Guidelines of tuberculosis preventive therapy for HIV-infected persons: a prospective, multicentre study

G. Antonucci*, E. Girardi*, M. Raviglione#, P. Vanacore*, G. Angarano¶, A. Chirianni+, G. Pagano§, F. Suter*f*, F.N. Lauria*, G. Ippolito*, and GISTA (Gruppo Italiano di Studio Tubercolosi e AIDS)

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ABSTRACT: The aim of this study was to assess the degree of implementation of national guidelines for isoniazid preventive therapy (IPT) among human immunodeficiency virus (HIV)-infected individuals and factors affecting the impact of the programme.

Twenty-eight infectious disease hospital units in Italy participated in this observational, multicentre, prospective cohort study. A number of HIV-infected subjects, (n=1,705) seen for the first time as outpatients, were included in this analysis.

Of the subjects considered, 1,215 out of the 1,705 completed purified protein derivative (PPD) screening. Variables independently associated with offering and completion of PPD screening included having acquired immune deficiency syndrome (AIDS), higher educational levels and currently receiving therapy. Overall, 103 subjects were identified as candidates for IPT. Of these subjects, five had tuberculosis and 15 had contraindications to IPT. Forty subjects agreed to start IPT, and 29 completed a full-course regimen. The incidence of tuberculosis among IPT candidates who either did not begin or discontinued IPT was 6.1 per 100 person-yrs, while no cases of tuberculosis were observed in subjects completing IPT.

Several factors may limit the implementation of an isoniazid preventive therapy programme for human immunodeficiency virus-infected persons. Physicians fail to offer purified protein derivative screening to patients with high degrees of immunodeficiency, and those with a more intense workload seem to pay less attention to this test. The high number of contraindications among patients and their low level of acceptance further affects the impact of isoniazid preventive therapy.
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*Dipartimento di Epidemiologia, Istituto Nazionale per le Malattie Infettive L. Spallanzani -IRCCS, Rome, Italy, #Programme on Communicable Diseases, World Health Organization, Geneva, Switzerland, ¶Clinica di Malattie Infettive, Policlinico di Bari, Bari, Italy, +Divisione di Malattie Infettive, Ospedale Cotugno, Napoli, Italy, §Divisione di Malattie Infettive, Ospedale S. Martino, Genova, Italy and *f*Divisione di Malattie Infettive, Ospedali Riuniti, Bergamo, Italy.

Correspondence: E. Girardi, Dipartimento di Epidemiologia, Istituto Nazionale per le Malattie Infettive "L. Spallanzani" -IRCCS, Via Portuense, 292, 00149 Roma, Italy.
Fax: 39 065582825

Patients infected with both the human immunodeficiency virus (HIV) and *Mycobacterium tuberculosis* are at extremely high risk of developing active tuberculosis [1]. Recent epidemiological studies using deoxyribonucleic acid (DNA) fingerprinting analysis of mycobacterial strains isolated in different populations, suggest that $\geqslant 50\%$ of cases of tuberculosis, in HIV-infected persons are due to reactivation of a latent infection [2–4]. The majority of these could be averted with the use of preventive therapy (recently renamed by some "treatment of latent infection") [5]. Several clinical trials have demonstrated that isoniazid preventive therapy (IPT) significantly reduces the risk of active tuberculosis in tuberculin-positive HIV-infected persons [6–10], and this intervention is recommended by national and international agencies [11–13]. However, several factors have emerged that limit its implementation. These include health system operational problems, the prevalence of conditions contraindicating preventive therapy, and low acceptance levels of preventive programmes by physicians and patients [14].

In Italy, national guidelines issued in November 1994 recommend IPT for all dually-infected persons [15]. In May 1995, a cohort study was established to evaluate the degree of implementation of national guidelines for preventing tuberculosis among persons with dual infection. The present study aims to assess factors affecting the impact of programme in an industrialized country with free access to healthcare, and to identify areas that should be targeted for further educational efforts.

