

**Title:** Antiretroviral therapy for prevention of HIV-associated tuberculosis: a systematic review and meta-analysis

## **Abstract**

**Background:** WHO reported that HIV infection increases the risk of tuberculosis 20-37 fold [1]. This increased risk of tuberculosis has fuelled the resurgence of tuberculosis, with latest WHO estimates indicating that deaths due to HIV-associated tuberculosis represent 24% of all tuberculosis deaths and 22% of all HIV-related deaths. ART has substantial potential to prevent HIV-associated tuberculosis. **Methods:** A systematic review on published articles will be undertaken. Qualitatively, we will summarise studies meeting inclusion criteria using a standardised data collection form and will assess for study bias using a validated tool [2]. There will be five categories based on CD4 at ART initiation for the quantitative portion of this review:  $\leq 200$ , 200-350, 351-500,  $>500$ , or not reported. We will assess for reporting biases, heterogeneity, and provide random-effects estimates in each of these CD4 categories. **Funding:** There will be no funding source for this manuscript.

## **Introduction**

### **Rationale**

Tuberculosis and human immunodeficiency virus (HIV) present a major combined threat to achieving the Millennium Development Goals [3]. In 2009 there were an estimated 1.2 million incident cases of tuberculosis [4] among the 33.3 million people living with HIV [5]. The 400,000 deaths among incident HIV-positive tuberculosis cases comprised 24% of all tuberculosis deaths [4] and 22% of all HIV-related deaths in 2009 [5].

WHO reported that HIV infection increases the risk of tuberculosis 20-37 fold [1]. This increased risk of tuberculosis has fuelled the resurgence of tuberculosis. Directly Observed Therapy, short-course, (DOTS) was largely developed in the pre-HIV era and provided an excellent strategy for eliminating tuberculosis during this time. However, DOTS is often not enough to control tuberculosis in countries tackling generalised HIV epidemics. In these countries, where over 80% of incident tuberculosis cases are HIV positive [1], additional interventions are needed.

WHO recommends twelve collaborative activities through which national HIV and tuberculosis programmes can address HIV-associated tuberculosis [6]. These include the *Three I's for HIV/TB*: intensified tuberculosis case-finding [7], isoniazid preventive therapy [7], and infection control for tuberculosis [8]. Given the risk of HIV-associated tuberculosis decreases as CD4

counts increase, and that antiretroviral therapy (ART) causes immune reconstitution [9], ART also has substantial potential to prevent HIV-associated tuberculosis.

Unfortunately, searches conducted in PubMed, Embase, and Google Scholar indicate that there are no systematic reviews on this topic.

## **Objective**

To systematically review the scientific literature on the effect of antiretroviral therapy on incident tuberculosis, in accordance with PRISMA guidelines [10]. This will be done by comparing rates of tuberculosis by antiretroviral therapy status in adults ( $\geq 13$  years) using retrospective cohort studies, prospective cohort studies, and randomised controlled trials.

## **Methods**

### **Inclusion criteria for studies**

*Participants:* People living with HIV at least 13 years of age.

In the quantitative portion of this systematic review, the outcome will be assessed in different strata of absolute CD4 count. In the paediatric HIV population, absolute CD4 counts exhibit variability, vary by age, and do not have the same diagnostic value as absolute CD4 counts in adults [11]. Therefore for immunological monitoring, clinicians use CD4 percentages in this population [12]. TB diagnosis in children also poses additional challenges [13]. Therefore, the paediatric population has been excluded from this review.

*Intervention:* Antiretroviral therapy (defined as three or more drugs for treatment of HIV).

Modern antiretroviral therapy uses three or more drugs for treatment of HIV [14]. Use of less than three drugs has been associated with poor durability and the development of antiretroviral resistance [15]. Since IPT may supplement ART's preventive effects, studies only assessing the effect of ART and IPT on incident tuberculosis will be excluded from the quantitative portion of this review.

*Comparator:* Placebo or no drugs.

There is considerable debate on appropriate methods to use for determining when to start antiretroviral therapy. One way has been to compare mortality rates in people who started ART at CD4 counts from 351-500 to mortality rates in people who started ART at CD4 counts greater than 500 [16, 17]. Another has been to compare mortality rates in CD4 strata, by

antiretroviral therapy status [18]. Given that tuberculosis rates differ by CD4 strata [9], an effective way to assess the effect of antiretroviral therapy on prevention of HIV-associated tuberculosis is by comparing rates of tuberculosis in different CD4 strata by antiretroviral therapy status.

