Tuberculosis infection and disease in people living with HIV in countries with low tuberculosis incidence

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Running head: TB in PLHIV in low-incidence countries

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Summary

In countries with low tuberculosis (TB) incidence, TB is concentrated in vulnerable populations, including people living with HIV (PLHIV) who have a substantially greater risk of TB than people without HIV.

We searched PubMed, EMBASE and Web of Science for studies evaluating risk factors for latent TB infection (LTBI) or active TB in PLHIV in countries with TB incidence ≤10/100,000 population. Due to the number of risk factors evaluated and heterogeneity in study designs, we present summary data and a narrative synthesis.

We included 45 studies; 17 reported data on risk factors for LTBI and 32 on active TB. Black, Asian or Hispanic ethnicity, birth or long-term residence in a country with high TB incidence, and HIV acquisition via injecting drug use or heterosexual sex were strong predictors of both LTBI and active TB. History of contact, a greater degree of immunosuppression at diagnosis or higher viral load increased TB risk.

Early HIV diagnosis to allow timely initiation of anti-retroviral therapy is essential for the prevention of TB in PLHIV. Screening and treating PLHIV for LTBI, to reduce risk of progression to active TB disease, should also be considered to further decrease the burden of active TB in low TB-incidence settings. Research to support the expansion of TB and HIV prevention and treatment globally is essential to eliminate TB in low-incidence settings.

Key words: tuberculosis, HIV, co-infection, low incidence countries, risk factors

Introduction

HIV is an important risk factor for tuberculosis (TB) disease; globally, people living with HIV (PLHIV) are at an estimated 26-31 times higher risk of TB than people without HIV infection.[1] HIV co-infection is associated with higher rates of progression from latent to active TB, more severe disease presentation, worse clinical outcomes and increased mortality. An estimated 12.5% of new TB cases in 2014 were among PLHIV and TB is the leading cause of death for PLHIV; responsible for around one third of deaths.[2] Globally, HIV-associated TB (HIV-TB) is concentrated in sub-Saharan Africa, which accounted for around three quarters of HIV-TB morbidity and mortality in 2015.[3] HIV-TB co-infection also remains a persistent public health problem in low TB incidence countries (defined by the World Health Organization [WHO] as less than 10 cases per 100,000 population),[4] where the changing epidemiology of TB has led to a concentration of disease in high risk groups. In 2012, an estimated 155,000 people fell ill with TB in low-incidence countries and 10,000 people died.[5]

TB transmission in the general population in low-incidence countries is generally minimal, with the majority of cases occurring in patients born abroad as a result of progression from previously acquired latent infection.[6] In addition to PLHIV, there is a disproportionate burden of TB among vulnerable populations such as recent migrants (particularly those from countries with high TB incidence) and people who are homeless, incarcerated, or have problems with substance abuse.[5] These sub-populations are often referred to as “hard to reach”, linked by poverty, social deprivation and difficulties accessing healthcare.[7]

Priority areas of the WHO’s action framework for TB in low-incidence countries include addressing TB in the most vulnerable and hard-to-reach groups, screening for latent and active TB in high-risk groups and ensuring continued patient-level surveillance and evaluation.[4] There is considerable overlap between these at-risk groups, as many people have multiple risk factors, and/or difficulties accessing healthcare services. Systematic

screening of PLHIV for active TB is recommended, but is not done in all low-incidence countries.[4] Systematic screening for LTBI is also recommended for PLHIV and other high-risk groups, but not widely implemented.[4]

Efforts to control HIV-TB are hampered by the significant proportion of PLHIV who are undiagnosed, diagnosed late, or not diagnosed until they present to healthcare service with other opportunistic infections such as TB. Managing TB in PLHIV is also more clinically complex, as a result of side effects of treatment, drug-drug interactions, and often a more severe presentation of disease.[8] Preventing TB in PLHIV is therefore of paramount importance. However diagnosing LTBI in PLHIV can be difficult, as diagnostic tests for LTBI (particularly the tuberculin skin test [TST]) are less sensitive at low CD4 counts.[9] Furthermore, pressure on resources, even in countries with low TB incidence, necessitates the targeting of preventative activities such as screening for LTBI and active TB. It is therefore critical to have a clear insight into risk factors for TB disease in PLHIV in countries with low TB incidence. This review provides an up-to-date synthesis of the evidence on risk factors for LTBI and TB disease among PLHIV.

