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The impact of HIV and antiretroviral therapy on tuberculosis risk in children: a systematic review and meta-analysis

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Tuberculosis; HIV; ART; paediatric; CD4

Word count:
3498

What is the key question?
What effects do HIV infection and anti-retroviral therapy (ART) have on tuberculosis (TB) risk in children?

What is the bottom line?
HIV infection increases the incidence of TB in children by a factor of around 8, increasing with degree of immunosuppression; ART reduces TB risk by around 70%, with protection continuing to increase over 1-2 years.

Why read on?
TB incidence in HIV infected children is very high, but no systematic review has quantified the effects of HIV or ART on TB risk in children.
ABSTRACT

Background Children (<15 years) are vulnerable to tuberculosis (TB) disease following infection, but no systematic review or meta-analysis has quantified the effects of HIV-related immunosuppression or antiretroviral therapy (ART) on their TB incidence.

Objectives Determine the impact of HIV infection and ART on risk of incident TB disease in children.

Methods We searched MEDLINE and Embase for studies measuring HIV prevalence in paediatric TB cases (‘TB cohorts’) and paediatric HIV cohorts reporting TB incidence (‘HIV cohorts’). Study quality was assessed using the Newcastle-Ottawa tool. TB cohorts with controls were meta-analysed to determine the incidence rate ratio (IRR) for TB given HIV. HIV cohort data were meta-analysed to estimate the trend in log-IRR versus CD4 percentage, relative incidence by immunological stage, and ART-associated protection from TB.

Results 42 TB cohorts and 22 HIV cohorts were included. In the eight TB cohorts with controls, the IRR for TB was 7.9 (95% confidence interval [CI]: 4.5-13.7). HIV-infected children exhibited a reduction in IRR of 0.94 (95% credible interval: 0.83-1.07) per percentage point increase in CD4%. TB incidence was 5.0 (95%CI: 4.0-6.0) times higher in children with severe compared to non-significant immunosuppression. TB incidence was lower in HIV-infected children on ART (hazard ratio: 0.30; 95%CI: 0.21-0.39). Following initiation of ART, TB incidence declined rapidly over 12 months towards a hazard ratio of 0.10 (95%CI: 0.04-0.25).

Conclusions HIV is a potent risk factor for paediatric TB, and ART is strongly protective. In HIV-infected children, early diagnosis and ART initiation reduces TB risk.

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INTRODUCTION

Children are at high risk of progression to tuberculosis (TB) disease following infection with *Mycobacterium tuberculosis*, particularly children in the first two years of life, who often develop non-pulmonary forms of TB.[1] The variety of presentation, difficulty in obtaining samples for laboratory testing and paucibacillary nature of disease mean that confirming a TB diagnosis 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 used mathematical modelling of exposure and disease progression risks to predict paediatric TB incidence.[2] WHO estimated that in 2014 one million children developed TB globally.[3]

Although programs to prevent mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) have reduced new cases of vertically infected infants, coverage is incomplete; in 2013, an estimated 199,000 (170,000-230,000) children were newly infected with HIV.[4] Children experience more rapid HIV disease progression than adults, making them highly susceptible to opportunistic infections.[5] Antiretroviral therapy (ART) can restore immune function and has enormously reduced morbidity and mortality among HIV-infected children. In 2015, World Health Organization (WHO) guidelines were revised, recommending all HIV-infected children should initiate ART, irrespective of clinical disease stage or degree of immunosuppression.[6] However, ART coverage among children lags behind adults, with only one-third of eligible children currently on ART, compared to two-thirds of adults.[4]

In adults, HIV is a known potent risk factor for developing TB, with incident rate ratios (IRR) greater than 5 when averaged across all levels of immunodeficiency.[7] Evidence synthesis suggests an exponential increase in the IRR with decrease in CD4 T-cell counts.[8 9] The effect of ART in reducing TB risk in adults living with HIV infection is well described.[10] 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.[9 11 12] In contrast to adults, 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. In the context of revised WHO treatment recommendations, our objective was therefore to systematically review the paediatric HIV/TB literature to quantify the effect of HIV and ART on TB risk in children.
METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement[13] (see supplementary checklist). A protocol was registered with PROSPERO (identification number: CRD42014014276) in October 2014.