Subjects and methods

Study design and selection of subjects

This multicentre, prospective, observational study was to assess the implementation of Italian guidelines regarding tuberculin screening and tuberculosis preventive therapy for HIV-infected persons [15]. These guidelines are in table 1.

Twenty-eight infectious disease units, which belong to an established research network on tuberculosis and HIV infection (the Gruppo Italiano di Studio Tubercolosi e AIDS or GISTA) participated in the study. These units are located in 13 of Italy's 20 regions, and all are in public hospitals, eight of which are university teaching hospitals. All of these clinical centres are experienced in HIV patient care. In Italy, National Health Service regulations dictate that acquired immune deficiency syndrome (AIDS) patients and HIV-infected persons receiving antiretroviral therapy be cared for in designated infectious disease units [16]. These units report ∼40% of the total number of AIDS cases notified in Italy (G. Rezza, Istituto Superiore di Sanità, Reparto AIDS e MST, Italy, personal communication).

Individuals (inpatients and outpatients) ⩾18 yrs of age, with confirmed HIV infection, seen for the first time in participating units May 1, 1995–April 30, 1996, were recruited into the cohort study, and a total of 2,160 subjects were considered. In the present analysis, the 1,705 subjects presenting for the first time as outpatients were included. Each of the participating centres sought ethical approval according to local regulations.

Table 1. – Summary of Italian guidelines on tuberculosis preventive therapy in human immunodeficiency virus (HIV)-infected persons

Candidates for preventive therapy
   Positive tuberculin reaction (induration ⩾5 mm at
     48–72 h) or
   Prior documented positive tuberculin reaction,
     untreated or
   Recent contacts with tuberculosis patients
Pretreatment evaluation
   Chest radiography and clinical examination
   Measurement of serum AST and bilirubin
   Microbiological examination for *Mycobacterium*
     tuberculosis only in presence of radiographical
     or clinical findings suspicious of active tuberculosis
Contraindications to preventive therapy
   History of adverse effects of isoniazid
   Severe or decompensated liver disease
   Serum AST above three times the upper limit of
     normal level
   Pregnancy
Recommended drug regimen
   Self-administered isoniazid (300 mg daily) plus
     pyridoxine (50 mg daily) for 6–12 months
Monitoring of treatment
   Monthly clinical examination and measurement of
     serum AST

AST: aspartate aminotransferase.

Data collection

At baseline, the following data were collected for each enrolled subject: age, sex, country of birth, place of residence, date of first positive HIV test, HIV-transmission category, history of active tuberculosis, history of tuberculin skin test, recent close contact with infectious active tuberculosis, and history of IPT. Data on current antiretroviral drug use, CD4+ lymphocyte count, and HIV clinical status were also recorded.

The medical charts of all HIV-infected subjects indicated for tuberculin screening were reviewed 2 months after enrolment to collect data on purified protein derivative (PPD) screening offered, performed, and read. Charts of candidates for IPT were also reviewed to verify whether tests were performed to exclude active tuberculosis, whether any other contraindications were recorded and to collect results. In addition, the date of IPT start, the presence of contraindications, or any other reason for not starting IPT were recorded.

In the present study, all follow-up data were recorded prospectively. For all subjects included in the study, data were abstracted twice a year from clinical charts to provide the most recent documentation regarding CD4+ lymphocyte count, diagnosis of active tuberculosis, antimycobacterial therapy including at least two antituberculosis agents, antiretroviral therapy, as well as the date of loss to follow-up or death.

The clinical charts of subjects receiving IPT were reviewed monthly. Self-reported data on pill taking, clinical data, results of aspartate aminotransferase (AST) and completion date of IPT or the date and cause of therapy discontinuation were recorded.

All data were collected using standardized forms. All forms were checked at the coordinating centre for logical errors.

Outcome variables and definitions

The main outcomes of this analysis were: offer and completion of PPD screening within 2 months following enrolment, and a new diagnosis of active tuberculosis during follow-up.

