Risk Factors for Development of Tuberculosis after Isoniazid Chemoprophylaxis in Human Immunodeficiency Virus–Infected Patients

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The long-term benefit of isoniazid chemoprophylaxis in human immunodeficiency virus (HIV)–infected patients and risk factors for isoniazid failure were studied in 131 HIV-infected patients who received >9 months of isoniazid preventive therapy. During a median follow-up of 43 months, 8 patients developed tuberculosis (TB) (6%; 0.61 cases per 100 patient-years). Only the persistence of risk factors for exposure to TB was statistically associated with development of disease (relative hazard, 3.17; 95% confidence interval, 1.56–17; $P < .001$). Our data suggest reinfection as the main cause of TB after isoniazid prophylaxis.

Because of defective cellular immunity, patients dually infected with *Mycobacterium tuberculosis* and HIV have a special susceptibility to the development of tuberculosis (TB), with an estimated incidence of 7%–10% each year [1, 2]. Therefore, identification and subsequent prophylaxis of HIV-infected patients at risk for TB constitute both a priority in the clinical management of the patients and an important public health measure.

A 12-month course of isoniazid, 5 mg/kg of body weight, has been shown effective in preventing TB in short-term studies. Recently, 9 months has been proposed as the standard duration for the treatment of latent infection with isoniazid [3]. Few data, however, have been reported about the duration of protection conferred by isoniazid administration in HIV-positive patients, even before the administration of highly active antiretroviral therapy (HAART) when patients uniformly developed progressive immunosuppression. Thus, it is difficult to estimate the risk of disease for patients who received isoniazid several years ago. In addition, despite abundant information on the short-term success of isoniazid as prophylaxis [2, 3], few data are available about causes of isoniazid failure. The aim of this study was to assess the long-term benefit of isoniazid prophylaxis and to identify risk factors associated to later development of TB in compliant HIV-infected patients who received an adequate course of isoniazid preventive therapy.

Methods. All HIV-infected patients who had a positive tuberculin skin test (TST), who completed ⩾9 months of isoniazid chemoprophylaxis, and who had a follow-up in our AIDS unit that lasted ⩾1 year after isoniazid chemoprophylaxis or until death, were included in this study. A positive TST was defined as the presence of ⩾5 mm of induration 72 h after the intradermal injection of 2 U of the RT-23 strain, applied by the Mantoux method [4].

Information collected from the patients' records included demographic data, initial $CD4^+$ cell count, compliance, toxicity, predisposing factors for TB infection before and after isoniazid, incidence of and time to development of TB, $CD4^+$ cell count at the time of the disease, and survival. Factors considered as predisposing conditions for TB infection included imprisonment, homelessness, alcohol abuse, continuation of active intravenous drug use, and intimate contact with a patient with TB disease.

Patients received daily self-administered isoniazid with as well as counseling and education, and close support of any problem was provided as warranted. In each visit, compliance was assessed by specific questions about intake of isoniazid. Patients who discontinued prophylaxis because of toxicity before 9 months of therapy were excluded from the study.

All patients were followed in our AIDS unit, even during the period of imprisonment, if any. Time to TB was considered from the time of completion of prophylaxis to the date of diagnosis of the disease. A diagnosis of TB was established when *M. tuberculosis* was isolated from a clinical specimen; those cases without a positive culture were not included. We also excluded patients who received prolonged treatment (>1 month) with agents with potential antituberculous activity. For the study, prison admission was considered as a risk factor for TB when the patient stayed within the institution for >1 month.