Cohort Definitions

For all studies, the exposure/intervention was HIV infection, with or without ART. We sought studies that either: (i) reported HIV prevalence in children with TB (‘TB cohorts’); or (ii) reported TB disease incidence in cohorts of children with HIV (‘HIV cohorts’). For TB cohorts, the outcome was HIV prevalence, and the comparator was HIV prevalence in control groups of children without TB. For HIV cohorts, the outcome was TB incidence, and the comparison was between subgroups of the same cohort with different levels of immune suppression, or ART exposure (all HIV-infected).

Search strategy, selection criteria, data extraction

To be eligible, a study had to present empirical data on more than 5 cases of TB in children (aged <15 years). Studies were excluded if they were not generally representative of paediatric TB cases in that population at that time, e.g.: studies that only addressed one form of TB; that only comprised hospitalized TB cases; studies explicitly focused on migrant populations; or autopsy studies. If the same cohort was published more than once, or individuals were described in more than one cohort, studies/children were only included once. Where explicit use of isoniazid preventive therapy (IPT) was stated, children receiving IPT were excluded. TB cohorts were excluded if the coverage of HIV testing was below 70% among TB cases. HIV cohorts were excluded if data were not reported that could be interpreted as an incidence (i.e. number of events and person-time).

MEDLINE and Embase were systematically searched without language, publication, or date restrictions using terms designed to capture Children & TB & (HIV or ART) on 20/12/2014 (see Appendix for full search). A combination of MeSH and EMTREE headings were used with free-text terms to enhance the sensitivity of the search. We further searched the Cochrane Controlled Trials Register and AIDSinfo for relevant studies. All references in review articles found by our database search were included. All citations listed in Google Scholar of the five most cited review articles found by our database search were screened. One additional study in press at the time of our systematic review, was brought to our attention after presenting draft results.[14] Two investigators (PJD and JAS) independently assessed titles and abstracts for inclusion. We further searched the Cochrane Controlled Trials Register and AIDSinfo for relevant studies. All references in review articles found by our database search were included. All citations listed in Google Scholar of the five most cited review articles found by our database search were screened. One additional study in press at the time of our systematic review, was brought to our attention after presenting draft results.[14] Two investigators (PJD and JAS) independently assessed titles and abstracts for inclusion. Full texts were independently assessed for inclusion and study type by PJD and JAS with disagreements resolved by discussion. Two investigators extracted the data for TB cohorts in tandem; PJD extracted the data for HIV cohorts with 25% of data checked by JAS.
For both study designs, the following were recorded: first author, publication year, study years, study country, number of TB cases, age range, number of male children. For TB cohorts, if local TB-free controls were reported in the study, the HIV prevalence among control children (numerator and denominator) was extracted. Other data extracted from the TB cohorts included: the coverage of HIV testing, the numerator and denominator of HIV prevalence in TB cases and the UNAIDS paediatric HIV estimate for corresponding country-year (if available; mid-point and uncertainty range). For HIV cohorts, the following were recorded: TB incidence (with uncertainty range), ART coverage at enrollment, estimate of protective effect of ART against TB (if present), and TB incidence in any ART- or immune-related stratum (with uncertainty range). Co-trimoxazole use was recorded where described. TB incidence by age band was extracted if present. Some studies recorded immune status using the WHO immunological classification[6] (not-significant, mild, advanced and severe immunosuppression), whereas others used alternative CD4% or CD4 count categories, which differed between studies. Mid-points and confidence intervals (assumed Poisson exact) were used to infer event numbers and person-time when aggregation was necessary. Some studies excluded incident TB within the first few months on ART, stating that they sought to exclude Immune Reconstitution Inflammatory Syndrome (IRIS) reactions and only determine true TB incidence.

Quality of individual studies was assessed using an adapted Newcastle-Ottawa quality assessment tool.[15] The version for case-control studies was used for TB cohorts; the version for cohort studies for HIV cohorts. For HIV cohorts, the quality for each study as input to each meta-analysis was assessed separately (Appendix pp.18-21) and reported as low/moderate/high quality (depending on whether few/some/most criteria were met) on domains of selection, comparability, and either outcome (for cohort studies) or exposure (for case-control studies).

**Statistical analyses**

For TB cohorts, we undertook a random-effects meta-analysis of the odds ratio (OR) for HIV prevalence given TB among those studies reporting HIV prevalence in controls. This OR can be interpreted as an incidence rate ratio (IRR) for developing TB disease if HIV positive[7] (Appendix p.7). We produced funnel plots to assess evidence of publication bias.

