

A systematic review of published literature describing factors associated with tuberculosis recurrence in people living with HIV in Africa

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Abstract

Background: A summary of factors associated with recurrent tuberculosis (TB) in the African HIV-infected population is lacking. We performed a systematic review to address this.

Methods: We performed a literature search within PubMed and The WHO Global Library with specific inclusion and exclusion criteria to identify manuscripts emanating from the African continent which potentially described factors associated with recurrent TB in persons living with HIV.

Results: The literature search yielded 52 unique manuscripts, of which only 4 manuscripts were included in the final systematic review following application of the inclusion and exclusion criteria. Baseline CD4 count, baseline HIV viral load, a positive tuberculin skin test, prior active TB disease, cutaneous hypersensitivity reaction to treatment, having < 3 lung zones affected by prior TB disease, and anaemia were associated with recurrent TB in HIV-infected individuals, whilst age and antiretroviral status were not.

Conclusion: The lack of studies describing recurrent TB in Africa which stratify results by HIV-status is a hindrance to understanding risk factors for recurrent TB in this population. This might be overcome by implementing guidelines related to the publishing of data from observational studies in peer-reviewed medical journals reporting recurrent TB in populations with a high-burden of HIV infection.

Keywords: published literature, tuberculosis recurrence, HIV, Africa.

DOI:<http://dx.doi.org/10.4314/ahs.v15i4.24>

Cite as: Moodley Y, Govender K. *A systematic review of published literature describing factors associated with tuberculosis recurrence in people living with HIV in Africa.* *Afri Health Sci.* 2015;15(4):1239-46. <http://dx.doi.org/10.4314/ahs.v15i4.24>

Introduction

Tuberculosis (TB) is a global health problem, with the African population amongst the populations with the highest burden of TB disease.¹ This appears to be related to the high burden of HIV on the African continent. Indeed, HIV infection substantially increases the risk of developing future TB disease.¹ Therefore, even HIV-infected individuals with a previous history of TB who might have been cured or successfully completed their TB treatment might develop TB again during their lifetime. This “recurrent” TB infection might be due to 1) a newly acquired infection with *Mycobacterium tuberculosis* following prior successful treatment for active TB disease, or 2) activation of latent *M. tubercu-*

losis from a previous exposure which did not result in active TB disease, or 3) activation of latent *M. tuberculosis* which remained following treatment completion for a prior episode of active TB disease.² Persons with HIV infection have a higher risk of recurrent TB disease.¹ In addition, there is significant mortality from TB infection in HIV infected persons.³ It is therefore important to identify additional factors associated with recurrent TB in the HIV-infected population to aid in the development of efficient risk-reduction interventions. The aim of this study was to conduct a systematic review of the published literature in order to identify additional risk factors for recurrent TB infection in people living with HIV/AIDS in Africa.

Methods

A formally registered protocol for this systematic review is unavailable. Briefly, we conducted a parallel search of PubMed and The WHO Global Library. In PubMed we searched using a combination of phrases/keywords and using a set of relevant MeSH terms (Table 1).

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Table 1. Electronic search strategy

Database	Query	Search Terms	Number of Items Returned
PubMed	1	Recurrence [MeSH Terms]	150497
	2	Tuberculosis[MeSH Terms]	162792
	3	HIV [MeSH Terms]	83568
	4	Risk Factors [MeSH Terms]	592615
	5	Africa [MeSH Terms]	191475
	6	((((Recurrent) OR Recurrence) OR Recurring) OR Relapse [All Fields]	560062
	7	Tuberculosis [All Fields]	219757
	8	HIV [All Fields]	287733
	9	(Risk Factors) OR Predictors [All Fields]	1024743
	10	Africa [All Fields]	249634
	11	(((((Query #1) AND Query #2) AND Query #3) AND Query #4) AND Query #5	5
	12	(((((Query #6) AND Query #7) AND Query #8) AND Query #9) AND Query #10	51
	13	(Query #11) OR Query #12	51
WHO Global Health Library	1	(Recurrence [MeSH Terms]) AND (Tuberculosis [MeSH Terms]) AND (HIV [MeSH Terms]) AND (Risk Factors [MeSH Terms]) AND (Africa [MeSH Terms])	12

We had chosen to search PubMed with both these options to improve the sensitivity of the search. In addition to the PubMed literature search, we also performed a search of literature in the World Health Organisation's (WHO) Global Medical Library using the same MeSH

terms used in the PubMed search. We were unable to search EMBASE as our institution does not have access to the database. Abstracts of studies identified from the literature search were screened using the inclusion and exclusion criteria specified in Table 2.