Methods

We systematically searched PubMed, EMBASE and Web of Science on 4th May 2017 for articles on risk factors for LTBI or active TB disease among people living with HIV in countries with low TB incidence (defined as ≤10 cases per 100,000 population, based on 2015 WHO data).[4] The search terms included variations of "tuberculosis", "HIV" and the low-incidence countries; full details of the search strategy and results are shown in Appendix 1. We excluded studies presenting data on multi-country cohorts if any country contributing to the cohort did not have low TB incidence. No limits were placed on year or language of publication.

The search results were de-duplicated and screening was done by title, abstract and then full-text, by two reviewers (JW and AA) with 10% overlap. Any disagreements were resolved by consensus. The reference lists of included articles and relevant review articles were screened for additional papers. We provide a narrative synthesis of our findings. The review was registered on PROSPERO (CRD42017069544).

Findings and Implications

Search results and included studies

After de-duplication, the search yielded 5,804 results. After title, abstract and full-text screening, 45 studies were included (Figure 1). Initial reviewer agreement was 99.3%, resolved to 100% after comparing the discrepant papers against the inclusion criteria. Of the 45 included studies (summarised in detail in supplementary table 1), 17 provided data on risk factors for LTBI,[10-26] 32 included data on risk factors for active TB,[23-54] and 4 studies contained data on both.[23-26] The studies spanned the period 1977-2014. Risk factors for LTBI are summarised in Table 1 and risk factors for active TB disease are summarised in Table 2.

Sociodemographic factors associated with tuberculosis

Sex

Globally, the risk of TB is higher for men than women,[55] however data on the effect of sex on risk of TB among PLHIV in this review were mixed. Of the nine studies which reported no association between sex and risk of LTBI, none adjusted for other factors such as route of HIV infection, which may have biased associations of risk of TB towards women; people who acquire HIV through heterosexual sex usually have higher rates of TB than MSM, as black African ethnicity and birth in countries with high TB incidence can be confounders for route of HIV infection. The HIV epidemic in sub-Saharan Africa disproportionately affects women, whilst the Western epidemic has predominantly affected men who have sex with men. As HIV-TB in low-incidence settings is mainly an issue for migrants from high-incidence countries, the higher number of heterosexual women than men diagnosed with HIV affects that observed patterns of HIV-TB.

Ethnicity and Country of Birth

We found that the risk of both LTBI and active TB was greatest among PLHIV from ethnic minorities; particularly those of black African, South Asian or Hispanic ethnicity.[13,15,17,19,23,25,31,32,37,43,44,46,49,52,53] Similarly, PLHIV who were born in, or long-term residents of, countries with high TB incidence had higher rates of LTBI and active TB.[10-13,17,18,22-24,26,45,56] Few studies examined the effects of country of birth and ethnicity independently of each other; those that did found no independent associations between ethnicity and country of birth and active TB[34,46] or LTBI.[14,17] However, a more recently published study stratified the risk of developing active TB by ethnicity and the TB incidence in country of birth and demonstrated that ethnicity and the incidence of TB in the patient's country of birth independently increase the risk of developing TB for PLHIV. TB incidence among black African PLHIV born in high-incidence countries was higher than that of PLHIV with only one of these risk factors.[57] Both ethnicity and country of birth are proxy measures

for long-term exposure to TB; visiting a TB-endemic country was not associated with the risk of LTBI, although the association between the length of visit and risk of LTBI was not explored.[45]

One study observed that the risk of TB among migrants decreased with increasing time since entry to the country. This could reflect reversion of previously acquired infection, as the risk of LTBI in PLHIV born abroad decreased with time since migration.[45] It could also be attributed to the fact that there is an increased risk of TB amongst people who were infected with HIV abroad,[46] and that the likelihood of HIV infection remaining undiagnosed decreases with time, and therefore the risk of TB decreases as patients become aware of their HIV infection and initiate ART. This is supported by the fact that the risk of active TB increased with increasing time from entry to the study country to HIV diagnosis.[41] As the majority of PLHIV born abroad are likely to have been infected with HIV in their country of birth,[58] the increased risk of TB with time from migration to HIV diagnosis is likely a reflection of late HIV diagnosis and low CD4 count.