For TB cohorts where UNAIDS estimates of national HIV prevalence in the <15 year age group were available for the same year and country as the study, we undertook a Bayesian meta-analysis using both the UNAIDS data and control data. This analysis modelled the relationship between UNAIDS HIV prevalence and HIV prevalence in study controls from studies where both were available, and used this relationship to predict individual study ORs where controls were not available. For comparison, a Bayesian version of the meta-analysis of studies with controls was conducted (Appendix pp.8-11).

For HIV cohorts reporting TB incidence by immune stage, we undertook a random-effects meta-analysis of the IRR for each stratum relative to the ‘not-significant’ WHO immune stage. For HIV cohorts reporting incidence by >1 CD4% category
(using the mid-point of the CD4\% category in which the incidence was reported), or
an analysis of the relation between CD4\% and IRR for TB, we undertook a Bayesian
meta-analysis to estimate the gradient of logarithmic IRR with respect to CD4\%
(Appendix pp.13-15). We averaged the IRR implied by this point estimate over
CD4\% between 0\% and 50\% to compare with our IRR from the TB cohort analysis.
For HIV cohorts reporting an estimate of the protection against TB from ART as a
hazard ratio (HR), we performed a random-effects meta-analysis. For HIV cohorts
reporting TB incidence by >1 category of time-since ART-initiation, we fitted a non-
linear mixed effects model to estimate the temporal dependence of ART protection,
using the mid-point of the time window in which the incidence was reported to model
incidence (Appendix pp.15-16).

Bayesian techniques were employed where greater flexibility was required over
standard software implementations to utilise all the data. All statistical analyses were
undertaken using in R;[16] random effects meta-analysis was performed using the
rma command in the metafor package implementing the restricted maximum-
likelihood estimator.[17]

RESULTS

Search results

The systematic review process is presented in Figure 1. Of the 311 full-text articles
screened, 65 were included in this review. The most common reasons for exclusion
were HIV test coverage <70\% for TB cohorts (n=46), and TB incidence not reported
for HIV cohorts (n=22). Of the 65 included studies, 42 were classified as TB cohorts
(see Table 1), 22 were classified as HIV cohorts (see Table 2), and 1 study included
both a TB and HIV cohort.[18] Thirty-one of the 42 TB cohorts (74\%) and 17 of the
22 HIV cohorts (77\%) were from sub-Saharan Africa.

Of the TB cohorts, 8 included HIV prevalence in controls without TB and could be
used in the random-effects meta-analysis; 35 had relevant UNAIDS estimates and
could be included in the Bayesian meta-analysis, including all 8 studies with controls.

Of the HIV cohorts, 7 could be included in the meta-analysis of CD4\% influence, 3
could be included in the analysis of the influence of immunological staging, 10 were
included in the analysis of time on ART, and 6 were included in the pooled estimate
of ART efficacy against TB. Only 3 HIV cohorts reported co-trimoxazole use.[14 19
20]

HIV prevalence in TB cohorts ranged between 5\% and 94\% (Appendix p.5). TB
incidence in HIV cohorts ranged from 0.3 to 25.3 per 100 person-years (Appendix
p.6). Insufficient data were available in either group of cohorts to stratify results by
age.
Table 1: TB cohorts (ns = not stated; na=not applicable; * = data from years with high enough HIV testing rates used; age range obtained where stated, for eligibility otherwise; ** = adapted Newcastle-Ottawa score for case-control studies with some questions (and the comparability domain) not applicable to studies without controls: A=high quality; B=moderate quality; C=low quality; see Appendix pp.18-19, 24-25)

