Short- and long-term mortality and causes of death in HIV/tuberculosis patients in Europe

Daria N. Podlekareva[1], Alexander M. Panteleev[2], Daniel Grint[3], Frank A. Post[4], Jose M. Miro[5], Mathias Bruyand[6], Hansjakob Furrer[7], Niels Obel[8], Enrico Girardi[9], Anna Vasilenko[10], Marcelo H. Losso[11], Alejandro Arenas-Pinto[12], Joan Caylá[13], Aza Rakhmanova[14], Indra Zeltina[15], Anne Marie Werlinrud[1], Jens D. Lundgren[1,8], Amanda Mocroft[3], Ole Kirk[1,8] and the HIV/TB study group[16]

Affiliations: [1]Copenhagen HIV Programme, University of Copenhagen, Copenhagen, and [8]Epidemiklinikken, Rigshospitalet, Copenhagen, Denmark. [2]TB Hospital #2, St Petersburg, and [14]St Petersburg AIDS Centre, St Petersburg, Russia. [3]University College London, London, [4]King's College London School of Medicine, London, and [12]Centre for Sexual Health and HIV Research, University College London, London, UK. [5]Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona, and [13]Servicio de Epidemiología, Agencia de Salud Pública de Barcelona, CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain. [6]University of Bordeaux, ISPED, Centre Inserm U897 – Epidemiologie–Biostatistique, Bordeaux, France. [7]Clinic for Infectious Diseases, Bern University Hospital and University of Bern, Bern, Switzerland. [9]Instituto Nazionale Malattie Infettive L. Spallanzani, Rome, Italy. [10]Minsk State Medical University, Dept of Infectious Diseases, Minsk, Belarus. [11]Hospital J.M. Ramos Mejia, Servicio de Immunocomprometidos, Buenos Aires, Argentina. [15]Infectology Centre of Latvia, Riga, Latvia. [16]A full list of the HIV/TB Study Group investigators can be found in the acknowledgements section.

Correspondence: D.N. Podlekareva, Copenhagen HIV Programme, Faculty of Health Sciences, University of Copenhagen, The Panum Institute/Building 21.1, Blegdamsvej 3B, 2200 Copenhagen N, Denmark. E-mail: dpo@cphiv.dk

ABSTRACT Mortality of HIV/tuberculosis (TB) patients in Eastern Europe is high. Little is known about their causes of death.

This study aimed to assess and compare mortality rates and cause of death in HIV/TB patients across Eastern Europe and Western Europe and Argentina (WEA) in an international cohort study. Mortality rates and causes of death were analysed by time from TB diagnosis (<3 months, 3–12 months or >12 months) in 1078 consecutive HIV/TB patients. Factors associated with TB-related death were examined in multivariate Poisson regression analysis.

347 patients died during 2625 person-years of follow-up. Mortality in Eastern Europe was three- to ninefold higher than in WEA. TB was the main cause of death in Eastern Europe in 80%, 66% and 61% of patients who died <3 months, 3–12 months or >12 months after TB diagnosis, compared to 50%, 0% and 15% in the same time periods in WEA ($p<0.0001$). In multivariate analysis, follow-up in WEA (incidence rate ratio (IRR) 0.12, 95% CI 0.04–0.35), standard TB-treatment (IRR 0.45, 95% CI 0.20–0.99) and antiretroviral therapy (IRR 0.32, 95% CI 0.14–0.77) were associated with reduced risk of TB-related death.

Persistently higher mortality rates were observed in HIV/TB patients in Eastern Europe, and TB was the dominant cause of death at any time during follow-up. This has important implications for HIV/TB programmes aiming to optimise the management of HIV/TB patients and limit TB-associated mortality in this region.

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Introduction

Tuberculosis (TB) is the most common opportunistic infection in HIV-positive people worldwide, often leading to death. High mortality has been reported among HIV-positive people treated for active TB (HIV/TB patients), particularly in patients with advanced disease [1, 2]. Combination antiretroviral therapy (cART) treatment is associated with a marked reduction of mortality in HIV/TB patients, although access and availability are far from equal around the world [3–6]. Deaths among HIV/TB patients may result from a number of causes, depending on the degree of immunosuppression and the availability of adequate TB treatment and cART. While TB may directly contribute to early mortality, other opportunistic and nonopportunistic infections and comorbidities may play an important role in those who receive appropriate TB treatment [1, 7–9]. Liver failure due to hepatic toxicity of anti-TB and anti-HIV drugs may also play a role; this is of particular concern in patients with pre-existing liver impairment due to hepatitis B virus (HBV)/hepatitis C virus (HCV) co-infection and/or alcoholism [10, 11].

The causes of death in HIV/TB patients treated for active TB have not yet been studied in detail. Previous studies have reported TB itself as the leading cause of death and other infections play a relatively rare role in death aetiology [7, 9, 12–14]. These studies, however, were conducted in (sub)tropical regions (Africa, Thailand and Brazil), were limited by their small sample size, were retrospective in nature and/or lacked standardised methodology for the evaluation of causes of death. Information on causes of death in HIV/TB patients in Europe, particularly in Eastern Europe, is missing. This is critical because the mortality rate of HIV/TB patients in this region is one of the world's highest [15, 16] and Eastern European countries are those most affected by the multidrug resistant (MDR)-TB epidemic [17–19]. We have reported a mortality rate of 30% within the first year of TB diagnosis in this region, which was up to fivefold higher than that in Western European countries and Argentina [16]. The aim of the current analyses was to define and compare short- and long-term mortality rates and causes of death in HIV/TB patients according to the region of follow-up (Eastern Europe *versus* other parts of Europe and Argentina).

Methods

The HIV/TB study and patient population

The HIV/TB study is a collaboration of HIV and TB clinicians from 11 European countries and Argentina. Details of the study have been published elsewhere [16].

Patients aged $\geqslant$16 years were included if they were HIV-infected and had started TB treatment between January 1, 2004 and December 31, 2006. Patients with confirmed TB (*Mycobacterium tuberculosis* on culture or PCR), probable TB (acid-fast bacilli on smear or granulomatous inflammation on biopsy specimens) and presumptive TB (TB treatment initiated and TB not subsequently ruled out) were included. Detailed data on TB disease and HIV infection, including demographic, clinical and laboratory parameters, outcomes and TB recurrences (defined as new TB diagnoses following completion of TB therapy), were collected retrospectively on standardised case report forms (www.cphiv.dk).