A case of tuberculosis was defined as the presence of clinical signs and symptoms suggestive of tuberculosis, confirmed by the isolation of *M. tuberculosis* in culture or by clinical and radiological improvement in response to antituberculosis therapy.

The clinical status of HIV infection was classified according to the 1993 Centers for Disease Control and Prevention (CDC) system [17]. AIDS cases were defined as only subjects meeting the clinical criteria of the CDC 1993 AIDS case definition [17].

Statistical analysis

Descriptive statistical methods were used to provide a general profile of the study population and a description of the subjects who initiated and completed the tuberculin screening and IPT.

Univariate analysis was performed to examine characteristics of centre possibly determining differences in offer and completion of PPD screening. The Chi-squared test was used to compare proportions.

Logistic regression analysis was used to identify determinants of completion of PPD screening. Two different models, were fitted. In the first model, the outcome variable was the offer of PPD by a physician. In the second model the outcome variable was the acceptance of PPD skin test and returning for test reading. All demographic and clinical characteristics collected at baseline were entered in both models. Variables were included in the model as indicator variables. Age was categorized as follows: 18–29 yrs, 30–34 yrs and $\geqslant 35$ yrs, years of education as: <6, 6–8, >8; CD4+ cells count as: $\geqslant 500$ μL^{-1}, 499–200 μL^{-1} and <200 μL^{-1}; time since first HIV-positive test as: $\leqslant 3$ months and >3 months between the first HIV-positive test and enrolment; and origin as: born in Italy or foreign born. Clinical centres of enrolment were also included in both models as indicator variables, and the joint significance of the clinic variable was determined using the log-likelihood test. In all analyses, a p-value of <0.05 was considered statistically significant.

To compute the incidence of tuberculosis, subjects were excluded with active tuberculosis at baseline examination or those who developed tuberculosis within 4 weeks from enrolment. Subjects who died, those who were lost to follow-up, or subjects initiating antimycobacterial therapy within the same 4-week period were also excluded. Each subject's observation period began on the date of enrolment and ended on the earliest of the following dates: diagnosis of tuberculosis; initiation, for any reason, of a course of antimycobacterial therapy including at least two antituberculosis agents; the last documented visit before loss to follow-up; or the last follow-up visit during the period January 1, 1998–June 30, 1998 for subjects completing the study. Incidence rates of tuberculosis were calculated per 100 person-yrs of observation according to IPT status.

Confidence intervals (CI) for the incidence rates were computed using the Poisson distribution. Statistical analyses were performed using standard statistical software.

Results

Of the 1,705 HIV-infected subjects considered for the present study, 1,211 (71.0%) were male, 1,588 (93.1%) were born in Italy, and the median age was 33 yrs (range: 18–75). The mode of HIV infection was intravenous drug use in more than half of the subjects (865, 50.7%); sexual exposure accounted for 42.6% of the study population, with heterosexual contacts representing 66.4% of this group. The first HIV-positive test was performed a median of 14.4 months (range 0–178.5) before enrolment. At baseline, CD4+ lymphocyte count was performed in 1,682 (98.7%) subjects. The CD4+ lymphocyte count was <200 μL^{-1} in 527 (30.9%) subjects, 200–499 μL^{-1} in 690 (40.5%), and $\geqslant 500$ μL^{-1} in 465 (27.3%) subjects; 177 (10.5%)

had clinically defined AIDS (1993 CDC class C). At enrolment, only 495 (21.0%) individuals were receiving antiretroviral therapy.

Purified protein derivative screening

Of the 1,705 enrolled subjects, 31 (1.8%) reporting a history of active tuberculosis, three (0.2%) with a history of antituberculosis therapy, six (0.4%) who had already completed a full course of IPT, and 13 (0.8%) subjects who had a documented previous positive PPD test were not considered for PPD skin test screening. Nine hundred and fifty-three subjects (55.6%) had the PPD skin test performed for the first time >3 yrs after the first HIV-positive test.