<table>
<thead>
<tr>
<th>First Author, Year</th>
<th>Country</th>
<th>Years of study</th>
<th>Study Description</th>
<th>Control HIV tested</th>
<th>Control with HIV</th>
<th>Children with TB</th>
<th>TB cases tested for HIV</th>
<th>TB cases with HIV</th>
<th>TB cases male</th>
<th>Age range</th>
<th>Quality assessment *(selection/ comparability / exposure)</th>
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<td>Berggren Palme, 2004[22]</td>
<td>Ethiopia</td>
<td>1995-1997</td>
<td>Prospective study recruiting all children investigated for TB at one hospital over a 13 month period</td>
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<td>355</td>
<td>54</td>
<td>ns</td>
<td>0-14</td>
<td>B/-/C</td>
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<td>1995-1997</td>
<td>Case control study, prospectively recruiting all children diagnosed with TB over a one year period at one children’s hospital, with a control group recruited concurrently amongst children undergoing elective surgery</td>
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<td>377</td>
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<td>186</td>
<td>0-14</td>
<td>B/A/A</td>
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<td>Controls Description</td>
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<td>Controls(s)</td>
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<tr>
<td>Bhat, 1993[24]</td>
<td>Zambia</td>
<td>1991-1991</td>
<td>Case control study, prospectively recruiting all children diagnosed with TB over a nine month period at one hospital, with a control group recruited from outpatients clinics and amongst surgical inpatients</td>
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<td>134</td>
<td>18</td>
<td>116</td>
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<td>58</td>
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<td>Cathebras, 1998[27]</td>
<td>Central African Republic</td>
<td>1997-1998</td>
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<td>Chintu, 1993[28]</td>
<td>Zambia</td>
<td>1990-1991</td>
<td>Case control study of all children treated for TB over an 18 month period in one teaching hospital. Controls were recruited from the emergency department or inpatient surgical wards</td>
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<td>242</td>
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<td>265</td>
<td>237</td>
<td>88</td>
<td>125</td>
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<td>Chintu, 1998[29]</td>
<td>Zambia</td>
<td>1992-1993</td>
<td>Case control study of all patients (adults and children) presenting with diarrhoea over an 8 month period at one teaching hospital. Cases were HIV-infected with controls HIV-uninfected. Paediatric analysis restricted to children under 5 years</td>
<td></td>
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<td>Nigeria</td>
<td>1999-2003</td>
<td>Retrospective study of all children diagnosed with TB at a TB centre over a five year period.</td>
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<td>Dominican Republic</td>
<td>1991-1994</td>
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<td>92</td>
<td>1-5</td>
<td>B+/C</td>
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<td>Feldacker, 2012[34]</td>
<td>Malawi</td>
<td>2008-2010</td>
<td>Retrospective study of all patients (adults and children) treated for TB at one TB treatment centre over a three year period.</td>
<td>na</td>
<td>na</td>
<td>364</td>
<td>338</td>
<td>148</td>
<td>168</td>
<td>0-14</td>
<td>C+/C</td>
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<td>Gava, 2013[35]</td>
<td>Brazil</td>
<td>1997-2006</td>
<td>Retrospective review of routinely collected data for all children treated for TB in one state over a ten year period</td>
<td>na</td>
<td>na</td>
<td>356</td>
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<td>183</td>
<td>0-14</td>
<td>C+/C</td>
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<tr>
<td>Geoghen, 2004[36]</td>
<td>Jamaica</td>
<td>1999-2002</td>
