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Association of HIV infection with extrapulmonary tuberculosis: a systematic review

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Abstract

Purpose—HIV/AIDS is a known risk factor for the development of pulmonary tuberculosis (PTB). However, the association is less clear between HIV and extrapulmonary tuberculosis (EPTB). We conducted a systematic review to determine the association between HIV and EPTB.

Methods—We searched the electronic databases Medline, Embase and relevant conference literature using defined search terms for EPTB and HIV. Only publications in English and only studies reporting adjusted estimates were included while our search criteria did not include restriction by age or geographic location of study participants. Qualitative and quantitative analyses (including I^2 test for heterogeneity) were performed.

Results—16 studies (15 cross-sectional and 1 case-control) conducted from 1984-2016 were included in the final analyses after screening 5163 articles and conference abstracts. Our qualitative analysis showed heterogeneity in study design and study population characteristics along with a medium/high risk of bias in the majority of studies. While most of the individual studies showed increased odds of EPTB compared with PTB among HIV-infected individuals, we did not provide an overall pooled estimate, as the I^2 value was high at 93% for the cross-sectional studies.

Conclusions—While an association between HIV and EPTB is observed in most individual studies, the high heterogeneity and risk of bias in these studies highlight the need for further well-designed prospective cohort studies to assess the true risk of EPTB in the HIV infected patient population.

Keywords

HIV; TB; EPTB; Pulmonary TB; systematic review

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Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest

Introduction

Over thirty years after its discovery, HIV continues to exert a heavy burden of disease on global health. In 2015, there were approximately 2.1 million people newly infected with HIV; in addition, there were 1.1 million deaths due to HIV infection and 36.7 million people were living with HIV/AIDS worldwide [1]. Tuberculosis (TB), caused by *Mycobacterium tuberculosis* is the leading cause of death in HIV infected individuals, accounting for 20% of all AIDS related deaths[1]. HIV is a known risk factor for overall active TB; HIV infected people are approximately 30 times more likely to develop disease compared to individuals without HIV [2].

While the association between HIV and overall TB (including PTB) is well characterized [2], the relationship between EPTB and HIV is less clear. The World Health Organization defines extrapulmonary TB as “a patient with tuberculosis of organs other than the lungs” [3]. EPTB has undergone a resurgence in recent years, with the majority of cases in regions with concomitantly high HIV incidence [4]. However, this trend is also evident in other regions with lower HIV prevalence. For example, in the US and Europe, although total TB cases have decreased, high rates of EPTB cases have remained relative to total TB cases [5-7]. On an individual level, in patients with HIV, EPTB correlates with clinical stage 4 disease, the most advanced phase of TB [8]. Moreover, those who are co-infected with HIV and EPTB are diagnosed later and exhibit poorer survival outcomes relative to EPTB patients without HIV [4]. A meta-analysis by Naing and colleagues [9] conducted in 2013 demonstrated an association between HIV and EPTB. However, this meta-analysis included multiple studies that conducted univariate analyses that did not control for any confounders. In addition, in that review, there were cross-sectional studies misclassified as case-control or cohort studies, as many of the included studies had a different primary research question (which was addressed using a cohort or case-control study design), but also assessed the relationship of HIV and EPTB as a secondary analyses in a cross-sectional manner.

This systematic review seeks to provide an updated review on the association of HIV with EPTB while using different search and inclusion criteria to address some of the limitations (e.g., misclassification and confounders) of the prior study. Evidence for an association has the potential to further encourage clinicians to consider and test for HIV infection in those with EPTB and to monitor those with HIV for EPTB, with the aim of reducing morbidity and mortality from both these diseases.

Methods

The search criteria and assessment of articles were conducted by the study authors using an internal protocol (unpublished) with relevant sections described below. The results of the systematic review are presented based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [10].

Inclusion and exclusion criteria

Types of Studies Included—Case reports and case series were excluded while cross-sectional, case-control, cohort and randomized controlled trial studies were included.

