**Title:** The influence of human immunodeficiency virus infection and antiretroviral therapy on risks of tuberculosis disease among children.

p.j.dodd@shef.ac.uk; james.seddon@imperial.ac.uk

**Abstract:**

**Background:** Human immunodeficiency virus (HIV) infection is one of the most significant risk factors for developing tuberculosis (TB) disease, and its influence on TB incidence has been quantified across different CD4 counts in adults. The protective effect of antiretroviral therapy (ART) against TB incidence has also been evaluated in adults. There is no comparable quantitative understanding of the influence of HIV and ART on TB incidence in children.

**Methods:** Systematic review of the literature to identify available data on TB incidence in HIV-infected children, as well as HIV infection prevalence in cohorts of children with TB. The available data will be synthesized using meta-analysis allowing for a quantitative objective test across studies of the influence of ART and HIV on TB in children. As moderating variables we will collect data on mean cohort age and CD4 percentage and all statistics will be performed using mixed-effect meta-analysis.

**Introduction**

**Rationale**

Children (those younger than 15 years) are at high risk of progression to tuberculosis (TB) disease following infection by *Mycobacterium tuberculosis* (1). This is particularly true for children in the first two years of life, who often develop non-pulmonary forms of TB (1). The variety of presentation and difficulty in obtaining viable samples for laboratory testing mean that confirming the diagnosis of TB in children can be challenging. This adds to difficulties in understanding the natural history and epidemiology of disease. Recent indirect approaches to burden estimation have made use of mathematical modelling of exposure and disease progression risks to predict the number of paediatric TB cases (2).

In adults, human immunodeficiency virus (HIV) infection is known to be a potent risk factor for developing TB, with incident rate ratios (IRR) of over 5 averaging across all levels of immune system deficiency (3). Evidence synthesis suggests an exponential increase in the IRR with decrease in the count of CD4-positive lymphocytes (4,5). The protective effect of antiretroviral therapy (ART) in reducing the risk of developing TB, in those living with HIV infection, is increasingly well quantified. This quantitative understanding of the effects of HIV and ART on TB progression has
been widely used by modellers, e.g. in predicting the impact of HIV interventions on TB incidence, e.g. (4–6).

While HIV infection is less common in children than adults, preliminary modelling suggests that in several sub-Saharan African countries, around 18% or more of paediatric TB is HIV-associated (2). However these estimates are associated with large uncertainty parameters as the impact of HIV infection and ART on TB progression in children is poorly quantified; no systematic reviews have been performed to evaluate this relationship.

**Objective**

To determine the effect of HIV infection on TB disease incidence in children, and to evaluate how this is affected by ART.

**Methods**

**Inclusion criteria for studies**

We will consider published articles written in English or French. If there are articles in other than these languages we will seek support to include them, although this is not expected.

**Participants:**

Children aged under 15 years.

**Exposure:**

HIV infection or HIV infection and ART.

**Study designs:**

i. *(TB cohorts)* Cohorts of children constructed on the basis of incident or prevalent TB where HIV and ART status of children is known, and where local or UNAIDS estimates of HIV prevalence and ART coverage in children of the same age are available.

ii. *(HIV cohorts)* Cohorts of HIV-infected children with either:
   a. controls (either HIV-negative or on ART)
   b. measurements of CD4 count and/or CD4 percentage or clinical staging and age and ART status

iii. *(RCTs)* Randomized controlled trials evaluating:
   a. ART vs. no ART in HIV-infected children
   b. in cohorts of HIV-infected children, co-trimoxazole therapy or other interventions with no established effect on TB incidence
Comparator:

i. (TB cohorts) HIV prevalence in children without TB
ii. (HIV cohorts) TB disease incidence in children of the same age in the same population
iii. (RCTs) Children of the same age and CD4 status, not on ART

Outcome:

i. (TB cohorts) HIV prevalence
ii. (HIV cohorts) TB disease incidence
iii. (RCTs) TB disease incidence

Search methods for identification of studies:

We will search the following databases from 1980 to 2014.

• MEDLINE
• EMBASE
• Cochrane Controlled Trials Register
• AIDSinfo

A draft search strategy for MEDLINE and EMBASE is shown in Table 1. A complete search strategy will be developed in with advice from an information specialist.

