

# Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection

Enrico Girardi<sup>a</sup>, Giorgio Antonucci<sup>a</sup>, Paola Vanacore<sup>a</sup>,  
Marco Libanore<sup>b</sup>, Isabella Errante<sup>c</sup>, Alberto Matteelli<sup>d</sup>,  
Giuseppe Ippolito<sup>a</sup> and the Gruppo Italiano di Studio  
Tubercolosi e AIDS (GISTA)\*

**Objective:** To assess the association between use of different antiretroviral regimens and incidence of tuberculosis among HIV-infected individuals.

**Design:** Observational, multicenter, prospective cohort study.

**Setting and patients:** Twenty-eight infectious diseases hospital units in Italy. A total of 2160 HIV-infected persons were considered for enrolment in a study on the implementation of tuberculosis preventive therapy between 1 May 1995 and 30 April 1996. The 1360 subjects who completed tuberculin screening at base-line were included in this analysis. Information on the use of antiretroviral therapies over time was collected. The median duration of follow-up was 104 weeks and 997 subjects (73.3%) completed the study.

**Main outcome measure:** Incidence of active tuberculosis according to different types of antiretroviral therapy.

**Results:** Eighteen cases of tuberculosis were observed with an overall incidence rate of 0.79 per 100 person-years of observation [95% confidence interval (CI), 0.51–1.31]. Tuberculin positivity and low CD4+ lymphocyte count were the only base-line variables independently associated with the risk of tuberculosis. During follow-up, 637 patients took double combination antiretroviral therapy and 387 took triple combination therapy. After adjusting for base-line characteristics of enrolled individuals, the relative hazard of tuberculosis was 0.16 (95% CI, 0.03–0.74) for double combination therapy and 0.08 (95% CI, 0.01–0.88) for triple combination therapy compared with no therapy or monotherapy.

**Conclusions:** Combination antiretroviral therapy significantly reduced the risk of tuberculosis in HIV-infected persons. In industrialized countries, the widespread use of this treatment may determine a decrease in the incidence of HIV-associated tuberculosis, possibly contributing to a reduction in the overall incidence of tuberculosis.

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From the <sup>a</sup> Centro di Riferimento AIDS - Servizio di Epidemiologia delle Malattie Infettive, IRCCS L. Spallanzani, Rome, the <sup>b</sup>Divisione di Malattie Infettive, Arcispedale S. Anna, Ferrara, the <sup>c</sup>Divisione di Malattie Infettive, Ospedale Niguarda, Milan and the <sup>d</sup>Clinica di Malattie Infettive e Tropicali, Spedali Civili, Brescia, Italy. \*See Appendix.

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Correspondence to Dr. Enrico Girardi, Centro di Riferimento AIDS- Servizio di Epidemiologia delle Malattie Infettive, IRCCS L. Spallanzani, Via Portuense, 292 - 00149 Rome, Italy.

Tel: +39 065594223; fax: +39 065594224; e-mail: craids@tiscalinet.it

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## Introduction

Tuberculosis is a frequent manifestation of immunosuppression due to infection with the human immunodeficiency virus (HIV), and the HIV epidemic has substantially contributed to the resurgence of tuberculosis both in developing and industrialised countries [1].

Parallel to the increasing use of double and triple antiretroviral combination therapy, a substantial decrease in the incidence of HIV-associated illnesses has been observed in several industrialized countries. In particular, a striking reduction of the risk of opportunistic infections typically occurring in advanced stages of immunosuppression, such as *Pneumocystis carinii* pneumonia, *Mycobacterium avium* complex infection, and cytomegalovirus retinitis [2], has been reported in observational studies among HIV-infected patients receiving combination antiretroviral therapy. However, only a few data are available regarding the impact of the combination antiretroviral therapy on the risk of HIV-associated tuberculosis, a disease that may occur over a wide range of immunosuppression levels. In a cohort of individuals with CD4+ lymphocyte count  $< 200 \times 10^6/l$ , a stable incidence of tuberculosis during the period 1992–1996 has been observed, in the context of a decreased incidence of other opportunistic infections and of a broader use of combination therapies since 1994 [3]. Conversely, in the United States data from a sentinel surveillance project show, among HIV-infected persons, a more than two-fold decrease in incidence of tuberculosis from 1992 to 1997, primarily related to advances in HIV-related therapy [4]. Because of the nature of their design these studies did not measure the direct effect of combination therapy on the incidence of tuberculosis in HIV-infected persons.