Qualitative or quantitative analyses reporting adjusted rather than crude effect estimates were included. In studying the association of HIV with EPTB, age and gender were required covariates, however we also included studies which adjusted for additional factors. Studies were not excluded based on the specific gender, age, or racial characteristics of study participants or based on study site or geographical characteristics.

Exposure and Outcome—The exposure of interest was HIV infection or AIDS, confirmed by standard diagnostic methods including serology and PCR. However, studies (such as state or country surveys) that did not specify their diagnostic method, were also included as long as the infection was diagnosed by a clinician. The exposure comparison group was HIV-uninfected individuals. Thus, this study required both HIV infected and uninfected participants for comparison purposes.

The outcome of interest was extrapulmonary TB (EPTB), defined as TB other than pulmonary tuberculosis (PTB) alone [11]. If a patient had both EPTB and PTB, they were classified as EPTB. For studies that presented regression analysis separately for “EPTB only” (exclusively EPTB) group and “EPTB+PTB only” (exclusively ones who have both EPTB + PTB), we only used the adjusted effect estimates from the “EPTB only” group. For inclusion, the TB diagnosis had to be made by a clinician. The comparator outcome group was “no EPTB”, including PTB alone [11], healthy controls, or any other group without EPTB. Thus, to be included in our review, studies had to include patients with EPTB as well as a comparison group without EPTB.

Databases and Search strategy

We conducted our search using two electronic databases: MEDLINE (PubMed) and EMBASE. This was performed on February 12, 2014 and included any articles present in the databases during that time (1984-2014) using our search terms (**Appendix**). Given the time between the original search and manuscript acceptance, an updated search using the same search terms (with filters on English language and date since last search) on PubMed was performed on August 25, 2016. A broad search strategy was employed using only two search terms: HIV and EPTB without restrictions on study or subject type (**Appendix**). Abstracts and titles from each article were independently screened by two reviewers to determine eligibility for full-text review. Each full-text article was thoroughly read by two reviewers to assess whether the inclusion and exclusion criteria were met. Discrepancies between two reviewers were addressed by discussion between all authors. After selection of the final articles, double data entry was performed in Microsoft Excel (based on prior piloting of the form), and relevant information was collected. To obtain additional data not provided in the paper, contact was attempted with the authors. Forward searching of additional articles using Web of Science was performed on the selected articles. We also searched all available abstracts from the prior three years for the following conferences: Infectious Disease Society of America (2011-13), International AIDS Society (2011-13), Union World Conference on Lung Health (2011-13) and Conference on Retroviruses and Opportunistic Infections (2014). As there are many conferences relevant to HIV and TB, we picked two representative international and two US-focused conferences.

Qualitative synthesis

We summarized the selected studies using a qualitative analysis of the study design, population characteristics, and the risk of bias in the studies. Clinical and methodological heterogeneity was determined by assessing differences in study design (case-control or cross-sectional), number of study participants, gender, age, country, other geographic details (urban or rural), presence of TB treatment, presence of HIV treatment, method of HIV and TB diagnosis, type of EPTB diagnosed, time to follow-up, as well as confounders (age, gender and any other variables).

Risk of bias assessment

Each selected study was assessed for risk of bias using the Newcastle-Ottawa scale [12] based on the published "Meta-analysis of observational studies in epidemiology" (MOOSE) guidelines [13-15]. Two reviewers rated the articles based on the Newcastle-Ottawa scale for assessing risk of bias in non-randomized studies for meta-analyses [12]. This yielded scores for selection bias, information bias, and analytical bias. We divided the risk of bias section according to the study design. We assessed each study based on various characteristics and gave them a final risk of bias score as low, medium or high, based on the key described in **Appendix Table 1**.

