Research article

Full title: The impact of HIV infection on treatment outcome of tuberculosis in Europe

Short title (running head): Treatment outcome of TB in HIV-patients

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Abstracts

Background: The effect of HIV on tuberculosis (TB) treatment outcomes (TO) has not been well established. We aimed to assess the impact of HIV infection on TB TO by using data from notifiable disease surveillance in Europe.

Methods: We analyzed the TO of TB cases reported from nine European countries during 2010-2012. We investigate the effect of HIV on TB TO using a multilevel and a multinomial logistic models, and considering the interaction between HIV and multidrug-resistant (MDR)-TB.

Results: A total of 61138 TB cases including 5.5% HIV-positive were eligible for our analysis. In the multilevel model adjusted for age and an interaction with MDR-TB, HIV was significantly associated with lower treatment success in all MDR strata [Non-MDR-TB: odds ratio (OR) 0.24 CI 0.20-0.29; Unknown MDR-TB status: OR 0.26 CI 0.23-0.30; MDR-TB: OR 0.57 CI 0.35-0.91]

In the multinomial regression model, HIV-positive cases had significantly higher relative risk ratio (RRR) for death [Non-MDR-TB: RRR 4.30 CI 2.31-7.99; Unknown MDR-TB status: 5.55 CI 3.10-9.92; MDR-TB: 3.59 CI 1.56-8.28] and being “still on treatment” [Non-MDR-TB: RRR 7.27 CI 3.00-17.6; Unknown MDR-TB status: 5.36 CI 2.44-11.8; MDR-TB: 3.76 CI 2.48-5.71]. We did not find any significant association between HIV and TB treatment failure [Non-MDR-TB: RRR 0.50 CI 0.15-1.67; Unknown MDR-TB status: 1.51 CI 0.86-2.64; MDR-TB: 0.51 CI 0.13-1.87]

Conclusion: This large study confirms that HIV is a strong risk factor for an adverse TB treatment outcome, which is mainly manifested by an increased risk of death and still being on TB treatment.

Keywords: HIV; Tuberculosis; Coinfection; Treatment outcome; Europe

Introduction

Tuberculosis (TB) and HIV comorbidity remains a serious challenge to public health worldwide including in the European region [1,2]. On one hand, HIV is a strong risk factor for TB increasing the risk of progression to active TB and reactivation of latent TB [3]. On the other hand, TB adversely affects the natural course of HIV infection in co-infected patients by increasing both viral replication and viral heterogeneity [4]. Furthermore, the HIV epidemic may have contributed to the emergence of drug-resistant strains of TB [5]. A meta-analysis showed that HIV-positive cases have higher risk of having MDR-TB by 24% [6]. The introduction of combination antiretroviral therapy (ART) was associated with a significant reduction in rates of AIDS and associated death in developed countries [7]. However, limitations of ART in reducing TB risk have been observed, and TB rates in HIV-positive patients remain substantial even among those who initiated ART [8]. In the EU/EEA, limited data are available on the risk factors for TB/HIV co-infection. A systematic review carried out by Pimpin et. al.[9] showed that co-infection was associated with male sex, adults, foreign-born person, the homeless, injecting drug users and prisoners. However this review indicated that only seven studies (from three countries: Spain, France and the Netherlands) of 61 studies included in the review provided risk factor information on TB/HIV co-infection, furthermore marginalized population was under-represented in the data [9].

In 1991, the 44th World Health Assembly set the international target for TB treatment success at >85% [10]. In principle the treatment of TB in HIV co-infected patients should not be different from HIV-negative TB patients [11,12]. Early clinical response to therapy and the time to sputum culture conversion from positive to negative appear to be similar for those with HIV infection and those without HIV infection [12]. However, the impact of HIV infection on TB treatment outcome

74 at the population level appears inconclusive. While some studies showed lower TB treatment
75 success among HIV co-infected TB cases and demonstrated HIV infection as a risk factor for an
76 unsuccessful TB treatment outcome [13-18], other studies reported comparable TB treatment
77 success and observed no significant association of treatment outcome with HIV infection [19-24].
78 These studies were limited by a number of factors. Many of them were conducted in high-burden
79 settings of TB and HIV with restricted access to ART [20-22], or had a small sample size [15,19,23].
80 Most of studies that reported similar TB treatment success rates in HIV-positive and HIV-negative
81 cases had excluded cases still on treatment from the treatment outcome analysis [13,15,17,18].
82 This procedure might overestimate treatment success and can neglect the effect of HIV on the
83 duration of TB treatment. Studies that concluded that TB treatment success was negatively
84 associated with HIV infection did not assess confounding by multidrug resistant (MDR)-TB or the
85 impact of the interaction between HIV and MDR-TB on treatment success [20-23]. These studies
86 may bias the effect of HIV since they do not distinguish between the effect of HIV and MDR status
87 on treatment outcome.

88 Based on data from notifiable disease surveillance in Europe, we aimed to assess the impact of HIV
89 infection on TB treatment success considering the interaction between HIV and MDR-TB.
90 Additionally, we investigated the impact of HIV on each treatment outcome category, comparing
91 HIV co-infected TB cases with non-HIV infected TB cases.