Patient follow-up was censored on 31 December 1996, in order to avoid the influence of HAART in the incidence of TB. Time to development of TB was estimated using Kaplan-Meier method, and comparison between curves was assessed using

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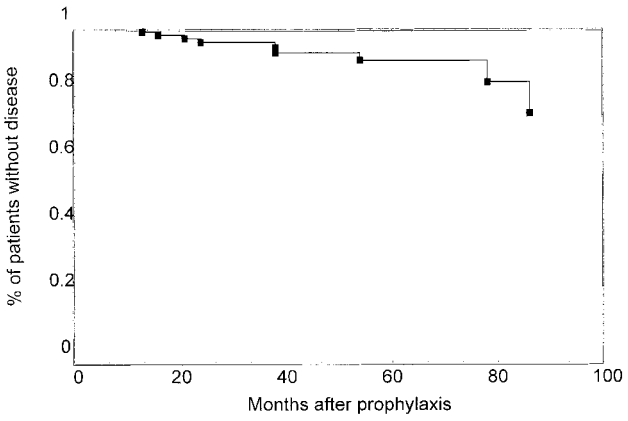

Figure 1. Kaplan-Meier estimates of development of tuberculosis in HIV-infected patients after isoniazid chemoprophylaxis.

log-rank test. For analysis, persistence of risk factors for exposure to TB was defined as a dichotomous variable. A Cox proportional hazards method was developed to determine the factors associated with later development of disease, after adjustments were made for $CD4^+$ cell count.

Results. From 1987 through 1996, a total of 131 patients were included in the study (418 person-years). Mean age was 35 years (range, 21–58 years), and 78% were male. The predominant risk factors for HIV infection were injection drug use (in 82% of patients), homosexuality (8%), heterosexual intercourse with an infected partner (6%), and unknown (4%). Overall, median $CD4^+$ cell count at the time of prophylaxis was 405 cells/mL (interquartile range [IQR], 266–616 cells/mL), 60% of patients were in AIDS Centers for Disease Control and Prevention (CDC) stage A, and only 5 patients (3%) had a prior AIDS-defining illness. No virus load determinations were available in the clinical routine during the period of follow-up.

Although all the patients had a positive TST, a predisposing factor for TB infection was identified in 116 patients (89%), especially drug addiction (83%), prior imprisonment (21%, or 28 cases), or close contact with a patient recently diagnosed with TB (10%). Of note, 38 patients (21%) had >1 factor for TB infection.

Median follow-up was 43 months (range, 14–118 months), with 38% of patients having a >5 years of follow-up. After isoniazid chemoprophylaxis, persistence of risk factors for exposure to TB was observed in 41 patients (33%): drug addiction in 33, new prison admission in 8, and homelessness in 3 cases. TB developed in 8 patients (6%) a median of 33 months after the completion of prophylaxis (0.61 cases per 100 patient-years of follow-up), without differences between patients receiving 9 or 12 months of isoniazid therapy ($P = .42$). Kaplan-Meier estimates of the probability of remaining free of TB was 95% after 3 years and 73% after 8 years of follow-up (figure 1). In these 8 cases, no *M. tuberculosis* strain was isoniazid resistant.

At the date of censoring, median $CD4^+$ cell count in this cohort of patients was 387 cells/μL (IQR, 233–520 cells/μL), and 19 patients (15%) had progressed to a worse AIDS CDC stage. Only 10 patients (8%) died during the study period. In a univariate analysis, injection drug use as risk factor for HIV infection ($P = .02$), lower initial mean $CD4^+$ cell count (186 cells/μL vs. 425 cells/μL; $P = .03$), and persistence of risk factors for TB infection ($P = .04$) were statistically associated with development of disease. In the Cox proportional hazards method, however, only the persistence of predisposing conditions for TB after isoniazid was statistically associated with the development of TB (relative hazard, 3.17; 95% CI, 1.56–17; $P < .001$; table 1).

Discussion. Long-term benefit of isoniazid chemoprophylaxis to prevent reactivation TB has been demonstrated in immunocompetent patients with a positive TST [5]. Also, the efficacy of isoniazid in preventing TB in HIV-infected patients has been shown in both retrospective and prospective studies [2, 6, 7]. The degree of protection described after isoniazid, however, ranged from no cases between 27 patients for a median follow-up of 25 months [6] and 8.9 per 100 patient-years 3–27 months after prophylaxis [7]. These differences could, at least in part, be due to the HIV population included (proportion of patients at highest risk, such as injection drug users [IDUs] or prison inmates) or the criteria established for diagnosis of TB (culture positive vs. clinical definition) [8]. In addition, the long-term benefit of isoniazid has not been established, and concern exists about reactivation of the disease as soon as $CD4^+$ cell counts fall [7, 9].