Quantitative synthesis (meta-analyses)

Effect measures (odds ratio and relative risk) and confidence intervals were collated for each study. A priori we decided not to calculate overall estimates if the I-squared values (a measure of heterogeneity between studies where higher values indicate greater heterogeneity) were above 50%, which is considered moderate heterogeneity [16]. Random-effects models were used to determine the I-squared values. STATA version 13.0 was used to conduct these analyses and create graphs. Three different sensitivity analyses were performed: 1) comparing: "EPTB only" vs. "PTB only" (removing analyses with EPTB +PTB), and 2) having "PTB only" as the comparator group (instead of "no EPTB" that also included health controls" and 3) removing studies with outlier values.

RESULTS

Search results

Using a search strategy combining the two terms of HIV and EPTB (**Appendix**), we obtained 2249 articles from a PubMed search and 3278 articles from an Embase search (**Figure 1**) conducted in February 2014. Once the duplicates were removed, we screened the titles and abstracts of 4913 articles using our inclusion and exclusion criteria and selected 258 citations for full-text screening. After the full-text review, ten articles [17-25, 11] were initially included in this review (**Figure 1**). An updated search was conducted in August 2016 yielding an additional 250 articles for title and abstract screening, 21 articles for full-text screening and 6 additional articles included in this review for a total of 16 articles. The most common reasons for removing articles included: the absence of effect estimates; study design (e.g., case studies or review articles); languages other than English; and the use of unadjusted estimates.

Qualitative synthesis

Characteristics of Included studies—From the sixteen studies selected for final review, fifteen were cross-sectional studies [17-31] and one was a case-control study [11] (**Table 1**). Most of these publications included an effect measure of the association of HIV with EPTB as a secondary analysis rather than the primary one. Nine of these studies were based on surveillance data or on analyses of city or statewide registry data [27, 17-20, 23, 24, 29, 11]. Seven studies were conducted in hospitals [26, 28, 21, 22, 30, 31, 25], although a few studies were more rigorous and included only incident cases at the hospital.. Study settings were also heterogeneous, ranging from Asia (Taiwan), South America (Brazil), Europe (Spain and Portugal), Africa (Ethiopia, South Africa, Zambia and Cameroon) and North America (US states of Florida, Maryland, Tennessee, Texas and Arkansas) (**Table 1**). The sample sizes of the included studies varied greatly, from 125 [26] to 213,336 participants [18], and participant ages ranged from 0 to 65. The gender distributions were similar among studies with a greater proportion of males (54-81%) than females (**Table 1**).

The type of EPTB investigated in the papers was not consistent. In four studies, descriptions were missing [21, 24, 26, 31], while in other studies the organ tissues with EPTB varied. Only one study [26], which had 50% of the study population on antiretroviral therapy (ART), reported on whether patients were receiving ART. While the study by Fortun [28] did not adjust for gender, they did assess for gender differences in a univariate analysis and found no differences suggesting that adjusting for gender would not have significantly altered their effect estimates. Finally, the effect measures in all of the studies were odds ratios except for a cross-sectional study, which reported a relative risk [25] (**Table 1**).

Risk of bias—Using the modified Newcastle-Ottawa criteria (**Appendix Table 1**), four of the studies [17, 20, 25, 29] had a low risk of bias, ten [18, 19, 21, 22, 24, 26-28, 30, 31] had a medium risk of bias and two [23, 11] had a high risk of bias. Despite the cross-sectional design, studies by Wilkinson and Moore; Gonzalez et al.; Fiske et al.; and Sama et. al. had a low risk of bias (**Table 2**). The study by Gonzalez and colleagues [20] was well designed and clearly described how outcome and exposure were assessed. The only weakness for risk of bias was their selection of controls, which were from hospitals rather than the community. The study by Wilkinson and Moore [25] was also well designed and very clear on the definition and diagnosis of cases and controls. Exposure was measured in all TB patients in a hospital, so exposure in cases and controls was measured consistently. Another important factor is that they only assessed HIV status in patients with incident TB. As it is highly unlikely that participants developed HIV infection and TB disease simultaneously, HIV likely preceded TB disease, adding a temporal component to this study. One weakness of this study was the lack of TB diagnosis by culture positivity. However, TB diagnosed by other means such as clinical features was clearly described. The study by Fiske, et al. [17] also had a low risk of bias, however, the ascertainment of HIV exposure from prior medical records was a weakness as there was no description of how HIV was diagnosed and missing HIV status was imputed. The case definition was also a weakness as it was based on record linkage rather than independent validation. The study by Sama et. al. (effect estimates obtained based on personal communication with corresponding author) was also well designed and had a low risk of bias. In addition to the strengths of representativeness and