<td>Retrospective review of all children 0-12 years treated for TB at one hospital over a four year period</td>
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<td>C+/C</td>
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<td>Henegar, 2013[37]</td>
<td>Democratic Republic of Congo</td>
<td>2006-2007</td>
<td>Prospective study of all patients (adults and children) starting treatment for TB at 14 clinics over a 17 month period</td>
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<td>na</td>
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<td>Case-Control</td>
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<tr>
<td>Hesseling, 2009[38]</td>
<td>South Africa</td>
<td>2004-2006</td>
<td>Prospective laboratory data collected from 3 hospitals over a three year period, used to estimate the incidence of TB in infants (&lt;12months) with HIV and without HIV</td>
<td>na na 245 175 53 133 0-1</td>
<td>C/-/C</td>
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<td>Hussain, 2007[39]</td>
<td>India</td>
<td>2003-2004</td>
<td>Prospective study of all children admitted to one hospital for the treatment of TB, over a two year period</td>
<td>na na 270 270 23 154 0-15</td>
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<td>Iriaso, 2005[40]</td>
<td>Uganda</td>
<td>2003</td>
<td>Cross-sectional study of all children aged 2-60 months, investigated for TB at one hospital over a 12 week period</td>
<td>na na 126 126 62 63 0-5</td>
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<tr>
<td>Jain, 2013[41]</td>
<td>India</td>
<td>2010-2012</td>
<td>Prospective study of all children &lt;5 years investigated for suspected TB, at one hospital over a 20 month period</td>
<td>na na 26 21 6 15 0-5</td>
<td>C/-/C</td>
<td></td>
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<tr>
<td>Jensen, 2012[42]</td>
<td>Spain</td>
<td>1997-2008</td>
<td>Case-control study. Details of all HIV-infected children (&lt;17 years) hospitalised anywhere in the country over a 12 year period were extracted from a central database. 4 HIV-uninfected controls, matched on age and gender, were extracted for each case. Rates of mycobacterial diseases were compared between cases and controls</td>
<td>na na 30 30 20 ns 0-17</td>
<td>C/-/C</td>
<td></td>
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<td>Llerena, 2010[43]</td>
<td>Colombia</td>
<td>2001-2009</td>
<td>Cross-sectional study of data from one laboratory of all children with culture-confirmed TB diagnosed over an 8 year period</td>
<td>na na 128 128 7 62 0-14</td>
<td>C/-/C</td>
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<td>Luo, 1994[44]</td>
<td>Zambia</td>
<td>1991-1992</td>
<td>Prospective study of all children treated for TB at one hospital over an 8 month period. Controls were children with traumatic injuries, selected from the emergency department or from the surgical wards</td>
<td>167 16 120 110 67 70 0-14</td>
<td>B/C/A</td>
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<tr>
<td>Madhi, 1999[45]</td>
<td>South Africa</td>
<td>1996-1997</td>
<td>Prospective study of all children (2 months to 12 years) treated for TB at hospitals attached to an academic department of paediatrics over a 5 month period.</td>
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<td>na</td>
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<td>130</td>
<td>52</td>
<td>85</td>
<td>0-12</td>
<td>C/-/C</td>
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<td>Tanzania</td>
<td>2005-2007</td>
<td>Randomised controlled trial of multivitamin supplementation in children with TB. All children (6 weeks to five years) treated for TB at one clinic were included and randomised over a 30 month period</td>
<td>na</td>
<td>na</td>
<td>255</td>
<td>255</td>
<td>87</td>
<td>139</td>
<td>0-5</td>
<td>B/-/C</td>
</tr>
<tr>
<td>Miranda, 2011[47]</td>
<td>Brazil</td>
<td>2000-2006</td>
<td>All cases of paediatric TB recorded on a state register over a 6 year period were included. Matching with the state AIDS database then performed</td>
<td>na</td>
<td>na</td>
<td>411</td>
