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Long-term effectiveness of diagnosing and treating latent tuberculosis infection in a cohort of HIV-infected and at risk injection drug users

Jonathan E. Golub, PhD, MPH^{1,2}, Jacquie Astemborski, MPH², Mohammed Ahmed, MPH², Wendy Cronin, PhD³, Shruti H. Mehta, PhD, MPH², Gregory D. Kirk, MD, PhD, MPH^{1,2}, David Vlahov, PhD, RN⁴, and Richard E. Chaisson, MD^{1,2}

¹Johns Hopkins University School of Medicine

²Johns Hopkins Bloomberg School of Public Health

³Maryland Department of Health & Mental Hygiene

⁴New York Academy of Medicine

Abstract

Introduction—Between 1990 and 1998, tuberculin skin testing (TST) and isoniazid preventive therapy (IPT) was provided to injection drug users participating in the AIDS Linked to the Intravenous Experiences (ALIVE) cohort.

Methods—A registry match was conducted with the ALIVE cohort database and the Maryland State Department of Health and Mental Hygiene tuberculosis registry.

Results—Of 2,010 participants, 1,753(74%) had a TST placed and read; 536(31%) were positive. TST positivity was 16% in HIV-positives;39% in HIV-negatives($p<0.01$). Overall, 299(56%) TST reactors started IPT; 165(55%) completed six months. Three tuberculosis cases were diagnosed among HIV-negatives (IR=0.16/1,000PYs); 19 among HIV-positives (1.94/1000PYs; IRR=12.3 (3.61–64.70)). Within the entire cohort, tuberculosis rates were 0.8/1000PYs for those not receiving IPT, 0.48/1000PYs for those receiving any IPT, 0.29/1000PYs for those completing at least 30 days and 0/1000PYs for completers. Ten cases of tuberculosis occurred in HIV-infected individuals with negative TSTs.

Discussion—IPT was associated with protection against tuberculosis, but uptake was modest. While it is likely that tuberculosis incidence would have increased, especially in HIV-positive subjects, if the IPT program had not occurred, more significant declines in tuberculosis incidence in this population will require improved methods for ensuring uptake and completion of IPT and preventing disease in TST-negative individuals.

Keywords

tuberculosis; latent tuberculosis infection; HIV

INTRODUCTION

Isoniazid preventive therapy (IPT) has long been known to markedly reduce the risk of reactivation of latent *Mycobacterium tuberculosis* infection^{1,2}. More recently, IPT has proved effective for HIV-infected patients with latent tuberculosis infection (LTBI) who are at considerable risk of progressing to active tuberculosis disease^{3,4}. Despite the documented efficacy at the individual level, the effectiveness of IPT as a strategy to reduce tuberculosis incidence at the population level is not clear.

Mathematical models have suggested that preventive therapy could significantly reduce tuberculosis incidence in populations with high tuberculosis prevalence⁵. Guidelines in the United States recommend targeted tuberculin skin test (TST) screening and IPT in TST-positive high risk populations, including HIV-infected individuals⁶. Globally, more widespread use of IPT for HIV-infected people at risk for tuberculosis has been endorsed^{7,8}. There are many logistical challenges with implementing a community-level IPT program, including the difficulty of placing and interpreting the tuberculin skin test (TST), ruling out active tuberculosis, and promoting adherence to treatment. As a result, IPT is underutilized in high-risk populations.

Injection drug use is an important risk factor for HIV infection and for tuberculosis infection and disease in the United States^{9,10}. In populations where HIV infection overlaps with injection drug use, tuberculosis is an important opportunistic disease^{11,12}.

In 1990, a campaign was launched to provide TSTs and IPT to over 2,000 injection drug users (IDUs) who participated in the AIDS Linked to the Intravenous Experiences (ALIVE) cohort in Baltimore, Maryland. In 1996, a preliminary report found that expanded access to treatment for LTBI in this cohort of IDUs reduced tuberculosis incidence from 6/1,000 (1991) to 0 over the two year period between mid-1992 and mid-1994¹³. The campaign continued through May, 1998. We investigated the long term effectiveness of the TST/IPT campaign through its completion in 1998 and an additional six years of follow-up through December 31, 2004.