comparability, this study also had information on whether individuals had HIV exposure data or not. Weaknesses of the paper include the lack of independent ascertainment of outcomes and exposures as the cases were defined based on record linkage and exposure was based on medical records (based on Baltimore city health department data of all TB cases).

The two studies with a high risk of bias (Prado, et al. and Yang, et al.) used data from registries and did not have any information on the diagnoses and definitions of cases and controls [23, 11]. They also did not assess the cases and controls for comparability and in general lacked necessary details needed for our study (**Table 2**). The ten studies with a medium risk of bias were more detailed than the low risk of bias studies, but were lacking in one or more components, such as case or control definitions, selection of controls, ascertainment of exposure, or non-response rates (**Table 2**). In addition to these components, the study by Culqui-Levano [27] defined individuals with PTB+EPTB as PTB (in contrast to all of the other papers), resulting in a further increase in the risk of bias in both qualitative and quantitative analysis.

Quantitative synthesis

As with the qualitative synthesis, we separated our studies based on study design (15 cross-sectional and 1 case-control) (**Figure 2**). For both the cross-sectional and case-control studies, the effect estimates for all of the studies except for one by Namme, et al. [22] showed a positive association (and a significant association for 12 studies) of HIV with EPTB (in comparison to PTB) with odds ratios that ranged from 1.03 to 16.83. Although our study protocol defined the comparison/control group to be no EPTB (even individuals without TB), the comparison group in all of the included studies were individuals with PTB alone, except for one study [26] which had no EPTB (including individuals with PTB and no TB) as the control group.

The individual studies suggested an increased odds of EPTB among HIV-infected individuals, however there was excessive heterogeneity ($I^2 = 94\%$ for cross-sectional studies) between the included studies that did not allow for a meaningful estimate of the magnitude and distribution of the overall effect size, and we could not make conclusions based on the quantitative estimates. Thus, we did not include an overall estimate (**Figure 2**), and we defer to our qualitative synthesis for conclusions. Results were similar for a sensitivity analysis where “PTB only” was used as the comparator group instead of “no EPTB”. High heterogeneity remained in another sensitivity analysis where EPTB was defined as “EPTB only” (“EPTB+ PTB” cases were excluded from the analysis). When the Gomes paper [19] was excluded in another sensitivity analysis because it had much higher estimates of the odds ratio compared to other studies, high heterogeneity persisted (data not shown).

Discussion

We were not able to definitively conclude, based on both qualitative and quantitative synthesis, whether or not there is an increased risk of EPTB with concomitant HIV infection. Qualitative synthesis of the studies included in this systematic review showed

medium to high risk of bias along with heterogeneity in study design and population characteristics between the studies. Additionally, although most individual studies suggested an increased risk of EPTB compared to PTB among HIV-infected individuals, high quantitative heterogeneity did not allow for pooled estimates. The medium to high risk of bias and the high heterogeneity between studies is likely due to the cross-sectional design of most of the existing studies. Future well-designed prospective cohort studies are needed to address this potential association of HIV and EPTB. While conducting a prospective study could be challenging, it could be feasible in high-risk populations and would provide valuable information. If such an association can be confirmed, this will have both clinical and public health implications. For the clinician, there would be increased urgency to assess patients for HIV or EPTB if a patient has either one of the diseases. From a population health perspective, a potential connection between EPTB and HIV would provide strong evidence for public health officials to determine strategies to reduce EPTB among HIV-infected individuals and implement integrated initiatives to target both diseases.