<td>411</td>
<td>27</td>
<td>191</td>
<td>0-14</td>
<td>C/-/C</td>
</tr>
<tr>
<td>Mukadi, 1997[48]</td>
<td>Côte d'Ivoire</td>
<td>1994-1995</td>
<td>Prospective study of all children (0-9 years) diagnosed with TB in two TB centres and two hospitals over a 21 month period</td>
<td>161</td>
<td>0</td>
<td>161</td>
<td>160</td>
<td>31</td>
<td>84</td>
<td>0-9</td>
<td>A/A/A</td>
</tr>
<tr>
<td>Berggren Palme, 2002[49]</td>
<td>Ethiopia</td>
<td>1995-1997</td>
<td>Prospective study of all children diagnosed with TB at the outpatient clinic or from the inpatient wards at one paediatric hospital over a 13 month period</td>
<td>na</td>
<td>na</td>
<td>517</td>
<td>517</td>
<td>58</td>
<td>259</td>
<td>0-14</td>
<td>B/-/C</td>
</tr>
<tr>
<td>Panigatti, 2014[50]</td>
<td>India</td>
<td>2009-2010</td>
<td>Prospective study of all children (0-12 years) diagnosed with TB at one hospital over an 18 month period, treated using a DOTS regimen</td>
<td>na</td>
<td>na</td>
<td>93</td>
<td>93</td>
<td>7</td>
<td>45</td>
<td>0-12</td>
<td>C/-/C</td>
</tr>
<tr>
<td>Rachow, 2012[51]</td>
<td>Tanzania</td>
<td>2008-2010</td>
<td>Prospective study of all children diagnosed with TB at one research facility over a 31 month period</td>
<td>na</td>
<td>na</td>
<td>164</td>
<td>164</td>
<td>84</td>
<td>86</td>
<td>0-14</td>
<td>C/-/C</td>
</tr>
<tr>
<td>Author, Year</td>
<td>Country</td>
<td>Year</td>
<td>Study Details</td>
<td>Results</td>
<td>Age Group</td>
<td>Case Classification</td>
<td></td>
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<tr>
<td>Ramos, 2010[52]</td>
<td>Ethiopia</td>
<td>2007</td>
<td>Retrospective data collection from TB registers and treatment cards of all patients (adults and children) treated for TB over a 10 year period at one private hospital</td>
<td>na</td>
<td>na</td>
<td>187</td>
<td>158</td>
<td>149</td>
<td>ns</td>
<td>0-14</td>
<td>C-/C</td>
</tr>
<tr>
<td>Rose, 2012[53]</td>
<td>Tanzania</td>
<td>2008-2010</td>
<td>Prospective study of all children with suspected TB at one district hospital over a 27 month period</td>
<td>93</td>
<td>22</td>
<td>33</td>
<td>33</td>
<td>18</td>
<td>24</td>
<td>0-14</td>
<td>A/C/A</td>
</tr>
<tr>
<td>Sassan-Morokro, 1994[54]</td>
<td>Côte d'Ivoire</td>
<td>1989-1990</td>
<td>Prospective study of all children diagnosed with TB at two outpatient treatment centres over an 18 month period</td>
<td>na</td>
<td>na</td>
<td>289</td>
<td>289</td>
<td>34</td>
<td>ns</td>
<td>1-14</td>
<td>B-/C</td>
</tr>
<tr>
<td>Schaaf, 2014[55]</td>
<td>South Africa</td>
<td>2009-2011</td>
<td>Retrospective study of all children (&lt;13 years) with culture-confirmed TB at one teaching hospital over a two year period</td>
<td>na</td>
<td>na</td>
<td>340</td>
<td>288</td>
<td>63</td>
<td>177</td>
<td>0-13</td>
<td>C-/C</td>
</tr>
<tr>
<td>Seddon, 2012[56]</td>
<td>South Africa</td>
<td>2007-2009</td>
<td>Retrospective study of all children (&lt;13 years) with culture-confirmed TB at one teaching hospital over a two year period</td>
<td>na</td>
<td>na</td>
<td>294</td>
<td>217</td>
<td>63</td>
<td>156</td>
<td>0-13</td>
<td>C-/C</td>
</tr>
<tr>
<td>Shahab, 2004[57]</td>
<td>India</td>
<td>1999-2000</td>
<td>Prospective study of all children (&lt;12 years) treated for TB in the outpatient and inpatient departments of one tertiary hospital over a 17 month period</td>
<td>na</td>
<td>na</td>
<td>250</td>
<td>250</td>
<td>5</td>
<td>174</td>
<td>0-12</td>
<td>C-/C</td>
</tr>
<tr>
<td>Thomas, 2014[58]</td>
<td>South Africa</td>
<td>2009-2010</td>
<td>Prospective study of all children (6 months to 12 years) with possible probable or confirmed TB recruited from outpatient and inpatient settings of one district hospital over a 17 month period</td>
<td>na</td>
<td>na</td>
<td>33</td>
<td>26</td>
<td>17</td>
<td>19</td>
<td>0-12</td>
<td>B-/C</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Country</td>
<td>Year</td>
<td>Study Design &amp; Population Details</td>
<td>Age (years)</td>
<td>Children (n)</td>
<td>Sequencing (A/B/C)</td>
<td></td>