Table 2. Inclusion and exclusion criteria for this systematic review

Inclusion Criteria	Exclusion Criteria
Original manuscripts published in English in peer reviewed journals	Unpublished data, review manuscripts, case reports, commentaries, non-English manuscripts
Research conducted in Africa	Research conducted outside Africa
Studies reporting risk factors for recurrent TB in people living with HIV/AIDS	Studies which do not report risk factors for recurrent TB in people living with HIV/AIDS
Studies conducted in the general population	Research which does not involve the general population or focusses on specific population groups (For example, miners)
Research in adults	Research in children

The reference lists of included manuscripts were also hand searched for relevant studies which might not

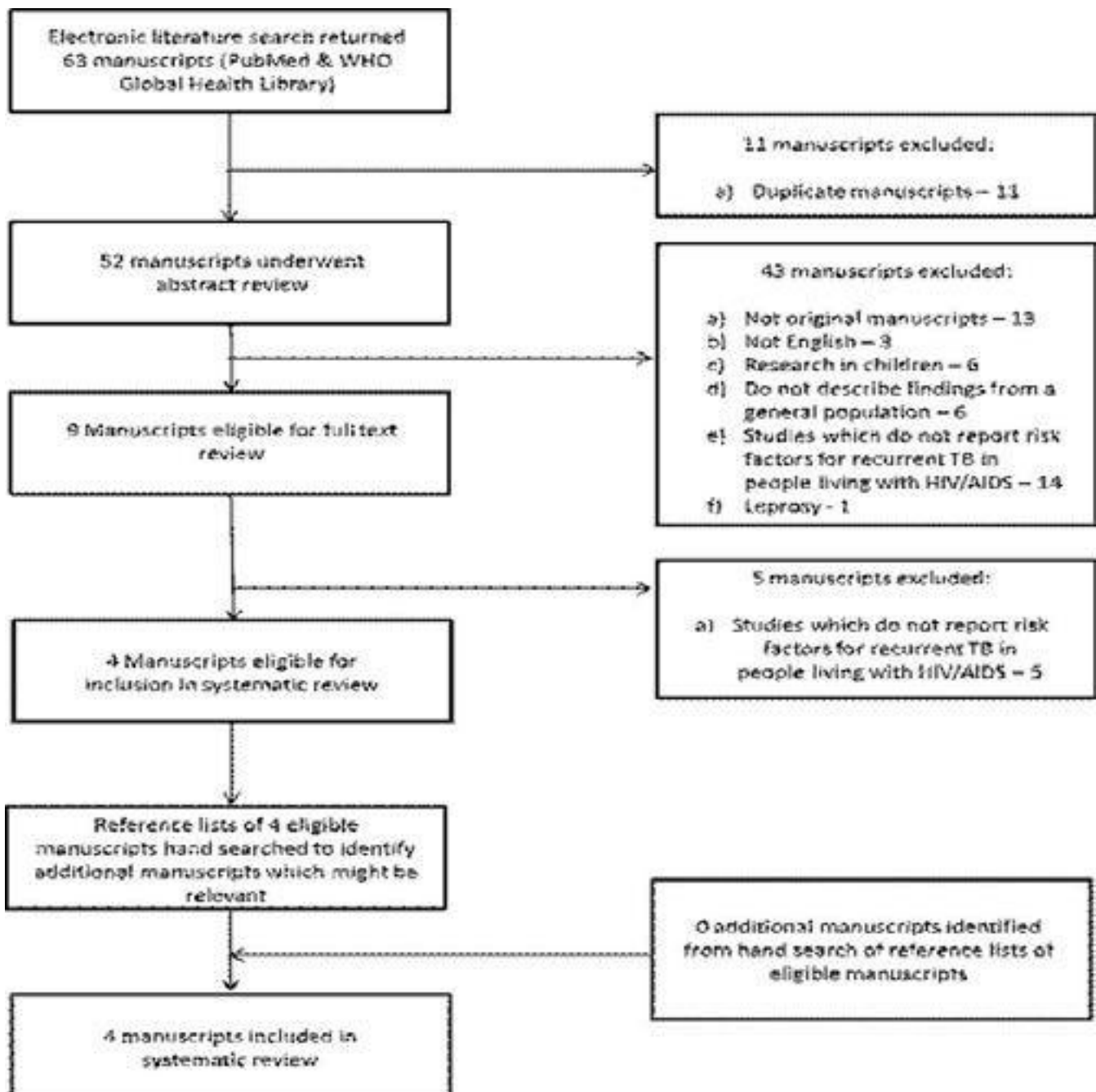
have been identified during the literature search. The quality of included studies was evaluated using the