Our results differed from the systematic review of the association between EPTB and HIV published by Naing, et al. [9]. Of the 19 studies included in their review, three were selected for our review. The differences in study selection are mainly due to the misclassification of the study designs in the review by Naing and colleagues (some cross-sectional studies were described as case-control or cohort), their inclusion of studies with unadjusted ORs (a major reason for fewer studies in our review), and the differences in our search strategy and inclusion criteria. Another reason for the disparity was our inclusion criterion of non-HIV subjects in studies, which Naing, et al. did not have. Despite the differences, the individual studies included in both the reviews suggest that there might be an association between HIV and EPTB. If these findings can be confirmed, future studies are needed to determine if there is a pathophysiological explanation for this association or whether there are other explanations such as finding more EPTB in HIV-infected individuals because they are screened for TB. Regardless of the explanation, these findings would add emphasis to screen for EPTB specifically, since most of the focus has been on diagnosing PTB.

As mentioned, the majority of the studies in our review were cross-sectional studies, which precluded the ability to comment on the temporality of the relationship between HIV and EPTB. Furthermore, many studies did not clearly define how the diagnoses of TB and HIV were made. In some cases, clinical suspicion was used for the diagnosis of TB, thus possibly overestimating the prevalence of TB. Moreover, many of our included studies used data from registries, which lacked detail on the method or order of diagnoses of PTB, EPTB, and HIV. There is clearly an unmet need for studies of higher quality in this field. Specifically, large, prospective cohort studies in a population without EPTB or HIV would shed more light on the actual risk of developing EPTB among HIV-infected and uninfected individuals. There is a need for such studies to have rigorous, widely accepted methods of diagnosing TB and HIV, which many of our studies did not have or did not mention. Moreover, future studies will also have to address the difficulty in diagnosing EPTB given the invasive procedures to collect samples and the limited sensitivity of the methods.

Our review and analysis have several limitations. Because the topic was broad (any type of EPTB included, control group could be PTB or even no TB, etc.), we anticipated that there

would be excessive heterogeneity in our results; this prediction was borne out in the data. When further studies on this topic are published, future reviews could focus on specific types of EPTB (such as TB meningitis or peritoneal TB; or separate out analyses where EPTB+PTB individuals are classified as EPTB as opposed to a separate group) to decrease the heterogeneity. In addition, data on important indicators such as ART or TB treatment as well as a description of potential biological plausibility for this association were also missing in these studies. Finally, our exclusion of non-English studies might or might not have held key information that could have potentially altered our results.

Ultimately, while there is a robust literature on HIV, TB, and EPTB, there are relatively few studies on the specific association of EPTB and HIV. Individual studies do suggest an increased association of HIV with EPTB, however these studies have a high risk of bias and there is substantial heterogeneity between the studies. Thus, to assess the relationship of HIV with EPTB, there is a need for prospective cohort studies that use well-validated, widely accepted methods of diagnosing HIV, TB, and EPTB that also collect information on other important risk factors to account for confounding.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. PRISMA diagram of search strategy for systematic review

Figure 1 Legend: Flow chart showing the search strategy utilized in this study. Articles from PubMed and EMBASE were screened for full-text review. The most common reasons for removing articles included: the absence of effect estimates; study design (e.g., case studies or review articles); languages other than English; and the use of unadjusted estimates. The remaining 16 citations are the basis of the articles used in this systematic review. Two separate searches were performed for this study. The first search was performed on February 2014 and the figure shows the number of articles screened and full-text read resulting in final selection of 10 articles. The second search was performed on August 2016 as an update since the first search. For this search, 250 articles were screened and 9 articles went full-text review to select 6 new articles.

Figure 2. Forest Plot of the association of HIV with EPTB

Figure 2 Legend: Forest plot showing the association of HIV with EPTB (relative to PTB or no EPTB [26]). The x-axis shows the effect estimate (ES) and 95% confidence intervals (CI). The weight, based on sample size, is shown along with the study design, I-squared value, study year and author. Overall effect estimates are not shown due to the high degree of heterogeneity between studies.

