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Short and long term mortality and causes of death in HIV/TB 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, 7], Hansjakob Furrer[8],Niels Obel[9], Enrico Girardi[10], Anna Vasilenko[11], Marcelo H. Losso[12], Alejandro Arenas-Pinto[13], Joan Caylá[14], Aza Rakhmanova[15], Indra Zeltina[16], Anne Marie Werlinrud[1], Jens D. Lundgren[1,9], Amanda Mocroft[3],Ole Kirk[1,9] and the HIV/TB study group[a, b]

1. University of Copenhagen, Copenhagen HIV Programme, Denmark
2. TB Hospital #2, St. Petersburg, Russian Federation
3. University College London, London, UK
4. King's College London School of Medicine, London, United Kingdom
5. Hospital Clinic - IDIBAPS, University of Barcelona, Barcelona, Spain
6. University Bordeaux, ISPED, Centre Inserm U897- Epidemiologie-Biostatistique, Bordeaux, France.
7. INSERM, ISPED, Centre Inserm U897- Epidemiologie-Biostatistique, Bordeaux, France.
8. Clinic for Infectious Diseases, Bern University Hospital and University of Bern, Switzerland
9. Epidemiklinikken, Rigshospitalet, Copenhagen, Denmark
10. Instituto Nazionale Malattie Infettive L Spallanzani, Rome, Italy
11. Minsk State Medical University, Department of Infectious Diseases, Minsk, Belarus
12. Hospital JM Ramos Mejia, Servicio de Immunocomprometidos, Buenos Aires, Argentina
13. University College London, Centre for Sexual Health & HIV Research, Mortimer Market Centre, London, United Kingdom
14. Servicio de Epidemiología. Agencia de Salud Pública de Barcelona. CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
15. St. Petersburg AIDS Centre, St. Petersburg, Russia
16. Infectology Centre of Latvia, Riga, Latvia

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[#]corresponding author
Daria Podlekareva

Copenhagen HIV Programme
University of Copenhagen, Faculty of Health Sciences
The Panum Institute/Building 21.1, Blegdamsvej 3B
2200 Copenhagen N, Denmark Tel: +45 35 45 57 57 Fax: +45 35 45 57 58 e-mail: dpo@cphiv.dk

[a] Contribution of each member of the HIV/TB Study Writing group is described in the 'Acknowledgement' section

[b] Investigators are listed in the appendix

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Abstract

Background: Mortality of HIV/TB patients in Eastern Europe (EE) is high. Little is known about their causes of death (COD).

Objectives: To assess and compare mortality rates and COD in HIV/TB patients across EE and Western Europe and Argentina (WEA) in an international cohort study.

Methods: Mortality rates and COD were analysed by time from TB diagnosis (<3/3-12/>12 months) in 1078 consecutive HIV-/TB patients. Factors associated with TB-related death were examined in multivariate Poisson regression analysis.

Results: 347 patients died during 2625 PYFU. Mortality in EE was 3-9-fold higher than in WEA. TB was the main COD in EE in 80%, 66% and 61% of patients who died <3, 3-12, 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 (IRR 0.12 [95% CI 0.04–0.35]), standard TB-treatment (0.45 [0.20-0.99]) and antiretroviral therapy (0.32 [0.14–0.77]) were associated with reduced risk of TB-related death.

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

Key sentence (130 characters):

High TB-related death rates in HIV patients from Eastern Europe call for measures to improve clinical management of these patients.

Background

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 tuberculosis (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 is far from equal around the world (3-6). Deaths among HIV/TB patients may result from a number of causes, depending on degree of immunosuppression and availability of adequate TB-treatment and cART. While TB may directly contribute to early mortality, other opportunistic and non-opportunistic infections and co-morbidities 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/C coinfection and/or alcoholism (10;11).

The causes of death in HIV/TB patients treated for active TB have not yet been studied in details. Previous studies have reported TB itself as the leading cause of death and other infections played a relatively rare role in death etiology (7;9;12-14). These studies, however, were conducted in (sub)tropical regions (Africa, Thailand, Brazil), were limited by their small sample size, retrospective nature, and/or lack of standardized methodology for 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 highest (15;16) and Eastern European countries are those most affected by the multi-drug 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 5-fold higher compared to 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 vs. other parts of Europe and Argentina).