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<tr>
<td>Yassin, 2011[59]</td>
<td>Ethiopia</td>
<td>2009</td>
<td>Cross-sectional study of all children (1-15 years) with TB symptoms and a TB source case who were investigated at two health centres and one hospital. TB-exposed but asymptomatic and unexposed children were also recruited as controls.</td>
<td>1-15</td>
<td>153 3 164 141 14 105 1-15 A/C/B</td>
<td></td>
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<tr>
<td>Kwara, 2015[60]</td>
<td>Ghana</td>
<td>2012-2014</td>
<td>Prospective pharmacokinetic study of all children (3 months to 14 years) starting treatment for TB disease at one teaching hospital over a two year period</td>
<td>0-14</td>
<td>na na 62 62 28 32 0-14 C/C/C</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Lopez-Varela, 2015[61]</td>
<td>Mozambique</td>
<td>2011-2012</td>
<td>Prospective study from one health district where all children (&lt;3 years) with presumptive TB were recruited over a 12 month period</td>
<td>0-3</td>
<td>na na 32 32 18 15 0-3 B/C/C</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Perfura Yone, 2012[62]</td>
<td>Cameroon</td>
<td>2005-2010</td>
<td>Retrospective study all children (&lt;15 years) diagnosed with TB and treated as inpatients at one hospital over a 5 and a half year period</td>
<td>0-15</td>
<td>na na 101 101 25 50 0-15 B/C/C</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>First author, year</td>
<td>Country</td>
<td>Years of study</td>
<td>Study Description</td>
<td>Number of TB cases</td>
<td>Number in cohort</td>
<td>Patient-years</td>
<td>TB incidence, per cent per year (95% CI)</td>
<td>ART at enrollment (%)</td>
<td>Number male</td>
<td>Age range</td>
<td>Quality, TB incidence (selection/outcomes)</td>
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<tr>
<td>Abuogi, 2013[63]</td>
<td>Kenya</td>
<td>2009-2010</td>
<td>Prospective cohort study of HIV-infected children (6 weeks to 14 years, some on ART and some not) followed up for the incidence of clinically diagnosed TB. Study at two urban clinics with children recruited over a two year period</td>
<td>10</td>
<td>686</td>
<td>720</td>
<td>1.39 (0.75-2.58)</td>
<td>74</td>
<td>322</td>
<td>0-14</td>
<td>B/A</td>
</tr>
<tr>
<td>Alarcon, 2012[64]</td>
<td>Brazil</td>
<td>2002-2007</td>
<td>Prospective cohort study of HIV-infected children (&lt;21 years) at 17 sites in Latin America; children recruited over a five year period and followed for the incidence of a number of opportunistic infections, including TB</td>
<td>7</td>
<td>731</td>
<td>2523</td>
<td>0.28 (0.07-0.48)</td>
<td>67</td>
<td>325</td>
<td>0-22</td>
<td>B/B</td>
</tr>
<tr>
<td>Auld, 2014[65]</td>
<td>Cote D’Ivoire</td>
<td>2004-2006</td>
<td>A nationally representative retrospective cohort study of children (&lt;15 years) starting ART over a five year period at 29 facilities</td>
<td>56</td>
<td>1960</td>
<td>4190</td>
<td>1.34(1.03-1.74)</td>
<td>100</td>
<td>1058</td>
<td>0-14</td>
<td>C/C</td>
</tr>
<tr>
<td>Study</td>
<td>Country/Locations</td>
<td>Time Period</td>
<td>Description</td>
<td>Sample Size</td>
<td>ART Start (%)</td>
<td>CD4 (%)</td>
<td>Viral Load (%)</td>
<td>Follow-up</td>
<td>Genotype</td>
<td>Resistance</td>
<td></td>
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<tr>
<td>Bakeera-Kitaka, 2011[66]</td>
<td>Uganda</td>
<td>2003-2006</td>
<td>Retrospective cohort study of children and adolescents starting ART over a three and a half year period at one specialist clinic</td>
<td>311</td>
<td>1806</td>
<td>1690</td>
<td>18.4(17.1-20.3)</td>
<td>100</td>
<td>932</td>
<td>ns</td>
<td>C/C</td>
</tr>
<tr>
<td>Braitsstein, 2009[67]</td>
<td>Kenya</td>
<td>2001-2007</td>
<td>Retrospective observational study of all children (&lt;13 years) enrolled in a network of HIV clinics over a 5 year period</td>
<td>765</td>
<td>6301</td>
<td>4368</td>
<td>17.6(16.3-18.8)</td>
<td>19</td>
<td>3144</td>
<td>0-13</td>
<td>C/C</td>
</tr>
<tr>
<td>Brennan, 2014[68]</td>
<td>South Africa</td>
<td>2004-2011</td>