Methods

Data source and case definitions

All European Union and European Economic Area (EU/EEA) countries report their available data on TB to the European Surveillance System (TESSy) hosted by the European Centre for Disease Prevention and Control (ECDC). Since 2010, TESSy data have included information on HIV status for TB cases. The cohort eligible for our analysis included TB cases reported to TESSy from EU/EEA countries that reported treatment outcome and HIV status for TB cases with at least one HIV-positive case in each year between 2010 and 2012.

Treatment outcomes of notified TB cases are reported 12 months after the start of treatment and 24 months after start of treatment for MDR-TB cases. We categorized treatment outcomes in accordance with the joint World Health Organization Regional Office for Europe/ECDC surveillance and monitoring report 2015 [25]:

- Cured: treatment completion and culture-negative samples taken at the end of treatment and on at least one previous occasion.
- Completed: treatment completed, but does not meet the criteria to be classified as cure or treatment failure.
- Successful outcome (treatment success): refers to the combined treatment outcome categories cured and completed.
- Died: death before cure or treatment completion, irrespective of cause.
- Still on treatment: patient still on treatment at 12 months without any other outcome during treatment and at 24 months for MDR-TB cases.

- Failed: culture or sputum smear remaining positive or becoming positive again five months or later into the course of treatment.
- Defaulted: treatment interrupted for two months or more, not resulting from a decision of the care provider.
- Transferred out: patient referred to another clinical unit for treatment and information on outcome not available.
- Unknown: information on outcome not available, for cases not known to have been transferred.

For the purpose of our analysis, we defined "cases lost to follow-up" as the combination of cases that defaulted, were transferred out, or had an unknown treatment outcome.

Statistical analysis

Categorical variables were described using absolute and relative frequencies and compared by the $\chi 2$ test regarding group differences. Continuous variables were described using medians with interquartile ranges (IQR) and compared by the Mann-Whitney U-test for differences between groups. All tests were two sided and considered significant if $p<0.05$.

To investigate the effect of HIV infection on TB treatment success, we used a multilevel logistic regression model involving two levels (TB cases nested within countries) corrected with a random intercept and a random slop for HIV effect at the country level [26]. In this model, "cases lost to follow-up" were excluded and treatment outcome was dichotomized as unsuccessful treatment (i.e. death, still on treatment, and treatment failure) versus treatment success (i.e. cure, and treatment completion). Independent variables available in TESSy data (age, gender, geographical origin, MDR-TB, major site of TB, previous treatment of TB, culture confirmation, microscopy

result, and reporting year) were tested as possible confounders in the relationship between TB treatment success and HIV infection. Independent variables that led to a ≥10% change in the HIV regression coefficient were considered as confounders and retained in the final multilevel multivariable model. We evaluated the interaction term between HIV and MDR-TB at a p-value of 0.1 [26]. To illustrate the MDR-HIV interaction term, we calculated the odds ratios for each MDR-TB strata separately [26], and graphed the adjusted probability of TB treatment success by HIV infection and stratified by MDR-TB status [27].

A multinomial logistic regression model with adjusted relative risk ratio (RRR) was built to investigate the effect of HIV infection on each treatment outcome category (death, still on treatment, treatment failure, and loss to follow-up) relative to treatment success. To illustrate the results, we plotted the adjusted probability for each category of TB treatment outcome in relation to HIV infection and stratified by MDR status [28].

All analyses were performed using STATA (version13, StataCorp, LP, TX, USA) software.

Ethical statement

The study was based on data collected on the basis of statutory notification in each EU country and reported anonymously to the ECDC on the basis of decision No 2119/98/EC of the European Parliament and of the Council.

Results

Cohort characteristics

Between 2010 and 2012, nine EU/EEA countries (Belgium, Bulgaria, Czech Republic, Estonia, Ireland, Lithuania, Portugal, Romania, and Spain) reported treatment outcome and HIV status for their TB cases and had at least one HIV-positive case in each year between 2010 and 2012. These countries reported a total of 106545 cases. Of these, 45407 (42.6%) cases had an unknown HIV status and were therefore excluded (see table, Supplemental-Digital-Content 1).

Hence, a total of 61138 cases with known HIV status were eligible for our analysis; including 3347 (5.5%) cases known as HIV-positive. The cases' characteristics stratified by HIV status are presented in Table 1.

Comparison of tuberculosis treatment outcome by HIV status

HIV co-infected cases had a lower TB treatment success rate compared to HIV-negative cases (56.9% vs. 78.7% respectively; p<0.001). Compared to HIV-negative cases, more HIV co-infected cases died while being treated for TB (13.5% vs. 6.2% respectively; p<0.001). Of the cases who died while on TB treatment, HIV co-infected TB cases tended to be younger compared to HIV-negative cases (median age: 38 years vs. 61 years respectively; p<0.001). A higher proportion of cases "still on treatment" was observed among HIV-positive cases compared to HIV-negative ones (7.4% vs. 1.9% respectively; p<0.001). Treatment failure was higher in HIV-negative cases compared to HIV-positive cases (2.4% vs. 1.5% respectively; p=0.001). A higher proportion of HIV co-infected cases were lost to follow-up compared to HIV-negative cases (20.2% vs. 10.2% respectively; p<0.001) (Fig. 1a).

After excluding cases that were lost to follow-up (i.e. defaulted, transferred or with unknown outcome), the proportion of successfully treated cases remained higher in HIV-negative cases compared to HIV co-infected cases (88.3% vs. 71.7% respectively; p<0.001) (Fig. 1b). The treatment success among HIV co-infected TB cases was lower than in HIV-negative ones in all subgroups and did not reach the global target of an 85% treatment success rate using different inclusion criteria (see Figure, Supplemental-Digital-Content 2).