Methods

The HIV/TB study and patients 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 16 years or older were included if they were HIV-infected and had started TB-treatment between January 1st 2004 and December 31st 2006. Patients with confirmed TB (*Mycobacterium tuberculosis* (MTB) 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 (CRFs, 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 (Box 1) (20). Detailed information on the clinical conditions preceding death was collected on the CoDe CRF, in addition to the clinical information as described above. Where available, autopsy reports were used to inform the CoDe process. All CoDe CRFs were reviewed by two medical doctors (internal reviewers, D.N.P. and A.V.) at the 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 CRFs were sent to independent external reviewers (HIV/TB clinicians at participating clinics, F.P., H.F. and J.M.M.). 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 (Box 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 patients 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 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 (EE) (Belarus, Latvia, Romania, Russia and Ukraine) and Western Europe or Argentina (WEA) (Argentina, Denmark, France, Italy, Switzerland, Spain and the United Kingdom), and their characteristics at baseline and death were described. Argentina was analyzed together with the above mentioned European countries because of the sample size and similar HIV epidemiology or access to health care (availability of cART), particularly with 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, gender, region of follow-up, history of injection drug use (IDU), hepatitis B (HBV, HBsAg positive) and C (HCV, HCV antibody positive) status, TB drugs used for initial TB treatment (any rifamycins, isoniazid, pyrazinamide [RHZ-based] vs. other),

resistance to TB drugs (rifamycin (R) resistance vs. other), initiation of cART prior to or up to one month after TB diagnosis; and CD4-cell count and HIV-RNA as time-updated variables.

All analyses were performed using SAS (Statistical analysis software, Cary, NC, USA) version 9.2.

Results

Patient characteristics and mortality rate

In total 585 patients from EE and 493 from WEA were included in the study. The patient characteristics are shown in Table 1. The median follow-up was 8.5 (IQR 5.7 – 37.1) months for patients in EE 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 EE and 63 (12.8%) in WEA, p<0.0001, with a median interval between TB diagnosis and death among those who died of 8.7 (2.5-19.5) months in EE and 5.1 (1.6 – 13.5) months in WEA, p=0.11. Recurrent TB was diagnosed in 99 patients: 81 in EE (13.8%) and 18 (3.7%) in WEA, p<0.0001.

Baseline characteristics were compared for patients who had died or not in each region (Table 1). In both EE and WEA, patients who died had significantly lower CD4-cell counts at TB diagnosis. In EE, those who died were more likely to be males, had a history of IDU, extra-pulmonary 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 1). At the time of death, patients in EE and WEA had similar CD4-cell counts (median [IQR]: 92 [37-222] vs. 80 [32-170] cells/mm^3, p=0.18). However, patients in EE were less likely to have initiated cART (29% vs. 68%, p<0.0001).

In both regions, crude mortality rates were highest in the first 3 months following TB diagnosis (61.4 [95% CI: 53.1-69.7] and 18.6 [11.6-25.7]/100 PYFU in EE and WEA respectively), and subsequently decreased over time, with a test of trend p-value of <0.0001 in both regions (Figure 1). However, mortality rates remained higher in EE 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 CRFs (92% of 347 deaths) were available for the present analysis, with 273 (85%) from EE and 47 (15%) from WEA. Deaths without a CoDe CRF were more likely to have occurred in WEA (Odds ratio (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 EE and 13% of deaths in WEA. Figure 2 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 EE and WEA respectively were categorised as TB-related. TB remained the main cause of death for patients in EE in later time periods (66 % in months 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 (Figure 2). Of note, among TB-related deaths >12 months after the TB diagnosis, 39 (56%) in EE and 2 (100%) in WEA occurred due to TB-recurrence. The proportion of TB-related deaths in EE decreased slightly, whereas the proportion of unknown deaths increased significantly with time since TB diagnosis (from 1% to 18%, p=0.0003).

In EE TB-related deaths occurred in the context of a multi-organ 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 were classified as TB-related in those with presumptive TB diagnosis, 42% vs. 66% and 70%in those with a confirmed and probable TB diagnosis, respectively, p=0.0005.

In adjusted analyses (Figure 3), follow-up in WEA was associated with an 88% (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% (0.45 [0.20-0.99]) and initiation of cART with a 68% (0.32 [0.14–0.77]) reduction in TB-related deaths. Patients with CD4-cell count $\leq$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 (3.80 [1.18-12.17]). R-resistant TB was a significant predictor for TB-related death in univariate analysis only, likely 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 EE (p=0.049, test for interaction).

Figure 4 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 3, although CD4-cell count modeled as continuous variable to provide a better fit of the model. After adjustment, patients from EE were at a significantly higher risk of dying from TB-related causes within the period more than 3 months after the TB diagnosis compared to the initial 3 months following TB diagnosis (figure 4, upper part). 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 (figure 4, lower part).

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 (2.65 [1.29-5.46], p=0.008). Also, in an analysis including R-resistance data up to 2 months after the TB diagnosis, the results remained similar, although the role of initial RHZ-based treatment was no longer significantly associated with TB-related death (0.87 [0.64-1.18]).