Our study shows that isoniazid preventive therapy provides a long-term benefit in HIV-infected patients (0.61 per 100 patient-years), with a cumulative probability of TB <5% 3 years after isoniazid in the HIV population at highest risk for TB (IDUs with positive TSTs). These data are consistent with previous reports on isoniazid prophylaxis [2, 10, 11] and support that the use of isoniazid provides >90% drop in TB incidence. This low rate of TB after isoniazid is similar to that described in a small study of 29 patients who were followed for a median of 89 months (1.6 per 100 patient-years) [12]. Recently, Gourevitch et al. [11] described a rate of 0.51 per 100 patient-years in a similar population of IDUs with a positive TST.

It is not known whether development of TB after prophylaxis

Table 1. Multivariate model of risk factors for tuberculosis after isoniazid prophylaxis.

Variable	Relative hazard (95% CI)	*P* value
$CD4^+$ cell count (per each unit of increase)	0.995 (0.992–1.003)	.06
Persistence of predisposing factors for tuberculosis	3.17 (1.56–17)	.0002

is secondary to reactivation of a latent infection or to a newly acquired infection. It has been suggested that isoniazid cannot eradicate the whole population of *M. tuberculosis*. Thus, despite isoniazid chemoprophylaxis, cases of active TB could be anticipated in long-term surviving HIV-infected patients with progressive immunosuppression. There is, however, evidence of transmission in centers for HIV-infected patients [13, 14], and up to 40% of cases in New York City were apparently due to recent infections [15]. Our study shows that the persistence of predisposing conditions for TB infection, such as drug addiction or new prison admissions, was the main risk factor for TB in our population, with >3-fold increase in the risk of TB. This fact is not surprising, in view of the high incidence of TB transmission between IDUs or prison inmates in our area [16, 17] and suggests reinfection as the main cause of TB after isoniazid chemoprophylaxis. In this way, a recent randomized study in our area has found a relative risk of TB 9-fold higher in prisoners despite the completion of a 12-month cycle of isoniazid [18]. Also, reinfection, not relapse, has been identified as the main reason for TB in a cohort of HIV-infected mineworkers who had successfully completed treatment [19], and a recent study has shown the utility of continuing isoniazid chemoprophylaxis for avoiding recurrence after completion of TB treatment [20].

There are 2 inherent biases in our study. First, most of our patients received isoniazid chemoprophylaxis early in the course of HIV infection, as confirmed by the median $CD4^+$ cell count and AIDS CDC stage, and they had a low rate of progression of HIV infection. Because of this relatively maintained immunological status, we cannot estimate the effect of important $CD4^+$ count drop on the rate of TB. This limitation, however, may not be significant at present, because the immunodeficiency of most patients lessens after treatment with HAART. Second, a high incidence of TB might be found shortly after isoniazid in noncompliant patients, in whom reactivation of dormant bacilli may be the cause of TB [21]. We selected for the study compliant patients who received $\geqslant$9 months of isoniazid chemoprophylaxis and were not receiving HAART and in whom the decline in the rate of disease can be fully attributed to isoniazid therapy. Higher decrease in the rate of TB after isoniazid may be anticipated, because the introduction of HAART, in view of the immune restoration associated with actual antiretroviral treatment. In a recent study, Girardi et al. [22] have found a significant reduction in the risk of TB for patients receiving triple combination therapy. Only 7% of patients in their study had a positive TST, however, and tuberculin positivity remained the main risk factor for TB.

In summary, the present study confirms the long-term benefit reached with 9–12 months of isoniazid prophylaxis in compliant HIV-infected patients with positive TSTs and gives further support to current recommendations. Compliance with therapy should be ensured, even in directly observed programs [23, 24], and specific strategies should be directed to avoid TB reinfection rather than periodic or lifelong prophylaxis. Thus, implementation of infection control guidelines in the prison setting, or methadone maintenance programs for IDUs at risk for TB, may be as important as isoniazid chemoprophylaxis.

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