METHODS

ALIVE

The ALIVE study recruited a cohort of injection drug users from community settings in Baltimore, MD beginning in 1988^{13,14}. In brief, both HIV-infected and uninfected study participants have semi-annual visits to the clinic where they undergo a series of interviews, a clinical examination and have blood drawn for laboratory tests. Included in these interviews are questions regarding history of diagnosis or treatment of tuberculosis. Any self-report of tuberculosis is confirmed through medical record review with standardized abstraction. Initial inclusion criteria for ALIVE was age ≥ 18 years, no history of an AIDS-defining illness, and use of injection drugs within the previous 11 years. The current analyses includes participants who were enrolled in the initial (1988–89) and second (1994–1995) recruitment waves.

Intervention

The TST/IPT campaign began in March, 1990 and continued through March, 1998. During this period, participants were invited to receive a TST and to return for a reading 2–3 days later^{13,15}. Repeat TST testing was offered during the testing interval to TST negative participants on return visits. A positive test was defined as ≥ 5 mm diameter induration for HIV-positive participants and ≥ 10 mm induration for HIV-negative participants. All participants with a positive result were screened for active tuberculosis disease with a symptom review and chest radiograph. All TST positive participants not diagnosed with active tuberculosis disease were offered isoniazid preventive therapy. For the first year of the study, IPT was self-administered.

However, as treatment expanded, participants received directly observed preventive therapy (DOPT) twice or thrice weekly. Treatment was considered complete if the participant was adherent to treatment for at least 26 weeks.

Outcomes

A registry match was conducted with the ALIVE cohort database and the Maryland State Department of Health and Mental Hygiene (DHMH) tuberculosis registry. All tuberculosis cases diagnosed in the state are reportable to DHMH, and reports are submitted by physicians, laboratories, pharmacies and health departments. Local health departments perform evaluations to verify the accuracy of diagnoses prior to submitting reports to DHMH. Only cases reported through the DHMH tuberculosis registry were considered as tuberculosis cases in the current analysis.

Statistical Analysis

Three time periods were considered for the current analysis: Pre-TST-era (1988 — Feb. 28, 1990), TST-era (March 1, 1990 — May 31, 1998) and Post-TST-era (June 1, 1998 — December 31, 2004). Annual and era-specific incidence rates for tuberculosis were calculated per 1,000 person-years of follow-up from study enrollment through December 31, 2004 or from the beginning to the end of each era. Incidence rate ratios compared tuberculosis incidence in the different eras. Cox proportional hazards models were used to investigate factors associated with a diagnosis of tuberculosis. Participants who were diagnosed as tuberculosis cases more than one year after their last ALIVE visit were not included in the Cox models because their risk factors close to time of diagnosis could not be ascertained. All analyses were conducted using SAS (Version 9.1, Cary, NC) and Stata (Version 9.1, College Station, Texas).

RESULTS

A total of 2,376 patients had visited the ALIVE clinic between 1988 and 1998. During the TST-era (March 1990 to May, 1998), 2,010 (84.6%) participants were interviewed by a tuberculosis study nurse during a study visit. Among those who were interviewed by a tuberculosis study nurse, the majority were males (75%), median age =36.3 (IQR=31.6, 41.1) and black (94%). 682 of the 2,010 participants (34%) were HIV-positive and 1,327 (66%) were HIV-negative at baseline. There were 118 (5.9%) participants who seroconverted for HIV antibodies during follow-up. Participants who were not interviewed did not differ in demographic or clinical characteristics compared to those that were interviewed (data not shown).

TST and IPT results

Overall, among 2,376 participants, 1,753 (74%) had at least one TST placed and read, and 536 (31%) had a positive TST result. Among 800 HIV-positive participants, 649 (81%) had a TST placed and read compared to 1,104 (70%; $p<0.01$) among 1,576 HIV-negatives (Table 1). TST positivity differed significantly between HIV-positive participants (16%) and HIV-negatives (39%; $p<0.01$). Among HIV-positives, TST positivity had an inverse association with CD4 count, with 4.1% of those with $CD4 < 200/mm^3$ having a positive result at first visit compared to 11.0% among participants with $CD4 > 200/mm^3$ ($p=0.02$).