Newcastle-Ottawa Scale. We did not extend our search to “grey area” literature. Our decision to exclude data from “grey area” literature might have introduced publication bias, however the “grey area” literature is often not peer reviewed and in the case of conference abstracts, may not have provided enough information to be included in the review. Two authors independently screened the articles for inclusion in the review, and the opinion of an expert would be sought in the event of a dispute.

Manuscripts describing findings from HIV-positive

populations (either studies solely of HIV-infected populations, or studies which stratified results by HIV status) were reviewed and the relevant data abstracted where possible. In addition to key risk factors for recurrent TB in HIV-infected individuals, the following data elements were extracted from all included manuscripts: Author, country where the study was conducted and year of publication; study design; size of HIV infected population; incidence of recurrent TB; % of cohort which was female; age; and CD4 count summary. Risk factors obtained from each study are primarily presented as a narrative. The characteristics of included studies are presented as descriptive statistics.

Figure 1. Flow chart showing study selection



Results

The results of our literature search of the two databases are illustrated in Figure 1.

Our search yielded a total of 63 manuscripts. A total of 11 of these manuscripts were duplicates. Following review of the abstracts of the remaining 52 unique manuscripts,^{4,55} 9 manuscripts^{7,15,18,23,25,26,31,33,35} were selected to undergo full text review. Reasons for exclusion of 43 manuscripts included: Not original manuscripts – 13 manuscripts,^{6,8,10,16,29,32,38,39,42,46,49,50,53} Not English – 3 manuscripts;^{30,40,45} Research in children – 6 manuscripts;^{4,12,17,27,47,48} Do not describe findings from a general population – 6 manuscripts,^{5,14,21,37,41,51} Studies which do not report risk factors for recurrent

TB in people living with HIV/AIDS – 14 manuscripts.^{9,11,13,19,20,22,24,28,36,43,44,52,54,55} In addition there was one manuscript which reported on leprosy.³⁴

Following full text screening of the 9 manuscripts,^{7,15,18,23,25,26,31,33,35} there were 5 manuscripts which were found not to specifically report risk factors for recurrent TB in people living with HIV/AIDS.^{7,15,26,33,35} In addition, we screened the reference lists of the remaining 4 manuscripts^{18,23,25,31} in order to identify other potentially eligible studies for inclusion in our systematic review, which did not yield any additional manuscripts. Therefore, this systematic review was comprised of 4 eligible manuscripts.^{18,23,25,31}

A description of all eligible manuscripts evaluated in this systematic review is shown in Table 3.

