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TB-HIV co-infection in EU and EEA countries

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Abstract (Maximum 200 words- now at 199)

In order to ensure the availability of resources for tuberculosis (TB) and HIV management and control, it is imperative that countries monitor and plan for co-infection to identify, treat, and prevent TB-HIV co-infection thereby reducing TB burden and increasing healthy life years of people living with HIV.

A systematic review was undertaken to determine the burden of TB-HIV infection in the European Union and European Economic Area (EU/EEA). Data on the burden of HIV-infection in TB patients and risk factors for TB-HIV co-infection from studies that collected information in 1996 and later, regardless of the year of initiation of data collection, in EU/EEA were extracted and a narrative synthesis presented.

The proportion of HIV-co-infected TB patients varied from 0 to 15%. Western and Eastern countries had higher levels and increasing trends of infection over time compared to Central EU/EEA countries. Groups at higher risk of TB-HIV co-infection were males, young adults, foreign-born persons, homeless, injecting-drug users and prisoners.

Further research is needed into the burden and associated risk-factors of co-infection in Europe, to help plan effective control measures. Increased HIV testing of TB patients and targeted and informed strategies for control and prevention could help curb the co-infection epidemic.

Keywords *(6 max, alphabetically listed in full, no abbreviations)* co-infection, Europe, Human immunodeficiency virus, risk factors, tuberculosis, surveillance.

Introduction Tuberculosis (TB) and HIV are global public health problems with considerable interaction. TB has been identified as one of the leading causes of death among HIV-infected persons(1). People living with HIV/AIDS (PLWHA) infected with *Mycobacterium tuberculosis* are at ten-times greater risk of developing TB compared to HIV-uninfected persons(2). Tuberculosis is often difficult to diagnose in a person infected with HIV due to the atypical presentation of the disease(3;4). The presence of TB also complicates HIV infection through a number of mechanisms including increased viral replication and CD4/CD8 cell proliferation(5). In addition, TB-HIV co-infection complicates the management of both diseases, with drug interactions, overlapping toxicity profiles, immune reconstitution inflammatory syndrome and a high tablet burden required to treat both diseases, which may reduce adherence(6). Nevertheless, data suggest that early TB treatment in HIV-infected people reduces morbidity and mortality and appropriate treatment regimes are often successful(7).

In order to respond to the increasing commitment to provide comprehensive care and support to HIV-infected TB patients, information is needed on the burden of co-infection and how this changes over time, particularly among at-risk populations. This information can influence policy and help secure resources for preventing, detecting and treating TB-HIV co-infection. In the European Union/European Economic Area (EU/EEA), information on the burden of TB-HIV co-infection and risk groups appears limited. To our knowledge, there are no published systematic reviews on this topic. Annual data collection rounds of the European Centre for Disease Prevention and Control (ECDC) have estimated levels for 2008 in EU/EEA countries to range between 0% of TB cases in Central EU countries to 14.6 % in Portugal(8;9) However, 16 of the 30 EU/EEA countries did not report numbers of TB cases with HIV infection to ECDC in 2008. We conducted a systematic review to improve understanding of TB-HIV co-infection levels and risk factors in EU/EEA countries.

Methods

We performed a systematic review of published literature and other sources not commercially published or peer-reviewed, such as reports, government and academic data- “grey literature”,- which provided information on the burden of TB-HIV co-infection and/or risk factors for co-infection in EU/EEA counties in all European languages.

Search strategy

Nine academic literature databases were searched, including, Medline; Scopus; BIOSIS; EMBASE; CINHAL: web of science; DARE; global health; index to theses; EDLIS, between September and October 2009. We included different terms for “TB”, “HIV”, “HIV/AIDS”, and “Europe” in a number of European languages (e.g. SIDA, tuberculose, etc). These were combined with the following qualifiers: “co-infection”, “coinfection”, “surveillance”, “prevalence”, or “incidence”.

Google Scholar was used for a general search of the grey literature and the 'related topics' search on all relevant information was used to maximise findings. Additionally, all EU/EEA countries' Ministry of Health/Statistics web sites were searched for TB and HIV reports published in the last 10 years, and any reports/manuscripts on TB-HIV co-infection. We also asked ECDC national TB and HIV contacts to identify additional reports or documents on TB-HIV co-infection for their country in our survey of national contact points(10). While the association of TB disease with HIV infection could more appropriately be referred to as "co-morbidity", the term "co-infection" is most widely used in the literature and was therefore used here to signify the concurrent presence of TB disease with HIV infection.

The primary concern of the initial search was sensitivity. Specificity was ensured by abstract/title and full document review. Relevant studies were obtained without language restrictions.

Inclusion/ exclusion criteria

Titles and abstracts of all documents identified were screened by one main reviewer (LP) for TB-HIV co-infection incidence, prevalence or risk factor data within EU/EEA countries. Second reviewers (LD/MK) validated the inclusion process by screening 50% of the titles/abstracts, demonstrating that no potential publications were missed. All documents fulfilling the initial criteria, and those lacking abstracts, were retrieved in full-text. These were reviewed by one main reviewer, with 10% assessed by a second reviewer, identifying no disagreements. All documents meeting inclusion criteria for title/abstract review and reporting on 1) the number/proportion and/or rate of HIV co-infection among TB cases or 2) risk factors for TB-HIV co-infection compared to mono-infected HIV or TB cases, or non-diseased persons were included.

Only the most complete and recent information was extracted in instances where there were multiple published estimates of the same data to avoid duplication. National publications were given precedence over international publications, as these were considered to be closer to the source, regardless of differences in data reported. Studies from any non-EU/EEA countries were excluded, as were literature reviews, summaries, and case reviews. Studies providing data collected before 1996 only were excluded as the aim of this review was to examine current trends in co-infection in the post-HAART era. However, publications covering periods both before and after 1996 were included to capture as much information as possible.

Data extraction

Data were extracted using a pre-defined Excel database by one reviewer, with 10% validation by a second reviewer. Information collected included study and participant characteristics, numbers and proportions of co-infection and/or risk factors, as well as potential biases and points raised in the discussion such as testing/screening methods and coverage assessment of co-infection status and other relevant background information.

Data analysis

Estimates of co-infection were expected to differ between countries and data sources (i.e. national surveillance and local or hospitals populations). No attempt was therefore made to pool data, a descriptive synthesis was undertaken, and recent trends described.