The effect of HIV on treatment success of tuberculosis

Out of all statistically evaluated covariates (gender, geographical origin, MDR-TB, major site of TB, previous treatment of TB, culture confirmation, microscopy result, and reporting year), only adding age to the model led to predefined change (≥10%) in the regression coefficient for HIV and therefore we retained age in the multivariable model as a potential confounder. The overall interaction between HIV and MDR-TB was significant (p<0.001) and therefore separate results regarding MDR-TB status are reported (Table 2). In the adjusted model, HIV co-infected cases had a lower chance of treatment success compared to HIV-negative TB cases in all MDR strata [Non-MDR-TB: odds ratio (OR) 0.24 CI 0.20-0.29; Unknown MDR-TB status: OR 0.26 CI 0.23-0.30; MDR-TB: OR 0.57 CI 0.35-0.91] (Table 2).

The age-adjusted probabilities of TB treatment success by HIV infection and stratified by MDR status are presented in the Figure 2.

HIV impact on each treatment outcome category of tuberculosis

In the multinomial regression model adjusted for age and corrected for clustering within countries, HIV-positive cases had significantly higher risk for death (Non-MDR-TB: RRR 4.30 CI 2.31-7.99; Unknown MDR-TB status: 5.55 CI 3.10-9.92; MDR-TB: 3.59 CI 1.56-8.28) and “still on treatment”

(Non-MDR-TB: RRR 7.27 CI 3.00-17.6; Unknown MDR-TB status: 5.36 CI 2.44-11.8; MDR-TB: 3.76 CI 2.48-5.71) relative to being successfully treated compared to HIV-negative ones. We did not find any significant association between HIV infection and TB treatment failure (Non-MDR-TB: RRR 0.50 CI 0.15-1.67; Unknown MDR status: 1.51 CI 0.86-2.64; MDR-TB: 0.51 CI 0.13-1.87). In HIV-positive cases, the relative risk of lost to follow-up over treatment success was significantly higher for both non-MDR-TB cases (RRR 2.30 CI 1.71-3.10) and cases with unknown MDR status (RRR 2.84 CI 1.73-4.64), but not for MDR-TB cases (RRR 0.85 CI 0.47-1.52) (Table 3).

Stratified by MDR status, the age-adjusted probabilities for each outcome category by HIV infection are presented in the Supplemental-Digital-Content 3.

Discussion

This study investigated the impact of HIV infection on TB treatment outcomes using European notification data. The strength of our work is that it is based on a large cohort from nine EU/EEA countries and applies a multilevel model in order to handle the correlation of TB cases within each country and therefore controlling for unobserved heterogeneity between countries [26]. Additionally, a systematic statistical evaluation of potential confounders and the HIV/MDR interaction allowed us to close the level of incertitude of the findings from other studies and confirm with high precision that HIV infection is a risk factor for an adverse TB treatment outcome. We found that the adjusted probability of TB treatment success was significantly lower among HIV-positive compared to HIV-negative TB cases in all MDR strata. The unsuccessful TB treatment was mainly manifested by an increased risk of death and being “still on treatment” (>12 months for non-MDR-TB; >24 months for MDR-TB) among HIV co-infected patients. We did not observe any statistically significant association between HIV infection and TB treatment failure.

The lower TB treatment success rate in HIV co-infected patients can be explained by difficulties in TB diagnosis and treatment in HIV co-infected patients. Alternation of the clinical manifestation of TB and lack of a rapid and sensitive TB diagnostic test in HIV co-infected patients might be responsible for delayed diagnosis and thus delayed treatment initiation, resulting in some of the negative treatment outcomes [11,29]. Treatment of TB in HIV co-infected patients presents with major challenges regarding the drug interactions between the rifamycins and some antiretroviral agents, overlapping toxic effects, and the occurrence of immune reconstitution inflammatory syndrome (IRIS) [30]. Malabsorption of antituberculosis drugs is common among patients with

advanced HIV [31], leading to low serum concentrations of drugs and therefore to unfavorable treatment outcomes.

The probability of TB treatment success was much lower among MDR-TB compared to non-MDR-TB both for HIV-negative and HIV-positive cases in our study population. In Europe, MDR-TB cases are known to have lower treatment success and there is an inverse association between TB treatment outcome and MDR-TB status [32]. This effect can be explained largely by the fact that treatment regimens for MDR-TB are less efficient and less well tolerated, in consequence, making treatment adherence difficult for patients [33].

The statistically significant interaction between MDR-TB and HIV on treatment success in our data suggests that considering the interaction is necessary when investigating the effect of HIV infection on TB treatment outcome in order to obtain a correct estimation. Our data show that HIV infection impacts the treatment success of MDR-TB cases to lesser extent than in non-MDR-TB cases but nevertheless significantly. This could be due to the fact that co-infection with HIV and MDR-TB may result in more care and adherence support to the patients. Existing data on treatment outcome of MDR-TB have shown inconsistent findings regarding the effect of HIV. In some studies, HIV was a predictor for poor treatment outcome among MDR-TB cases [34-36], while others did not indicate any association [37-40]. Age was a confounder in the relationship between HIV and treatment success in our analysis. It is well-known that increased age is a risk factor for an inadequate treatment outcome in the general population in the EU/EEA [32], and HIV co-infected TB cases were significantly younger compared to HIV-negative TB cases in our data. Also, delay in TB diagnosis and more advanced disease at presentation are common among elderly and contribute to increased mortality among them [41].