A number of subjects (n=1,652) were eligible for PPD screening and their progression through each step of the procedure is summarized in figure 1. Among the 437 (26.5%) subjects eligible for PPD screening and not completing this procedure, 187 (42.8%) were not tested because medical staff failed to offer the test, 160 (36.6%) refused the screening, and 90 (20.6%) did not return for reading. Eighty-one (6.7%) of the 1,215 screened subjects had a positive PPD skin test. The proportion of PPD positive subjects was significantly higher among those with a baseline CD4+ lymphocyte count >199 μL^{-1} (73 out of 832, 8.8% *versus* eight out of 377, 2.1%; p<0.001).

Characteristics associated with purified protein derivative screening

The proportion of subjects to whom PPD screening was offered varied greatly among participating centres, ranging 58.9–100%. Twenty out of 28 centres offered PPD screening to >95% of enrolled subjects. The only characteristics of centres offering PPD was the number of reported AIDS cases during the enrolment period (table 2). The proportion of subjects completing PPD screening also varied among centres,
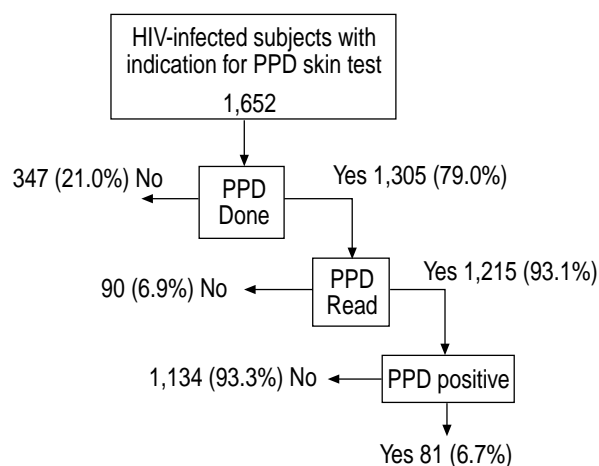

Fig. 1.–Outcomes for 1,652 human immunodeficiency virus (HIV)-infected subjects eligible for purified protein derivative (PPD) skin testing.

Table 2. – Distribution of participating centres by proportion of subjects to whom purified protein derivative (PPD) screening was offered and who completed PPD screening

Characteristics of centres	PPD screening offer			PPD screening completion		
	<95%	>95%	p-value	<95%	≥95%	p-value
Centres offering PPD screening n	8	20		22	6	
Number of AIDS cases reported during the enrolment period						
≤100	1 (7.1)	13 (92.9)		11 (78.6)	3 (21.4)	
>100	7 (50.0)	7 (50.0)	0.03	11 (78.6)	3 (21.4)	NS
Geographical location in Italy						
North	5 (33.3)	10 (66.7)		11 (73.3)	4 (26.7)	
Central	1 (14.3)	6 (85.7)		7 (100.0)	0 (0.0)	
South	2 (33.3)	4 (66.7)	NS	4 (66.7)	2 (33.3)	NS
Hospital						
Non-teaching	6 (30.0)	14 (25.0)		15 (75.0)	5 (25.0)	
Teaching	2 (70.0)	6 (75.0)	NS	7 (87.5)	1 (12.5)	NS

Data are presented as n (%) unless otherwise stated. AIDS: acquired immune deficiency syndrome; NS: nonsignificant.

ranging 50.0–100%, with a median value of 88%. No associations were found between the types of centres and proportion of PPD screening completion (table 2). To identify patient characteristics associated with effective PPD testing, baseline demographic and clinical variables of the 1,630 potential candidates for PPD were entered into a logistic regression model. In this analysis, which accounted also for variations between centres, having AIDS and currently undergoing antiretroviral therapy were the variables independently associated with PPD offering (table 3). A similar analysis was also performed to identify patient characteristics associated with PPD test completion. This analysis included the 1,445 subjects with an indication for PPD to whom the test was offered. Concomitant antiretroviral treatment and higher educational levels were associated independently with acceptance and completion of PPD screening.