Assessment of causes of death

The Coding Causes of Death in HIV (CoDe) methodology was used for the collection and central adjudication of causes of death (fig. 1) [20]. Detailed information on the clinical conditions preceding death was collected on the CoDe case report form, in addition to the clinical information as described above. Where available, autopsy reports were used to inform the CoDe process. All CoDe case report forms were reviewed by two medical doctors (internal reviewers, D.N. Podlekareva and A. Vasilenko) at the

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Conflict of interest: Disclosures can be found alongside the online version of this article at www.erj.ersjournals.com

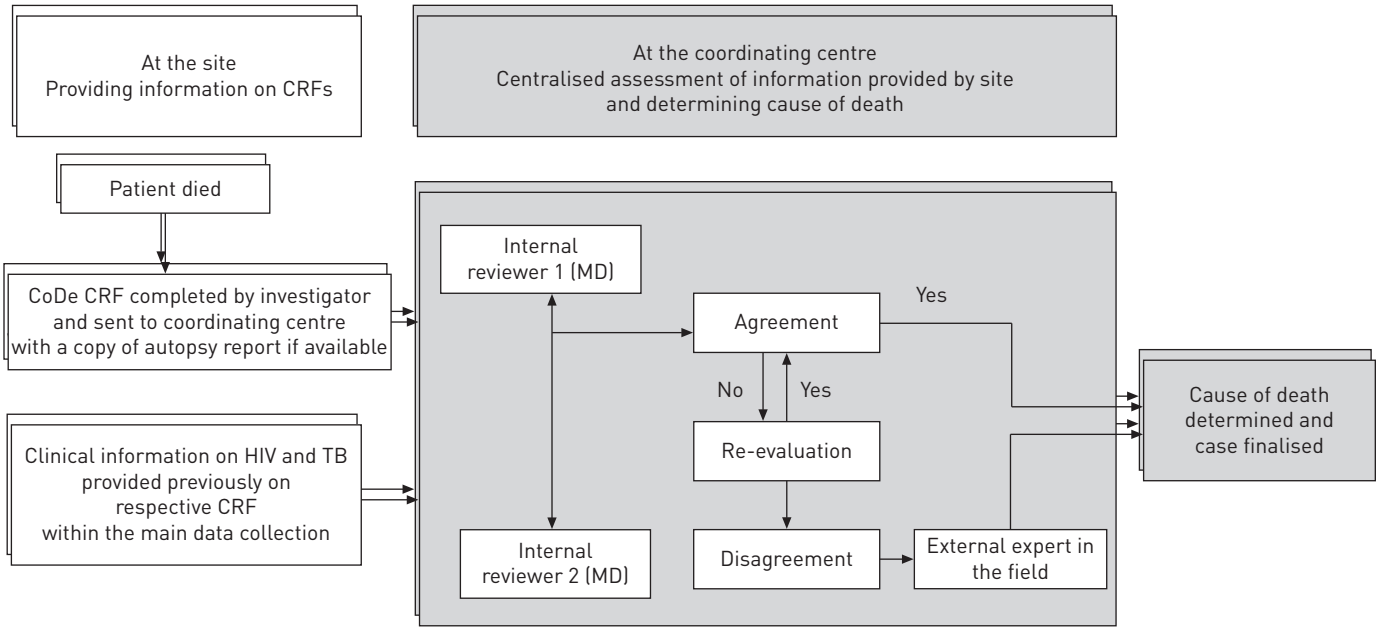

FIGURE 1 Determining cause of death in the HIV/tuberculosis (TB) study: the Coding Causes of Death in HIV (CoDe) methodology adapted from KOWALSKA *et al* [20]. The following sources were used for cause of death assessment: CoDe case report form (CRF), clinical information on TB and HIV and autopsy reports where available. Clinical case examples are provided in table 1. MD: medical doctor.

coordinating centre. Based on the information provided, the immediate and up to four contributing and underlying causes of death were assigned. Complex cases with several concomitant clinical conditions and a random sample of 10% of CoDe case report forms were sent to independent external reviewers (HIV/TB clinicians at participating clinics, F. Post, H. Furrer and J.M. Miro). Internal and external reviewers had to agree on the causes of death. In case of disagreement, the reviewers discussed the case and an adjudication process was used to reach consensus (fig. 1) [20].

The immediate cause of death was the main focus of the current analysis, defined as the disease/injury that directly led to death [21]. When assigning the immediate cause of death, terminal conditions describing the mechanism of death were avoided. For example, TB meningitis was assigned as the immediate cause of death if a patient died of cerebral oedema as a consequence of TB meningitis.

Statistical methods

Baseline was defined as the date of TB diagnosis, which was defined as the date at which TB treatment was initiated, or the first smear or culture positive sample was obtained, whichever occurred earlier [16]. Patients with known HIV infection or who were diagnosed up to 6 months after TB diagnosis were included in the present analysis. Follow-up continued until date of death or the last date when the patient was known to be alive or July 2010, whichever occurred first. The analysis was based on 1078 consecutive HIV/TB patients, stratified according to the region of follow-up: Eastern Europe (Belarus, Latvia, Romania, Russia and Ukraine) and Western Europe or Argentina (WEA) (Argentina, Denmark, France, Italy, Switzerland, Spain and the UK), and their characteristics at baseline and death were described. Argentina was analysed together with the above-mentioned European countries because of the sample size and similarity of HIV epidemiology or access to healthcare (availability of cART), particularly to South European countries.

Mortality rates were calculated per 100 person-years of follow-up (PYFU) in consecutive intervals from TB diagnosis: $<$3 months, 3–12 months and $>$12 months, to analyse death rates during intensive and continuation TB treatment phases, and during the post-treatment period. Deaths were categorised as TB-related or TB-unrelated, based on the identified immediate cause of death. Deaths classified as unknown were categorised as TB-unrelated, with sensitivity analyses excluding these deaths. Poisson regression models were used to assess factors associated with TB-related death. Models were adjusted for the following baseline variables, chosen *a priori*: age at TB diagnosis, sex, region of follow-up, history of injection drug use (IDU), HBV (hepatitis B surface antigen positive) and HCV (HCV antibody positive) status, TB drugs used for initial TB treatment (any rifamycin, isoniazid and pyrazinamide (RHZ)-based *versus* other), resistance to TB drugs (rifamycin resistance *versus* other), initiation of cART prior to or up to 1 month after TB diagnosis, and CD4 cell count and HIV RNA as time-updated variables.