*Outcome:* Incident tuberculosis.

There are many ways to diagnose tuberculosis. The gold standard is culture confirmation. Other methods include using acid fast bacilli smears, chest radiography, nucleic acid amplification tests, or clinical symptoms. This review will include studies regardless of diagnosis method used. However, the Newcastle-Ottawa Quality scale will assess for in-study measurement bias by downgrading studies that do not microbiologically confirm TB cases.

*Study design:* Randomised trials, prospective cohort studies, and retrospective cohort studies.

Randomised trials, prospective cohort studies, and retrospective cohort studies will be used since their study arms (i.e. participants on ART and participants off ART) are from the same source population.

**Search methods for identification of studies:** Electronic searches of abstracts and titles will be conducted in PubMed and Embase. The Cochrane Central Register of Controlled Trials, the International Standard Randomised Controlled Trial Number Register, and ClinicalTrials.gov will be searched for future/ongoing studies. We also plan to contact experts in the field to identify unpublished research or ongoing studies. Since Embase searches both the Embase and PubMed databases, it will be used for the systematic searches (Table 1).

All retrieved abstracts will be screened independently by two reviewers. Disagreements will be resolved by inclusion of the controversial article (with the understanding that systematic application of the inclusion criteria will exclude irrelevant studies). Full articles of abstracts identified by the reviewers will be assessed for eligibility using the inclusion criteria.

**Table 1.** Search strategies for PubMed and Embase databases

Search number	Search strategy for Embase and PubMed databases
1	antiretroviral
2	anti-retroviral
3	HAART
4	cART
5	ART
6	ARV
7	1 or 2 or 3 or 4 or 5 or 6
8	tuberculosis
9	TB
10	8 or 9
11	risk*
12	rate*
13	hazard*
14	incidence*
15	11 or 12 or 13 or 14
16	7 and 10 and 15

### Qualitative summaries

**Data extraction and management:** Author, year of publication, study population, inclusion and exclusion criteria (including what screening for tuberculosis was done prior to ART initiation), intervention and comparator, information on follow-up, outcome data, and study design will be collected in a standardised spreadsheet.

**Assessment of bias in included studies:** The Newcastle-Ottawa Quality Assessment Scale (NOS) will be used to assess bias in cohort studies [2]. This scale rates studies from 0-10 based on nine criteria in the three sources of bias. Each criterion is worth one point except confounding, which is worth two points. Selection bias will be assessed using four criteria: (1) representativeness of the cohort on ART to the average adult on ART in the community from which study participants were drawn, (2) representativeness of the cohort off ART to the cohort on ART, (3) ascertainment of ART use, and (4) demonstration that prevalent tuberculosis was not present at the start of follow up and that cases developed during the first three months of ART are considered prevalent rather than incident episodes. For studies not reporting analyses in CD4 strata, adjustment for baseline CD4 will be used to judge whether appropriate methods have been used to address confounding. For studies reporting analyses in CD4 strata, adjustment for body mass index will be used to assess confounding. Measurement bias will be assessed by three criteria: (1) microbiological confirmation of TB cases, (2) adequate follow up to detect

ART's preventive effect on TB (i.e. median follow up of at least one year [19]), and (3)  $\leq 30\%$  of participants were lost to follow up during the study.

### **Quantitative analyses**

ART is already recommended in people living with HIV with CD4s  $\leq 350$  [14]. Therefore, to make this systematic review and meta-analysis useful to clinicians, policy makers, and programme managers, we plan to have five categories based on CD4 at ART initiation for the quantitative portion of this review:  $\leq 200$ , 200-350, 351-500,  $>500$ , or not reported.

**Assessment of publication biases:** A funnel plot with the effect measures on the x-axis and the standard error of the log for the effect measures on the y-axis will be created for each of the five CD4 categories. The Egger and Begg tests will be used to test the symmetry of the funnel plots.

**Assessment of heterogeneity:** Chi-square with a significance level of 0.10 will be used to test for heterogeneity if all studies meeting inclusion criteria, in each of the CD4 categories, present outcome data by ART status. I-squared estimates will be used to test for heterogeneity if all studies meeting inclusion criteria, in each of the CD4 categories, present effect estimates and 95% confidence intervals. I-squared estimates greater than 50% will indicate moderate levels of heterogeneity.