Results

---Figure 1 – Flowchart of inclusion of manuscripts for the primary and secondary outcomes. ---

Following removal of duplicates and initial abstract review we identified 380 papers for full text retrieval from 6,632 references in the published and grey literature. After full inspection 61 documents were included (54 on burden of TB-HIV only, six providing risk factor information only, and one presenting both). The full details of the article retrieval process is summarised in figure 1. Nine studies provided data on the number of PLWHA co-infected with TB, which are not included in this study.

Study characteristics

All 55 documents providing information on the burden of TB-HIV co-infection reported prevalence of HIV in TB patients, with one also measuring incidence(11). The majority of papers provided national estimates (37/55, 67%), the remaining regional or local. The greatest number of studies was from Spain, followed by France. For 19 countries the only sources of data were from four international surveillance reports (8;12-14). Information on socio-demographic characteristics of patients was provided in 26 studies.

The seven risk factor studies were from Spain (5/7), France and the Netherlands. Most were longitudinal studies (4/7), one was cross-sectional and two were obtained from surveillance studies. The majority of papers (5/7) presented risk factors for co-infection, with PLWHA as the baseline population.

Overall burden of TB-HIV co-infection

---Figure 2- Map of most recent data on proportion of TB patients co-infected with HIV in EU/EEA countries. ---(8;13;15-19)

Data on HIV co-infection among TB patients was identified for 23 of the 30 EU/EEA countries. The most recent national estimates are shown in Figure 2. Prevalence varied between 0% in Bulgaria, Slovenia and Slovakia to 15% in Portugal and Iceland. In general, a very low level of co-infection was observed in Central EU/EEA countries. Information on the burden of co-infection in capital cities was available for four countries. Prevalence was 7.3% in London

(2005), 7.5% in Paris (2001), 8.6% in Brussels (2008), and 14.3% in Madrid (2003). Except for London, where prevalence was the same as the national average, the co-infected proportion in these cities was higher than the national average.

Trends in TB-HIV co-infection

---Figure 3- Trends in the prevalence of HIV co-infection in TB patients in EU/EEA countries by year of reporting. ---

Between 2000 and 2008, Estonia, Latvia, Lithuania, Belgium, Denmark and England and Wales, as well as the Czech Republic and Romania reported increasing proportions of HIV co-infection among TB patients, although in some this plateau in the latest years of observation (Figure 3). Data for France is also suggestive of an increase in co-infection, but additional time points are required to confirm this. Spain and Portugal show a decline in co-infection levels, and Finland may be exhibiting a downward trend.

Characteristics of co-infected cases

---Figure 4 - Socio-demographic characteristics of co-infected cases compared to mono-infected TB cases (most recent data). ---(11;15;18;20-28)

Demographic characteristics were reported for few countries, the most recent data is shown in Figure 4. The majority of co-infected cases were male and young adults (Figure 4A and B), and their proportion was larger than in non co-infected patients. In North-western EU countries, cases were mostly foreign-born while in Spain and Italy around 30% were foreign-born.

In Spain, a large proportion of co-infected cases were IDU compared to all TB cases 59% vs. 8% respectively. Although no comparable mono-infected data was available, Latvia showed a similarly high proportion of IDU co-infected cases.

---Table 1-Association between age group and TB-HIV co-infection and male gender and TB-HIV co-infection. ---(23;29-33)

---Table 2- Association between CD4 count and TB-HIV co-infection and HIV transmission route and TB-HIV co-infection. ---(29-33)

---Table 3- Association between risk behaviour and TB-HIV co-infection. ---(23;32-34)

Risk factors for TB-HIV co-infection

In the seven papers that statistically examined risk factors for TB/HIV co-infection, gender, age, CD4 count at HIV diagnosis, HIV transmission route and TB risk groups were most often studied (Tables 1-3). Co-infection was associated with male gender in three of five studies (Table 1).Younger adults (aged 25-30 to 45) tended to have a higher risk of TB co-infection compared to children and older adults, but this was statistically significant in only two of the four relevant studies (Table 1).

The risk of TB disease was higher in PLWHA who presented with lower CD4 cell counts (below 200 cells/mm^3) at HIV diagnosis in three studies (Table 2). A fourth study among AIDS patients found that TB was more likely to be reported as the AIDS-defining illness at higher CD4 counts (200-350 cells/mm^3) than other AIDS defining illnesses.

Acquiring HIV through injecting drug use was significantly associated with higher risk of TB co-infection than acquisition through sexual contact in three of the four studies investigating probable route of HIV infection(29;33;35).

Combinations of risk behaviours and lifestyles, including homelessness, imprisonment, alcohol-abuse, sharing syringes and close contact with a TB case, were associated with an increased risk of being TB-HIV co-infected (Table 3)..

Two studies investigated the risk of co-infection by place of birth or citizenship, showing contradictory evidence of whether being foreign-born conferred increased risk of co-infection. One study from France(29), found an increased risk of TB in foreign-born PLWHA. Conversely, a Dutch study, demonstrated that TB patients of Asian and Eastern EU/EEA citizenship had a decreased risk of HIV diagnosis among TB patients compared with Dutch nationals(23). When comparing such data it should be considered that the definition of citizenship might vary between countries and the ethnic distribution may vary as well. Both studies also looked at area of residence, showing a higher risk of co-infection in the urban areas ($p<0.001$ (23;29).

Discussion

Published data on the proportion of TB patients co-infected with HIV show levels are highest in Iceland and Portugal (15%) and lowest in central EU/EEA countries (<1%). Increasing trends were observed in the Baltic States as well as Western EU countries, the Czech Republic and Romania. Socio-demographic characteristics and risk factors for TB-HIV co-infection were only reported for a handful of countries. In these countries males, young adults, IDU, homeless, prisoners, those living in urban areas and, in some countries, foreign born persons were at higher risk of co-infection.

Strengths and limitations

This review used a sensitive approach identifying a large number of publications to ensure all information was captured. Although we were not able to check for evidence of publication bias, the comprehensive search undertaken minimised the potential for missing studies. A limitation is the inherent observational nature of surveillance studies associated with biases and confounding. Comments in our survey of national HIV and TB contacts to the ECDC suggest that surveillance systems may under-represent marginalised populations(9;10). The majority of studies presenting data on risk factors and demographic characteristics were conducted in Spain, and data were only available for a small number of countries. The heterogeneous nature of the populations and infrastructures within the EU/EEA, hinder the generalisation of this information to the whole of Europe. Furthermore, differences in the design of and populations covered by these studies only allowed for a descriptive synthesis of the evidence available. We included both demographic data from surveillance reports, and risk factor data from observational studies which increases heterogeneity of this data. However because of the limited number of observational studies, the demographic information was obtained to strengthen our results. Despite these limitations, findings were in agreement with knowledge on risk groups for TB and/or HIV separately, and/or studies from outside the EU/EEA, and countries with similar populations and infrastructure may be found to have similar risk groups.