247 The probability of death during TB treatment was significantly higher among HIV co-infected TB
248 cases than among HIV-negative TB cases. It is well-documented in both developed and developing
249 countries that HIV co-infected TB cases suffer of high mortality while on TB treatment
250 [13,15,21,22]. A study from Southern Ethiopia found that there was no significant difference in the
251 risk of death regarding HIV status during the intensive phase of TB treatment, but the risk was
252 significantly higher among HIV co-infected cases in the continuation phase [42]. This increased
253 mortality can be due to the fact that TB progresses more rapidly in HIV co-infected patients
254 resulting in some excess mortality among them [43]. Immunological studies have also shown that
255 TB is associated both with increased HIV viral load and HIV diversity; leading to accelerated HIV
256 disease progression and early mortality [4]. However, many clinical and observational studies
257 attributed a high proportion of death among HIV co-infected TB cases to HIV-related complications
258 other than TB [21,22,30,42,44]. A meta-analysis showed that receiving ART reduces the mortality
259 during TB treatment for HIV-positive TB cases by between 44 to 71% [45]. In EU/EEA, it was
260 estimated that more than 85% of those diagnosed with HIV received ART in 2012 [46]. Data
261 available on the TB/HIV co-infected patients on ART are limited. According the *WHO Global*
262 *Tuberculosis Report 2013*, three of the nine countries included in our analysis provide information
263 on ART coverage among TB/HIV co-infected patients including Estonia, Portugal and Romania with
264 62%, 100% and 90% respectively [47].

265 Our data show that the risk of being “still on treatment” (>12 months for non-MDR-TB; >24
266 months for MDR-TB) was significantly higher among HIV co-infected patients than HIV-negative
267 patients. The treatment of TB in HIV-positive patients may be intermittent and extended due to
268 intercurrent diseases frequent in individuals infected with HIV, concerns of treatment failure or
269 relapse, potential drug interactions, clinical deterioration from IRIS, overlapping side-effects

and high pill burden compromising treatment adherence [11]. A study from the United States demonstrated that HIV was a risk factor for failing to complete TB treatment in time (≤12 months) [48] ,and in a French study HIV was associated with extensively long treatment of TB [49]. In Zaire, an observational study showed a high relapse rate after one year of standard TB therapy among HIV co-infected cases [50], while a clinical trial showed that extending TB treatment from 6 months to 12 months significantly reduced the rate of relapse among HIV co-infected cases [51]. A meta-analysis showed that longer duration of rifamycin therapy (at least 8 months) might be associated with better outcomes [52]. Since the majority of studies on TB treatment outcome excluded cases "still on treatment" from the analysis, there are only limited data that provide evidence for the effect of treatment duration on treatment outcome. The World Health Organization recommends that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients acknowledging that the data quality of the studies included in the evidence base was low [53]. Thus very basic questions on treatment of active TB in HIV co-infected patients, including duration of treatment remain unresolved, and future randomized clinical trials are urgently needed [52].

No statistically significant difference in the risk of treatment failure was observed between HIV-positive and HIV-negative TB cases. This is consistent with other findings from studies that showed that treatment failure of TB was not related to HIV infection [21,54]. Among non-MDR-TB cases, the risk of loss to follow-up was higher among HIV-positive cases than HIV-negative ones. That can be attributed to some underlying factors correlated with HIV infection such as intravenous drug use (IDU) as indicated in a study done in Spain [15].

Our data show that the treatment success of TB among HIV co-infected cases in EU/EEA settings was markedly low and did not reach the global target of 85% treatment success rate; the application of different inclusion criteria did not change this result. This confirms that, even in settings like the EU/EEA where ART is available and accessible, the TB/HIV co-epidemic presents a serious threat to public health. Since such patients are treated for two diseases, special case management is strongly recommended in order to achieve the optimal outcome in terms of treatment response and prevention of drug resistance for both diseases [11]. However, our data showed that the treatment success among HIV-negative cases was also below the global target. A current study evaluating the TB treatment outcome in the EU/EEA over 10 years showed the overall treatment success was 78% and none of the EU/EEA countries included in our analysis reached the global target in any years between 2002 and 2011 [32].

There are some limitations to this study. Early initiation of ART among co-infected patients is known to decrease mortality [11] and ART during TB treatment can be a protective factor against default from TB treatment [55]. Due to the unavailability of information on ART we could not assess its effects on our findings. However, by using multilevel model corrected with a random slop we could control for the different relationship between HIV and TB treatment outcome for the different countries (among other factors also the unobserved heterogeneity of ART coverage and availability between countries) and therefore enhance the generalizability of our findings. Also, we could not explore whether CD4+ cell count, HIV viral load, homelessness, alcoholism, drug use, or comorbidities were associated with TB treatment outcome since these data are not collected at the EU/EEA level. According to a study from Spain, drug use substantially affects mortality and many HIV-positive patients were also drug users [15], hence drug use might be a potential confounder in the analysis for which we could not correct. Collecting information on risk