Route of HIV infection

Both LTBI and active TB were more likely to occur in study participants who acquired their HIV infection through heterosexual sex, injecting drug use or mother-to-child transmission than by sex between men, and having a partner who injected drugs was also associated with increased risk of LTBI.[15,19,24,26,31,32,34,35,38,41,51] Children with TB were more likely to have mothers who acquired HIV through injecting drug use than heterosexual sex or other routes of transmission, compared to HIV-infected children without TB.[52] Injecting drug use was associated with increased risk of TB,[33,43,49] as was long term tobacco use,[39] however alcohol misuse was not.[59] It is likely that routes of HIV infection other than sex between men are confounders for exposure to TB, which was an important risk factor for both LTBI and active TB, but one which few studies examined directly. In particular, HIV

acquisition through heterosexual sex is strongly correlated with birth in countries with high TB incidence,[60] discussed previously.

Other social risk factors

Homelessness, and living or working in a collective group or institution, were associated with higher risks of LTBI,[10,13,18,19] Proximity to persons with TB was also important; close contact with a TB case increased the risk of LTBI[10,11,19,21,45] and active TB,[25,29,40] and a study set in a prison demonstrated that closer proximity was associated with increased risk.[25]

Clinical risk factors for HIV-TB

CD4 count, viral load and ART

CD4 counts of <500 cells/µl were overwhelmingly inversely associated with greater risk of developing active TB.[23,24,27,28,30,31,33-38,42-44,46,49-51] ART was highly protective against active TB for PLHIV,[24,27,30,34,35,46,51] with a time-dependent decrease in risk of TB during ART documented in multiple studies.[27,31,43,44] Conversely, though the data were conflicting, high viral loads were associated with increased risk of active TB in most studies.[27,31,32,35,36] Together, these findings highlight the fundamental importance of early diagnosis and treatment of HIV in preventing HIV-TB. As recommended in existing guidelines, this may require screening programmes to be implemented in groups of people at high risk.

LTBI

Anergic patients and patients with a positive TST result had significantly higher risk of TB than TST-negative and/or non-anergic patients.[24,28,30,38,47,48] However, diagnosing LTBI in PLHIV is challenging, particularly among those with low CD4 counts. There was no consistent association with the risk of LTBI for CD4 count, HIV viral load, or ART. Low CD4 count was not associated with an increased risk of LTBI among PLHIV, [10-12,17,22] and some studies (particularly those which used TSTs to diagnose LTBI) reported higher rates of LTBI

in participants with high CD4 counts.[14,16,24,26] This is likely due to lower sensitivity of diagnostic tests for LTBI at lower CD4 counts, which is well documented for TSTs but less so for interferon-gamma release assays (IGRAs). This difficulty diagnosing LTBI at low CD4 count means that it is not established as to whether HIV increases the risk of becoming infected with TB (as opposed to progression to active disease, the evidence for which is definitive). Known LTBI was associated with increased risk of TB disease, [24,28,30,38,47,48] although this risk was lessened by preventive therapy.[24,26,47] A longer duration of preventive therapy was more protective.[48] The difficulty diagnosing LTBI at low CD4 counts means that preventive TB therapy for PLHIV at high risk of exposure to pulmonary TB patients is important, since low CD4 counts can prevent diagnosis of LTBI and there is a high risk of progression to active TB if latent infection is established.

History of previous TB

Two studies examined the relationship between prior active TB disease and the risk of active TB; an observational cohort reported that prior TB was associated with higher risk of TB,[28] however a study in a prison of an outbreak which occurred as a result of infection from a single source patient found no association between prior TB and risk of TB. This may suggest that prior TB increases the risk of active TB either because it is a marker for other risk factors relating to risk of exposure to TB or progression from LTBI to active TB. These factors could include higher background rates of TB, low CD4 count, unsuccessful treatment of prior disease or development of drug resistance during treatment of the previous disease.

Strengths and limitations of the study design and findings

The systematic search strategy enabled a comprehensive review of the literature. Due to the high number of records found by our search, 10% of results were screened by two reviewers. Between-reviewer agreement was high and the discrepant articles were generally excluded after reviewing them against the inclusion criteria. Accordingly, our strategy demonstrated a high sensitivity.