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TABLE 1 Clinical case examples

Patient A	
Information on CoDe form	Patient died due to liver failure as a consequence of HCV infection
	Patient had clinical signs of liver failure in the 3 weeks prior to death
	CD4 cell count prior to death 48 cells·mm^{-3}
	HIV RNA no data
	Autopsy not performed
Additional clinical information	
TB	Pulmonary TB diagnosed 3 years earlier, bacteriologically confirmed, fully susceptible to anti-TB drugs
	Completed RHZE treatment, no TB recurrence reported
HIV	Known HIV positive for 13 years
	CD4 cell count at TB diagnosis 245 cells·mm^{-3}
	HIV RNA 500 000 copies·mL^{-1}
	No ART
CoDe review process	Immediate COD was coded as ''liver failure due to HCV infection''
Patient B	
Information on CoDe form	Patient died due to dissemination of TB with multiorgan failure
	Condition had deteriorated during the last 1.5 months due to irregular treatment
	Autopsy: macrofocal pulmonary TB with haematogenous dissemination; medium and small caverns with caseous necrosis in upper lung lobes bilateral, drained to bronchi; TB in kidneys, spleen, intra- and extrathoracic lymph nodes; tuberculous meningitis with brain oedema. Patient died due to brain oedema and multiorgan failure
Additional clinical information	
TB	Disseminated MDR-TB diagnosed 14 months earlier
	Anti-TB treatment RHZ combined with amikacin and ethionamide, but poor adherence to treatment and several episodes of treatment interruptions
HIV	Known HIV-positive for 8 years
	ART initiated after TB diagnosis, but interrupted after 6 months at patient's wish
	CD4 cell count at TB diagnosis 78 cells·mm^{-3} and at time of death 255 cells·mm^{-3}
	HIV RNA not measured
CoDe review process	Immediate COD was coded as ''disseminated TB with TB meningitis''
Patient C	
Information on CoDe form	Patient died after progressive pulmonary failure over a month
	No signs of TB progression
	Autopsy: signs of PCP
	No evidence for active TB process
Additional clinical information	
TB	Presumptive (without positive culture and thus no susceptibility tests available) pulmonary TB diagnosed 1.5 years earlier with involvement of intra- and extrathoracic lymph nodes
	Initial anti-TB treatment was RH with the addition of Z and amikacin 2 months later for a total treatment duration of 8 months
	No recurrence of TB reported
HIV	Known HIV positive for 8 years
	CD4 cell count 5 months prior to TB diagnosis 410 cells·mm^{-3}, at time of death 135 cells·mm^{-3}
	HIV RNA not measured
	Patient did not receive ART
	PCP was not diagnosed while patient was alive and PCP treatment/prophylaxis not prescribed
CoDe review process	Immediate COD was coded as ''non-TB AIDS defining condition, PCP''

CoDe: Coding Causes of Death in HIV; TB: tuberculosis; HCV: hepatitis C virus; R: rifamycin; H: isoniazid; Z: pyrazinamide; E: ethambutol; COD: cause of death; ART: antiretroviral therapy; MDR: multidrug resistant; PCP: *Pneumocystis jirovecii* pneumonia.

All analyses were performed using Statistical Analysis Software (SAS Institute, Cary, NC, USA) version 9.2.

Results

Patient characteristics and mortality rate

In total 585 patients from Eastern Europe and 493 from WEA were included in the study. Patient characteristics are shown in table 2. The median (interquartile range (IQR)) follow-up was 8.5 (5.7–37.1) months for patients in Eastern Europe and 38.9 (19.2–52.1) months for those in WEA ($p<0.0001$). Overall, 347 patients had died by July 2010: 284 (48.5%) in Eastern Europe and 63 (12.8%) in WEA ($p<0.0001$), with a median (IQR) interval between TB diagnosis and death among those who died of 8.7 (2.5–19.5) months in Eastern Europe and 5.1 (1.6–13.5) months in WEA ($p=0.11$). Recurrent TB was diagnosed in 99 patients: 81 in Eastern Europe (13.8%) and 18 (3.7%) in WEA ($p<0.0001$).

TABLE 2 Baseline characteristics of HIV/tuberculosis (TB) patients according to vital status following TB diagnosis in Eastern Europe and Western Europe and Argentina

	Eastern Europe			Western Europe and Argentina		
	Dead	Alive	p-value	Dead	Alive	p-value
Total	286 (49)	301 (51)		61 (12)	430 (88)	
Male	220 (77)	199 (66)	0.0023	40 (63)	274 (64)	0.97
Age years	30 (26–34)	31 (26–35)	0.67	37 (32–44)	37 (32–43)	0.96
HCV antibody positive	140 (49)	128 (43)	0.10	11 (17)	72 (17)	0.89
HBsAg positive	34 (12)	28 (9)	0.29	5 (8)	21 (5)	0.31
History of IDU	223 (79)	196 (65)	0.0003	19 (30)	93 (22)	0.13
Origin same as country of follow-up	270 (94)	293 (97)	0.073	36 (59)	213 (50)	0.17
Definite TB[#]	171 (60)	149 (50)	0.012	42 (69)	290 (67)	0.83
Presumptive TB[¶]	59 (21)	104 (35)	0.0002	12 (20)	88 (20)	0.89
Rifamycin resistance at baseline[+,§]	11 (52)	9 (18)	0.0037	1 (5)	6 (4)	0.83
Rifamycin resistance within 2 months after baseline[+,§]	56 (63)	23 (21)	<0.0001	3 (8)	7 (3)	0.13
RHZ initial treatment	105 (37)	160 (53)	<0.0001	48 (76)	362 (84)	0.11
Extrapulmonary/disseminated TB	205 (72)	169 (56)	<0.0001	43 (68)	284 (66)	0.73
TB recurrence	50 (17)	32 (11)	0.017	4 (7)	13 (3)	0.16
Prior non-TB AIDS[ƒ]	41 (14)	38 (13)	0.52	21 (33)	106 (25)	0.14
Started cART prior to/at TB diagnosis	30 (11)	68 (23)	<0.0001	30 (63)	223 (52)	0.53
On cART at TB diagnosis	30 (11)	66 (22)	0.0003	28 (46)	215 (50)	0.55
CD4 cell count cells·mm^{-3}	148 (59–322)	311 (143–514)	<0.0001	86 (28–200)	140 (55–289)	0.0056
HIV RNA log$_{10}$ copies·mL^{-1}	5.40 (4.54–5.90)	4.94 (4.22–5.62)	0.089	5.21 (3.03–5.71)	4.82 (3.41–5.52)	0.10

Data are presented as n (%) or median (interquartile range), unless otherwise stated. Baseline was defined as the date of TB diagnosis. HCV: hepatitis C virus; HBsAg: hepatitis B surface antigen; IDU: injecting drug use; RHZ: rifamycin, isoniazid and pyrazinamide; cART: combination antiretroviral therapy. [#]: diagnosis confirmed by either positive culture for *Mycobacterium tuberculosis* or PCR; [¶]: cases where TB therapy initiated and TB not subsequently ruled out; [+]: resistance to at least rifamycin; [§]: percentage of those with drug susceptibility tests available; [ƒ]: history of at least one of the AIDS-defining (except TB) diseases according to the 1993 Centers for Disease Control and Prevention classification of HIV disease.