Quantification of the impact of new antiretroviral regimens on the risk of developing tuberculosis may help in defining the trends of the epidemic of the HIV-associated tuberculosis in countries where these treatments are being widely used.

In 1995 we started an observational study to assess the degree of implementation of tuberculosis preventive therapy national guidelines for persons with HIV-infection [5]. Individuals included in this observational study who received a tuberculin skin test and who were evaluated for potential risk factors for tuberculosis were followed up until 1998. For these individuals, information on the use of antiretroviral therapies over time was collected. This article presents an analysis of

the relationship between different antiretroviral regimens and the incidence of tuberculosis.

## Material and methods

### Study population

A multicentre, prospective, observational study was conducted in 28 infectious diseases hospital units in Italy to assess the implementation of National Guidelines [6] regarding tuberculin screening and tuberculosis preventive therapy for HIV-infected persons. A total of 2160 individuals (inpatients and outpatients) aged 18 years or older, with confirmed HIV infection, and seen for the first time in participating units between 1 May 1995 and 30 April 1996 were considered for inclusion in this study.

In the present analysis, we did not include 524 individuals who did not complete the base-line tuberculin screening, 74 individuals with a previous episode of active tuberculosis (within the past 24 months) or found to have active tuberculosis at base-line examination, four who had completed a full course of isoniazid preventive therapy (at least 6 months), and eight individuals taking at least two anti-tuberculosis drugs at base-line. To further exclude prevalent cases of tuberculosis, three individuals who developed tuberculosis within 4 weeks from enrolment were excluded from the present analysis. One hundred eighty-seven individuals who died or were lost to follow-up within the same 4-week period were also excluded. The remaining 1360 HIV-infected individuals formed the study population.

At enrolment, all individuals were tested for tuberculin reactivity with 5 tuberculin units of purified protein derivative (PPD), using the Mantoux procedure. Any palpable induration at 48–72 h was measured and recorded.

At base-line, the following data were collected: age, sex, country of birth, place of residence, HIV-transmission category, prior history of active tuberculosis, recent ( $< 2$  years) contact with persons with active tuberculosis, results of tuberculin skin test, CD4+ lymphocyte count, HIV-clinical status, prior tuberculosis preventive therapy and current antiretroviral therapy regimen. Results of chest radiographs and microbiological examinations for mycobacteria were also collected for individuals with any of the following signs or symptoms suspicious of active tuberculosis: persistent

cough ( $\geq 2$  weeks), haemoptysis, fever, night sweats, significant weight loss ( $\geq 10\%$  of body weight) and for any subject in which these examinations were performed if attending physicians considered them necessary to exclude active disease on the basis of other signs or symptoms.

Follow-up data were collected approximately at 6-month intervals and included medical history, physical examination, CD4+ lymphocyte count, use of tuberculosis preventive therapy and antiretroviral therapy. Detailed clinical and microbiological data were also collected for individuals who, at any time during the study period, presented with signs or symptoms suspicious of active tuberculosis. Clinical and laboratory data of all individuals who were lost to follow-up or died during the study period were abstracted from clinical charts to obtain the latest documented information regarding CD4+ lymphocyte count, diagnosis of tuberculosis and use of antiretrovirals, as well as the date and the cause of death.

All data were collected onto standardized forms. All forms were checked for logical errors by scientific staff at the co-ordinating centre. Each of the participating centres sought ethical clearance according to local ethical regulations.

### Definitions and outcome variable

Clinical status of HIV infection was classified according to the 1993 Centers for Diseases Control and Prevention (CDC) classification system [7]. An induration in response to PPD of at least 5 mm was considered a positive response [8]. Individuals were classified according to the number of antiretrovirals used into four categories: none, one drug, two drugs and three or more drugs.