This is the first comprehensive overview of this subject in EU/EEA and provides useful data for planning and evaluation of control measures.

Trends in TB-HIV co-infection

The distribution of co-infection across EU/EEA is in agreement with what is reported by ECDC and in our survey of national contacts(8;10). The burden of co-infection follows the national prevalence of HIV in these countries(8) and the country-specific prevalence of drug users. Some of the observed time-trends may be due to changes in testing activity and reporting practices, and may not represent an increase in the true number of HIV-infected TB patients, but in the diagnosed burden. However, it is interesting to note that countries such as Spain and Italy with higher levels of co-infection in IDU and homeless populations, show decreasing rates of TB-HIV co-infection, while countries with higher levels of HIV-infection in foreign-born people had increasing rates. This suggests that the increases in some countries may be related to migration and decreases to strengthened control in IDU and homeless populations. Further efforts are required to control TB in other parts of the world to reduce the risk in migrant populations in these countries.

HIV prevalence in TB patients was generally higher in capital cities and urban areas were found to be associated with an increased risk of co-infection. This is in agreement with previous data from non-EU countries(36) and may be related to the greater number of high-risk individuals for TB and/ or HIV co-infection in these areas(37;38). Urban conditions such as poverty and overcrowding have also long

been associated with TB(39;40). Studies of hospital in-patients also tended to show a higher prevalence of HIV co-infection than the national average. This is to be expected as TB-HIV co-infected patients are more likely to have complex needs, drug interactions and toxicities, and are therefore more likely to be in contact with hospitals.

Risk factors/groups for TB-HIV co-infection

The higher risk of co-infection in males found in 4 studies is consistent with the observation that both TB(8) and HIV(41) are more common among men in Europe(13). This reflects the more prominent transmission of HIV through MSM, and via injection drugs, of which a higher proportion of users is male (30, 32). Co-infection was more prevalent in the 15-45 age group in 5 studies, reflecting the higher proportion of HIV in this group, or more frequent HIV testing in young adult TB cases (23,29,31). Five of seven countries where the data were available showed a majority of the TB-HIV co-infected patients to be born abroad. These countries have high levels of migration from parts of the world with generalised TB and HIV epidemics. Countries where the majority of migrants originate from areas with concentrated epidemics, for example Spain which receives more migrants from Latin American countries, show a different pattern of co-infection. Based on three Spanish studies, people living with HIV/AIDS with lower CD4 counts, mainly as a result of late diagnosis, were more likely to have TB disease compared to those with a higher CD4 count (32). Among persons diagnosed with an AIDS defining illness in France, TB was diagnosed at higher CD4 cell counts than other AIDS defining illnesses. This is consistent with findings that TB occurs earlier in HIV infection than other opportunistic diseases (42;43), highlighting the need to monitor PLWHA for TB throughout the course of their infection.

Several countries have highlighted the diversity in the level of co-infection across population groups. These findings provide evidence for more robust monitoring of co-infection in EU/EEA countries to develop targeted strategies to reduce HIV and TB infection. Although demographic and clinical data pertaining to persons living with HIV and/or TB is available in many countries they are not always reported on. Reporting of this information and analysis to determine statistical associations between co-infection and demographics analysis of statistics association would provide much needed information to tailor effective control strategies.

Clinical implications

The results of this review highlight how some population groups affected by TB and HIV co-infection are particularly vulnerable, suggesting that efforts for identifying, treating and raising awareness for both diseases, should be considered by countries with high levels of co-infection in these populations. The survey of TB and HIV

contact points shows limited overlap in risk groups targeted for TB and for HIV screening; IDUs and prisoners are screened for both infections in eight countries, and migrants in nine(10). In order to capture and effectively treat all co-infected patients, some countries with higher co-infection burdens might benefit from screening risk groups for both infections. In addition, various studies have shown that many TB patients are not tested for HIV(10;44-46). Further improvements in offering HIV testing to all TB patients as recommended by WHO are needed(47).

Conclusion

Co-infection levels in EU/EEA countries ranged from 0 to 15% and were in the same range as those reported from comparable parts of the world, (e.g. the United States 12% HIV-positive TB cases in 2007, Canada (5.7%) Australia (3.2%) and Japan (0.5%) (48-51). The increasing levels observed in a number of EU/EEA countries are concerning, efforts to scale up control of both infections as well as further monitoring of the trends of co-infection are therefore required.

Men, young adults, foreign-born people, those living in urban areas, as well as injecting drug users, homeless and prisoners were identified as higher risk groups for TB-HIV co-infection. The information obtained in this review indicates that a diverse and varied approach is required to deal with the burden and population groups at risk of TB-HIV co-infection in EU/EEA countries. Greater use of available demographic and clinical data, as well as further, standardised, Europe-wide research would help increase our understanding of co-infection risk.

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References

(1) Sharma SK, Mohan A, Kadhiravan T. HIV-TB co-infection: epidemiology, diagnosis & management. Indian J Med Res 2005 Apr;121(4):550-67.

(2) Liberato IR, de Albuquerque MF, Campelo AR, de Melo HR. Characteristics of pulmonary tuberculosis in HIV seropositive and seronegative patients in a Northeastern region of Brazil. Rev Soc Bras Med Trop 2004 Jan;37(1):46-50.

(3) Mendelson M. Diagnosing tuberculosis in HIV-infected patients: challenges and future prospects. Br Med Bull 2007;81-82:149-65.

(4) Sterling TR, Pham PA, Chaisson RE. HIV infection-related tuberculosis: clinical manifestations and treatment. Clin Infect Dis 2010 May 15;50 Suppl 3:S223-S230.

(5) Toossi Z. Virological and immunological impact of tuberculosis on human immunodeficiency virus type 1 disease. J Infect Dis 2003 Oct 15;188(8):1146-55.

(6) Pozniak AL, Collins S, Coye KM, Freedman AR, Johnson MA, Lipman MCI, et al. British HIV Association guidelines for the treatment of TB/HIV co-infection 2009. London: BHIVA (in consulation); 2010.