For the purposes of our inclusion criteria, countries were defined as 'low incidence' based on the TB incidence of TB in 2015; this was a pragmatic choice as many studies spanned several years and TB incidence changed over time. Consequently we may have included studies from periods where the TB incidence was above 10/100,000 population, or excluded studies conducted where TB incidence was less than 10/100,000 prior to 2015 but not in 2015. This is particularly relevant for small countries, where a small change in the number of cases reported could result in a substantial fluctuation in incidence. We excluded multi-country studies where not all the countries had low TB incidence and data were not presented stratified by country, which led to the exclusion of some large studies of active TB incidence among PLHIV. However, the findings of these studies were consistent with those of this review; the HIV-CAUSAL study, the EuroSIDA cohort and the ART Cohort Collaboration reported that higher TB incidence was associated with low CD4 count, high viral load, HIV acquisition by injecting drug use or heterosexual sex (compared to MSM), and being born in Africa.[61-64]

We did not report on the magnitude of associations between the various risk factors and LTBI or active TB due to the considerable heterogeneity in the design and statistical analyses of the included studies, particularly variation in how variables were categorised, which category was used as the baseline, and which other variables (if any) were adjusted for. There were no clear differences in the directions of associations between risk factors and the outcome in studies which conducted multivariable analyses and those which only reported univariable associations; accordingly, this does not appear to be a source of bias. The majority of studies were large cohorts or utilised national surveillance data and so would have used standard definitions for active TB, although this was generally not stated specifically.

The majority of the literature included in this review was from Western Europe and North America. The risk factors for TB in PLHIV discussed here may therefore not be

generalisable to other low-incidence settings with different migration patterns, such as Australia. Many of the risk factors for TB identified in this study will also apply to people who are not infected with HIV. In particular, people born in countries with high TB incidence have high rates of TB even without HIV infection. Consequently, incorporating HIV testing and care into screening programmes targeted to those at high risk of TB is important to ensure that preventive measures are being offered to all those with a high risk of TB.

Opportunities for Prevention

Early HIV diagnosis and ART initiation

Early diagnosis of HIV is fundamental to the prevention of HIV-TB, as early initiation of ART is highly protective against TB disease. Early diagnosis of HIV also provides an opportunity to test and treat PLHIV for LTBI before active TB can develop. However, there are challenges at all stages of the continuum of HIV care; diagnosing HIV, linking patients to HIV care, initiating ART, and viral suppression. This highlights the importance of the UNAIDS 90-90-90 targets.[65] Despite the UK exceeding the overall UNAIDS target for the proportion of PLHIV that are virally suppressed, a substantial number of TB diagnoses in PLHIV are in people who are not aware of their HIV infection prior to their TB diagnosis.[46,57] Scale-up of targeted HIV testing of populations at high risk of both HIV and TB disease such as migrants from high-burden countries and people who inject drugs may facilitate earlier diagnosis of HIV, which may allow prevention of many cases of TB among these populations.

HIV testing could also be incorporated alongside screening initiatives for other diseases with overlapping risk profiles, including TB, hepatitis B and C. These may including active case finding programmes targeting vulnerable groups (including the homeless, prisoners, high-risk drug users and migrants).[66] One study found that HIV-positive children with TB were more likely to have mothers who acquired HIV through injecting drug use than

through heterosexual sex or other routes of transmission than HIV-positive children without TB. This suggests that antenatal HIV screening and preventive treatment for TB are not being effectively delivered to “hard to reach” women who acquired HIV infection through injecting drug use, resulting in a higher risk of TB for their children than for the children of heterosexual women with HIV. Improving support to access antenatal HIV screening could help prevent mother-to-child HIV transmission in hard to reach populations and reduce the susceptibility of mothers and their children to TB.

Pre-entry screening of migrants from countries with high TB incidence for pulmonary TB is now required for migrants moving to the UK, Australia, Canada, New Zealand and the USA, and other countries could consider adopting these guidelines to reduce the incidence of active TB. However, this strategy cannot prevent TB among migrants who arrive via irregular routes (who may be among those at highest risk of disease), and pre-entry screening does not include testing for LTBI or HIV. Promoting integrated screening for HIV infection and LTBI to migrants from countries with high TB incidence, particularly those who have recently entered the country, could also be an effective measure to both diagnose HIV sooner and prevent LTBI from progressing into active TB disease.