314 factors such as co-morbidities, substance use and social determinants are necessary to increase
315 our understanding, empower tailored interventions and develop targeted responsive strategies
316 [56]. Our study included data from nine of 31 EU/EEA countries which represent 49% of all TB
317 cases reported to the ECDC from EU/EEA for the period 2010-2012 [25]. Therefore, our data
318 pertain to our nine EU/EEA countries and are not necessarily generalizable to the whole of
319 EU/EEA. Finally, 41% of the cases reported from the nine EU/EEA countries in our analysis were of
320 unknown HIV status and therefore excluded. Since the reason for the absence of a HIV test result
321 is unknown, it is not possible to hypothesize how this affects our findings. Notably, the proportion
322 of cases of foreign origin was twofold higher in TB cases with known HIV status (included cases)
323 than in cases with unknown HIV status (excluded cases). However, it is known that the treatment
324 success rate was slightly higher among native cases than among cases of foreign origin in the
325 EU/EEA [32].

326 In conclusion, this large study confirms that HIV infection is a strong risk factor for an adverse TB
327 outcome in all MDR-TB strata. Our findings strongly reinforce the evidence that HIV infection is
328 associated with higher mortality in TB co-infected patients than HIV-negative TB patients.
329 Additionally, an increased risk of still being on treatment (>12 months for non-MDR-TB; >24
330 months for MDR-TB) is another indicator of less successful TB regimens in HIV-positive patients.
331 This result encourages future studies including randomized clinical trials to investigate the optimal
332 duration of TB treatment in HIV co-infected individuals.

Abbreviations

TB: Tuberculosis; MDR: Multidrug resistant; ART: Antiretroviral therapy; IRIS: Immune reconstitution inflammatory syndrome; ECDC: European Centre for Disease Prevention and Control; EU/EEA: European Union and European Economic Area; TESSy: The European Surveillance System; IQR: Interquartile range; CI: Confidence interval; OR: Odds ratio; RRR: Relative risk ratio.

Note

The views and opinions of the authors expressed herein do not necessarily state or reflect those of the ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data.

Author's contributions

Concept and design (BK, WH), literature search (BK), statistical analysis (BK), interpretation of the data (BK, WH, GK, SC, MvdW, VH), drafting the manuscript (BK) and critical revision of the manuscript for important intellectual content (BK, WH, GK, SC, MvdW, VH, OH). All authors read and approve the final manuscript.

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Supplemental-Digital-Content 1. Comparison of tuberculosis characteristics between cases with known HIV status to those with unknown HIV status in nine EU/EEA countries, TESSy 2010-2012

Characteristics	Tuberculosis cases with unknown HIV status	Tuberculosis cases with known HIV status	P-value
Total cases 100% (N=106545)	42·6% (N=45407)	57·4% (N=61138)	
Age in years, Median [IQR]	44 [30-59]	42 [30-56]	<0·001*
Male gender	66·3%	67·9%	<0·001†
Cases of foreign origin	6·0%	12·9%	<0·001†
Extrapulmonary TB	20·9%	17·8%	<0·001†
Multidrug-resistant TB	9·1%	9·6%	0·098†
Previously treated TB	19·6%	16·2%	<0·001†
Bacteriology confirmed TB	72·7%	77·9%	<0·001†
Treatment success	74·8%	76·7%	<0·001†

***Obtained using the Mann-Whitney U-test for difference in the sum of ranks.**
†Obtained using the χ2 test for difference in percentage.
EU/EEA: European Union and European Economic Area; TESSy: The European Surveillance System; TB: tuberculosis.

Table 1. Characteristics of tuberculosis cases stratified by HIV status in nine EU/EEA countries, TESSy 2010-2012

Demographic and clinical characteristics of TB cases N=61138 (100%)	Non-HIV co-infected TB cases N=57791 (94·5%)	HIV co-infected TB cases N=3347 (5·5%)	P-value
Gender	57789	3347	<0·001*
Female	18695 (32·4%)	905 (27·0%)	
Male	39094 (67·6%)	2442 (73·0%)	
Age in years			<0·001†
Median [IQR]	43 [30-57]	39 [31-45]	
Age group	57754	3343	
<15	2390 (4·1%)	21 (0·6%)	<0·001*
15-44	28612 (49·5%)	2386 (71·4%)	
45-64	17946 (31·1%)	854 (25·5%)	
>64	8806 (15·3%)	82 (2·5%)	
Geographical origin	57760	3343	<0·001*
Native	50701 (87·8%)	2491 (74·5%)	
Foreign	7059 (12·2%)	852 (25·5%)	
Major site of TB	57769	3345	<0·001*
Pulmonary	47778 (82·7%)	2448 (73·2%)	
Extrapulmonary	9991 (17·3%)	897 (26·8%)	
Multidrug-resistant TB	21147	976	0·003*
No	19157 (90·6%)	837 (85·8%)	
Yes	1990 (9·4%)	139 (14·2%)	
Previously treated for TB	56866	3247	<0·001*
No	47704 (83·9%)	2646 (81·5%)	
Yes	9162 (16·1%)	601 (18·5%)	
Culture confirmed	52418	2824	<0·001*
No	11669 (22·3%)	541 (19·2%)	
Yes	40749 (77·7%)	2283 (80·8%)	
Reporting year	57791	3347	<0·001*
2010	18144 (31·4%)	1170 (35·0%)	
2011	19839 (34·3%)	1114 (33·3%)	
2012	19808 (34·3%)	1063 (31·7%)	
EU/EEA countries‡	57791	3347	<0·001*
Low TB incidence	15597 (27·0%)	1466 (43·8%)	
High TB incidence	42194 (73·0%)	1881 (56·2%)	
EU/EEA countries	57791	3347	<0·001*
Belgium	2175 (3·8%)	146 (4·4%)	
Bulgaria	4973 (8·6%)	10 (0·3%)	
Czech Republic	449 (0·8%)	14 (0·4%)	
Estonia	764 (1·3%)	125 (3·7%)	
Ireland	284 (0·5%)	51 (1·5%)	
Lithuania	3429 (5·9%)	71 (2·1%)	
Portugal	5892 (10·2%)	953 (28·5%)	
Romania	27136 (46·9%)	722 (21·6%)	
Spain	12689 (22·0%)	1255 (37·5%)	