Discussion

The results of our study show consistently higher mortality rates among HIV/TB patients in EE, 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 EE, therefore, may improve the outcome of patients with HIV/TB. This study adds to the knowledge on on-going 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 EE 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 EE. In contrast, the fact that patients in WEA were more likely to die of other conditions (either infections or non- infections), suggests that TB was well managed and other diseases (including liver and renal failure, cardio-vascular 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 EE 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 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 of 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 second-line drugs if MDR-TB was suspected). Use of non-standard 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 was under-used in Eastern Europe, but the reasons are unclear and deserve further investigation (16;30). Interestingly, after adjustment for R-resistance obtained within 2 months after TB diagnosis (thus, increasing number of patients), the role of RHZ-based initial treatment was no longer significant in patients' survival. This finding underlines that the identification of 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), R-resistance rather than MDR was included in the models, as rifamycins are a cornerstone of TB-treatment, therefore susceptibility of *Mycobacterium tuberculosis* to these drugs play an important role in determining treatment outcome. (28) Currently there are several rapid tests available for detection of R-resistance only and studies have shown that R-resistance is highly predictive for MDR-TB. (32-34) Sensitivity analyses limited to MDR-TB cases gave similar results (data not shown).

The majority of patients who died in EE were severely immunosuppressed and had disseminated TB with CNS involvement and/or TB-sepsis. Intensified case-finding for TB, 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 EE had a history of injecting drug use, HCV-coinfection 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 collinearity 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 multi-disciplinary 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 EE, the median follow-up time was shorter, which could be explained by high early mortality rates, but also a high rate of lost to follow-up (38% of patients with no data reported beyond 1 year after TB diagnosis and not known to have died in EE 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 maintain patients' retention within healthcare. Patients lost to follow-up may be the sickest and most likely to die, thus the mortality rate in EE might be even higher than reported here (38). Severely sick patients could have other AIDS conditions in addition to TB, which were not diagnosed, however it 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

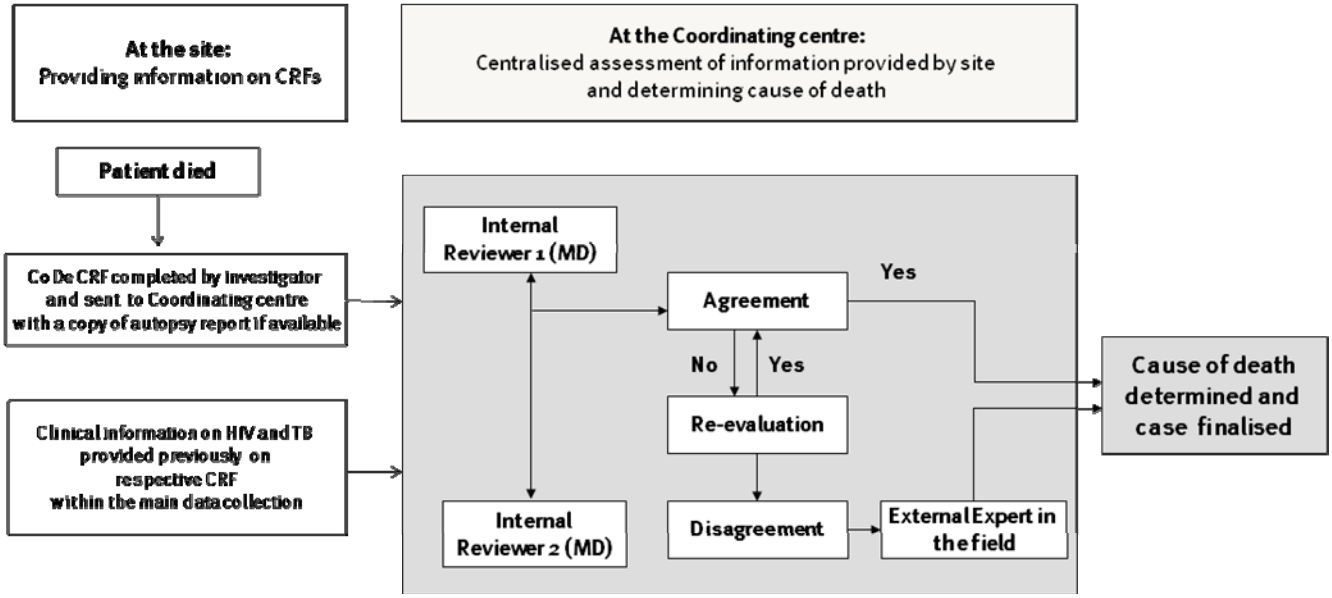
vital status through liaison with health care facilities, death registers and phone calls to relatives/friends were used to improve data collection and allowed establishment of the cause of death in the majority of patients. Cause of death was ascertained using a standardised method for assessment of 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 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 coinfected patients.

Conclusion

We have demonstrated high early and late TB-related mortality rates among HIV/TB patients in EE. Our findings call for urgent measures and further research to improve the clinical management using a multi-disciplinary approach in order to improve survival of HIV/TB patients EE 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).

Box 1

Determining cause of death in the HIV/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, autopsy reports where available.

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 was not performed.

Additional clinical information:

Ad TB: pulmonary TB diagnosed 3 years earlier, bacteriologicaly confirmed, fully susceptible to anti-TB drugs. Completed RHZE treatment, no TB recurrence reported.