(7) Schiffer JT, Sterling TR. Timing of antiretroviral therapy initiation in tuberculosis patients with AIDS: a decision analysis. J Acquir Immune Defic Syndr 2007 Feb 1;44(2):229-34.

(8) European Centre for Disease Prevention and Control/WHO RegionalOffice for Europe. Tuberculosis surveillance in Europe 2008. Stockholm; 2010.

(9) Kruijshaar M, Pimpin L, Abubakar I, Rice R, Delpech V, Drumright LN, et al. The burden of TB-HIV in the EU/EEA - how much do we know? A survey of TB-HIV surveillance practices and results. 2011.

(10) European Centre for Disease Prevention and Control/ World Health Organization Europe. Survey on TB-HIV Co-infection in EU/EEA Countries 2009/2010. Stockholm: European; 2011.

(11) Baussano I, Bugiani M, Gregori D, Pasqualini C, Demicheli V, Merletti F. Impact of immigration and HIV infection on tuberculosis incidence in an area of low tuberculosis prevalence. Epidemiology and Infection 2006;134(6):1353-9.

(12) EuroHIV. HIV/AIDS Surveillance in Europe. Mid-year report 2006. Saint-Maurice: French Institute for Public Health Surveillance; 2007. Report No.: 74.

(13) Lazarus JV, Olsen M, Ditiu L, Matic S. Tuberculosis-HIV co-infection: policy and epidemiology in 25 countries in the WHO European region. HIV Medicine 2008 Jul;9(6):406-14.

(14) World Health Organization. Global tuberculosis control : epidemiology, strategy, financing : WHO report 2009. Geneva: World Health Organization; 2009.

(15) French CE, Glynn JR, Kruijshaar ME, Ditah IC, Delpech V, Abubakar I. The association between HIV and antituberculosis drug resistance. European Respiratory Journal 2008;(3):718-25.

(16) KNCV tuberculosefonds. 'Tuberculosis in the Netherlands 2008' Surveillance report of the Tuberculosis situation in the Netherlands. 2009.

(17) Fonds des Affections Respiratoires. Registre Belge de la Tuberculose 2008. Brussels; 2010.

(18) Statens Serum Institute. Tuberculosis 2008, Part I. Copenhagen; 2009.

(19) World Health Organization. WHO Tuberculosis Data. 2008. 5-4-2010.

(20) Garcia Sanchez I, Perez de Oteyza C, Gilsanz Fernandez C. Tuberculosis epidemiological study in a third level hospital during 2001. Anales de Medicina Interna 2005;5-226.

(21) Che D, Campese C, Decludt B. Cases of tuberculosis declared in France in 2002. Bulletin Epidémiologique Hebdomadaire 2004 Apr 13;-16.

(22) Wanlin M, Uydebrouck M, Vermeire P, Bartsch P, Schandevyl W, Dierckx P. Recent trends in tuberculosis incidence in Belgium. Archives of Public Health 2000;5-251.

(23) Haar CH, Cobelens FG, Kalisvaart NA, Van Der Have JJ, van Gerven PJ, Van Deutekom H. HIV prevalence among tuberculosis patients in The Netherlands, 1993-2001: trends and risk factors. International Journal of Tuberculosis and Lung Disease 2006 Jul;10(7):768-74.

(24) Rose AM, Sinka K, Watson JM, Mortimer JY, Charlett A. An estimate of the contribution of HIV infection to the recent rise in tuberculosis in England and Wales. Thorax 2002 May;57(5):442-5.

(25) Cailhol J, Che D, Campese C, Decludt B. Cases of tuberculosis declared in France in 2001. Archives de Pédiatrie 2003 May;10(5):476-81.

(26) Morozova I, Riekstina V, Sture G, Wells C, Leimane V. Impact of the growing HIV-1 epidemic on multidrug-resistant tuberculosis control in Latvia. International Journal of Tuberculosis and Lung Disease 2003;7(9):903-6.

(27) Ruiz-Navarro MD, Espinosa JA, Hernbndez MJ, Franco AD, Carrillo CC, GarcÆa AD, et al. Effects of HIV status and other variables on the outcome of tuberculosis treatment in Spain. Archivos de Bronconeumologia 2005;41(7):363.

(28) Instituto de Salus CarlosIII. Casos de tuberculosis declarados a la red nacional de vigilancia epidemiologica. Espana 2008. Boletin Epidemiologico Semanal 2009;17(11):121-4.

(29) Lot F, Pinget R, Cazein F, Pillonel J, Leclerc M, Haguy H, et al. Frequency and risk factors for tuberculosis as an AIDS-defining illness, in France. Bulletin Epidémiologique Hebdomadaire 2009 Dec 13;-113.

(30) Moreno S, Jarrin I, Iribarren JA, Perez-Elias MJ, Viciana P, Parra-Ruiz J, et al. Incidence and risk factors for tuberculosis in HIV-positive subjects by HAART status. International Journal of Tuberculosis and Lung Disease 2008 Dec;12(12):1393-400.

(31) Muga R, Ferreros I, Langohr K, de Olalla PG, Del Romero J, Quintana M, et al. Changes in the incidence of tuberculosis in a cohort of HIV-seroconverters before and after the introduction of HAART. AIDS 2007 Nov 30;21(18):2521-7.

(32) Diez M, Diaz A, Bleda MJ, Aldamiz M, Camafort M, Camino X, et al. Prevalence of M-tuberculosis infection and tuberculosis disease among HIV-

infected people in Spain. International Journal of Tuberculosis and Lung Disease 2007;11(11):1196-202.

(33) Martin V, Cayla JA, Bolea A, Castilla J. Mycobacterium tuberculosis and human immunodeficiency virus co-infection in intravenous drug users on admission to prison. International Journal of Tuberculosis and Lung Disease 2000;4(1):41-6.

(34) Casado JL, Moreno S, Fortun J, Antela A, Quereda C, Navas E, et al. Risk factors for development of tuberculosis after isoniazid chemoprophylaxis in human immunodeficiency virus-infected patients. Clin Infect Dis 2002 Feb 1;34(3):386-9.

(35) Caminal Montero L, Trapilla Martinez L, Telenti Asensio M, Fernandez Bernaldo de Quiros J. Characteristics of tuberculosis in a general hospital during the period 1993-1998. Analysis of resistence and HIV coinfection. Enfermedades Infecciosas y Microbiologia Clinica 2002;2-73.