LTBI testing and treatment for PLHIV

Recent clinical trials in high TB-incidence settings have demonstrated the efficacy of isoniazid preventive therapy for reducing TB incidence among PLHIV.[67] However, in low-incidence settings, there are challenges in determining who should be offered preventive therapy, and in increasing uptake of testing and treatment for LTBI.[68] In low-incidence settings, the WHO recommend systematic testing for and treatment of LTBI among PLHIV,[4] prioritising those with recent infection, and those who have recently migrated from high- to low-burden settings. National guidelines have followed suit, with the CDC recommending testing all PLHIV for LTBI at the time of HIV diagnosis, and treating those who test positive or who are close contacts of infectious pulmonary TB patients.[69] For PLHIV who are

diagnosed with HIV with a CD4 count <200 cells/μl, the CDC also recommend re-testing for LTBI once the CD4 count has risen to ≥200.[69] Similarly, the UK recommend screening PLHIV for LTBI according to criteria based on CD4 count, time on ART, and country of birth;[70,71] however, these guidelines are not widely implemented.[68] Further research is required to understand whether the barriers to testing and treating LTBI are occurring at the clinic level (i.e., whether testing and treatment for LTBI are being offered) or at the patient level, and how these barriers can be overcome to improve the uptake of LTBI testing and treatment.

Systematic screening for active TB

The WHO recommend screening for active TB in high-risk groups, such as PLHIV, due to both the high risk of developing TB and the high likelihood of severe consequences if TB diagnosis and treatment are delayed.[4] Earlier diagnosis of active TB as a result of screening programmes may also reduce onwards transmission. General WHO guidance on systematic screening for active tuberculosis includes a strong recommendation to screen PLHIV for active TB at each visit to a health facility.[72] In low-incidence settings (where the majority of PLHIV are receiving ART and virologically suppressed), this is unlikely to be an efficient use of resources; indeed the WHO action framework for low-incidence countries[4] does not specify the frequency at which PLHIV should be screened for active TB. The risk of TB has been shown to decrease over time following HIV diagnosis,[27,35,57] therefore screening for active TB at, or soon after, HIV diagnosis may be the most efficient use of resources. Cost-effectiveness analyses would be useful to investigate the efficacy and impact of such screening programmes, to inform guidelines.

Conclusions

Important sociodemographic risk factors for HIV-TB include black African ethnicity, birth in a country with high TB incidence (particularly sub-Saharan Africa) and HIV acquisition through injecting drug use. Clinical risk factors for HIV-TB include low CD4 count,

high viral load and failure of (or late) initiation of ART. This highlights a number of critical opportunities for the prevention of HIV-TB in low TB-incidence settings. These include early HIV diagnosis and timely initiation of effective ART, testing and treatment of PLHIV for LTBI, along with prompt diagnosis and treatment of those who develop HIV-TB.

TB ultimately cannot be eliminated in low-incidence countries without addressing the global epidemic of HIV-TB. While considerable progress has been made in the main approaches to manage HIV infection, there remain considerable challenges in implementation and programmatic research even in high income settings. Research to support more rapid expansion of HIV diagnostics globally including self-testing, measures to ensure the scaling-up of access to ART to the nearly 17 million PLHIV currently not on treatment, and approaches to deliver isoniazid preventative therapy for PLHIV are crucial to global HIV-TB control efforts. Furthermore, TB-HIV programmes should ensure better access to ART for pre- and post-exposure prophylaxis, effective needle exchange programmes, and support a wider range of community interventions promoting behaviour changes to prevent HIV.

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JRW, ALA and IA designed the study and the search terms. JRW ran the searches. JRW and ALA de-duplicated and screened the search results and extracted the data. JRW drafted the paper. All authors critically revised the paper and approved the final version for publication.