Table 1: Draft Ovid search strategy for EMBASE and MEDLINE

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Hand searching of the following journals will also be performed:

- Journal of Tuberculosis and Lung Disease
- Paediatric infectious disease journal

The reference lists from identified primary research articles and review articles will be searched for new studies to be evaluated for inclusion. Google Scholar will be used to search citations indexed in Web of Science for new reports.

Finally, authors of key studies will be contacted to ask if they know of any unpublished data that can inform our question.

**Qualitative summaries**

**Data extraction and management**

Two reviewers will independently assess articles identified by the above search strategy. They will first review the title and abstract of each paper and evaluate each against pre-specified criteria. Reasons for exclusion will be recorded. The union of the two selections will be taken forward and full text versions will be obtained. The two reviewers will then independently review studies for inclusion based on pre-specified inclusion criteria; conflicts will be resolved by discussion. We will follow the results guidance in the PRISMA statement (7). A spreadsheet will be used to collate information on author, publication date, year(s) of data collection, study population, study type, inclusion and exclusion, the relevant moderators (TB and HIV prevalence, BCG vaccination coverage and study latitude), reported follow-up and outcomes. Later analyses of the raw data will be made using custom R scripts.

**Assessment of quality in included studies:**

The NIH quality assessment tool for cohort and cross-sectional studies (8) will be used as a guide in assessing the quality of included studies.

**Narrative summary:**
We will provide a narrative summary of studies included and discuss their quality for answering our question.

**Quantitative analyses**

*Meta-analysis:*

Contingent on the identification of sufficient studies with appropriate data, data will be analysed as follows for each of the corresponding study designs described above:

i. Let: $H$ be the fraction of TB cases in children that are HIV-positive; $h$ be the fraction of comparable children in the general population who are HIV-infected; $IRR^H$ the incidence rate ratio for HIV-infected not on ART vs HIV-uninfected children; $IRR^A_H$ the incidence rate ratio for HIV-infected on ART vs HIV-infected children not on ART; and $f_H$ the fraction of HIV-infected children in the general population who are on ART. The relationship:

$$\frac{H/(1-H)}{h/(1-h)} = IRR^H \cdot f_H + IRR^A \cdot (1 - f_H)$$

is expected to hold, where $IRR^A = IRR^A_H$, $IRR^H$. Incidence rate ratios $IRR^A$ and $IRR^H$ will be estimated by random effects logistic regression, the data graphed and a heterogeneity statistic reported. ART and background HIV prevalence ($f_H$ and $h$) will be treated as perfectly known parameters, but sensitivity to varying them considered.

ii. If there are sufficient studies in each category that report relevant data, the following quantitative syntheses will be performed:

   a. For cohorts with controls, direct estimates of $IRR^H$ (where controls are HIV-uninfected) and $IRR^A_H$ (where controls are HIV-infected but on ART) will be displayed on a forest plot and a random effects overall measure calculated.

   b. For cohorts reporting TB incidence by CD4-percentage/count the log(incidence) or incidence (as judged most appropriate from graphing the data) will be regressed against CD4-percentage/count with a random effect for the slope and separate intercepts for each study in order to estimate the dependence of TB incidence on CD4 degradation.

iii. Where there are sufficient studies reporting other relevant data, these data will be analysed as in ii) a.

If sufficient data are reported by age, CD4 percentage, or BCG vaccination status of the child, these analyses will be carried out by subgroup or by incorporating these quantities as explanatory variables.

**Assessment of publication biases**

Bias in meta-analysis will be assessed using Egger regressions and rank tests of the sampling variance against the effect sizes extracted. If any asymmetry due to publication bias is suspected, trim and fill methods will be applied.
**Assessment of heterogeneity**

$I^2$ statistics will be computed separately for each measure from the previous section of effect, where sufficient studies were available to estimate a pooled effect. An $I^2$ value of 50% will be regarded as substantial heterogeneity.

**Sensitivity analysis:**

If an $I^2$ value is greater than 50%, reasons for potential heterogeneity will be discussed. Population TB and HIV prevalence, BCG vaccination coverage and study latitude will be considered as specific quantitative causes.

**Start date:**

November 2014

**References**