In both of these logistic regression models, differences among centres were statistically significant ($p<0.001$) (table 3).

Screening for tuberculosis and contraindications to isoniazid

The progression of the subjects who were candidates for IPT through each step of the procedure is summarized in figure 2. Overall, 103 subjects were identified as candidates for IPT (6.0% of 1,705 subjects): 81 had positive PPD at baseline, 13 had a history of positive tuberculin skin test, and nine were in close contacts with an infectious tuberculosis patient. Of these 103 subjects, 10 (9.7%) did not undergo screening to exclude active tuberculosis and other contraindications to IPT. Of the 93 subjects

Table 3. – Logistic regression analysis of predictors of purified protein derivative (PPD) screening offer and completion among human immunodeficiency virus (HIV)-infected patients*

Characteristics	PPD screening offer[#]					PPD screening completion[¶]				
	Subjects offered PPD	Subjects not offered PPD	OR	95% CI	p-value	Subjects completing PPD	Subjects noncompleting PPD	OR	95% CI	p-value
Subjects n	1445	185				1209	236			
Years of education										
<6	319 (22.1)	55 (29.7)	1.00			256 (21.2)	63 (26.7)	1.00		
6–8	682 (47.2)	92 (49.8)	1.68	0.99–2.84	NS	564 (48.6)	118 (50.0)	1.67	1.10–2.51	0.01
>8	444 (30.7)	38 (20.5)	1.55	0.86–2.78	NS	389 (32.2)	55 (23.3)	2.65	1.65–4.25	<0.001
AIDS diagnosis										
No	1315 (91.0)	160 (86.5)	1.00			1098 (90.8)	217 (91.9)	1.00		
Yes	130 (9.0)	25 (13.5)	0.30	0.16–0.58	<0.001	111 (9.2)	19 (8.1)	1.36	0.75–2.46	NS
Antiretroviral therapy										
No	1015 (70.2)	132 (71.4)	1.00			835 (69.1)	180 (76.3)	1.00		
Yes	430 (29.8)	53 (28.6)	1.59	1.03–2.45	0.04	374 (30.9)	56 (23.7)	1.49	1.01–2.18	0.04

Data are presented as n (%) unless otherwise stated; OR: odds ratio; CI: confidence interval; NS: nonsignificant; AIDS: acquired immune deficiency syndrome; *: Sex, age, origin, HIV transmission category, occupation, CD4+ cell count, time since first HIV-positive test, and clinical centres are included in the models; [#]: includes 1,630 patients for whom PPD screening was indicated; [¶]: includes 1,445 patients to whom PPD screening was offered.
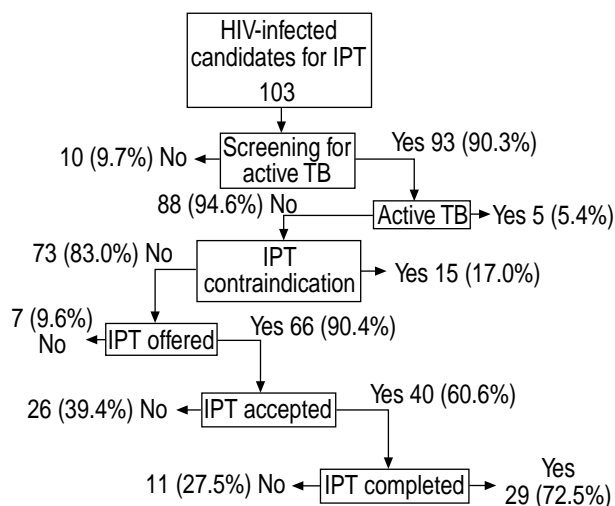
Fig. 2. – Screening for contraindications to isoniazid preventive therapy (IPT), initiation of IPT and completion of IPT among 103 human immunodeficiency virus (HIV)-infected candidates for IPT. Candidates for IPT included 81 purified protein derivative (PPD)-positive subjects, 13 subjects with a documented history of PPD positivity, and nine PPD-negative close contacts with an infectious tuberculosis (TB) patient.

screened, five had active tuberculosis and 15 had contraindications (three had severe chronic liver disease, 10 had elevated AST serum levels, and two females were pregnant). Of the 73 candidates (83.0%) with no contraindications for IPT, two were not offered IPT because of chronic alcoholism, and five because of infection with hepatitis B or hepatitis C virus. Thus, IPT was offered to 66 patients, 40 (60.6%) of whom agreed to begin therapy.

