreased in recent years due to public health efforts such as hospital isolation policies and directly observed therapy, but it still remains an important problem in patients with HIV, with an estimated 6000 to 9000 new cases annually in the US.

Higher susceptibility to tuberculosis in HIV-positive patients is thought to be due to reduced T-1 lymphocyte response. T-1 lymphocytes produce interferon-gamma, which is an important mediator of anti-mycobacterial immune defense. Tuberculosis, in turn, may accelerate HIV replication by inducing macrophages to produce TNF-alpha, IL-1 and IL-6. The mortality rate among patient with coinfection with HIV and tuberculosis is high (four times higher than in HIV-negative patients with tuberculosis), and it appears to be due to progressive HIV infection rather than tuberculosis. Tuberculosis can occur in less advanced stages of immune deficiency, but low CD4 cell counts, and prior opportunistic infections are associated with increased mortality.

Because HIV-positive patients are at a higher risk of developing active tuberculosis, HIV infected patients with a positive PPD skin test (TB infection, not active TB disease - negative chest x-ray and no symptoms), or negative PPD but contact with persons with active tuberculosis, are given prophylaxis for tuberculosis with isoniazid for 9 months. For HIV-positive patients who develop active tuberculosis, the current guidelines of the Centers for Disease Control (CDC) recommend treatment for 6 months with the standard multi-drug therapy, most commonly the 4-drug regimen including isoniazid, rifampin, pyrazinamide and ethambutol. Longer treatment is recommended only when there is delayed clinical and bacteriologic response to antituberculous medication. The recommendations for treatment for active tuberculosis are identical to that for HIV-negative patients with tuberculosis. There is no recommendation for more intensive tuberculosis therapy for HIV-positive patients, and no recommendation for post-treatment prophylaxis. This is in contrast to treatment of other opportunistic infections in HIV disease, such as *Pneumocystis carinii* pneumonia, *Cryptococcus neoformans* and *Toxoplasma gondii*, where treatment regimens are often longer and include post-treatment prophylaxis.

Studies have shown that there may be a higher rate of recurrence of tuberculosis among HIV-positive patients than among HIV-negative patients, although the data are not clear-cut. In the six prospective studies evaluating outcomes of the 6-month regimen for tuberculosis treatment in

HIV-positive patients, and three studies in HIV-negative patients, the relapse rate for tuberculosis in the HIV-positive patients ranged from 0-10% in the six studies and from 0-3.6% in the HIV-negative patients. In three studies, the relapse rate in HIV-positive patients was less than 5%, while in the other three studies the relapse rate was greater than 5 percent.

Since cure rates in the re-treatment of recurrent tuberculosis are substantially lower, and patients with HIV who develop tuberculosis have a four-fold mortality compared with HIV-negative patients, it is important to consider whether giving post-treatment prophylaxis to HIV-positive patients after curative treatment for one episode of tuberculosis can decrease the recurrence rate of tuberculosis.

There is one study of post-treatment prophylaxis with isoniazid in HIV-positive patients after curative treatment of tuberculosis. In this randomized trial conducted in Haiti, the rate of recurrent tuberculosis was 10-fold higher in HIV-positive patients (4.8 percent per year vs. 0.4 percent per year), and secondary prophylaxis with isoniazid reduced the recurrence rate of tuberculosis from 7.8 to 1.4 percent per year. This study, however, does not report whether any of these patients were on antiretroviral therapy, and has incomplete data on patients' CD4 counts. Only 58 percent of patients had CD4 counts reported.

The purpose of the proposed study is to evaluate whether secondary prophylaxis with isoniazid will decrease the recurrence rate of tuberculosis in the HIV-positive population in the US, and whether CD4 counts at baseline are good predictors for recurrence of tuberculosis. The population in the US is different from the population studied in Haiti 'in that most of the patients are on highly active antiretroviral therapy (HAART) and have better access to health care. Our hypothesis is that secondary prophylaxis with isoniazid will decrease the recurrence rate of tuberculosis by 80 percent, and that patients with lower CD4 counts at baseline will have a higher rate of recurrence of tuberculosis.

B. Study Design and Statistical Analysis

a. Study Design

Prospective, randomized, double-blinded, placebo-controlled, multi-center trial of isoniazid.

b. Population

450 HIV-positive patients with curative treatment for first episode of pulmonary tuberculosis. This number was determined by calculations to power the study at 0.80 and to allow for a 10 percent attrition rate among subjects. Estimates for the rate of relapse were made using data from the previously mentioned study done in Haiti, with 7.8 percent relapse in the isoniazid group and 1.4 percent in the placebo group.

C. Statistical Analysis

Comparison of two proportions will be done using Chi-square tests, or Fisher's exact test when expected cell values are less than five. There will be intention-to-treat analysis with no cross over of subjects from one group to the other. Adverse events experienced by the patient or observed by the investigator will be reported whether or not they are considered to be related to the study drug.

D. Study Subjects

a. Inclusion Criteria

1. Documented HIV infection by ELISA or Western Blot.
2. Previous documented tuberculosis infection by *Mycobacterium tuberculosis* culture in sputum.
3. Documented cure after treatment as defined by sputum culture negative for MTB and complete resolution of symptoms (fever, night sweats, cough, hemoptysis, lymphadenopathy), with completion of treatment with directly observed therapy within the last three months.