Ad HIV: known HIV+ for 13 years. At TB diagnosis CD4 cell count was 245 cells/mm^3; HIV-RNA 500.000 copies/ml and the patient did not receive antiretroviral therapy (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 multi-organ failure. Patient’s condition deteriorated during the last 1,5 months due to irregular treatment.

Autopsy report: 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 multi-organ failure

Additional clinical information:

Ad TB: disseminated MDR-TB diagnosed 14 months earlier. Anti-TB treatment was RHZ combined with amikacin and ethionamide, but the patient had poor adherence to treatment and there were several episodes of treatment interruptions.

ad HIV: known HIV+ for 8 years. ART initiated after TB diagnosis, but was interrupted after 6 months as per patient’s wish. CD4 cell count at TB diagnosis was 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 report revealed signs of *pneumocystis jirovececii* pneumonia (PCP). No evidence for active TB process.

Additional clinical information:

Ad TB: presumptive (without positive culture and thus no susceptibility tests available) pulmonary TB diagnosed 1,5 year earlier with involvement of intra- and extrathoracic lymph nodes. Initial anti-TB treatment was RH with addition of Z and amikacin two month after for a total treatment duration of 8 months. No TB recurrence reported.
Ad HIV: known HIV+ for 8 years. CD4 cell count 5 months prior to TB diagnosis was 410 cells/mm^3, at time of death 135 cells/mm^3. HIV-RNA not measured. Patient did not receive ART, and PCP was not diagnosed while patient was alive and PCP treatment/ prophylaxis was not prescribed.
CoDe review process: immediate COD was coded as "non-TB AIDS defining condition, PCP".

Table 1. Baseline characteristics of HIV/TB patients according to vital status following the TB diagnosis in Eastern Europe and Western Europe & Argentina.

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

Baseline was defined as the date of TB diagnosis

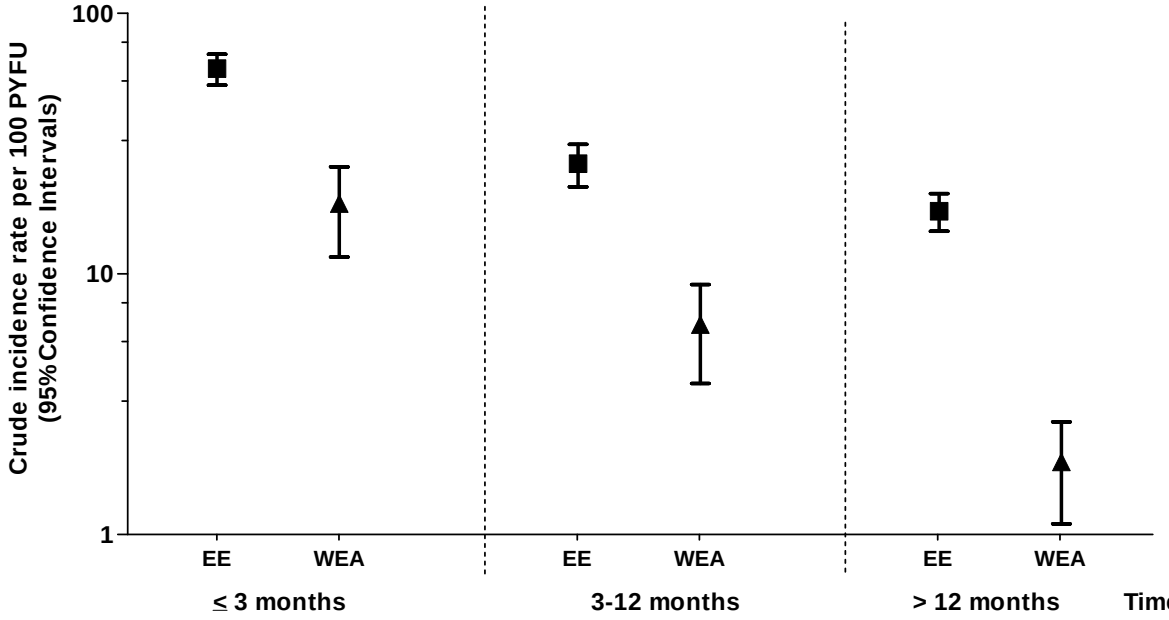
IQR, interquartile range; IDU, injecting drug use; HC/BV, hepatitis C/B virus

Definite TB, TB diagnosis confirmed by either positive culture for *mycobacterium tuberculosis* or PCR; Presumptive TB, cases where TB therapy initiated and TB not subsequently ruled out; R-resistance, resistance to at least rifamycin; RHZ, rifamycin, isoniazid, pyrazinamide

Prior non-TB-AIDS, history of at least one of the AIDS-defining (except TB) diseases according to the 1993 CDC classification of HIV disease; cART, combination antiretroviral therapy