The outcome of interest in the analysis was a new diagnosis of active tuberculosis. A case of tuberculosis was defined as the presence of clinical signs and symptoms suggestive of tuberculosis, confirmed by the isolation of *Mycobacterium tuberculosis* in culture or by clinical and radiological improvement in response to specific antituberculosis therapy.

### Statistical analysis

The period of observation for each individual 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; initiation of a full course of isoniazid preventive therapy (6 months); death; the last documented visit before unavailability for follow-up; or the last follow-up visit during the period between 1 January 1998 and 30 June 1998 for the individuals who completed the study.

Incidence rates of tuberculosis were calculated per 100 person-years (p-y) of observation. Confidence intervals (CI) for the incidence rates were computed using the Poisson distribution.

The  $\chi^2$  test was used to compare categorical variables. Cox regression was used to calculate hazard ratios for tuberculosis by baseline characteristics and by antiretroviral therapy that was included in the model as a time-dependent covariate considered as in an intention-to-treat approach, i.e. each individual was considered to be on a given therapy from the date of starting that therapy until the end of period of observation or until the therapy was changed to a more complex scheme (for example from single-drug to two-drug therapy). The potential for violation of the proportional-hazards assumption was assessed (i) by comparing the survival curve of each level of a variable with the survival curve of the referent group for that variable, and (ii) by fitting models containing an interaction term between the variable of interest and a log-time variable.

Data analysis was performed with Epi-info version 5.1 (USD Inc., Stone Mountain, Georgia, USA) and Egret software (Statistics and Epidemiology Research, Seattle, Washington, USA).

## Results

Main demographic and base-line characteristics of the 1360 individuals included in this analysis are reported in Table 1. At entry into the study, the majority of individuals (837, 61.7%) had asymptomatic HIV infection (class A), 298 (21.9%) individuals had symptomatic HIV infection without an AIDS-defining condition (class B) and 223 individuals (16.4%) had clinically defined AIDS (class C). The CD4+ lymphocyte count was lower than  $200 \times 10^6/l$  in 38.8% of individuals, between 200 and  $499 \times 10^6/l$  in 38.4%, and greater than  $499 \times 10^6/l$  in 22.8%. Based on skin tests results, 95 individuals (7.0%) were tuberculin positive. The mean age was 34.3 years (range, 18–74 years). Almost all (94.0%) were born in Italy. Compared with individuals considered for enrolment in the study on preventive therapy but not included in the present analysis, those included in the analysis were less likely to be foreign born (6.0 versus 9.8%;  $P < 0.01$ ), to be intravenous drug users (50.2 versus 55.3%;  $P = 0.02$ ), and to have clinically defined AIDS (16.4 versus 25.4%;  $P < 0.01$ ).

The median duration of follow-up was 104.3 weeks (range, 4–154.6 weeks). Of the 1360 individuals enrolled, 864 (63.5%) completed the study, 133 (9.8%) died before the end of the follow-up period, and 363 (26.7%) were lost to follow-up, a median of 44.4 weeks