Baseline characteristics were compared for patients who had died or not in each region (table 2). In both Eastern Europe and WEA, patients who died had significantly lower CD4 cell counts at TB diagnosis. In Eastern Europe, those who died were more likely to be male, have a history of IDU, extrapulmonary or disseminated TB and to be infected with rifamycin-resistant isolates. Patients who died were less likely to have received initial TB treatment containing RHZ or cART at TB diagnosis (table 2). At the time of death, patients in Eastern Europe and WEA had similar CD4 cell counts (median (IQR) 92 (37–222) cells·mm^{-3} *versus* 80 (32–170) cells·mm^{-3}, p=0.18). However, patients in Eastern Europe were less likely to have intiated cART (29% *versus* 68%, p<0.0001).

In both regions, crude mortality rates were highest in the first 3 months following TB diagnosis (61.4 per 100 PYFU, 95% CI 53.1–69.7 and 18.6 per 100 PYFU, 95% CI 11.6–25.7 in Eastern Europe and WEA, respectively), and subsequently decreased over time, with a test-of-trend p-value of <0.0001 in both regions (fig. 2). However, mortality rates remained higher in Eastern Europe for all time periods, with statistically significant differences (p<0.0001) for all comparisons.

Causes of death and risk factors for TB-related death

A total of 320 CoDe case report forms (92% of 347 deaths) were available for the present analysis, with 273 (85%) from Eastern Europe and 47 (15%) from WEA. Deaths without a CoDe case report form were more likely to have occurred in WEA (OR 3.94, 95% CI 1.33–11.65; p=0.013) and these patients were more likely to have started cART prior to TB diagnosis (OR 3.65, 95% CI 1.43–9.28; p=0.0065) than those with an accompanying CoDe form. Among those with a CoDe form, autopsy reports were available for 63% of deaths in Eastern Europe and 13% of deaths in WEA. Figure 3 describes the causes of death among HIV/TB patients according to the interval between TB diagnosis and death. In the first 3 months after TB diagnosis, 80% and 50% of deaths in Eastern Europe and WEA, respectively, were categorised as TB-related. TB remained the main cause of death for patients in Eastern Europe in later time periods (66% in months

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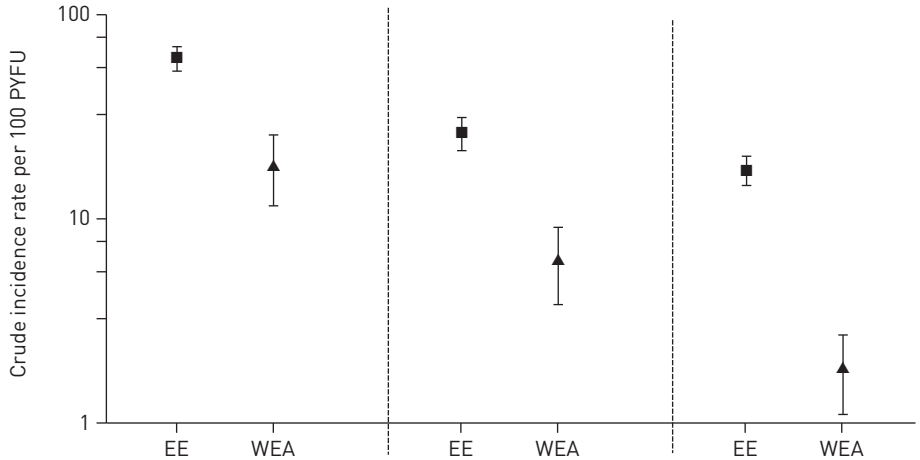

Deaths n (of those TB recurrences)	81 (0)	22 (0)	83 (0)	21 (0)	120 (49)	20 (5)
Follow-up n	585	493	493	461	363	412
PYFU	132	118	313	327	688	1046
Incidence rate	61.4	18.6	26.5	6.4	17.4	1.9

FIGURE 2 The crude mortality rate in HIV/tuberculosis (TB) patients stratified by time from TB diagnosis and region of follow-up. Error bars represent 95% confidence intervals; EE: Eastern Europe; WEA: Western Europe and Argentina; PYFU: person-years of follow-up.

3–12 and 61% >12 months after TB diagnosis), whereas for patients in WEA who died at a later stage, the predominant causes of death were non-TB-related or unknown (fig. 3). Of note, among TB-related deaths, >12 months after the TB diagnosis, 39 (56%) in Eastern Europe and 2 (100%) in WEA occurred due to TB recurrence. The proportion of TB-related deaths in Eastern Europe decreased slightly, whereas the proportion of unknown deaths increased significantly with time since TB diagnosis (from 1% to 18%, p=0.0003).

In Eastern Europe, TB-related deaths occurred in the context of a multiorgan failure in 28%, disseminated TB where TB-meningitis led to death in 23%, and disseminated TB without further specification in 25% of patients. A similar distribution was observed among the 11 TB-related deaths in WEA (data not shown). A smaller proportion of deaths was classified as TB-related in those with presumptive TB diagnosis, 42% *versus* 66% and 70% in those with a confirmed and probable TB diagnosis, respectively (p=0.0005).

In adjusted analyses (fig. 4), follow-up in WEA was associated with an 88% (incidence rate ratio (IRR) 0.12, 95% CI 0.04–0.35) reduced risk of TB-related death. Initiation of RHZ-based TB treatment was associated with a 55% (IRR 0.45, 95% CI 0.20–0.99) reduction and initiation of cART with a 68% (IRR 0.32, 95% CI 0.14–0.77) reduction in TB-related deaths. Patients with CD4 cell count ⩽50 cells·mm^{-3} had a 3.8-fold increased risk of TB-related death compared with those having CD4 cell count 200–350 cells·mm^{-3} (IRR 3.80, 95% CI 1.18–12.17). Rifamycin-resistant TB was a significant predictor for TB-related death in univariate analysis only, probably due to the lack of statistical power. There was some evidence that the incidence of TB-related death differed through the time periods in WEA compared to Eastern Europe (p=0.049, test for interaction).