* % of those with drug susceptibility tests available

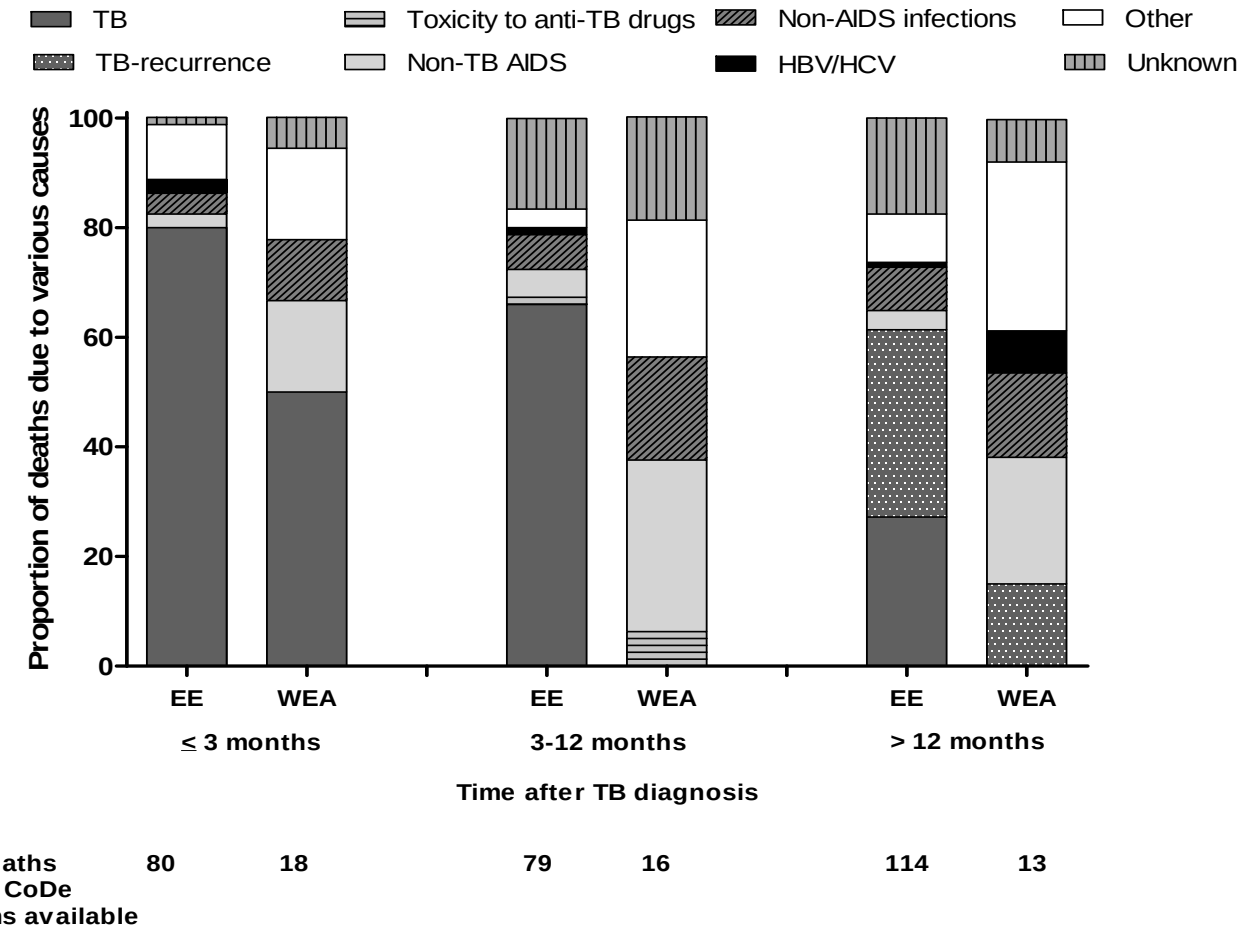
Figure 1: The crude mortality rate in HIV/TB patients stratified by time from TB diagnosis and region of follow-up



N deaths (of those TB recurrences)	**81 (0)**	**22 (0)**	**83 (0)**	**21 (0)**	**120 (49)**	**20(5)**
N under FU	**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**