Similar proportions of TST-positive HIV-positives (59%) and HIV-negatives (55%; $p=0.45$) started IPT. Additionally, the proportions completing therapy were similar between HIV-positives (60%) and HIV-negatives participants (54%; $p=0.28$). Overall, 31 percent of all participants with a positive TST completed 6 months of IPT (35% HIV-positive, 30% HIV-negative; $p=0.28$). The majority of participants starting (80%) and completing (78%) IPT were HIV-negative. Participants with a positive TST who started IPT did not differ from those who

did not start IPT by age, gender, race, HIV status or drug use. Among those starting IPT, 20 (7%) self administered all doses, 134 (45%) had all doses directly observed, and the remaining 145 (48%) received a combination of direct observation and self-administered therapy.

Tuberculosis Incidence Rates by TST/IPT status

Among participants who visited the clinic at least once between 1990 and 1998, 28 cases of tuberculosis were recorded. Six of these were excluded because they had no visits in the PPD era (4 of these 6 had a baseline visit only) and were therefore not given the opportunity to receive a TST or IPT. A total of 22 tuberculosis cases were included in the analysis.

Of the 22 patients who developed tuberculosis, 19 were HIV-positive and three were HIV-negative. Among the 19 HIV-positives, 13 had a TST, of whom three were reactive and 10 were non-reactive. Two of the three HIV-positive reactors initiated IPT: one received IPT for one week and was diagnosed with tuberculosis three months later and the other received IPT for 20 weeks and was diagnosed with tuberculosis three years later. Two of the three HIV-negatives had a TST and both were reactive. Neither of the HIV-negative reactors initiated IPT.

The incidence of tuberculosis was calculated for participants who never had IPT, those who started IPT, those who completed at least 30 days and those who completed at least 6 months of IPT (Table 2a). Among patients who completed at least 30 days of IPT, but did not complete the 6 month course, the median duration of therapy was 15 weeks. Among the full cohort, participants who never started IPT contributed 24,585 person-years and had 20 cases of tuberculosis diagnosed for an incidence rate (IR) of 0.81/1000PYs. Those who started IPT experienced two cases during 4,185 person-years for an IR of 0.48/1000PYs and those with at least 30 days of IPT had an IR of 0.29/1000PYs. Finally, among those who completed 6 months of IPT, there were no cases of tuberculosis in 2,385 person-years of follow-up. These rates were higher when restricted to the HIV-positive subset; however, similar rates were seen in the no IPT group (1.92/1000PYs), the starting IPT group (2.15/1000PYs) and the 30 day group (1.30/1000PYs) versus no cases during 588 person-years in the group completing IPT (Table 2b).

Incidence rates were calculated according to HIV and TST status without considering IPT use. Among HIV-infected participants, those with a positive TST had an IR=1.93/1,000PYs compared to 1.56/1000PYs for TST negatives and 3.24/1000PYs for TST unknowns. Among HIV-negatives, TST positive participants had an IR=0.35/1000PYs compared to 0/1000PYs for TST negatives and 0.22/1000PYs for participants with an unknown TST result.

Temporal Trends in Tuberculosis Incidence

Two cases of tuberculosis were diagnosed in the Pre-TST era, 13 during the TST era, and 7 in the Post-TST era (Figure 1). Annual tuberculosis incidence fluctuated greatly throughout the 17 years, and the trends in the overall cohort and HIV-positive participants were quite similar. The overall incidence rate for the full cohort was 0.76/1000PYs. The incidence rates for the three time periods were: Pre-TST era= 0.72/1000PYs; TST era=0.88/1000PYs, Post-TST-era=0.62/1000PYs (**Table 3a**). The incidence rate ratio comparing the TST era to the Pre-TST era was 1.21 (95%CI: 0.34–10.02), while the Post-TST era saw a reduction in tuberculosis incidence when compared to the TST-era (IRR=0.71; 95% CI: 0.42–1.34) but this decrease was not statistically significant.