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Figure

Figure 1: Flow chart of the screening process and included studies

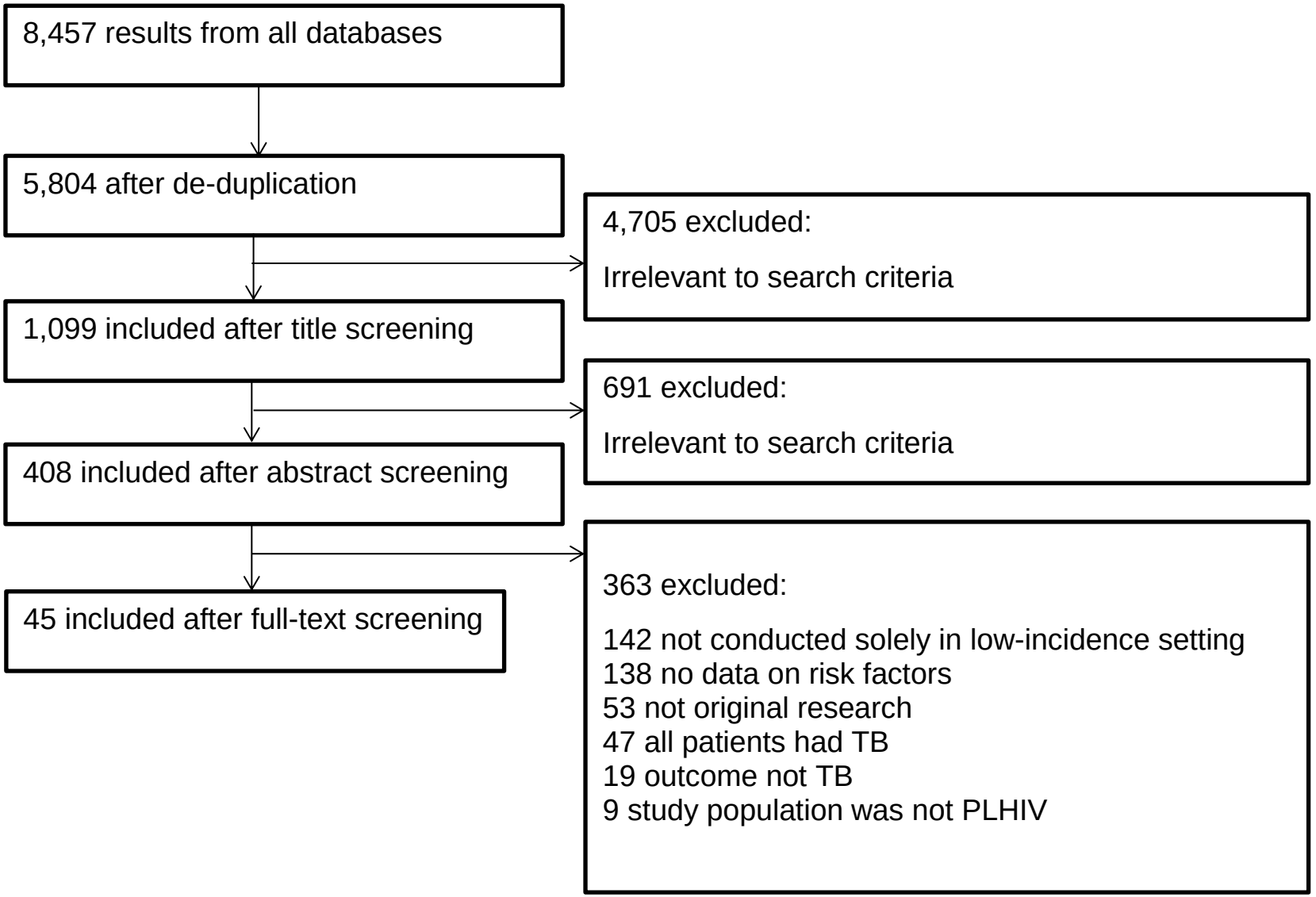

Table 1

Table 1: Summary of risk factors for latent tuberculosis infection among people living with HIV

Risk factor for LTBI	Summary of results
Sociodemographic factors	
Age	Greater risk with increasing age: 1 study [19]
	QFT-GIT-positive participants were significantly younger than QFT-GIT-negative participants: 1 study [11]
	No association: 11 studies [10,12,13,16-18,21-24,45]
Ethnicity	Greater risk for black participants than white participants: 4 studies [15,17,19,23]
	Greater risk for Asian participants than white participants: 2 studies [13,17]
	Greater risk for Hispanic participants than white participants: 1 study [15]
	No association: 2 studies [18,22]
Country of birth or residence	Greater risk of LTBI in participants who were born abroad: 4 studies [13,21,23,24]
	Greater risk of LTBI in participants born in Africa: 3 studies [23,24,26]
	Greater risk for participants who were born or long-term residents in countries with high TB incidence: 7 studies [10-12,17,18,22,45]
	Risk of TB decreased with time since migration: 1 study [45]
	No association with visiting a TB-endemic country: 1 study [45]
Sex	Greater risk for women: 2 studies [10,23]
	Greater risk for men: 1 study [24]
	No association: 9 studies [11-13,15-18,22,45]
	Single-sex studies: 4 studies [14,19,21,25]
Pregnancy	No association: 1 study [19]
	All participants were pregnant: 1 study [21]
Route of HIV infection	Higher rates of TST positivity among people who inject drugs and/or have a partner who injects drugs: 2 studies [15,24]
	Higher rates of TST positivity among people who acquired HIV through heterosexual sex than by sex between men: 1 study [24]
	Significant, but not described, differences in risk by infection route: 1 study [26]
	No association: 2 studies [22,23]
Drug misuse	Higher rates of illicit drug use amongst TST-positive participants than TST-negative participants: 1 study [19]
	No association between injecting or recreational drug use and