Table 1

Characteristics of included studies

Study, Year, reference	Country	Study Design	Clinical Setting	Sample size	Gender	Age distribution	Type of EPTB	HIV treatment (Y/N)	Primary effect measure
Rieder et al, 1989 [24]	USA	Cross-sectional	Florida Department of Health	8171	Male 71%; Females 29%	0-50+	Not reported	Not reported	Odds ratio
Wilkinson et al, 1996 [25]	South Africa	Cross-sectional	Hlabisa Health Ward, KwaZulu Natal (hospital and clinics)	297	Male 60%; Females 40%	Mean age of HIV (+) is 33.6	Pleural, disseminated, lymph node, pericardial, genitourinary, bone, TBM, peritoneal	Not reported	Relative risk
Gonzalez et al., 2003 [20]	USA	Cross-sectional	Houston TB initiative (surveillance program)	1878	Males: 67%; Females 33%	EPTB: <18, 112 (21%); >18, 426 (79%); PTB: <18, 57 (4%); >18 1060 (96%)	Lymph nodes, pleura, CNS, musculoskeletal system, genitourinary tract, gastrointestinal tract, other	Not reported	Odds ratio
Yang et al., 2004 [11]	USA	Case-control	Arkansas Department of Health: reported TB cases	354	Male: 63%; Female 36%	46% were over 65 years old	Bone and/or joint; lymphatic, other, military, genitourinary, peritoneal, meningial	Not reported	Odds ratio
Kung et al., 2009 [21]	Taiwan	Cross-sectional	National Taiwan University Hospital	1237	Males: 64%; Females: 36%	0 - >65	Not documented	Not reported	Odds ratio
Fiske et al, 2010 [17]	USA	Cross-sectional	Tennessee Health Department, state wide reporting	1571	Males: 67%; Females 33%	Median age is 49	Lymphatic, pleural, bone, genitourinary, military, meningial, peritoneal, other	Not reported	Odds ratio
Prado et. al., 2011 [23]	Brazil	Cross-sectional	Surveillance data from state of Espirito Santo	9165	Male 65.6%; Females: 34.4%	Median 38 IQR 27-50	Peripheral lymph node, meningial, pleural, other	Not reported	Odds ratio
Namne et. al, 2013 [22]	Cameroon	Cross-sectional	TB register at a tertiary health institution in Douala.	749	Males: 53.8%; Females: 46.2%	Mean: 37.8 (+/- 15.6)	Bones and joints, lymph nodes, pleural, peritoneum, CNS, meninges, other	Not reported	Odds ratio
Gomes et al., 2013 [19]	Brazil	Cross-sectional	Lab based state surveillance data from Espirito Santo	450	Males: 70%; Females: 30%	0-9, 1%; 10-19, 4%; 20-39, 58%; 40-60, 32%; >60, 5%)	Miliary, pleural, peripheral lymphatic, genitourinary, bone & joint, ocular, meningial, others	Not reported	Odds ratio
Gomes et al., 2014 [18]	Brazil	Cross-sectional	Brazilian Notifiable Diseases Surveillance System	213336	Males 81%; Females 19%	0-14, 15-24, 25-34, 35-44, 45-54, 55-64, >=65	Pleural, laryngeal, skin, meningial, military, eye, bone, genitourinary, lymph node	Not reported	Odds ratio