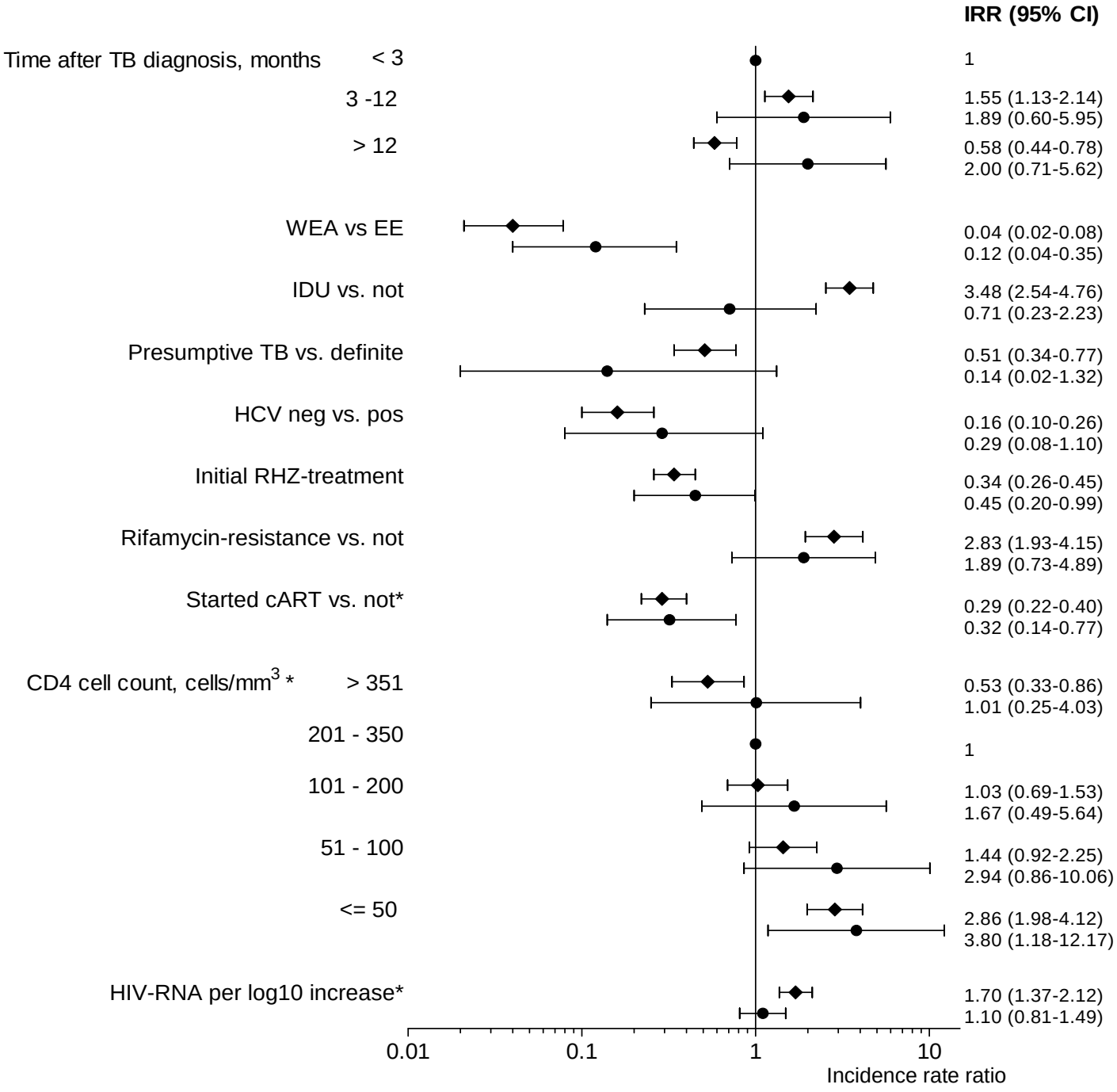
EE, Eastern Europe; WEA, Western Europe and Argentina; PYFU, person years of follow-up

Figure 2. Causes of death among HIV/TB patients according to the time interval between TB diagnosis and death and region of follow-up



EE, Eastern Europe; WEA, Western Europe and Argentina; CoDe, The Coding Causes of Death in HIV