Table 3. Characteristics of studies included in this systematic review

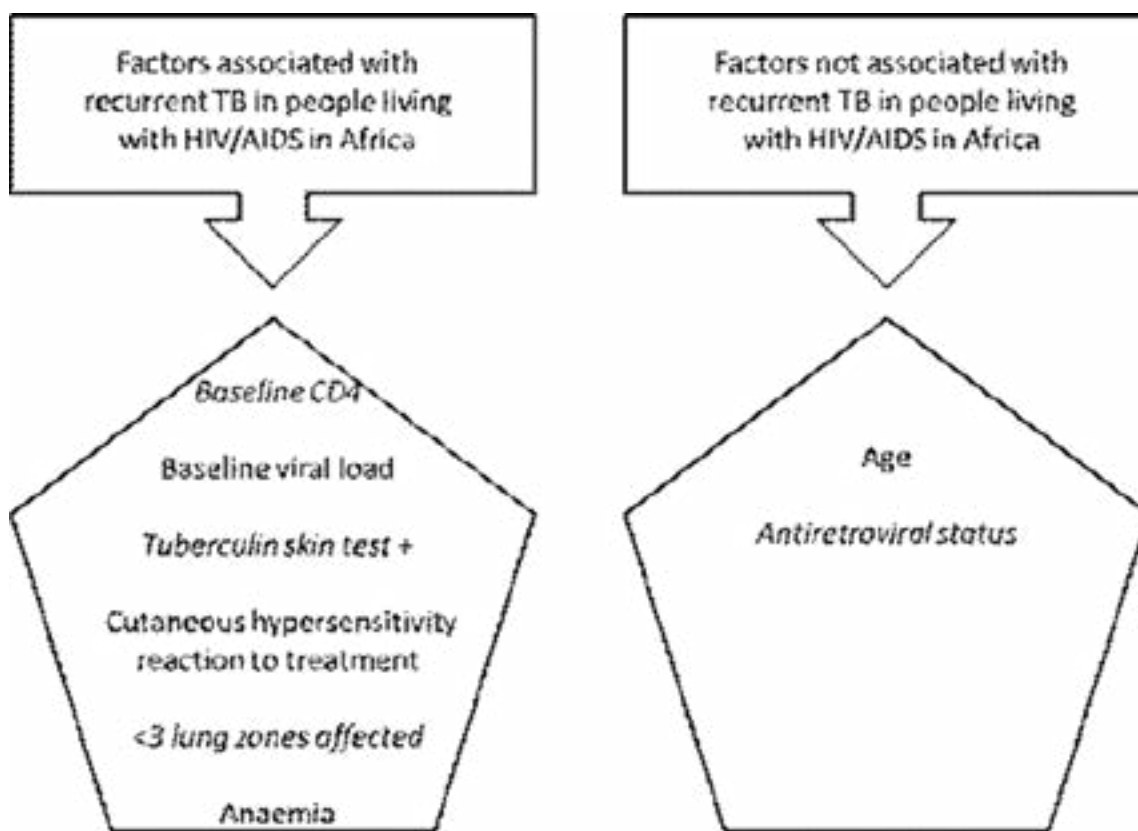
Authors (Country, Year)	Study Design	Total sample size analyzed (HIV-positives only)	Incidence of recurrent TB (/100 py)	% Female	Median Age	Median CD4+ count (Range)	Study Quality (Newcastle-Ottawa Scale Score)	Potential bias
Lahey et al. (Tanzania, 2013)	Prospective observational	979	HIV-positive with definite TB: 4.57 HIV-positive with definite/probable TB: 7.42	75.6	Median age of HIV-positive patients with prior history of TB: 36.4 years	HIV-positive patients with a prior history of TB: 347 (262– 549) cells/ μ L	7	Selection, performance
Houben et al. (Malawi, 2012)	Prospective observational	623	HIV-positive not on ART: 3.9 HIV-positive on ART: 3.0	53.7	Not specified. 50.6% of cohort <35	Not specified	8	Performance
Isanaka et al. (Tanzania, 2012)	Sub-analysis of randomized controlled trial data	Unclear	12 events/644 person months and 11 events/704 person months in HIV-infected persons with non-iron deficiency anaemia and iron deficiency anaemia, respectively.	Unclear	Unclear	Unclear	8	Selection, performance
Hawken et al. (Kenya, 1993)	Prospective observational	58	In patients with HIV-infection: 16.7	38.0%	Not reported. 65% of patients < 35 years old.	Not reported	8	Selection

Risk factors for recurrent TB in people living with HIV/AIDS were evaluated in participants from 4 studies conducted in 3 countries in Africa (Kenya, Malawi and Tanzania).^{18,23,25,31} Three of the eligible manuscripts describe prospective observational studies.^{18,23,31} One manuscript described the secondary analysis of data obtained from a randomized controlled trial.²⁵ Females comprised 38%,¹⁸ 54%²³ and 76%³¹ of HIV-infected participants described in three of the eligible manuscripts. The remaining manuscript did not stratify results for gender by HIV status.²⁵ The median age of HIV-infected participants in one manuscript was 36

years old.³¹ Although median age was not specified in two manuscripts, approximately half of the HIV-infected study population was <35 years old in one manuscript,²³ while this proportion was 65% in another manuscript.¹⁸ The remaining manuscript did not stratify results for age by HIV status.²⁵ Median CD4 counts were reported in one of the 4 manuscripts only.³¹

There were several factors associated with a higher risk of developing recurrent TB infection identified in this systematic review. Risk factors for recurrent TB in people living with HIV/AIDS obtained from the full text review of eligible manuscripts are shown in Figure 2.