Follow-up and tuberculosis incidence

Eleven subjects (27.5% of the 40 subjects starting IPT) discontinued IPT before the sixth month, four following adverse reactions (neuropathy in two cases, and increased AST serum levels in two) and seven by their own decision. IPT was eventually completed by 29 individuals: 1.7% of the 1,705 HIV-infected subjects initially considered for this study, and 72.5% of those starting IPT. Based on self-report, 10 subjects (34.5%) were considered to have been 100% compliant with the prescribed preventive regimen.

Among the 1,419 subjects with a follow-up period >4 weeks, tuberculosis was diagnosed in 10 patients (0.7%) over 2,522 person-yrs of observation, giving an overall incidence rate of 0.4 (95% CI 0.19–0.73) per 100 person-yrs. The incidence of tuberculosis among IPT candidates who either did not start or discontinued preventive therapy was 6.1 per 100 person-yrs (95% CI 1.97–14.15), while it was 0.2 per 100 person-yrs (95% CI 0.07–0.49) among non-IPT candidates. No cases of tuberculosis were observed among the 29 subjects completing IPT over 37.3 person-yrs of observation after IPT (95% CI of incidence rate, upper limit: 6.26 per 100 person-yrs).

Discussion

The present study highlights a number of pitfalls complicating the implementation of IPT guidelines for dually infected persons. More than a quarter of the subjects included in this study in whom tuberculin screening was indicated, failed to complete it. Physicians were more likely to offer PPD screening to patients taking antiretroviral treatment, and to patients in the less advanced stages of HIV infection upon enrolment. About 15% of candidates for IPT had contraindications to isoniazid, and ~10% of those without contraindications were not offered IPT by their supervising physicians. Furthermore, 55% of candidates who were offered IPT, either refused or decided to discontinue prior to completion. Finally, the incidence of tuberculosis among IPT candidates who either did not begin or did not complete preventive therapy was very high, while no cases were detected among those completing IPT.

Previous studies of the implementation of IPT programmes in high risk populations also reported a high proportion of failure to complete tuberculin screening [18–23]. In particular, a retrospective study conducted in a population of HIV-infected patients in New York City, NY, USA, showed that physicians failed to submit 40% of the potential candidates to tuberculin screening [24]. However, this study did not distinguish between subjects to whom the PPD test was not offered and those who refused the test or did not return for reading. The present study found that physician failure to offer a PPD skin test accounts, on average, for 40% of the total number of subjects missing this procedure, and this proportion varied widely among centres. It has been recently suggested that field experience in the care of HIV-infected patients may be the best predictor of physician compliance with a recommended tuberculin-skin test procedure [25]. Conversely, the authors observed a lower proportion offered the PPD skin test in those centres reporting higher number of AIDS cases, whilst routine tests such as CD4+ cell count were usually performed in the vast majority of HIV-infected individuals. A possible explanation for this apparent difference could be that, among physicians working in centres specialized in HIV care, those with a higher patient load pay less attention to other important recommendations such as the PPD skin test.

PPD screening was more likely to be offered to patients receiving antiretroviral treatment, and to those in the less advanced stages of HIV infection. These findings may reflect physicians' attitudes to offering the PPD test to HIV-infected persons attending centres more frequently, with deliberate avoidance of skin testing in the advanced stages of HIV infection, when the test is likely to be negative due to a high degree of immunocompromise [26].