**Meta-analysis:** Data will be entered on the log scale (generic inverse variance). All effect measures will be entered as  $\ln(\text{effect measure})$  and standard error as  $\ln(\text{upper limit}/\text{lower limit})/3.92$ . A random effects model will be used for generating summary estimates in each of the five CD4 categories.

**Sensitivity analysis:** If an I-square value greater than 50% is found in the analysis, its cause will be explored using sensitivity analysis. Differences in TB incidence [4], TB prevalence [4], or Human Development Index [20] in the countries where studies were conducted may be causes for heterogeneity.

**Start date:** 21 March 2011

## References

1. WHO. *Global Tuberculosis Control 2009: Epidemiology, Strategy, and Financing*. Available from: [http://www.who.int/entity/tb/publications/global\\_report/2009/pdf/full\\_report.pdf](http://www.who.int/entity/tb/publications/global_report/2009/pdf/full_report.pdf).
2. Wells, G., et al. *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses*. Available from: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).
3. UN. *United Nations Millennium Development Goals*. [cited 2011 7 February]; Available from: <http://www.un.org/millenniumgoals/>.
4. WHO. *Global Tuberculosis Control, WHO Report*. 2010; Available from: [http://whqlibdoc.who.int/publications/2010/9789241564069\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241564069_eng.pdf).
5. UNAIDS. *UNAIDS Report on the Global AIDS Epidemic*. 2010; Available from: [http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123\\_globalreport\\_en.pdf](http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20101123_globalreport_en.pdf).
6. WHO. *Interim Policy on Collaborative TB/HIV Activities*. 2004; Available from: [http://whqlibdoc.who.int/hq/2004/who\\_hm\\_tb\\_2004.330.pdf](http://whqlibdoc.who.int/hq/2004/who_hm_tb_2004.330.pdf).
7. WHO. *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*. 2010; Available from: [http://whqlibdoc.who.int/publications/2011/9789241500708\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf).
8. WHO. *WHO policy on TB infection control in health-care facilities, congregate settings, and households*. 2009 10 September 2010]; Available from: [http://whqlibdoc.who.int/publications/2009/9789241598323\\_eng.pdf](http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf).
9. Lawn, S.D., et al., *Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa*. *Aids*, 2009. **23**(13): p. 1717-25.
10. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration*. *PLoS Med*, 2009. **6**(7): p. e1000100.
11. CDC, *1994 Revised Classification System for Human Immunodeficiency Virus Infection in Children Less Than 13 Years of Age*. *MMWR*, 1994. **43**: p. 1-10.
12. Raszka, W.V., Jr., et al., *Variability of serial absolute and percent CD4+ lymphocyte counts in healthy children born to human immunodeficiency virus 1-infected parents*. *Military Pediatric HIV Consortium*. *Pediatr Infect Dis J*, 1994. **13**(1): p. 70-2.
13. Harries, A., D. Maher, and S. Graham. *TB/HIV: A Clinical Manual*. 2004; 2nd edition:[Available from: <http://whqlibdoc.who.int/publications/2004/9241546344.pdf>.
14. WHO. *Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach*. 2010; Available from: [http://whqlibdoc.who.int/publications/2010/9789241599764\\_eng.pdf](http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf).
15. Miller, V., et al., *Dual resistance to zidovudine and lamivudine in patients treated with zidovudine-lamivudine combination therapy: association with therapy failure*. *J Infect Dis*, 1998. **177**(6): p. 1521-32.
16. Kitahata, M.M., et al., *Effect of early versus deferred antiretroviral therapy for HIV on survival*. *N Engl J Med*, 2009. **360**(18): p. 1815-26.
17. Sterne, J.A., et al., *Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies*. *Lancet*, 2009. **373**(9672): p. 1352-63.
18. Ray, M., et al., *The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals*. *Aids*, 2010. **24**(1): p. 123-37.
19. Lawn, S.D., M. Badri, and R. Wood, *Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort*. *Aids*, 2005. **19**(18): p. 2109-16.
20. UN. *Human Development Report 2010 - 20th Anniversary Edition*. 2010 [cited 2011 24 February]; Available from: [http://hdr.undp.org/en/media/HDR\\_2010\\_EN\\_Complete\\_reprint.pdf](http://hdr.undp.org/en/media/HDR_2010_EN_Complete_reprint.pdf).