Figure 2. Factors associated with recurrent tuberculosis infection in persons living with HIV/AIDS in Africa



Most of these risk factors were identified from the study of Lahey et al,³¹ and included: Baseline CD4 count, baseline HIV viral load, and a positive tuberculin skin test. Factors which were not associated with a higher risk of recurrent TB in HIV-infected individuals reported in the study of Lahey et al,³¹ included ART status and age. In their study, Houben and colleagues conducted a sub-analysis of HIV-infected individuals but only investigated whether ART status was associated with recurrent TB infection in this population.²³ As

with the study of Lahey et al,³¹ the study of Houben and colleagues did not identify an association between ART status and recurrent TB in HIV-infected individuals.²³ In the study conducted by Hawken and colleagues, there were two factors associated with a higher risk of recurrent TB in HIV-infected patients who had completed treatment: cutaneous hypersensitivity reaction to treatment and < 3 lung zones affected by prior TB disease.¹⁸ Isanaka et al., found that anaemia with or without iron-deficiency was associated with a 4- to 7-fold

increased risk of recurrent tuberculosis in HIV-infected patients when potential confounders were accounted for.²⁵

Discussion

Despite the high burden of HIV-TB co-infection on the African continent, there appears to be very little published peer-reviewed literature related to identifying risk factors for recurrent TB in HIV-infected individuals emanating from Africa. It is possible that the complexity of sharing data between TB and HIV programs (which have traditionally been vertical programs at African health care facilities),⁵⁶ makes research related to HIV-TB co-infection very difficult. Therefore it is likely that collaborative activities between HIV and TB health services which have been shown to improve patient outcomes,⁵⁷ might also improve research efforts as a consequence.

The risk factors for recurrent TB in HIV-infected individuals identified in this systematic review were essentially extracted from four manuscripts^{18,23,25,31} and included baseline CD4 count, baseline HIV viral load, a positive tuberculin skin test, cutaneous hypersensitivity reaction to treatment, having < 3 lung zones affected by prior TB disease, and anaemia. The findings of this systematic review have identified a gap in the current literature and highlight the important role of future clinical studies studying recurrent TB in the HIV-infected population. Due to the insufficient number of published manuscripts identified during the literature search, we were unable to perform a meta-analysis which could have provided pooled risk estimates for risk factors associated with recurrent TB in HIV-infected individuals in Africa. This further highlights the need for more research initiatives aimed at identifying risk factors for recurrent TB in HIV-infected individuals living in Africa, and further efforts to disseminate the findings of these studies through peer-reviewed manuscripts to the wider scientific community. This systematic review was also unable to provide information related to the stratification of recurrent TB into re-infection with *M. tuberculosis* or TB relapse. Before risk factors can be identified for these pathways leading to recurrent TB disease, adequately-powered genetic studies in African populations are required to accurately determine the burden of re-infection with *M. tuberculosis* and TB relapse.

Unfortunately, the lack of studies describing recurrent TB in Africa which stratify results by HIV-status is a hindrance to understanding risk factors for recurrent TB in this population. It is possible that implementing guidelines related to the publishing of observational studies in peer-reviewed medical journals reporting recurrent TB in populations with a high-burden of HIV infection might be a worthwhile approach to generating higher-level evidence for risk factors for recurrent TB in the form of systematic reviews and meta-analyses.

Acknowledgment

This work was supported through postdoctoral funding awarded by the South African National Research Foundation. The funding source played no role in designing the study; in the collection, analysis, and interpretation of data; in writing the report; or in the decision to submit this article for publication. The authors declare that there are no conflicts of interest.

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