**Table 1.** Baseline characteristics and incidence of tuberculosis among 1360 HIV-infected individuals.

	No. with feature n (%)	No. with tuberculosis	Incidence per 100 person-years	Adjusted hazard ratio <sup>a</sup> (95% CI)
Age (years)				
18–29	383 (28.2)	5	0.77	1.00
30–34	466 (34.3)	5	0.62	0.49 (0.14–1.73)
>34	511 (37.6)	8	0.96	0.64 (0.19–2.14)
Sex				
Female	368 (27.1)	4	0.63	1.00
Male	992 (72.9)	14	0.85	1.56 (0.45–5.33)
HIV transmission category				
Injecting drug users	683 (50.2)	10	0.93	1.00
Homosexual/bisexual	381 (28.0)	5	0.73	0.51 (0.09–2.89)
Heterosexual contacts	215 (15.8)	2	0.53	0.90 (0.27–2.97)
Other/undefined	81 (6.0)	1	0.68	0.59 (0.07–4.84)
Place of birth				
Italy	1279 (94.0)	15	0.69	1.00
Other	81 (6.0)	3	2.64	3.41 (0.78–14.98)
Place of residence in Italy				
North	894 (65.7)	15	0.98	1.00
Centre	271 (19.9)	2	0.44	0.54 (0.12–2.42)
South	195 (14.3)	1	0.33	0.29 (0.04–2.30)
CDC clinical class				
A	839 (61.7)	7	0.46	1.00
B	294 (21.9)	4	0.86	0.94 (0.24–3.63)
C	223 (16.4)	7	2.28	2.20 (0.62–7.68)
CD4+ lymphocytes × 10 <sup>6</sup> /l				
≥ 500	311 (22.8)	1	0.18	1.00
200–499	522 (38.4)	3	0.33	2.14 (0.21–21.19)
0–199	527 (38.8)	14	1.72	14.02 (1.51–129.4)
Tuberculin skin test status				
Negative	1265 (93.0)	13	0.59	1.00
Positive	95 (7.0)	5	4.93	17.24 (5.12–58.2)

<sup>a</sup>Calculated in a Cox proportional hazards model. CI, confidence interval.

after enrolment (range, 4–136.6 weeks). Comparing demographic and base-line characteristics of individuals lost to follow-up with other individuals, those lost to follow-up were more likely to be intravenous drug users (63.6 versus 45.3%;  $P < 0.001$ ), have asymptomatic HIV-infection (67.5 versus 59.6%;  $P < 0.001$ ), have higher baseline CD4+ lymphocyte count (proportion of individuals with count greater than  $499 \times 10^6/l$ : 28.7 versus 20.6%;  $P < 0.001$ ).

During the study period 29 individuals completed a 6-month or longer course of isoniazid preventive therapy, 26 of whom were tuberculin positive at base-line. Of the remaining 69 tuberculin-positive individuals, 17 started preventive therapy but discontinued it before the sixth month, 25 did not consent to begin therapy, 22 were not offered preventive therapy because of contraindications to or increased risk of toxicity from isoniazid (mainly chronic liver diseases), and five had not indications for preventive therapy because of previous treatment of active tuberculosis completed more than 2 years before enrolment.

The total period of follow-up of individuals in the

study was 2271.9 p-y. Tuberculosis was diagnosed in 18 individuals and was pulmonary in 11 individuals, extrapulmonary in three, and concomitant pulmonary and extrapulmonary in four. The overall incidence rate was 0.79 per 100 p-y (95% CI, 0.51–1.31).

In multivariate analysis (Table 1) tuberculin positivity and a low CD4+ lymphocyte count, were the only base-line characteristics independently associated with the risk of developing tuberculosis.

At enrolment the majority of individuals (888, 65.3%) were not receiving antiretroviral therapy, 230 (16.9%) were on single-drug therapy, 226 (16.6%) on two-drug therapy and 16 (1.2%) on three-drug therapy. During follow-up an increasing number of patients started antiretroviral therapies or switched to a more complex therapeutic regimen. The overall number of patients who were at any time during follow-up on a different antiretroviral therapeutic regimen are shown in Table 2. Of the 387 patients who received a combination therapy with three or more drugs, 92% took at least one protease inhibitor.

**Table 2.** Adjusted hazard ratio of tuberculosis by antiretroviral therapy.

Antiretroviral therapy	No. individuals <sup>a</sup>	No. with tuberculosis	Adjusted hazard ratio (95% CI) <sup>b</sup>	
			Model 1 <sup>c</sup>	Model 2 <sup>d</sup>
No therapy	483	9	1.00	} 1.00
One drug	320	7	1.18 (0.38–3.63)	
Two drugs	637	1	} 0.14 (0.03–0.65)	0.16 (0.03–0.74)
Three drugs	387	1		0.08 (0.01–0.88)

<sup>a</sup>The number of patients who were, at any time during follow-up, not on therapy or on a different antiretroviral therapeutic regimen, is reported. <sup>b</sup>Calculated in a Cox proportional hazards model including therapy as a time-dependent covariate, and baseline variables listed in Table 1. <sup>c</sup>Patients on two- or three-drug combination therapy were considered combined in this model. <sup>d</sup>Patients not on therapy or on single drug therapy were considered combined in this model. CI, confidence interval.