Figure 5 shows the incidence rate ratios of TB-related death at 3–12 months and >12 months after TB diagnosis, compared with the first 3 months (reference group) for the two regions separately. The model was adjusted for the same covariates as shown in figure 4, although CD4 cell count was modelled as continuous variable to provide a better fit of the model. After adjustment, patients from Eastern Europe were at a significantly higher risk of dying from TB-related causes within the period >3 months after the TB diagnosis compared to the initial 3 months following TB diagnosis (fig. 5). In contrast, patients from WEA were much less likely to die from TB-related causes after 12 months, compared to the first 3 months following TB diagnosis (fig. 5).

Sensitivity analyses restricted to patients with definite TB (n=652), and to those for whom cause of death was determined as definite (n=1002) showed results consistent with the main model (data not shown). In the latter analysis, rifamycin-resistant TB was a significant predictor for TB-related death (IRR 2.65, 95% CI 1.29–5.46; p=0.008). In addition, in an analysis including rifamycin resistance data up to 2 months after the

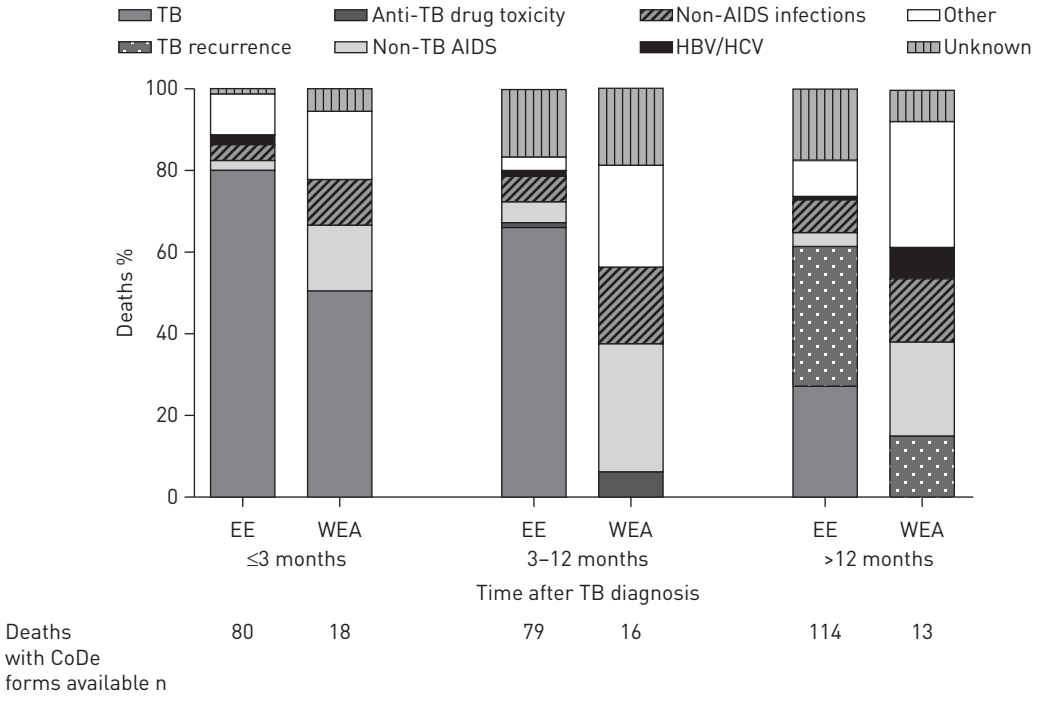

FIGURE 3 Causes of death among HIV/tuberculosis (TB) patients according to the time interval between TB diagnosis and death and region of follow-up. HBV: hepatitis B virus; HCV: hepatitis C virus; EE: Eastern Europe; WEA: Western Europe and Argentina; CoDe: Coding Causes of Death in HIV.

TB diagnosis, the results remained similar, although the role of initial RHZ-based treatment was no longer significantly associated with TB-related death (IRR 0.87, 95% CI 0.64–1.18).

Discussion

The results of our study show consistently higher mortality rates among HIV/TB patients in Eastern Europe, with a high proportion of deaths attributable to TB, irrespective of the interval between TB diagnosis and death. By contrast, mortality rates in WEA were lower and TB-related deaths were largely restricted to the first 3 months after TB diagnosis. TB-related mortality was significantly lower in patients who received RHZ-based TB-treatment and in those who initiated cART. Routine use of RHZ-based therapy and more widespread early use of cART in Eastern Europe, therefore, may improve the outcome of patients with HIV/TB. This study adds to the knowledge on ongoing clinical conditions prior to death in HIV/TB patients [7, 9, 12, 22], and more detailed information on these matters may allow for planning of effective interventions to improve patients' survival.

Our observation that the majority of deaths in HIV/TB patients in Eastern Europe are TB-related is consistent with earlier studies [7, 9, 12, 23]. Several studies also reported that at later stages after TB diagnosis or in recurrent TB cases, non-TB AIDS or non-AIDS infections were the main conditions leading to death [8]. Interestingly, in our study, other conditions, such as non-TB AIDS, HBV/HCV co-infection or drug toxicity did not appear to play a prominent role in the pathogenesis of death for patients in Eastern Europe. In contrast, the fact that patients in WEA were more likely to die of other conditions (either infections or noninfections), suggests that TB was well managed and other diseases (including liver and renal failure, cardiovascular disease, and diabetes) led to death. This is in line with recent findings from the EuroSIDA study showing that patients from Western Europe are more likely to die from non-AIDS conditions compared to patients from Eastern Europe [24]. Reasons for consistently higher TB-related long-term mortality in HIV/TB patients in Eastern Europe need further investigation. In our cohort, a large proportion of patients (>50%) was diagnosed with disseminated TB; many patients, particularly those with a history of IDU, alcohol consumption and imprisonment, had several treatment interruptions (data not shown), which potentially lead to extending treatment duration and a worse outcome.