The very high proportion of contraindications to isoniazid, mainly due to chronic hepatitis, observed in the present study is not unexpected in a population of HIV-infected persons largely composed of intravenous drug users. The high prevalence of co-infection with hepatitis B or hepatitis C viruses frequently leads to chronic hepatitis and cirrhosis [27, 28]. Moreover,

some candidates were excluded from IPT although they did not have established contraindications to isoniazid. This was largely justified by serological evidence of hepatitis B or hepatitis C virus positivity even without evidence of liver damage. This finding may reflect overestimation of the risk of fatal isoniazid-related hepatitis by physicians, although this risk is extremely low in closely monitored individuals with no contraindications [29].

The reluctance of HIV-infected subjects to complete PPD screening and preventive therapy represents a further factor hampering the full implementation of guidelines. A similar problem was observed in an inner-city population IPT programme carried out in the mid-1960s [18]. In the present study, the determinants of noncompletion of PPD skin testing were a low level of education and no concomitant antiretroviral treatment. These results may reflect attitudes of HIV-infected patients receiving care in clinical centres: high educational level and acceptance of antiretroviral treatment result in better understanding and a more serious attitude toward receiving care [30, 31]. Moreover, the significant variation among centres in the proportion of noncompletion of PPD screening observed in the present study suggests that the quality of counselling by health care providers may also influence acceptance of this procedure [32].

Finally, the ability of this IPT programme to identify HIV-infected persons with latent tuberculosis infection is further impaired by the length of time elapsing between the first HIV-positive test and the PPD procedure, which results in a greater number of false-negative tuberculin tests due to HIV-related immunosuppression [26].

The main consequence of the difficulty in the implementation of IPT guidelines to prevent tuberculosis among HIV-infected persons is obviously a high proportion of patients who do not take advantage of this well established tool. The observed high incidence of tuberculosis among IPT candidates noncompliant with IPT and, conversely, the absence of active tuberculosis among those who completed IPT, confirm its crucial role in decreasing the risk of tuberculosis among HIV-infected persons [6–10].

The main limitations of the present study need to be mentioned. Firstly, the study was not carried out on a random sample of Italian clinical centres caring for HIV-infected patients. Rather, it was done in those centres which belong to an established operational and epidemiological research network. However, centres, participating in this study accounted for ∼40% of the total number of AIDS cases reported in Italy during the study period. Secondly, a high proportion of subjects in the present study were intravenous drug users, as is the case for most HIV-infected persons in Italy. This may limit the generalizability of the presented findings to other industrialized countries. In particular, in populations with a lower proportion of intravenous drug users, a lower frequency of contraindications to IPT due to co-infection with hepatitis viruses would be expected. However, drug use was not a determinant of poor adherence to skin testing. Thirdly, for the purpose of the present study only PPD tests performed within the first 2 months of the first clinic visit were considered, and this may have led to underestimation of the true completion rate of screening. Nevertheless, follow-up data showed no evidence of initiation of IPT in patients other than those screened within the first 2 months after enrolment. Finally, physicians working in participating centres were not unaware that a study on implementation of IPT guidelines was being conducted, and this may have influenced their attitude toward the screening and treatment procedures.

The results of the present study clearly indicate the need for interventions aimed to improve the implementation of national guidelines for isoniazid preventive therapy among human immunodeficiency virus-infected persons. Firstly, educational and training programmes for healthcare providers, even for those experienced in human immunodeficiency virus care, should become a priority. These programmes should heighten awareness of the efficacy of isoniazid preventive therapy in dually-infected persons, emphasize the importance of early purified protein derivative screening, and properly address physicians' concerns for fatal isoniazid-related hepatitis. Secondly, interventions targeted to improve tuberculosis education among human immunodeficiency virus-infected persons are needed, as also suggested by previous studies [24]. Finally, to maximize adherence to isoniazid preventive therapy among high-risk human immunodeficiency virus-infected persons, new approaches are necessary. The recently published American guidelines recommending short-course regimens based on rifampicin and pyrazinamide are probably an effective means for improving patient adherence [5].

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