As reported in Table 2, the vast majority of cases of tuberculosis occurred in patients who were receiving no therapy or single-drug therapy and only one case occurred in patients receiving two- or three-drug therapy, respectively. The two individuals taking dual or triple antiretroviral therapy developed active tuberculosis 4 and 5 months after the initiation of therapy, respectively.

To estimate the relative hazard of tuberculosis by antiretroviral therapy regimen controlling for baseline characteristics, we fitted a Cox model including tuberculin skin test status, CD4+ lymphocyte count, sex, HIV transmission category, place of birth, place of residence in Italy, clinical status and antiretroviral therapy as time-dependent covariates. We first calculated the relative hazard of tuberculosis for patients receiving single-drug therapy and for those receiving any combination therapy compared with patients not receiving therapy. In this analysis, single-drug therapy was not associated with a significantly different risk of tuberculosis compared with no therapy, whereas combination therapy was associated with a significantly decreased risk of tuberculosis (Table 2). We then fitted another Cox model in which patients not on therapy or on single-drug therapy were considered combined. This latter analysis showed that dual and triple combination therapy were both independently associated with a significantly lower risk of tuberculosis (Table 2).

## Discussion

The data analysed in the present study were collected in the context of routine clinical practice during the time period when antiretroviral combination therapy was just being introduced in our country for the treatment of HIV infection and thus it was possible to

monitor the transfer from monotherapy to multi-drug therapy and evaluate the related magnitude of the effect on tuberculosis incidence. In fact, in Italy dual combination therapy was introduced in 1995 and triple combination with protease inhibitors during the summer of 1996 with an experimental programme followed by an expanded programme in 1997.

Our results show that the risk of developing tuberculosis is significantly decreased among HIV-infected persons receiving combination antiretroviral therapy. The incidence of tuberculosis, after adjusting for CD4+ lymphocyte count, tuberculin skin test status and other baseline characteristics, was reduced by approximately six times for patients receiving double combination therapy and ten times for those receiving triple combination therapy compared with individuals receiving no treatment or a single antiretroviral drug.

The different effects of dual and triple combination therapy most likely reflect their different antiretroviral potency and clinical efficacy. In fact, results of clinical trials show that double combination therapy with nucleoside analogues is effective in reducing mortality and morbidity among HIV-infected patients [9,10], and the addition of protease inhibitors produces a further striking benefit [11].

Independently from the effect of antiretroviral therapy, tuberculin positivity and a low level of CD4+ lymphocyte count were associated in our cohort with an increased risk of tuberculosis, consistently with the results of previous cohort studies [12–14].

Several limitations should be kept in mind when interpreting our results. Despite our large sample size and a median period of observation of 2 years, only 18 cases of tuberculosis were observed. This made it impossible to provide accurate estimates of the reduc-

tion of risk of tuberculosis associated with combination therapy, as suggested by the wide confidence intervals of the relative hazard in multivariate analysis. Moreover, patients were followed up while on combination therapy for a median time period of 1 year. Therefore, we could not estimate the long-term effect of antiretroviral combination regimens on tuberculosis risk. Most of the individuals in our cohort were injecting drug users, similar to the majority of AIDS cases reported in Italy in 1995 and 1996. This fact may limit the extent to which our results can be generalized to all HIV-infected individuals. The subjects lost to follow-up had a significantly higher CD4+ lymphocyte count than those who completed the study and this could have resulted in an overestimation of the risk of tuberculosis in our cohort. Some individuals in our cohort took an incomplete course of isoniazid preventive therapy, which may provide some degree of protection against tuberculosis [15]. The entire period of follow-up of these individuals was considered in the analysis, and this could have biased the estimates of the risk of tuberculosis. However, when in multivariate analysis these individuals were censored at the date of initiation of preventive therapy, similarly to those who took isoniazid for at least 6 months, hazard ratios of tuberculosis for double combination therapy and for triple-combination therapy were virtually unchanged. Finally, since the study was conducted in 28 clinical centres, variability in diagnostic procedures might have affected our findings. However, all participating centres agreed to follow national guidelines on tuberculosis screening and preventive therapy.