Initiation of TB-treatment with a RHZ-based regimen was associated with a 55% reduced risk of TB-related death, thus highlighting the importance of starting empiric rifamycin-based TB therapy, even in settings with high rates of MDR-TB [25, 26]. Initial RHZ-based treatment was used as a reference group, thus other anti-TB drugs could have been added to the empirical regimen (either ethambutol or streptomycin, or

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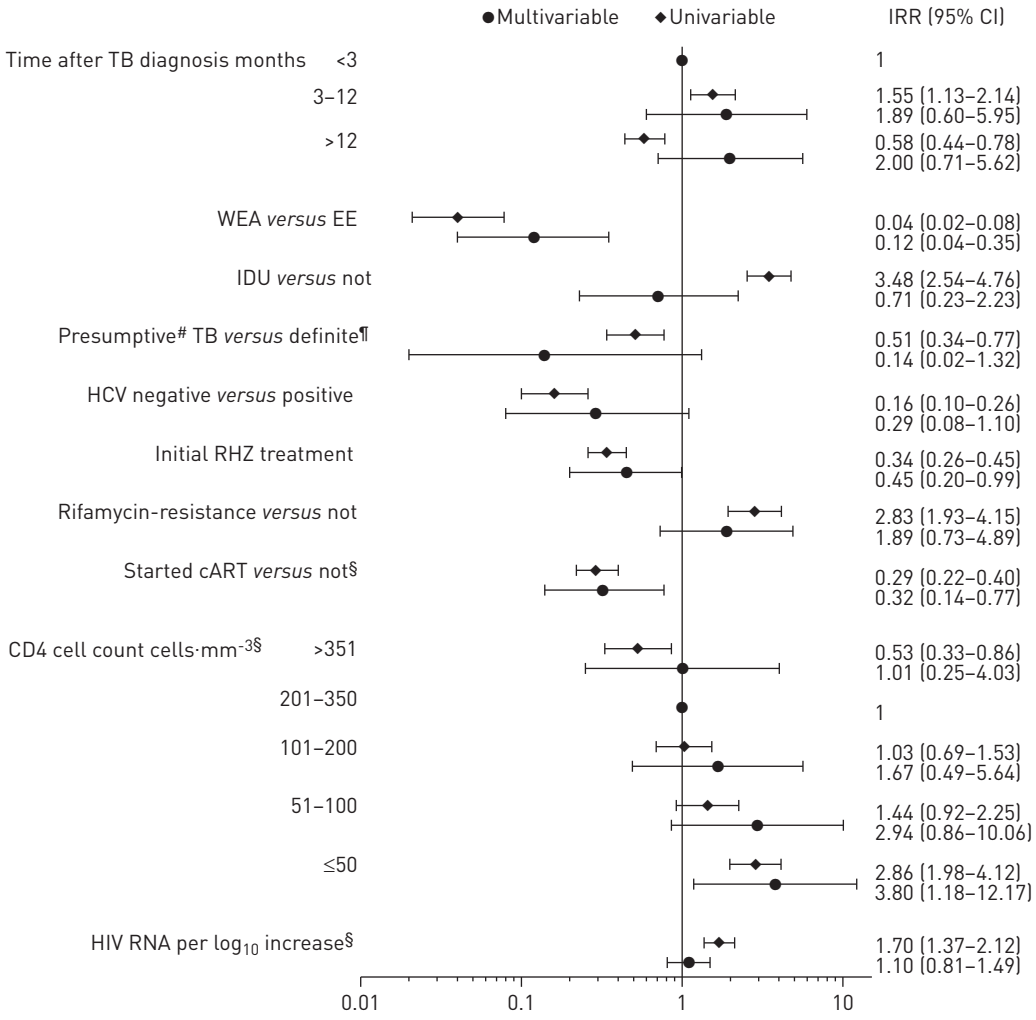

FIGURE 4 Incidence rate ratios (IRR) of tuberculosis (TB)-related death in HIV/TB patients. The model was also adjusted for baseline age, sex, hepatitis C virus (HCV) negative/unknown *versus* HCV positive, probable TB *versus* definite TB and rifamycin resistance unknown *versus* not. WEA: Western Europe and Argentina; EE: Eastern Europe; IDU: injecting drug use; RHZ: rifamycin, isoniazid and pyrazinamide; cART: combination antiretroviral therapy. #: cases where TB therapy initiated and TB not subsequently ruled out; ¶: TB diagnosis confirmed by either positive culture for *Mycobacterium tuberculosis* or PCR; §: latest values.

second-line drugs if MDR-TB was suspected). Use of nonstandard TB regimes was also associated with the increased risk of TB-related death in a Thai study [7]. Non-rifamycin based TB treatment regimens are associated with increased rates of treatment failure, and are less effective when given empirically to patients with unknown resistance patterns [27–29]. We have previously reported that RHZ-based treatment is underused in Eastern Europe, but the reasons are unclear and deserve further investigation [16, 30]. Interestingly, after adjustment for rifamycin resistance obtained within 2 months after TB diagnosis (thus, increasing the number of patients), the role of RHZ-based initial treatment was no longer significant in patient survival. This finding underlines that identifying drug susceptibility patterns as soon as possible is essential for initiation/adjustment of effective TB therapy, and for avoiding exposure to potentially ineffective drugs, thus minimising drug toxicities [26, 31]. In the current analysis, consistent with previous reports from the HIV/TB study [16, 30], rifamycin resistance, rather than MDR, was included in the models, as rifamycins are a cornerstone of TB treatment, therefore susceptibility of *M. tuberculosis* to these drugs plays an important role in determining treatment outcome [28]. Currently, there are several rapid tests available for detection of rifamycin resistance only and studies have shown that rifamycin resistance is highly predictive of MDR-TB [32–34]. Sensitivity analyses limited to MDR-TB cases gave similar results (data not shown).

The majority of patients who died in Eastern Europe were severely immunosuppressed and had disseminated TB with central nervous system involvement and/or TB sepsis. Intensified case-finding for TB,