Risk factor for LTBI	Summary of results
	LTBI: 8 studies [11-13,16,18,21-23]
Alcohol misuse	No association: 2 studies [11,13]
Homelessness	Greater risk among those who were homeless, or lived in group/institutional living or a homeless shelter: 3 studies [10,13,19]
	No association: 3 studies [12,18,22]
Imprisonment	No association: 4 studies [12,13,19,22]
	All participants were in prison: 1 study [25]
Contact with TB, or other close exposure to TB	Greater risk for those living or working in a homeless shelter, prison or drug rehabilitation unit: 1 study [18]
	Greater risk for participants with a contact with TB or smear-positive TB: 5 studies [10,11,19,21,45]
	Greater risk for prisoners closer to the source patient of an outbreak within a prison: 1 study [25]
	No association: 2 studies [12,18]
Level of education	No association: 1 study [19]
Income	No association between income and LTBI: 1 study [19]
	No association between receiving public social aid and LTBI: 1 study [22]
Occupation	No association: 1 study [12]
Clinical factors	
CD4 count and DTH result	Higher rates of LTBI at higher CD4 counts: 7 studies [13,16,22-24,26,45]
	No association between CD4 count and LTBI: 7 studies [10-12,14,17,18,25]
	No association between a positive DTH reaction and LTBI: 1 study [16]
Viral load	Greater risk with high viral load: 1 study [23]
	Lower risk with viral load: 1 study [24]
	No association: 9 studies [10-14,16,18,22,25]
Anti-retroviral therapy	Lower risk of LTBI for participants on ART: 3 studies [14,23,24]
	No association: 8 studies [11,12,17,18,22,25,26,45]
	All patients were on ART: 1 study [16]
BCG vaccination	No association: 2 studies [10,18]
Previous TB disease	Greater risk of LTBI for patients with prior active TB disease: 6 studies [10,11,18,22,23,45]
Latent tuberculosis infection	Greater risk of current LTBI for patients with a history of LTBI: 2 studies [10,18]
Previous treatment for LTBI	Participants with LTBI were more likely to have been previously treated for LTBI: 1 study [18]

Risk factor for LTBI	Summary of results
AIDS-defining illness	Higher risk of LTBI for patients with prior AIDS: 1 study [22]
	No association: 4 studies[11,16,21,45]
Other non-infectious co-morbidities	No association between diabetes and LTBI: 1 study [11]
Time since HIV diagnosis or duration of follow-up time	No association: 4 studies [11,21,22,45]

AIDS: acquired immunodeficiency syndrome. ART: anti-retroviral therapy. BCG: Bacillus Calmette-Guérin. DTH: delayed-type hypersensitivity. LTBI: latent tuberculosis infection. QFT-GIT: quantiFERON-gold in-tube. TB: tuberculosis. TST: tuberculin skin test.

Table 2

Table 2: Summary of risk factors for active tuberculosis disease among people living with HIV