***Obtained using the χ2 test for difference in percentage.**

†Obtained using the Mann-Whitney U-test for difference in the sum of ranks.

‡Low-incidence countries were defined as those with less than 20 TB cases per 100000 population (Belgium, Czech Republic, Ireland, and Spain), and high-incidence countries as those with 20 or more TB cases per 100000 population (Bulgaria, Estonia, Lithuania, Portugal, and Romania)

EU/EEA: European Union and European Economic Area; TESSy: The European Surveillance System; TB: tuberculosis.

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Table 2. Multilevel multivariable logistic regression model of the impact of HIV infection on the treatment success of tuberculosis in nine EU/EEA countries, TESSy 2010-2012

	Odds ratio [95% CI]	P-value
Non MDR-TB		
Crude	0·31 [0·25-0·39]	<0·001
Adjusted*	0·24 [0·20-0·29]	<0·001
Unknown MDR-TB status		
Crude	0·25 [0·22-0·29]	<0·001
Adjusted*	0·26 [0·23-0·30]	<0·001
MDR-TB		
Crude	0·68 [0·43-1·07]	0·101
Adjusted*	0·57 [0·35-0·91]	0·018

***Adjusted for age.**

Outcome coding: Unsuccessful treatment=0; Treatment success=1.

The model is corrected with both a random intercept and a random slope for HIV at the country level using an unstructured covariance matrix.

EU/EEA: European Union and European Economic Area; TESSy: The European Surveillance System; MDR: Multidrug-resistant; TB: tuberculosis.

546

Table 3. Multinomial logistic regression analysis of the effect of HIV infection on treatment outcome categories of tuberculosis in nine EU/EEA countries, TESSy 2010-2012

Treatment outcome categories	Non-MDR-TB	Unknown MDR status	MDR-TB
	Adjusted relative risk ratio (RRR)* [CI 95%]		
Treatment success	Base outcome (reference)		
Death			
HIV-negative	1		
HIV-positive	**4·30 [2·31-7·99]**	**5·55 [3·10-9·92]**	**3·59 [1·56-8·28]**
Still on treatment			
HIV-negative	1		
HIV-positive	**7·27 [3·00-17·6]**	**5·36 [2·44-11·8]**	**3·76 [2·48-5·71]**
Treatment failure			
HIV-negative	1		
HIV-positive	0·50 [0·15-1·67]	1·51 [0·86-2·64]	0·51 [0·13-1·87]
Lost to follow-up			
HIV-negative	1		
HIV-positive	**2·30 [1·71-3·10]**	**2·84 [1·73-4·64]**	0·85 [0·47-1·52]

Notes: Figures in bold are statistically significant at $p < 0·05$.

*The model was adjusted for age and corrected for clustering within countries.

EU/EEA: European Union and European Economic Area; TESSy: The European Surveillance System; MDR: Multidrug-resistant; TB: tuberculosis.