(36) Datiko DG, Yassin MA, Chekol LT, Kabeto LE, Lindtjorn B. The rate of TB-HIV co-infection depends on the prevalence of HIV infection in a community. BMC Public Health 2008;8:266.

(37) Story A, Murad S, Roberts W, Verheyen M, Hayward AC. Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 2007 Aug;62(8):667-71.

(38) Galea S, Rudenstine S, Vlahov D. Drug use, misuse, and the urban environment. Drug Alcohol Rev 2005 Mar;24(2):127-36.

(39) Elender F, Bentham G, Langford I. Tuberculosis mortality in England and Wales during 1982-1992: its association with poverty, ethnicity and AIDS. Soc Sci Med 1998 Mar;46(6):673-81.

(40) Mangtani P, Jolley DJ, Watson JM, Rodrigues LC. Socioeconomic deprivation and notification rates for tuberculosis in London during 1982-91. BMJ 1995 Apr 15;310(6985):963-6.

(41) European Centre for Disease Prevention and Control/WHO RegionalOffice for Europe. HIV/AIDS surveillance in Europe 2008. Stockholm: European Centre for Disease Prevention and Control; 2009.

(42) Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey-Faussett P, Shearer S. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. J Infect Dis 2005 Jan 15;191(2):150-8.

(43) Patel NR, Swan K, Li X, Tachado SD, Koziel H. Impaired M. tuberculosis-mediated apoptosis in alveolar macrophages from HIV+ persons: potential role of IL-10 and BCL-3. J Leukoc Biol 2009 Jul;86(1):53-60.

(44) Haar CH, Cobelens FG, Kalisvaart NA, Van Der Have JJ, van DH. [HIV-test policy for tuberculosis patients in the Netherlands]. Ned Tijdschr Geneeskd 2007 Dec 1;151(48):2674-9.

(45) van der Werf MJ, Yegorova OB, Chechulin Y, Hasker E, Veen J, Turchenko LV. HIV testing practices of TB patients after introduction of a new testing policy in Kiev City, Ukraine. Int J Tuberc Lung Dis 2005 Jul;9(7):733-9.

(46) Rodger AJ, Story A, Fox Z, Hayward A. HIV prevalence and testing practices among tuberculosis cases in London: a missed opportunity for HIV diagnosis? Thorax 2010 Jan;65(1):63-9.

(47) World Health Organization. Guidelines for HIV Surveillance Among Tuberculosis Patients, Second Edition. Geneva; 2004.

(48) World Health Organization. United States of American Tuberculosis Profile. 11-11-2010. Accessed 18-11-2010.

(49) World Health Organization. Canada Tuberculosis Profile. 11-11-2010. Accessed 18-11-2010.

(50) World Health Organization. Australia Tuberculosis Profile. 11-11-2010. Accessed 18-11-2010.

(51) World Health Organization. Japan Tuberculosis Profile. 11-11-2010. Accessed 18-11-2010.

Tables and figures

Figure 1 – Flowchart of inclusion of manuscripts for the primary and secondary outcomes

Figure 2- Map of most recent data on proportion of TB patients co-infected with HIV in EU/EEA countries

Figure 3- Trends in the prevalence of HIV co-infection in TB patients in EU/EEA countries by year of reporting.

Figure 4 - Socio-demographic characteristics of co-infected cases compared to mono-infected TB cases (most recent data).

Table 1-Association between age group and TB-HIV co-infection and male gender and TB-HIV co-infection.

Table 2- Association between CD4 count and TB-HIV co-infection and HIV transmission route and TB-HIV co-infection.

Table 3- Association between risk behaviour and TB-HIV co-infection

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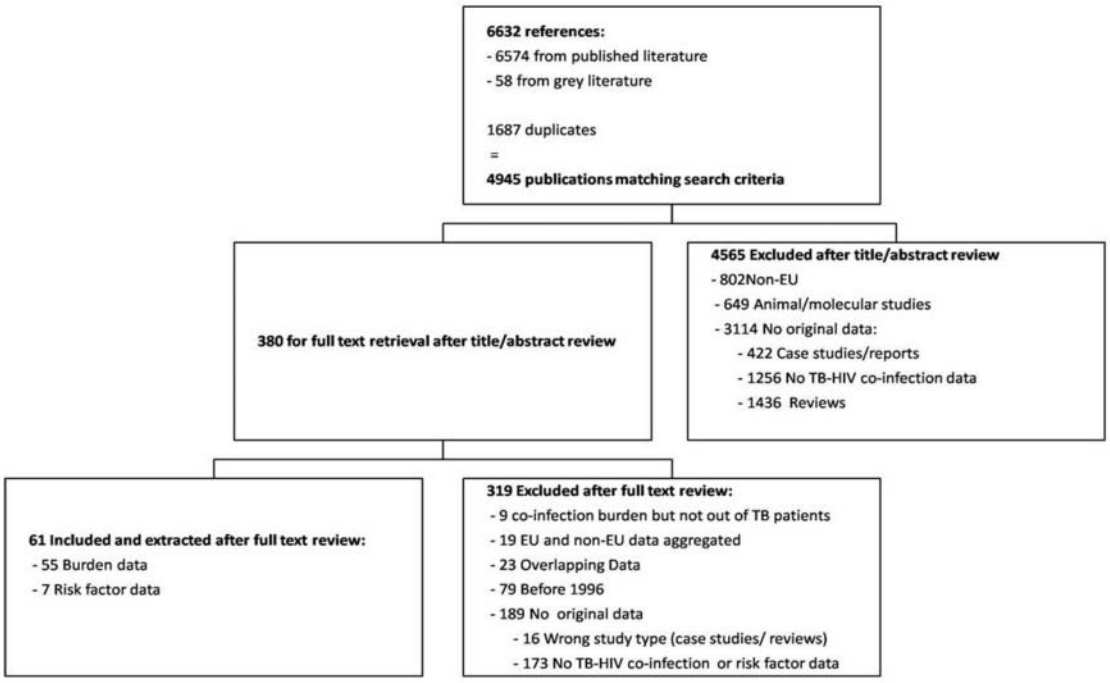