4. Laboratory parameters: transaminases within normal limits, creatinine <2.
5. Age >18
6. Able to give consent.

b. Exclusion Criteria

1. Two or more prior episodes of active tuberculosis
2. Extrapulmonary tuberculosis
3. Drug-resistant tuberculosis
4. Active liver disease
5. Daily alcohol use
6. Isoniazid hypersensitivity (fever, rash)
7. Pregnancy

E. Randomization

The patients will be stratified into two groups by CD4 cell count (<200 and >200), then randomized by a computer-generated random numbers list into isoniazid treatment arm (to receive isoniazid 300 mg and vitamin B6 25 mg daily for 9 months) and placebo arm (to receive vitamin B6 25 mg daily and a placebo pill for 9 months).

F. Outcome Measures

1. **Primary endpoint:** Recurrence of pulmonary tuberculosis, defined as Sputum culture positive for MTB.
2. **Secondary endpoints:**
 - a. Mortality, defined as death from any cause.
 - b. Relapse of previous strain of MTB vs. re-infection with new strain, as analyzed by RFLP analysis of MTB from sputum.

G. Study Procedures

At baseline, blood will be drawn and tests for CD4 cell count, hepatic function tests, and Chem 7 will be done. Patients will receive the study drug for the first 9 months. Patients will be seen in clinic every month during treatment with the study drug. Patients will be given packets with 45-day supply of the study drug (or placebo) for self-administration at home. Pill counts will be done on each clinic visit to monitor compliance. If a patient does not come to his clinic appointment, he will be called on the telephone. Patients will be given a packet of tokens on each clinic visit to maximize compliance with appointments. Liver function tests will be repeated every three months during isoniazid administration. If symptoms suggestive of liver damage appear, such as jaundice, abdominal pain, liver function tests will be done.

Duration of post-treatment follow-up will be 2 years. Patients will be seen every three months in clinic, and a thorough history and physical examination performed. Patients will be instructed to come to the clinic ahead of schedule if any symptoms of tuberculosis develop. A chest radiograph will be taken every six months. If symptoms suggestive of recurrence of tuberculosis are present at any visit, a chest radiograph and sputum smear and culture will be done.

Among patients who have a recurrence of pulmonary tuberculosis, restriction fragment length polymorphism testing will be conducted on Mycobacterium tuberculosis specimens from the sputum to determine whether the recurrence is due to relapse from the previous strain of MTB versus re-infection with a new strain.

H. Study Drugs

Isoniazid has been FDA approved for treatment of tuberculosis since 1952. Each patient in the treatment arm will receive a daily oral tablet of isoniazid 300 mg and vitamin B6 25 mg. The route and dosage of administration are according to standard use.

Peripheral neuropathy is the most common side effect of isoniazid. It is dose-related, occurs most often in the malnourished and 'in those predisposed to neuritis (e.g., alcoholics and diabetics). The patients in this study will receive vitamin B6 to prevent this complication. Nausea, vomiting, epigastric distress are other common side effects. Severe and sometimes fatal hepatitis associated with isoniazid therapy are rare but do occur and may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are: 0 per 1,000 for persons under 20 years of age, 3 per 1,000 for persons in the 20-34 year age group, 12 per 1,000 for persons in the 35-49 year age group, 23 per 1,000 for persons in the 50-64 year age group, and 8 per 1,000 for persons over 65 years of age.

I. Medical Devices

No medical devices are being used in this study.

F. Study Questionnaires

No questionnaires are being used in this study.

J. Recruitment of Subjects

Potential subjects will be identified by review of records of the Department of Health Chest Clinics in New York City. The patient's primary care physician will be approached to determine if the patient is appropriate and amenable to participation. The subjects will be approached regarding study enrollment, and informed consent will be obtained from all subjects prior to their enrollment.

K. Confidentiality of Study Data

Any information obtained during this study and identified with the patient will remain confidential. All subjects enrolled in the study will be given a unique identifier, which will be used for all further evaluations.

L. Potential Conflict of Interest

There is no potential conflict of interest among the investigators.

M. Location of the Study

The study will be conducted in the Department of Health Chest Clinics in New York city.

N. Potential Risks

There is a rare but potential risk of severe hepatic failure from isoniazid. The risk of developing hepatitis is age related. Approximate case rates by age are: 0 per 1,000 for persons under 20 years of age, 3 per 1,000 for persons in the 20-34 year age group, 12 per 1,000 for persons in the 35-49 year age group, 23 per 1,000 for persons in the 50-64 year age group, and 8 per 1,000 for persons over 65 years of age. There is also risk of more common, but less severe, side effects of isoniazid, such as nausea, vomiting, and neuropathy.

O. Potential Benefits

The patients may potentially benefit by preventing a recurrence of tuberculosis due to administration of the study drug.

P. Alternative Therapies

There are no approved alternative therapies for secondary prophylaxis of tuberculosis. The alternative would be to not participate in the study.

Q. Compensation to Subjects

Subjects will not be given monetary compensation. They will be given a packet of tokens worth 15 dollars each month when they come to their clinic appointment.

R. Costs to Subjects

There will be no additional costs to subjects as a result of participating in this study.

P. Minors as Research Subjects

No minors will participate in this study.

S. Radiation or Radioactive Substances

No radiation or radioactive substances will be used in this study.