547

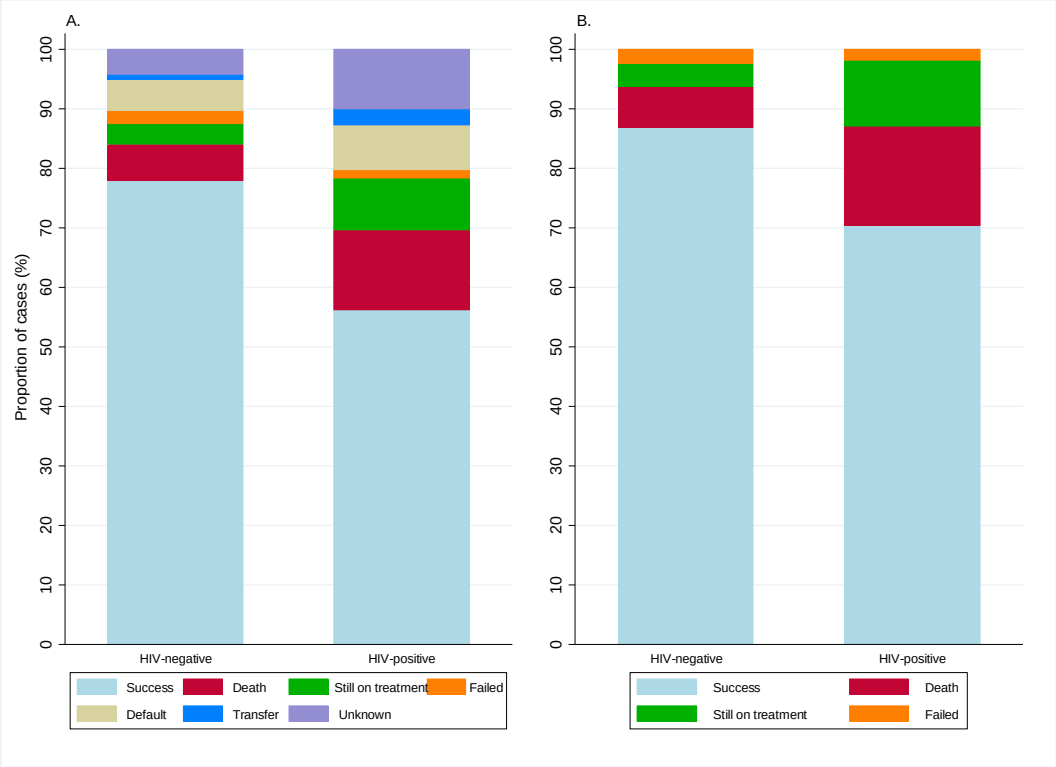
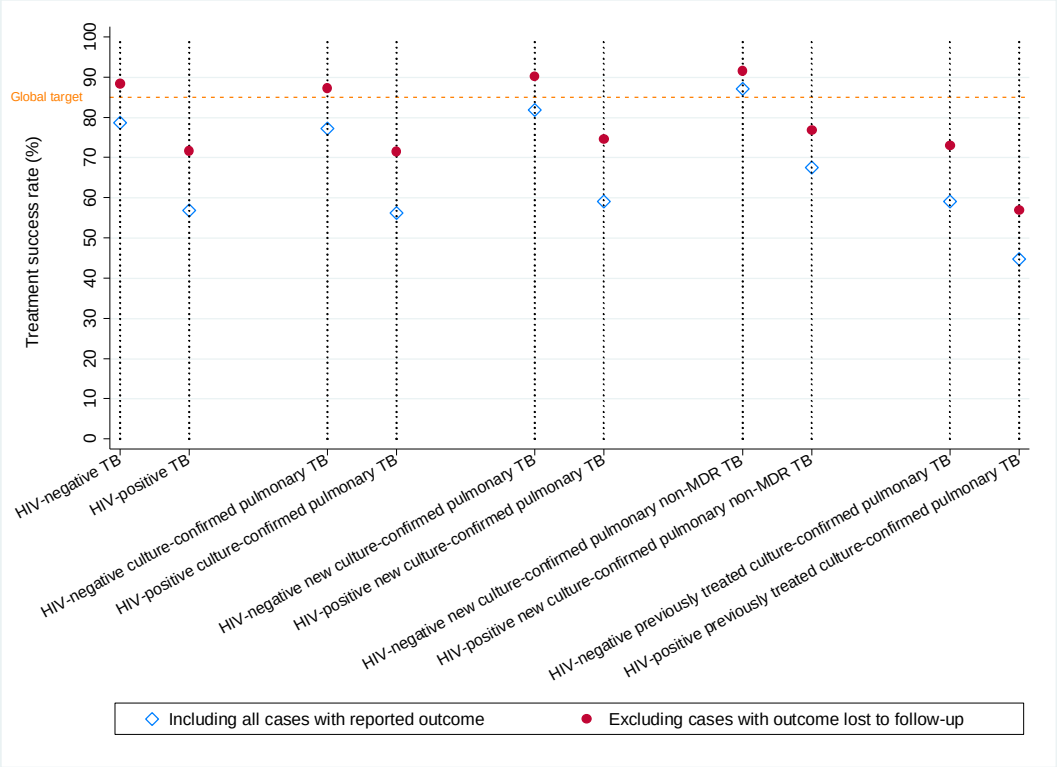