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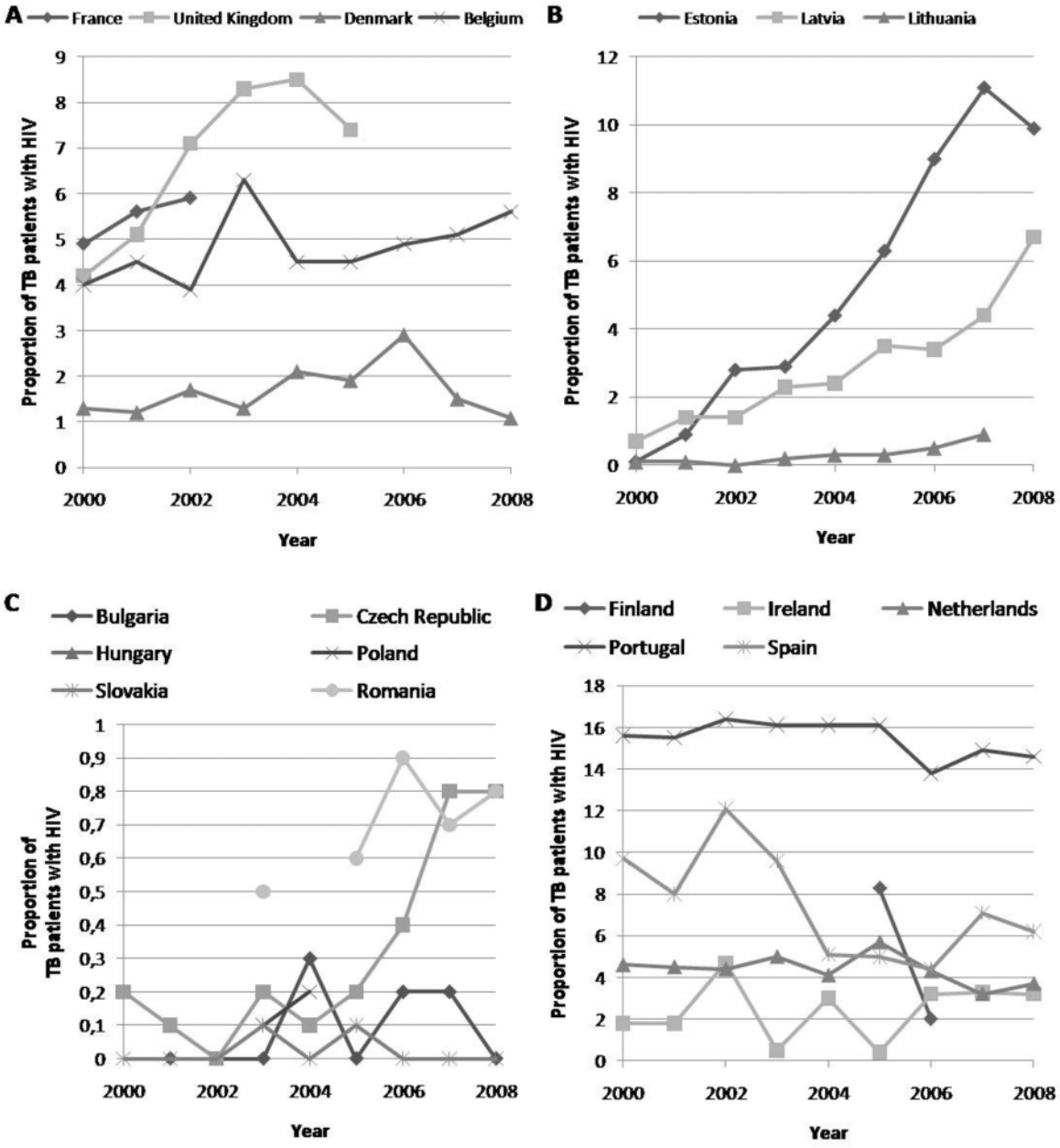
Figure 2- Map of most recent data on proportion of TB patients co-infected with HIV in EU/EEA countries

Country	Year	TB-patients with HIV % (n/N)
Austria (13)	2005	1.7% (16/942)
Belgium (17)	2008	5.6% (56/1006)
Bulgaria (8)	2008	0% (0/3151)
Cyprus (8)	2008	4% (2/50)
Czech Republic (8)	2008	0.8% (7/868)
Denmark (18)	2008	1.0% (4/367)
Estonia (8)	2008	9.9% (44/444)
Finland (8)	2006	2% (6/297)
France (8)	2001	5.6% (364/6465)
Iceland (8)	2006	15.4% (2/13)
Ireland (8)	2008	3.2% (15/470)
Italy (13)	2005	3.0% (121/3975)
Latvia (8)	2008	6.7% (72/1070)
Lithuania (8)	2007	0.9% (21/2408)
Malta (8)	2008	9.4% (5/53)
Netherlands (16)	2008	3.7% (37/997)
Poland (19)	2004	0.2% (15/9493)
Portugal (8)	2008	14.6% (438/2995)
Romania (8)	2008	0.8% (202/24786)
Slovakia (8	2008	0% (0/633)
Slovenia (8)	2008	0% (0/213)
Spain (8)	2008	6.2% (507/8214)
United Kingdom - E&W only(15)	2005	7.4% (233/3153)