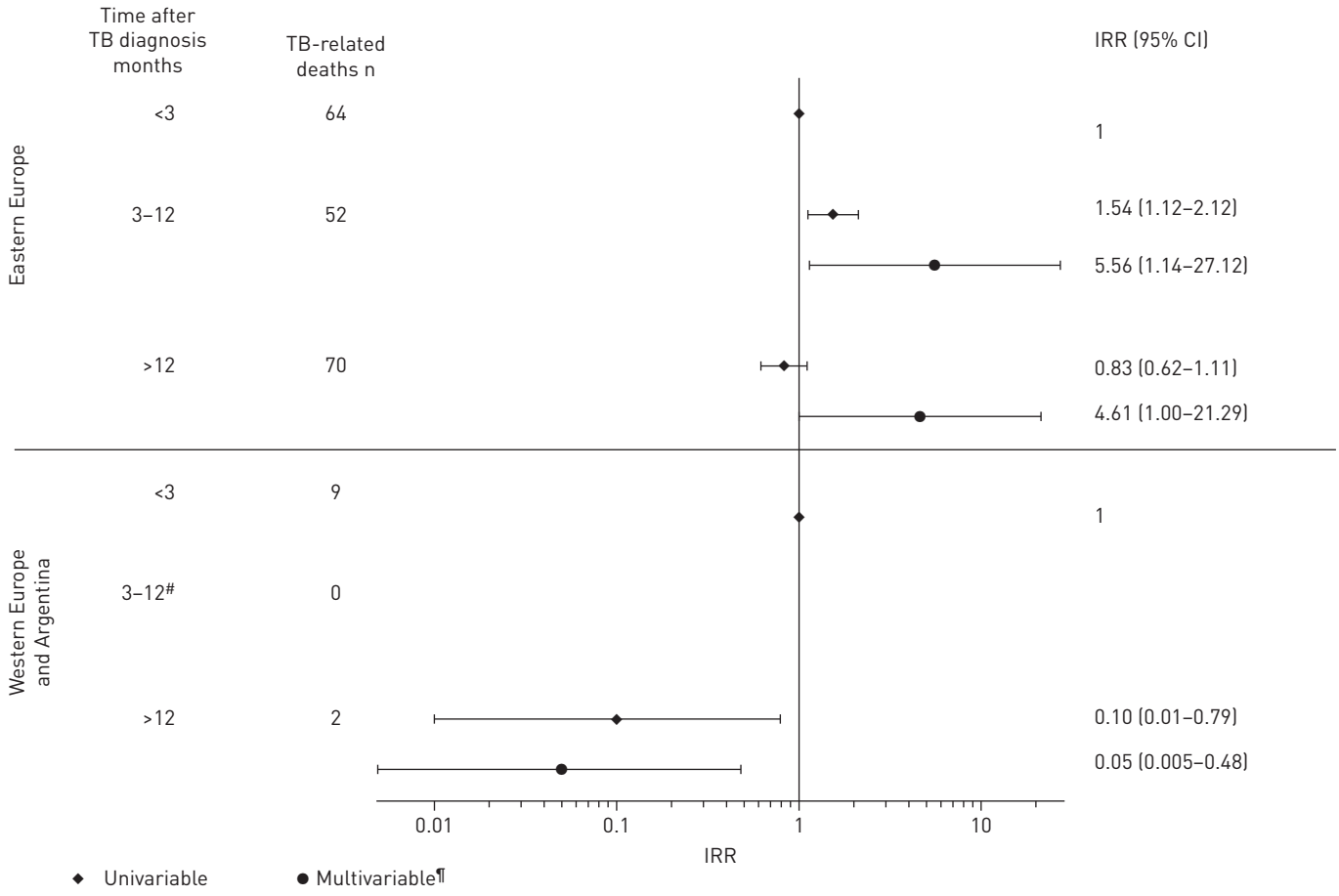

FIGURE 5 Incidence rate ratios (IRR) for tuberculosis (TB)-related death in HIV/TB patients stratified by time from TB diagnosis and region of follow-up. #: no TB-related death in Western Europe and Argentina in this time period; ¶: the model was also adjusted for: baseline age, sex, history of injecting drug use, hepatitis C virus status, certainty of TB diagnosis, TB drugs used for initial TB treatment, resistance to TB drugs, initiation of combination antiretroviral therapy and HIV-RNA. CD4 cell count was modelled as a continuous variable (per 100-cells·mm^{-3} increase).

access to RHZ-based therapy and rapid diagnostic tests to identify patients infected with rifamycin-resistant isolates should be an operational priority in this region [26].

The beneficial role of cART in the management of patients with HIV/TB is well documented [3, 5, 35]. The greatest benefit is in those with lowest CD4 cell counts, in whom cART initiation within 2 weeks of TB diagnosis is associated with reduced mortality [3, 5]. While some deaths in patients with advanced immunodeficiency who do not receive cART may be due to opportunistic infections, malignancies and other causes, our results showed a 68% reduction in TB-related deaths in those who started cART and suggest that some of the benefits of cART may be conferred through a reduction in TB-related mortality.

Finally, in our cohort, a large proportion of HIV/TB patients from Eastern Europe had a history of injecting drug use, HCV co-infection and specific socioeconomic characteristics (homeless and previously imprisoned, data not shown). History of IDU was significantly associated with TB-related death in the unadjusted analysis, but not in the adjusted model, due to the co-linearity with region of follow-up and HCV status. It is likely that optimising TB and HIV management alone for these patients will not resolve the high mortality rates. There is a need for a multidisciplinary approach, also involving access to opiate substitution therapy, social and psychological assistance [36, 37].

This study has several limitations. Due to its retrospective and observational design, some information was missing or not available. Sensitivity analyses, excluding patients with missing CoDe forms or those where cause of death was categorised as probable/likely or unknown, did not change our findings (data not shown). In Eastern Europe, the median follow-up time was shorter, which could be explained by high early mortality rates, but also a high rate of loss to follow-up (38% of patients with no data reported beyond 1 year after TB diagnosis and not known to have died in Eastern Europe compared to 16% in WEA, $p<0.0001$). The latter underlines the need to improve HIV/TB health systems in this region in order to

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maintain patient retention within health care. Patients lost to follow-up may be the sickest and most likely to die, thus the mortality rate in Eastern Europe might be even higher than reported here [38]. Severely sick patients could have other AIDS conditions in addition to TB that were not diagnosed; however, that did not seem to be the case among those with autopsy reports available. Nonetheless, an extensive quality assurance programme, which included queries to resolve data discrepancies and missing data as well as monitoring visits to the sites and ascertainment of vital status through liaison with healthcare facilities, death registers and phone calls to relatives/friends, was used to improve data collection and allowed establishment of the cause of death in the majority of patients. Cause of death was ascertained using a standardised method for assessment of causes of death in HIV patients and a central adjudication process [20]. Detailed information on the clinical situation during TB disease and at the time of death with the addition of autopsy reports, as well as an external review procedure allows for a more certain and detailed assessment of the cause of death. Finally, our cohort consists of patients diagnosed with TB in 2004–2006. Since then there have been updates in clinical management of HIV/TB co-infected patients.

Conclusion

We have demonstrated high early and late TB-related mortality rates among HIV/TB patients in Eastern Europe. Our findings call for urgent measures and further research to improve the clinical management using a multidisciplinary approach in order to improve survival of HIV/TB patients Eastern Europe and elsewhere. A prospective study of HIV/TB patients has recently been initiated and will further elucidate the situation of HIV/TB epidemic in Europe, Latin America, and particularly in Eastern Europe in the coming years (www.cphiv.dk).