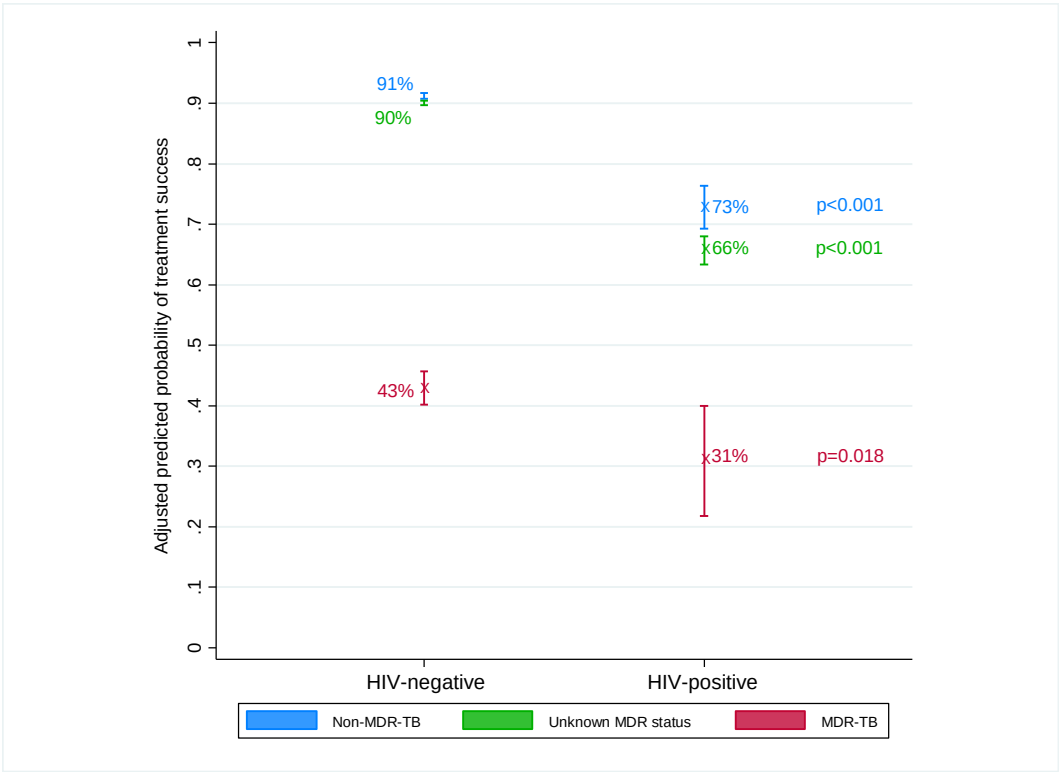
Figure 1. Treatment outcome of tuberculosis by HIV status in nine EU/EEA countries*, TESSy 2010-2012:
A. Including all cases with reported treatment outcome **B.** Excluding cases with treatment outcome lost to follow-up (i.e. defaulted, transferred or had an unknown outcome).
* Including: Belgium, Bulgaria, Czech Republic, Estonia, Ireland, Lithuania, Portugal, Romania, and Spain.
Treatment outcome was reported at 12-month follow-up, while for MDR-TB cases at 24-month follow-up.
EU/EEA: European Union and European Economic Area; TESSy: the European Surveillance System; MDR: multidrug resistant; TB: tuberculosis.



Supplemental-Digital-Content 2. Treatment success rate of TB cases stratified by HIV status in nine EU/EEA countries*, TESSy 2010-2012.

TB: tuberculosis; MDR: multidrug resistant; EU/EEA: European Union and European Economic Area; TESSy: the European Surveillance System.

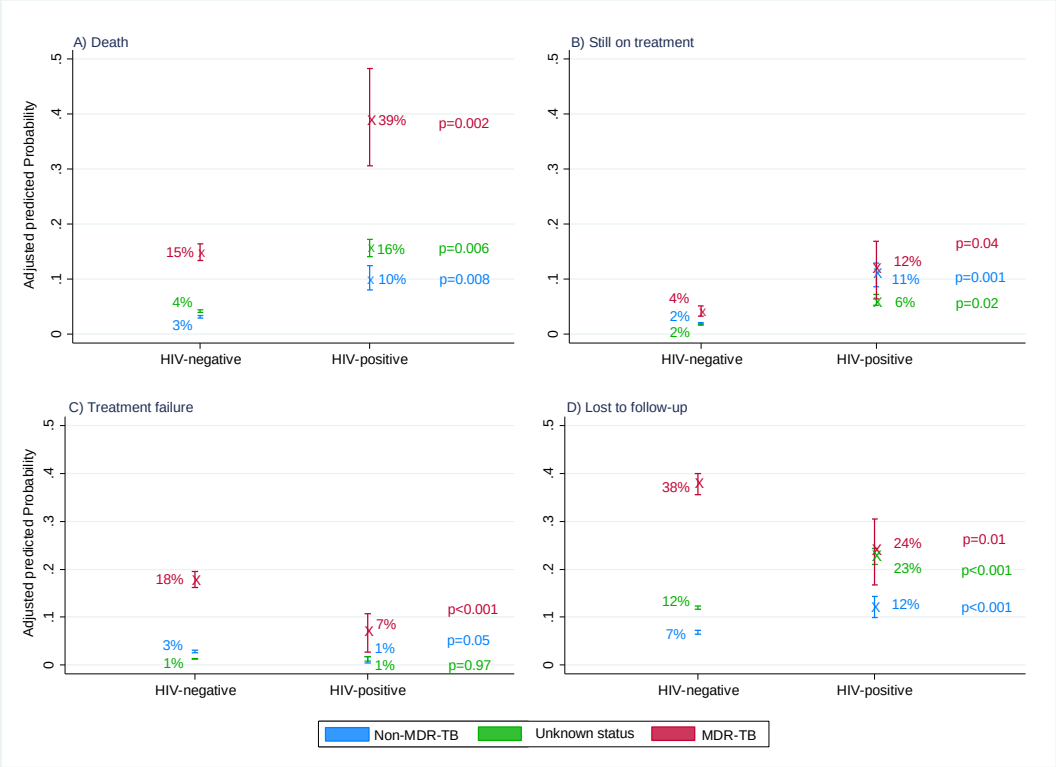
* Including: Belgium, Bulgaria, Czech Republic, Estonia, Ireland, Lithuania, Portugal, Romania, and Spain.



564

565 **Figure 2. Age-adjusted predicted probabilities of treatment success of tuberculosis by HIV infection and stratified by multidrug-**
566 **resistant TB status.**
567 TB: tuberculosis; MDR: multidrug resistant.

568



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570 **Supplemental-Digital-Content 3. Age-adjusted predicted probabilities by HIV infection and stratified by MDR status for tuberculosis**
571 **cases who A.** died while on TB treatment; **B.** were still being on TB treatment; **C.** had TB treatment failure; **D.** were lost to follow-up.
572 TB: tuberculosis, MDR: multidrug resistant
573