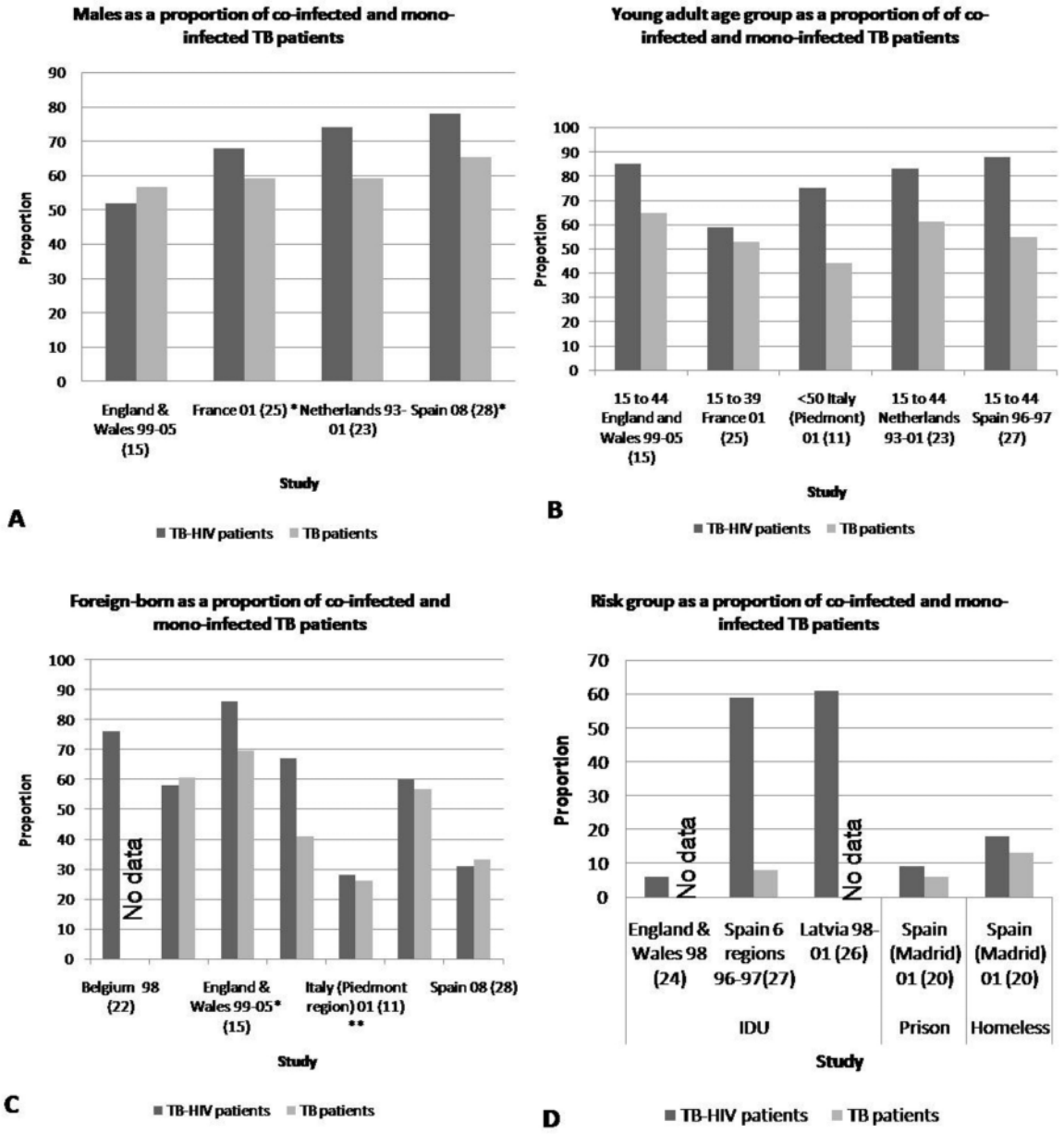
All data were based on national surveillance (2001 to 2008). The burden in some countries with low numbers of TB cases i.e. Iceland, must be interpreted with caution.

Figure 3- Trends in the prevalence of HIV co-infection in TB patients in EU/EEA countries by year of reporting.



Strong variations in the data for Cyprus, Iceland, Malta and Slovenia (not shown) are likely to be due to the small numbers of TB and HIV cases reported annually (8;41) can be found.

Figure 4 - Socio-demographic characteristics of co-infected cases compared to mono-infected TB cases (most recent data).



All data is from surveillance apart for [60], from a cross-sectional study in more than one hospital in Madrid; * unknown category not included; ** High TB prevalence countries include those in Sub-Saharan Africa, South east Asia and eastern Europe. Low TB prevalence countries include industrialised countries;

Table 1-Association between age group and TB-HIV co-infection and male gender and TB-HIV co-infection.

Country/study type	Year	Sample Size/patients	Outcome	Age group	Adjusted Estimate (C.I.)	Male gender	Adjusted Estimate (C.I.)	Adjusting factor
Netherlands (23) S	1993-2001	13269 TB patients	OR for HIV infection	0-14 15-24 25-34 35-44 45-54 55-64 ≥65	5.02 (1.67; 15.15) 9.45 (3.98; 22.5) 23.5 (10.3; 53.7) 28.9 (12.6; 66.1) 14.7 (6.25; 34.4) 4.66 (1.73; 12.5) 1**	Male Female	1.61 (1.3;2.0) 1**	Age, Sex, Year, Residence, Place of diagnosis, Citizenship, Site of disease, Risk group
France (29) S	1997-2007	16927 AIDS patients	OR for TB (AIDS defining)	15-30 30-39 ≥40	1.71 (1.49; 1.96) 1.27 (1.15; 1.39) 1**	Male Female	1.30 (1.16; 1.43) 1**	Age, Sex, CD4, Known serostatus + ARV,Transm. route, World region of origin, Residence
Spain(31) L (>1 H)	1980-2004	HIV sero-converters (23698 PY)	HR for TB disease	0-20 21-30 >30 ≥50	1 1.25 (0.83; 1.87) 1.38 (0.81; 2.36) 0.5 (0.1-4.0)	Male Female	1.61 (1.04;2.44) 1	Age at sero-conversion, Sex, Transmission route, Calendar period of TB
Spain (30) L (>1 H) (open)	1997-2003	3196 PLWHA (HAART naïve)	RR for TB disease	≤30 31-35 36-40 >40	1 0.84 (0.67; 1.05) 0.83 (0.54; 1.26) 0.96 (0.71; 1.29)			Age, Sex, Transmission route, Calendar period of observation, CD4 at entry, Viral load. HAART at follow up for HAART naïve
		1072 PLWHA (on HAART)	RR for TB disease	≤30 31-35 36-40 >40	1 0.83 (0.26; 2.65) 1.17 (0.38; 3.57) 0.97 (0.41; 2.29)			Age, Sex, Transmission route, Calendar period of observation, CD4 at entry, Viral load, HAART during follow-up
Spain(32) L (>1 H)	2000-2003	315 PLWHA (MTB infected)	OR for TB disease	≤29 30-39 40-49	1 1.6 (0.6; 4.4) 1.6 (0.5; 5.1)	Male Female	1.1 (0.42;3.33) 1	Age, Sex, SES, Occupation, CD4, Viral load, Transmission route, BCG scar, Hospital of study
Spain (NW) (33) X	1991-1997	980 IDU on admission to prison	OR for TB-HIV infection	16-24 25-29 >29	1 3.14 (1.71; 5.75) 3.67 (1.96; 6.86)	Male Female	0.58 (0.31; 1.1) 1	Age, Sex, Year, IDU status (former/present), Needle sharing, Tattoos, Time in prison

C.I. 95% Confidence Interval ; S: surveillance; X : cross-sectional study ; L (>1 H) : multi-centre cohort study ; L (>1 H) open : open multi-centre cohort study ; L (1H) : single hospital cohort study ; PY: person years ; PLWHA: people living with HIV/AIDS ; OR: odds ratio ; HR: hazard ratio ; RR : rate ratio ;
** : p<0.001;

Table 2- Association between CD4 count and TB-HIV co-infection and HIV transmission route and TB-HIV co-infection.