Among the subset of HIV-positives, the overall tuberculosis incidence was 1.94/1000PYs. The incidence rates in each era were 2.16/1000PYs (Pre-TST era), 1.84/1000PYs (TST-era) and 2.03 (Post-TST era; **Table 3b**). Though tuberculosis incidence in the TST era was lower than

that in the pre-TST era, the observed reduction was not statistically significant (IRR=0.85; 95% CI: 0.23–7.04).

Correlates of Incident Tuberculosis

Eighteen of 22 tuberculosis cases were included in the Cox proportional hazards models; three were excluded because tuberculosis was diagnosed more than one year after final visit and one other had only one visit prior to tuberculosis diagnosis. The strongest risk factor for tuberculosis in the full cohort was HIV infection (RH=8.4; 95% CI: 2.4–28.9; Table 3). There was no association between risk of tuberculosis and sex, age, education, homelessness, or employment status. Prior incarceration was associated with a decreased risk of tuberculosis. Among those with a positive TST, receiving any INH was protective of developing tuberculosis (Table 3); however, these associations were not statistically significant primarily because there was only one case of tuberculosis among participants who received at least 30 days of IPT. In multivariate analysis for all participants, HIV-infection (aHR: 6.0; 95% CI: 1.7–21.1) was associated with an increased risk and history of incarceration (aHR:0.24; 95% CI: 0.1–0.7) was associated with a decreased risk of tuberculosis.

Among the HIV-infected participants, there was no observed difference in tuberculosis risk by gender, age, education, employment or incarceration. In multivariate analysis, CD4+ cell count < 200 μ L/ml was the strongest risk factor for tuberculosis (aRH=13.6; 95% CI: 1.5–119.9) (Table 4). Although a potentially protective effect was suggested, antiretroviral treatment did not significantly affect tuberculosis risk (aRH=0.4; 95% CI: 0.1–1.4). Body mass index <21, measured only among the HIV-positive participants, was strongly associated with incident tuberculosis (aRH=4.6; 95% CI: 1.6–13.6) even after adjusting for advanced immunosuppression.

DISCUSSION

A program aimed at providing TSTs and IPT to a cohort of injection drug users contributed to reduced tuberculosis incidence for some participants, but did not eliminate tuberculosis from this high-risk population. While there were no cases of tuberculosis diagnosed among participants who completed at least 6 months of IPT, the overall incidence of tuberculosis within the cohort did not significantly change over time. Within the HIV-infected subjects, however, the expected rate of tuberculosis without IPT would have increased over time as cellular immunodeficiency progressed¹⁶, so the program most likely was beneficial at the population level. Nonetheless, although the intent of the program was to test and treat all participants infected with *Mycobacterium tuberculosis*, only 32% of those found to be TST-positive completed the recommended course of treatment. It is quite likely that with an increase in the proportion of participants starting and completing six months of IPT, tuberculosis could have been reduced more substantially than found in this analysis. Of note, however, is that 10 of 22 TB cases were in HIV-infected individuals with a negative TST. These people may have had false negative tests, or could have had new *M. tuberculosis* infections that progressed to disease following testing.¹⁷

In the initial report of this intervention in 1996, it was stated that tuberculosis was eliminated from this population for at least a two year period only two years after implementation¹³. Our analysis revealed that some TB cases occurred during that time period but were only captured by the registry match with DHMH. The methodology in this analysis differs from the initial report which included tuberculosis diagnoses reported by patients but not verified or matched to the state TB registry.

In the current analysis, we observed a reduction in TB incidence in the final two years of the intervention and temporary elimination in the two years immediately following completion of

the intervention. However, incidence increased again and 7 cases were diagnosed between 2000 and 2004, all among HIV-infected participants. Six of these participants received a TST at least 7 years prior to developing TB. Thus, it is possible that the cumulative effect of detecting and treating latent tuberculosis infection in almost 300 participants had an impact on reducing tuberculosis incidence over a four year period and that the observed rates of tuberculosis may have been even higher had the intervention not been initiated. Also, a prolonged period of TB elimination may have been observed if all these 7 patients had been detected and treated. Moreover, repeat TST may have detected latent infection in these (and other) patients.