Our data suggest that the use of combination antiretroviral therapy could result in a decrease in the incidence of HIV-associated tuberculosis, and could possibly contribute to a reduction in overall incidence of tuberculosis, in areas where these treatments are being increasingly used [4,16]. In the United States, where approximately 30% of the 28 000 excess cases of tuberculosis reported in 1985–1990 has been attributed to HIV infection [17], a decrease in incidence of tuberculosis was reported in 1992–1997 [18]. This decrease was particularly marked among those aged 25–44 years and in areas with a high incidence of AIDS, suggesting a possible reduction in HIV-associated tuberculosis. Although this reduction has been primarily attributed to stronger tuberculosis control programmes, it is possible that a wider use of combination antiretroviral therapy has also contributed to this phenomenon as suggested by sentinel surveillance data [4]. Similarly, a decrease in AIDS-associated tuberculosis cases has been reported since 1996 in most western European countries [19]. Nonetheless, a substantial proportion of HIV-infected patients may remain at very high risk of tuberculosis in spite of antiretroviral therapy. Cases of tuberculosis occurred in our cohort among patients receiving combination antiretroviral

therapy; they were observed in patients who did not show an increase in number of circulating CD4+ lymphocytes following antiretroviral therapy. In current practice, up to 40% of patients may not show an immunological response even when treated with protease inhibitor-containing therapeutic regimens [20] and therefore remain at high risk of developing opportunistic infections [21]. Moreover, cases of tuberculosis were reported also in patients showing an immunological and/or virological response to therapy [22]. This observation probably reflects the fact that tuberculosis may present also in HIV-infected patients with minor levels of immunosuppression, as shown also in this study (Table 1).

Whatever the magnitude of the effect of combination antiretroviral treatment on the incidence of tuberculosis, aggressive public health programmes, including preventive therapy for tuberculin-positive individuals and monitoring of adherence to treatment [23], will most likely continue to play a critical role in the control of the HIV-associated tuberculosis epidemic.

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## Appendix

### Members of the Gruppo Italiano di Studio Tubercolosi e AIDS (GISTA) and participating institution

Gioacchino Angarano, MD (Bari, 'Policlinico'), Sergio Babudieri, MD (Sassari, 'SS. Annunziata'), Claudio Cancellieri, MD (Forlì, 'GB Morgagni'), Sergio Carbonara, MD (Bari, 'Policlinico'), Antonio Chirianni, MD (Napoli, 'Cotugno'), Antonella Cingolani, MD (Roma, 'Policlinico Gemelli'), Michele De Gennaro, MD (Lucca, 'Campo di Marte'), Saverio Giomi, MD (Grosseto, 'Civile'), Sergio Lo Caputo, MD (Firenze, 'S. Maria Antella'), Giuseppina Liuzzi, MD (Napoli, 'II Policlinico'), Elio Manzillo, MD (Napoli, 'Cotugno'), Gabriella Meneghin, MD (Torino, 'Amedeo di Savoia'), Gabriella Pagano, MD (Genova, 'S. Martino'), Maria Bruna Pasticci, MD (Perugia, 'Policlinico'), Gianpietro Pellizzer, MD (Vicenza, 'S. Bortolo'), Tiziana Quirino, MD (Milano 'Sacco'), Guido Raineri, MD (Cuneo, 'S. Croce'), Mario Raviglione, MD (Geneva, 'WHO'), Marco Rizzi, MD (Bergamo, 'Riuniti'), Rosario Russo, MD (Catania, 'Ascoli-Tomaselli'), Bernardino Salassa, MD (Torino, 'Amedeo di Savoia'), Domenico Santoro, MD (Como, 'S. Anna'), Eliana Savalli, MD (Pisa, 'Cisanello'), Pier Giorgio Scotton, MD (Treviso 'Ca' Foncello'), Fredy Suter, MD (Busto Arsizio, 'Civile'), Antonio Traverso, MD (Aosta, 'USL 1').