Figure 3. Incidence rate ratios (IRR) of TB-related death in HIV/TB patients



♦ - Univariable ● - Multivariable

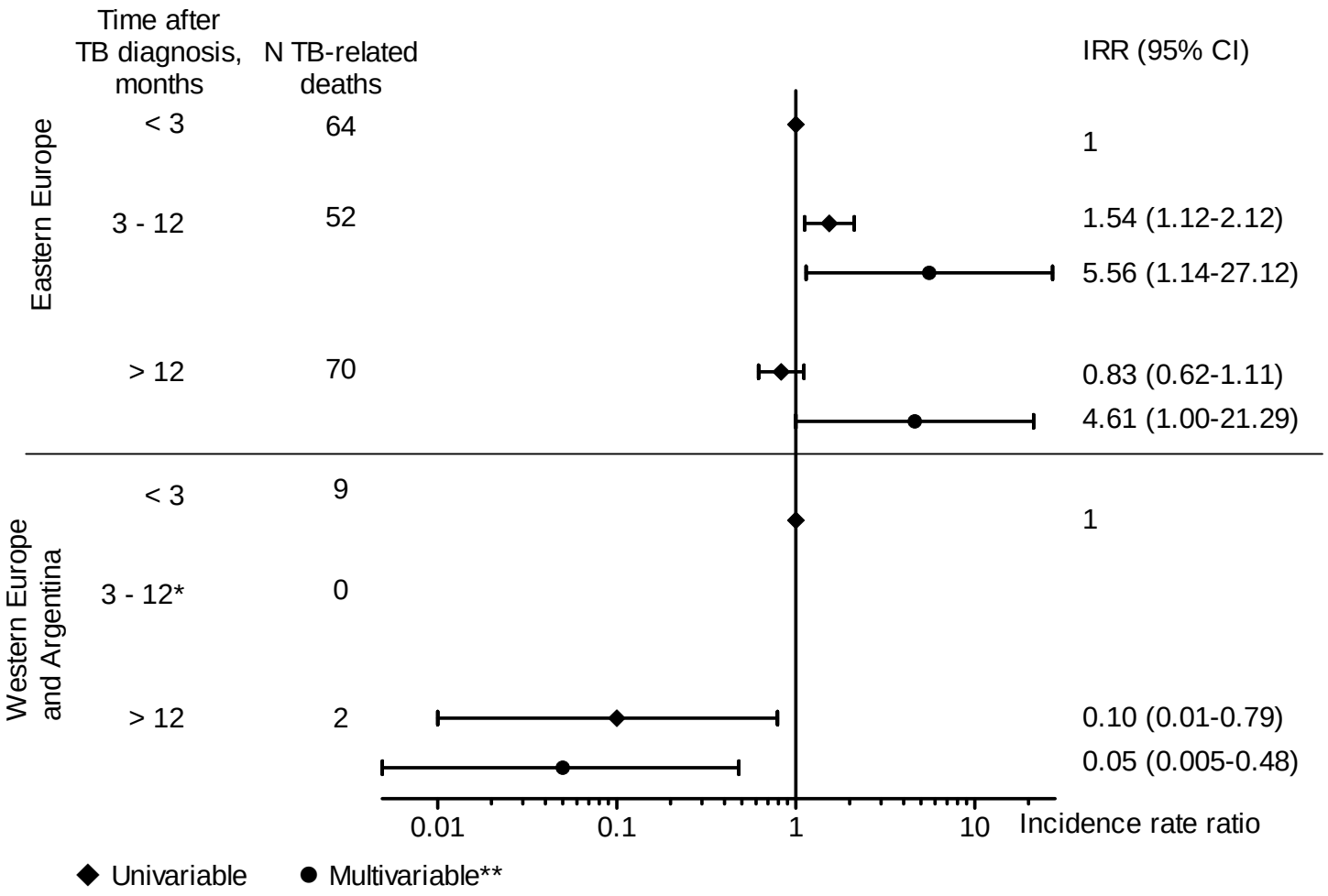
*-time up-dated

WEA, Western Europe and Argentina; EE: Eastern Europe; IDU – injecting drug use; Presumptive TB, cases where TB therapy initiated and TB not subsequently ruled out; Definite TB, TB diagnosis confirmed by

either positive culture for *mycobacterium tuberculosis* or PCR; HCV, hepatitis C virus; RHZ – rifamycin, isoniazid, pyrazinamide; cART – combination antiretroviral therapy.

The model was also adjusted for: baseline age, gender, HCV negative /unknown vs. HCV positive, probable TB vs. definite TB, Rifamycin-resistance unknown vs. not.

Figure 4. Incidence rate ratios (IRR) for TB-related death in HIV/TB patients stratified by time from TB diagnosis and region of follow-up



*- No any TB-related death in Western Europe and Argentina in this time-period

** - Multivariable models included all variables listed in legend to figure 3, although CD4-cell count modelled as continuous variable (per 100 cells/mm^3 increase)

Study group:

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

Argentina, Buenos Aires: M. H. Losso (PI); Project Manager: J. J. Toibaro; Hospital Interzonal General de Agudos DR. D.PROISSIEN: E. Warley, N. Tamayo, M. Cristina Ortiz; Hospital General. de Agudos Donación F. Santojanni: P. Scapelatto, E. Bottaro; Hospital Provincial Petrona V. de Cordero. San Fernando: F. Murano; Hospital San Juan de Dios (La Plata): M. Miachans, J. Contarelli, L. Massera; Hospital Interzonal HIGA Oscar Alende (Mar del Plata): J. Corral, M. Hualde, C. Miglioranza; Hospital de Infecciosas Francisco Muñiz: M. Corti, H. Metta; Hospital General. de Agudos Dr. T. Álvarez: A. Casiró, R. Cuini; Hospital Posadas: H. Laplume; Hospital Rawson (Cordoba): D. David, C. Marson; C.A.I.C.I: S. Lupo, L. Trape; Hospital Piñero: O. Garcia Messina, O. Gear; Hospital General de Agudos J.M.Ramos Mejía: J. J. Toibaro, J. M. Bruguera.