Of the 19 cases of tuberculosis diagnosed among HIV-infected participants in the ALIVE cohort, 6 (31%) never received a TST and 3 (16%) had a positive TST but did not receive the recommended course of IPT. Thus, about half of HIV-infected cases may be considered missed opportunities of the program. Of the 3 cases of tuberculosis among the HIV-negative participants, one never received a TST and the other two had a positive TST but never started IPT. False negative reactions to the TST are also a concern, especially among HIV-infected participants, leading to missed opportunities for prevention. During the TST-period of this study, the TST was the only available tool for diagnosing latent tuberculosis infection. New interferon- γ release assays may have greater sensitivity and specificity for latent tuberculosis infection¹⁸, though the performance of these assays in HIV-infected individuals needs to be more fully evaluated. Four of seven tuberculosis cases who were co-infected with HIV at tuberculosis diagnosis had CD4 lymphocyte counts less than 200 at the time of their negative TST result, a level that has been shown to have reduced sensitivity for detection of latent infection¹⁹. In our population, participants with CD4 counts $< 200/\text{mm}^3$ were less likely to have a positive TST compared to those with higher CD4 counts and HIV-negatives. This difference was likely due to the decreased sensitivity of the TST in HIV-infected patients.

In the initial analysis¹³, there were no tuberculosis cases in 418 person-years of follow-up among participants receiving at least 6 months of isoniazid. The extended follow-up in this study reveals no cases occurring among 2,385 person-years of follow-up among participants completing therapy and no cases occurring among 588 person-years of follow-up among the HIV-infected subset. It is noteworthy that among all participants who started IPT in this study, only 2 tuberculosis cases developed after 4,185 person-years of follow-up, and among those who took at least 30 days of IPT only one case of tuberculosis developed, suggesting benefits among IPT initiators even if the entire course is not completed²⁰⁻²². Of course, the goal of any IPT program should be completion of therapy to increase the efficacy of the treatment. Further, it should also be noted that this partial protection may differ by HIV status. Among HIV-infected participants who started IPT but did not complete at least 6 months, the incidence rate was similar to those who did not receive any IPT. Thus, for HIV-infected patients, it is imperative to ensure adherence to IPT. Importantly, isoniazid resistance was not detected among TB cases who had received any duration of IPT.

Participants with more advanced HIV disease ($\text{CD4} < 200$) had a much greater incidence of tuberculosis^{23,24}. However, we did not observe a significant reduction in tuberculosis incidence among HIV-infected participants who received antiretroviral therapy. Though several cohort studies have shown that tuberculosis incidence is reduced in HIV-infected patients receiving HAART, rates among these patients still remain alarmingly high^{23,25-27}. Although tuberculosis incidence did not differ by antiretroviral therapy use, the small number of cases in the study may have limited the ability to make this observation. Further, the majority of person-time, and almost all of the intervention time, was prior to the start of the HAART era. Thus, the cohort as a whole had increasingly progressive immune suppression.

Our study had several limitations. Though all participants in the ALIVE cohort were cross-matched with the Maryland State tuberculosis registry, it is possible that ALIVE participants

were diagnosed with tuberculosis outside the state of Maryland and were therefore not captured. If tuberculosis cases were missed, our reported incidence would be an underestimate of the true incidence. However, our study population is known to be restricted in movement out of the city and rarely seeks health care elsewhere. If any misclassification occurred, it was unlikely to be differential. Secondly, this intervention was at the program level and therefore did not include a control group. However, the primary analysis in this study was conducted to compare tuberculosis incidence by era among all ALIVE participants during this time period regardless of participation in the intervention. This conservative approach allows for a more realistic assessment of population-level effectiveness of a programmatic intervention that was intended to include as many participants as possible. Though a high proportion (74%) had a TST reading, we were limited by having significant numbers of participants who did not initiate or complete IPT. When analyzed further, the positive effects of isoniazid were considerably more pronounced when limited only to those receiving a TST and preventive therapy (data not shown). Further, our primary intention was to describe the effectiveness of the TST/IPT intervention and its potential effectiveness despite the relatively low uptake of the intervention. It is possible that those individuals who adhered to their IPT, were those at greatest TB risk, but this is difficult to assess with these data. Finally, despite the >30,000 person-years of follow-up and a high prevalence of latent tuberculosis infection, the number of tuberculosis cases detected among the ALIVE participants was relatively low.