Study, Year, reference	Country	Study Design	Clinical Setting	Sample size	Gender	Age distribution	Type of EPTB	HIV treatment (Y/N)	Primary effect measure
Fortun et. al., 2014 [28]	Spain	Cross-sectional	TB patients from Ramon y Cajal Hospital, Madrid	814	Males 65%; Females 35%	Mean: 43.7 ± 19	Lymphadenitis, military, multifocal; others	Not reported	Odds ratio
Tesgaye et. al., 2014 [31]	Ethiopia	Cross-sectional	TB cases in 14 randomly selected public and private health facilities in Addis Ababa	Not reported for this analysis	Not reported for overall	Median age is 29	Not reported	Not reported	Odds ratio
Sanches et. al., 2014 [30]	Portugal	Cross-sectional	All TB patients registered at the Pulmonology Diagnostic Center of Vila Nova de Gaia	386	Male 62%; Female 38%	Not reported for overall	Lymphatic, pleural, genitourinary, disseminated, others	Not reported	Odds ratio
Bates et. al., 2015 [26]	Zambia	Cross-sectional	Whole-body autopsies of inpatients in hospital in Lusaka	125	Male 64%; Female 36%	Median age is 35 years	Not reported	50% on ART	Odds ratio
Culqui-Levano et. al., 2016 [27]	Spain	Cross-sectional	All cases of TB reported to National Epidemiological Surveillance Network in Spain from 2007-2012	25688	Male 62%; Female 38%	Not reported for overall	Pleural, lymphatic, spine, others	Not reported	Odds ratio
Sama et. al., 2016 [29]	USA	Cross-sectional	All TB cases treated at Baltimore City Health Department	154	Male 61%; Female 39%	Mean: 47.3	Lymphatics, pleural, musculoskeletal, others	Not reported	Odds ratio

Table 1 Legend: For each of the sixteen selected articles, information is provided on the country of study, study design, clinical setting, sample size, gender and age distribution, the type of EPTB, information on antiretroviral use and the effect estimates.

Table 2
Modified Newcastle-Ottawa Criteria for Assessment of Bias in Case-Controls and Cross-Sectional Studies

	Case Definition Adequate	Representativeness of Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls	Ascertainment of Exposure	Same Method of Ascertainment	Non-Response Rate	Risk of bias score
Rieder 1989	B	A	A	A	AB	D	A	C	Medium Risk: 6 stars
Wilkinson 1996	A	A	B	A	AB	AB	A	A	Low Risk: 8 stars
Gonzalez 2003	B	A	A	A	AB	A	A	A	Low Risk: 8 stars
Yang 2004	B	A	C	B	AB	E	B	C	High Risk: 3 stars
Kung 2009	B	A	C	B	AB	A	A	A	Medium Risk: 6 stars
Fiske 2010	B	A	A	A	AB	D	A	A	Low Risk: 7 stars
Prado 2011	C	A	C	B	AB	E	B	C	High Risk: 3 stars
Namne 2013	A	B	C	B	AB	A	A	A	Medium Risk: 6 stars
Gomes 2013	B	A	A	A	AB	D	A	C	Medium Risk: 6 stars
Gomes 2014	C	A	A	A	AB	D	A	C	Medium Risk: 6 stars
Fortun 2014	A	A	B	B	AB	E	A	C	Medium Risk: 5 stars
Tesgaye 2014	B	A	B	A	AB	D	A	A	Medium Risk: 6 stars
Sanches 2014	B	A	A	A	AB	E	B	C	Medium Risk: 5 stars
Bates 2015	A	B	B	A	AB	D	A	C	Medium Risk: 5 stars
Culqui-Levano 2016	B	A	A	A	AB	E	B	A	Medium Risk: 6 stars
Samia 2016	B	A	A	A	AB	D	A	A	Low Risk: 7 stars

Table 2: Each of the sixteen studies are given a final risk of bias score based on the key in **Appendix Table 1**. The final score is based on individual scores for the following criteria: adequate case-definition, representativeness of cases, selection of controls, definition of controls, comparability of cases and controls, ascertainment of exposure, method of ascertainment and non-response rates. Studies

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can be awarded a maximum of 9 points; 1 star within each sub-category of the main categories of exposure and selection; up to 2 stars for comparability. Low risk of bias 7-9 stars; medium risk of bias 4-6 stars; 1-3 stars high risk of bias.