Belarus, Minsk: University Hospital of Infectious Diseases: I. Karpov (PI), A. Vasilenko; Research Institute of Pulmonology and Pulmonary Tuberculosis: E. Skrahina, A. Skrahin; Gomel: University Hospital of Infectious Diseases: V. Mitsura, E. Kozorez; University Hospital of Tuberculosis: D. Ruzanov, V. Bondarenko; Svetlogorsk: Gomel Region AIDS centre: O. Suetnov, D. Paduto

Denmark: Danish HIV Cohort: N. Obel (cohort PI and HIV/TB Study PI)

France: Aquitaine Cohort: F. Dabis (cohort PI); M. Bruyand (HIV/TB Study PI)

Italy: Brescia: Institute of Infectious and Tropical Diseases, University of Brescia: A Matteelli, AC Carvalho, R Basché; I Division of Infectious Diseases, Spedali Civili: IE Hamad, BA Ricci, Bergamo: F. Maggiolo, V Ravasio, Modena: Clinica di Malattie Infettive, C. Mussini, F. Prati, S. Castelletti; Rome: INMI 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 (coordinator), N. Petrosillo, L. Pucillo, V. Puro, P. Vanacore, R. Urso ; ICONA Cohort: A. d'Arminio Monforte (cohort PI); E. Girardi (HIV/TB Study PI); www.fondazioneicona.org/

Latvia, Riga: State Agency of TB and Lung Diseases: V. Riekstina (PI); Infectology Centre of Latvia: P. Aldins, I. Zeltina;

Romania, Bucharest: Spitalul de Boli Infectioase si Tropicale: D Duiculescu (PI)

Russia, St. Petersburg: Botkin Hospital of Infectious Diseases A. Rakhmanova (PI), E. Malashenkov, A. Kozlov, St. Petersburg City TB Hospital №2, A. Panteleev; Novgorod city AIDS Centre: S. Buzunova

Spain: Barcelona: Hospital Clinic – IDIBAPS, University of Barcelona J. M. Miro (PI), C. Manzardo, J. F. García-Goez, A. Moreno-Camacho, J. A. Martínez, J. González, F. García-Alcaide, I. Pérez, J. M. Gatell; Hospital del Mar: P. Sánchez, J. L. López-Colomes. Mutua de Terrassa: X. Martínez-Lacasa. Hospital Universitari Vall d'Hebrón: V. Falcó A. Imaz, I. Ocaña, R. Vidal. Hospital Universitari de Sant Pau: M. A. Sambeat. Agencia de Salud Pública de Barcelona: J. Caylà, A. Moreno-Martínez, JP Millet, L. Fina, L. del Baño, A. Orcau.

Switzerland: Swiss HIV Cohort: Barth J, Battegay M, Bernasconi E, Böni J, Bucher HC, Burton-Jeangros C, Calmy A, Cavassini M, Cellerai C, Egger M, Elzi L, Fehr J, Fellay J, Flepp M, Furrer H (HIV/TB Study PI), Fux CA, Gorgievski M, Günthard H (President of the SHCS), Haerry D , Hasse B, Hirsch HH, Hirschel B, Hösli I,

Kahlert C, Kaiser L, Keiser O, Kind C, Klimkait T, Kovari H, Ledergerber B, Martinetti G, Martinez de Tejada B, Metzner K, Müller N, Nadal D, Pantaleo G, Rauch A, Regenass S, Rickenbach M , Rudin C , Schmid P, Schultze D, Schöni-Affolter F, Schüpbach J, Speck R, Taffé P, Tarr P, Telenti A, Trkola A, Vernazza P, Weber R, Yerly S.

United Kingdom: London: King's Hospital: F. Post (PI), L Campbell; Mortimer Market Centre: R. Miller, A. Arenas-Pinto

Ukraine: Kiev City AIDS Centre: N. Chentsova (PI)

EuroSIDA cohort: J. D. Lundgren (HIV/TB Study PI); www.cphiv.dk

Coordinating centre (CHIP): D. Podlekareva, O. Kirk, A. Mocroft, D. Grint, J. Kjær, AM 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, J. J. Toibaro

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The role of each of the members of the writing group:

Daria Podlekareva contributed in project development and coordination, review of Cause of Death forms, data analysis and interpretation, and was responsible for writing the manuscript

Daniel Grint performed data analysis; contributed with ideas for data analysis and interpretation, and writing manuscript

Frank Post contributed with data collection and ideas for data analysis, review of Cause of Death forms, and writing the manuscript.

Jose M. Miro, Hansjakob Furrer, Anna Vasilenko contributed with national coordination, data collection, study design, review of Cause of Death forms and writing the manuscript

Alexander Panteleev, Mathias Bruyand, Niels Obel, Enrico Girardi, Anne Marie Werlinrud, Marcello Losso, Alejandro Arenas-Pinto, Joan Caylá, Aza Rakhmanova, and Indra Zeltina contributed with national coordination, data collection, study design, and with writing the manuscript.

Jens Lundgren proposed the project and contributed with ideas for the study design and data analysis, interpretation of data, and writing the manuscript.

Amanda Mocroft supervised data analysis; contributed with ideas for data analysis and interpretation, and writing manuscript.

Ole Kirk contributed with ideas for the study design, development, overall coordination, data analysis interpretation of data analysis as well as with writing manuscript and supervised the project.

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