Country/ Year/Study	Sample Size and source	Outcome	HIV Transmission Route	Adjusted estimate	CD4 count at HIV diagnosis	Adjusted Estimate (95%CI)	Adjusting factors
France (29) 97-07 S	16927 AIDS patients	OR for TB as AIDS defining-illness vs. other AIDS-defining illnesses)	MSM IDU Hetero O/U	1** 2.66 (2.26; 3.14) 2.31 (2; 2.67) 2.1 (1.76; 2.5)	<200 200-350 >350 Unknown	1** 3.04 (2.66; 3.47) 3.62 (3.11; 4.22) 1.73 (1.51; 1.99)	Age, Sex, CD4, Known serostatus + ARV, Transmission route, World region of origin, Residence
Spain(31) 1980-2004 L (>1 H)	HIV sero-converters (23698 PY)	HR for TB disease	Sexual IDU Clotting/ Haemophilia	1 3 (1.72; 5.26)** 0.4 (0.19; 0.88)			Age, Sex, SES, Occupation, CD4, Viral load, Transmission route, BCG scar, Hospital of study
Spain (Madrid)(33) 87-96 L (1H)	418 PY in PLWHA (after 9 months INH)	HR for TB disease			CD4 (unit increase)	0.995 (0.992; 1.003)[b]	Age at seroconversion, Sex, Transmission route, Calendar period of TB
Spain (30) 97-03 L (>1 H) (open)	3196 PLWHA (HAART naïve)	RR for TB disease	MSM M IDU M hetero M O/U F IDU F hetero F O/U	1** 2.01 (1.28; 3.16) 0.84 (0.55; 1.29) 0.94 (0.36; 2.47) 1.45 (0.81; 2.62) 0.92 (0.37; 2.30) 1.07 (0.67; 1.71)	<200 200-350 >350 unknown	1** 0.36 (0.28; 0.46) 0.18 (0.15; 0.21) 0.23 (0.13; 0.41)	Age, Sex, Transmission route, Calendar period of observation, CD4 at entry, Viral load, HAART during follow-up
	1072 PLWHA (on HAART)	RR for TB disease	MSM M IDU M hetero M O/U F IDU F hetero Female O/U	1** 0.61 (0.23; 1.62) 0.44 (0.13; 1.44) 0.68 (0.11; 4.06) 1.58 (0.77; 3.24) 0.40 (0.18; 0.91)** -	<200 200-350 >350 Unknown	1** 0.27 (0.09; 0.79) 0.17 (0.04; 0.62) 0.64 (0.06; 6.79)	Age, Sex, Transmission route, Calendar period of observation, CD4 at entry, Viral load
Spain (32) 00-03 L (>1 H)	315 PLWHA MTB infected	OR for TB disease	Hetero IDU MSM Transfusion Unknown	1 0.4 (0.2; 1.1) 1.8 (0.4; 7.4) 0.3 (0.0; 177.0) 1.6 (0.1;52.9)	<100 100-199 200-499 ≥500	83.4 (17.0; 409.3)* 4.3 (1.5; 12.0)* 1.4 (0.6; 3.2) 1	Age, Sex, SES, Contact with TB case, CD4 count, Transmission route, Hospital of study

C.I. 95% Confidence Interval ; S: surveillance; X : cross-sectional study ; L (>1 H) : multi-centre cohort study ; L (>1 H) open : open multi-centre cohort study ; L (1H) : single hospital cohort study ; PY: person years ; PLWHA: people living with HIV/AIDS ; MSM: men having sex with men; IDU : intra-venous drug use ; hetero: heterosexual; M – male ; F – female ; O/U : other/unknown;
OR: odds ratio ; HR: hazard ratio ;INH: Isoniazid RR : rate ratio ; ** : p<0.001; * p<=0.05 ; [b] : borderline

Table 3- Association between risk behaviour and TB-HIV co-infection

Country/ Year/Study type	Sample Size and source	Outcome & Measure Type	TB Group	Adjusted estimate (C.I.)	Adjusting factors
Netherlands(23) 1993-2001 S	13269 TB patients	OR for HIV infection	No risk group Illegal resident Homeless Drug users	1 1.67 (1.08; 2.4)* 1.55 (1.01; 2.4) [b] 5.13 (3.81; 6.89)**	Age, Sex, Year, Residence, Place of diagnosis, Citizenship, Site of disease, Risk group
Spain-Madrid (34) 1987-1996 L (>1 H)	418 PY (PLWHA after 9 month INH)	HR for TB disease	No risk group Any risk group	1 3.17 (1.56; 17)**	Risk group (incarceration, homelessness, alcohol abuse, IDU, intimate contact TB case), CD4
Spain (32) 00-03 L (>1 H)	1242 PLWHA	OR for TB *infection* (>1 H)	Living alone Living with family Homeless/ prison/ institution	1 1.3 (0.8; 2.1) 1.7 (1; 2.9) [b]	Age, Sex, SES, Contact with TB case, CD4 count, Transmission route, Hospital of study
Spain (NW) (33) 1991-1997 X	980 IDU on admission to prison	OR for TB-HIV infection	IDU Former IDU Not sharing Sharing syringes No Tattoos Tattoos 0 months in prison 1-23 months >23 months	1 1.87 (1.23; 2.82) 1 2.43 (1.57; 3.77) 1 1.56 (0.98; 2.49) 1 2.44 (1.28; 4.64) 4.94 (2.56; 9.55)	Age, Sex, Year, IDU status (former/ present), Needle sharing, Tattoos, Time in prison

C.I. 95% Confidence Interval ; S: surveillance; X : cross-sectional study ; L (>1 H) : multi-centre cohort study ; L (>1 H) open : open multi-centre cohort study ; L (1H) : single hospital cohort study ; PY: person years ; PLWHA: people living with HIV/AIDS ; OR: odds ratio ; HR: hazard ratio ; ** : p<0.001; * p<=0.05 ; [b] : borderline