There are several strengths to this analysis. The study population is a unique high risk population in the US, and one that is of high priority for tuberculosis control programs. IDUs are at high risk for both HIV and tuberculosis, and this analysis was able to determine the effectiveness of preventive therapy for both HIV-infected and uninfected populations. The ALIVE cohort is a long-standing cohort, thus long-term follow-up was able to be assessed because of the strong retention rate of study participants. Finally, the Maryland DHMH tuberculosis registry has a strong record of complete data collection.

Tuberculosis incidence can be reduced in a high risk population through programmatic implementation of tuberculin skin testing and isoniazid preventive therapy. For a program to achieve its maximum benefit, a high proportion of patients must be tested and high rates of treatment completion must be achieved among the eligible population. HIV-infected injection drug users will receive the greatest benefit and should be a high priority for targeted tuberculin testing and isoniazid preventive therapy in the US. In addition, efforts to identify better tests for LTBI in HIV-infected individuals and to prevent transmission of *M. tuberculosis* infection are important strategies for tuberculosis control.

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Figure 1.

Incidence rate (per 1000PYs) of TB in ALIVE cohort 1988 – 2004

Table 1

TST and IPT experience among full cohort

	HIV-positive (n=800)	HIV-negative (n=1,576)	Total (n=2,376)
TST placed and read	649 (81%)	1,104 (70%)	1,753 (74%)
TST positive	102 (16%)	434 (39%)	536 (31%)
IPT started	60 (59%)	239 (55%)	299 (56%)
IPT at least 30 days	48 (80%)	189 (79%)	237 (79%)
IPT completed	36 (60%)	129 (54%)	165 (55%)
% completing IPT among TST positive	35% (36/102)	30% (129/434)	31% (165/536)

Table 2a

Incidence rate of Tuberculosis by IPT experience in full cohort

IPT experience	# of TB cases	Person-years	IR* (95% Confidence Intervals)
No IPT	20	24,585	0.81 (0.50–1.26)
All starting IPT	2	4,185	0.48 (0.06–1.72)
IPT at least 30 days	1	3,358	0.29 (0.01–1.66)
All completing IPT	0	2,385	0 (0–1.55)

* Incidence rate per 1000PYs

Table 2b

Incidence rate of Tuberculosis by IPT experience in HIV-infected only

IPT experience	# of TB cases	Person-years	IR* (95% Confidence Intervals)
No IPT	17	8,867	1.92 (1.11–3.07)
All starting IPT	2	932	2.15 (0.26–7.75)
IPT at least 30 days	1	767	1.30 (0.03–7.26)
All completing IPT	0	588	0 (0–6.27)

* Incidence rate per 1000PYs

Table 3
Univariate predictors of tuberculosis in all participants

Risk factor	Hazard Ratio	95% CI
HIV-positive	8.4	2.4–28.9
Female	1.2	0.4–3.3
Age < 35 years	0.7	0.2–2.5
Education < high school	1.3	0.5–3.3
Homeless	1.2	0.5–3.1
Employed	1.8	0.7–4.9
Incarcerated past 10 years	0.3	0.1–0.7
TST-positive	1.2	0.4–3.8
Started IPT	0.5	0.1–4.1
Started IPT [*]	0.6	0.1–7.0
Received at least 30 days IPT	0.7	0.1–5.1
Received at least 30 days IPT [*]	0.9	0.1–9.5
Completed IPT	0.0	0.0
Completed IPT [*]	0.0	0.0

* Only among TST positives

Table 4

Univariate and adjusted predictors of tuberculosis in HIV-infected participants

Risk factor	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
BMI < 21	5.9 (2.0–17.3)	4.6 (1.6–13.6)
ARV therapy	0.6 (0.2–1.9)	0.4 (0.1–1.3)
CD4 < 200	12.9 (1.5–108.1)	13.6 (1.5–119.9)
CD4 200–499	3.1 (0.3–28.0)	3.3 (0.4–30.2)
CD4 ≥ 500	REF	REF