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The HIV/TB Study Group investigators are as follows. Argentina: M.H. Losso (principal investigator (PI)); J.J. Toibaro; E. Warley, N. Tamayo and M. Cristina Ortiz (Hospital Interzonal General de Agudos Dr D. Proissien, Buenos Aires); P. Scapelatto and E. Bottaro (Hospital General de Agudos Donación F. Santojanni, Buenos Aires); F. Murano (Hospital Provincial Petrona V. de Cordero San Fernando, Buenos Aires); M. Miachans, J. Contarelli and L. Massera (Hospital San Juan de Dios, La Plata); J. Corral, M. Hualde and C. Miglioranza (Hospital Interzonal HIGA Oscar Alende, Mar del Plata); M. Corti and H. Metta (Hospital de Infecciosas Francisco Muñiz, Buenos Aires); A. Casiró and R. Cuini (Hospital General de Agudos Dr T. Álvarez, Buenos Aires); H. Laplume (Hospital Posadas, Buenos Aires); D. David and C. Marson (Hospital Rawson, Cordoba); S. Lupo and L. Trape (CAICI, Buenos Aires); O. Garcia Messina and O. Gear (Hospital Piñero, Buenos Aires); J.J. Toibaro and J.M. Bruguera (Hospital General de Agudos J.M. Ramos Mejía, Buenos Aires). Belarus: I. Karpov (PI) and A. Vasilenko (University Hospital of Infectious Diseases, Minsk); E. Skrahina and A. Skrahin (Research Institute of Pulmonology and Pulmonary Tuberculosis, Minsk); V. Mitsura and E. Kozorez (University Hospital of Infectious Diseases, Gomel); D. Ruzanov and V. Bondarenko (University Hospital of Tuberculosis, Gomel); O. Suetnov and D. Paduto (Gomel Region AIDS Centre, Svetlogorsk). Denmark: N. Obel (cohort PI and HIV/TB Study PI) (Danish HIV cohort). France: F. Dabis (cohort PI) and M. Bruyand (HIV/TB Study PI) (Aquitaine cohort). Italy: A. Matteelli, A.C. Carvalho and R. Basché (Institute of Infectious and Tropical Diseases, University of Brescia, Brescia); I.E. Hamad and B.A. Ricci (I Division of Infectious Diseases, Spedali Civili, Brescia); F. Maggiolo and V. Ravasio (Bergamo); C. Mussini, F. Prati and S. Castelletti (Clinica di Malattie Infettive, Modena); L. Spallanzani, A. Antinori, G. Antonucci, C. Bibbolino, G. Bove, E. Busi Rizzi, S. Cicalini, A. Conte, G. Cuzzi, P. De Mori, A. Festa, E. Girardi (PI), D. Goletti, S. Grisetti, G. Gualano, F.N. Lauria, R. Maddaluno, P. Migliorisi Ramazzini, P. Narciso, L. Parracino, F. Palmieri, N. Petrosillo, L. Pucillo, V. Puro, P. Vanacore and R. Urso (INMI, Rome); A. d'Arminio Monforte (cohort PI) and E. Girardi (HIV/TB Study PI) (ICONA, Rome). Latvia: V. Riekstina (PI) (State Agency of TB and Lung Diseases, Riga); P. Aldins and I. Zeltina (Infectology Centre of Latvia, Riga). Romania: D. Duiculescu (PI) (Spitalul de Boli Infectioase si Tropicale, Bucharest). Russia: A. Rakhmanova (PI), E. Malashenkov and A. Kozlov (Botkin Hospital of Infectious Diseases, St Petersburg); A. Panteleev (St Petersburg City TB Hospital No 2, St Petersburg); S. Buzunova (Novgorod City AIDS Centre, Novgorod). Spain: J.M. Miro (PI), C. Manzardo, J.F. García-Goez, A. Moreno-Camacho, J.A. Martínez, J. González, F. García-Alcaide, I. Pérez and J.M. Gatell (Hospital Clinic – IDIBAPS, University of Barcelona, Barcelona); P. Sánchez and J.L. López-Colomes (Hospital del Mar, Barcelona); X. Martínez-Lacasa (Mutua de Terrassa, Barcelona); V. Falcó, A. Imaz, I. Ocaña and R. Vidal (Hospital Universitari Vall d'Hebrón, Barcelona); M.A. Sambeat (Hospital Universitari de Sant Pau, Barcelona); J. Caylà, A. Moreno-Martínez, J.P. Millet, L. Fina, L. del Baño and A. Orcau (Agencia de Salud Pública de Barcelona, Barcelona). Switzerland: J. Barth, M. Battegay, E. Bernasconi, J. Böni, H.C. Bucher, C. Burton-Jeangros, A. Calmy, M. Cavassini, C. Cellerai, M. Egger, L. Elzi, J. Fehr, J. Fellay, M. Flepp, H. Furrer (HIV/TB Study PI), C.A. Fux, M. Gorgievski, H. Günthard, D. Haerry, B. Hasse, H.H. Hirsch, B. Hirschel, I. Hösli, C. Kahlert, L. Kaiser, O. Keiser, C. Kind, T. Klimkait, H. Kovari, B. Ledergerber, G. Martinetti, B. Martinez de Tejada, K. Metzner, N. Müller, D. Nadal, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach, C. Rudin, P. Schmid, D. Schultze, F. Schöni-Affolter, J. Schüpbach, R. Speck, P. Taffé, P. Tarr, A. Telenti, A. Trkola, P. Vernazza, R. Weber and S. Yerly (SCHS cohort). UK: F.A. Post (PI) and L. Campbell (King's College Hospital, London); R. Miller and A. Arenas-Pinto (Mortimer Market Centre, London). Ukraine: N. Chentsova (PI) (Kiev City AIDS Centre, Kiev). EuroSIDA cohort: J.D. Lundgren (HIV/TB Study PI). Coordinating centre (CHIP): D. Podlekareva, O. Kirk, A. Mocroft, D. Grint, J. Kjær and A.M. Werlinrud. Steering committee: N. Chentsova, D. Duiculesku, H. Furrer, E. Girardi, M. Bruyand, M.H. Losso, J.D. Lundgren, A. Panteleev, R. Miller, J.M. Miro, N. Obel, F. Post, V. Riekstina, A. Skrahin and J. J. Toibaro. PI: principal investigator for the HIV/TB Study in the respective country/cohort. For participating HIV cohorts, only those cohort representatives who were directly involved in the HIV/TB Study are named.

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