Risk factor for active TB	Summary of results
Sociodemographic factors	
Age	Risk increases with age: 2 studies [33,41]
	Risk decreases with age: 1 study [26]
	Risk was highest in the middle age categories: 3 studies [32,53,54]
	No association: 17 studies [24,27-31,34-37,42-44,46,49-51]
Ethnicity	Greater risk for black or black African participants than white participants: 10 studies [25,31,32,37,43,44,46,49,52,53]
	Greater risk for Asian participants than white participants: 3 studies [32,46,53]
	Greater risk for Hispanic participants: 2 studies [49,53]
	No association: 4 studies [34,36,38,54]
Country of birth or residence	Greater risk among participants who were born or acquired HIV abroad: 8 studies [26,27,34,43,44,46,53,54]
	Greater risk among participants from Africa: 5 studies [24,27,33,35,51]
	Greater risk among participants from Asia: 2 studies [33,51]
	Greater risk among participants from South America: 1 study [33]
	Greater risk for participants from countries with higher TB incidence: 2 studies [36,50]
	Risk of TB increased with time since arrival for foreign-born participants: 1 study [41]
	No association: 2 studies [23,30]
Region	Risk of TB varied by region of country: 1 study [27]
	No association: 4 studies [28,30,38,54]
Sex	Greater risk for men: 5 studies [34,41,44,46,47]
	Greater risk for women: 2 studies [26,52]
	No association: 15 studies [24,28-30,32,35,37,38,42,43,49-51,53,54]
	Risk presented grouped with route of HIV infection: 2 studies [27,31]
	Single-sex studies: 1 study [40]
Route of HIV infection	Greater risk for people who acquired HIV through heterosexual sex than from sex between men: 7 studies [27,31,32,34,41,44,51]
	Greater risk for people who acquired HIV infection through injecting drug use than from sex between men: 5 studies [27,32,34,41,51]
	Greater risk for people who acquired HIV through mother-to-child transmission than from sex between men: 1 study [32]
	Greater risk among children with mothers who acquired HIV through

Risk factor for active TB	Summary of results
	injecting drug use: 1 study [52]
	No association: 7 studies [24,26,28,30,35,38,50]
	All participants were heterosexual: 1 study [46]
Drug misuse	Greater risk for participants who inject drugs: 3 studies [33,43,49]
	Greater risk for participants who used tobacco long-term: 1 study [39]
	No association: 1 study [29]
	All participants had a history of prior or current drug use: 2 studies [39,47]
Alcohol misuse	No association: 1 study [51]
Imprisonment	All participants were in prison: 2 studies [25,40]
Level of education	No association: 1 study [38]
Clinical factors	
Year of diagnosis	Greater risk among those who entered the cohort later: 1 study [27]
	Greater risk of TB if diagnosing with HIV during the ART era than prior to ART being introduced: 1 study [41]
	No association: 3 studies [31,51,54]
CD4 count	Greater risk at lower CD4 count: 22 studies [23,24,27,28,30-38,40,42-44,46,49-52]
	No association: 3 studies [25,26,39]
Viral load	Greater risk with higher viral load: 9 studies [23,24,27,31,32,35,36,43,44]
	No association: 6 studies [25,34,37,49,51,54]
Anti-retroviral therapy	Lower risk for patients on ART: 10 studies [23,24,27,30,34,35,43,44,46,51]
	Lower risk with increasing time on ART: 4 studies [27,31,43,44]
	No association: 7 studies [25,26,28,36,37,49,54]
	All patients were on ART: 1 study [32]
Previous TB disease	Greater risk for patients with a history of TB: 1 study [28]
	No association: 1 study [40]
LTBI infection and anergy	Greater risk for patients with known LTBI: 6 studies [24,28,30,38,47,48]
	Greater risk for anergic patients: 1 study [28] No association: 1 study [40]
Previous treatment for LTBI	Lower risk for patients who had been treated for LTBI: 4 studies [24,26,47,48]
	No association: 2 studies [34,40]
Contact with TB or other close exposure to TB	Greater risk for patients who had been exposed to active TB: 3 studies [25,29,40]
AIDS-defining illness or other opportunistic infections	Greater risk for patients with prior AIDS: 2 studies [27,34]
	Greater risk for patients with more clinical symptoms of AIDS: 1 study [23]

Risk factor for active TB	Summary of results
Time since HIV diagnosis or duration of follow-up time	No association: 4 studies [28-30,54]
	Lower risk for patients taking prophylactic co-trimoxazole: 1 study [33]
	Decreasing risk over time: 2 studies [27,35]
	Greater risk for patients with more follow-up time: 1 study [50]
	No association: 1 study [37]

AIDS: acquired immunodeficiency syndrome. ART: anti-retroviral therapy. BCG: Bacillus Calmette-Guérin. LTBI: latent tuberculosis infection. QFT-GIT: quantiFERON-gold in-tube. TB: tuberculosis. TST: tuberculin skin test.