<td>Retrospective cohort of all children (&lt;19 years) on ART enrolled over a 7 year period at 12 urban clinics</td>
<td>113</td>
<td>3329</td>
<td>2828</td>
<td>4.0(3.3-4.8)</td>
<td>100</td>
<td>1608</td>
<td>0-18</td>
<td>C/A/C</td>
</tr>
<tr>
<td>Ciaranello, 2014[69]</td>
<td>East Africa</td>
<td>2002-2008</td>
<td>All HIV-infected infants (&lt;12 months) enrolled over a 6 year period at 7 sites across 3 countries</td>
<td>128</td>
<td>847</td>
<td>738</td>
<td>17.4 (14.5-20.6)</td>
<td>0</td>
<td>418</td>
<td>&lt;1</td>
<td>C/C</td>
</tr>
<tr>
<td>Crook, 2016[14]</td>
<td>Uganda, Zimbabwe</td>
<td>2007-2012</td>
<td>Randomised controlled trial assessing different monitoring strategies for providing ART. All HIV-infected children (3 months to 17 years) enrolled from 4 centres in 2 countries over an 18 month period</td>
<td>69</td>
<td>969</td>
<td>3632</td>
<td>1.9(1.5-2.4)</td>
<td>100</td>
<td>488</td>
<td>0-17</td>
<td>B/B</td>
</tr>
<tr>
<td>Curtis, 2012[19]</td>
<td>8 countries</td>
<td>2002-2010</td>
<td>Data from 25 HIV treatment centres in 8 countries collected prospectively over an 8 year period. Adults and children included if starting ART at one of the centres. Data from children (&lt;15 years) disaggregated from adults</td>
<td>140</td>
<td>3946</td>
<td>1687</td>
<td>8.3(8.1-8.6)</td>
<td>100</td>
<td>ns</td>
<td>0-15</td>
<td>C/C</td>
</tr>
<tr>
<td>Study</td>
<td>Country</td>
<td>Period</td>
<td>Design and Methods</td>
<td>Incidence (95% CI)</td>
<td>Initiation</td>
<td>Follow-up</td>
<td>p-value</td>
<td>Genotype 1</td>
<td>Genotype 2</td>
<td>Genotype 3</td>
<td>Genotype 4</td>
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<tr>
<td>Dankne, 2001[70]</td>
<td>USA</td>
<td>1988-1998</td>
<td>Data from 13 studies over a period of 10 years with children (&lt;21 years) included. From pre-ART period. Wide range of opportunistic infections assessed.</td>
<td>0.4(0.3-0.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>C/C</td>
<td>na</td>
<td>C/C/C</td>
<td>na</td>
</tr>
<tr>
<td>De Beaudrap, 2013[71]</td>
<td>Burkina Faso/Cote d'Ivoire</td>
<td>2006-2007/2000-2004</td>
<td>Pooled data from a clinical trial (recruited over 1 year) and observational cohort (recruited over 4 years). Children (15 months to 15 years) enrolled at initiation of ART and followed for two years.</td>
<td>2.9(1.4-5.1)</td>
<td>100</td>
<td>66</td>
<td>ns</td>
<td>C/A</td>
<td>na</td>
<td>C/C/A</td>
<td>B/C/A</td>
</tr>
<tr>
<td>Edmonds, 2009[72]</td>
<td>Democratic Republic of the Congo</td>
<td>2004-2008</td>
<td>Prospective study of children (&lt;18 years) enrolled from one hospital clinic over a three and a half year period. All children ART-naive at baseline with some starting ART during follow up.</td>
<td>13.6(10.8-16.9)</td>
<td>0</td>
<td>172</td>
<td>ns</td>
<td>B/B</td>
<td>B/C/B</td>
<td>na</td>
<td>A/C/B</td>
</tr>
<tr>
<td>Gray, 2014[73]</td>
<td>South Africa</td>
<td>2005-2011</td>
<td>Control (placebo) arm of a randomised controlled trial of isoniazid preventive therapy. Children (over 8 weeks) recruited over a 4 year period from 3 sites.</td>
<td>2.9 (1.2-6.0)</td>
<td>100</td>
<td>42</td>
<td>ns</td>
<td>A/B</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Kouakoussui, 2004[74]</td>
<td>Cote d'Ivoire</td>
<td>2000--2003</td>
<td>All children recruited from 1 clinic and followed up for incident TB. All children in the study initiated ART at some point in the study to provide pre- and post-ART TB incidences.</td>
<td>3.4 (1.5-6.7)</td>
<td>65</td>
<td>153</td>
<td>1-16</td>
<td>C/B</td>
<td>na</td>
<td>C/C/C</td>
<td>na</td>
</tr>
<tr>
<td>Li, 2013[75]</td>
<td>Tanzania</td>
<td>2004-2011</td>
<td>Prospective study of all children (&lt;15 years) from 28 clinics recruited over a 7 year period. ART started based on local guidelines over follow up.</td>
<td>5.2(4.7-5.8)</td>
<td>51</td>
<td>2460</td>
<td>0-14</td>
<td>B/C</td>
<td>B/A/C</td>
<td>na</td>
<td>A/A/C</td>
</tr>
<tr>
<td>Author</td>
<td>Location</td>
<td>Date</td>
<td>Study Description</td>
<td>Cases</td>
<td>Incidence (95% CI)</td>
<td>Age Group</td>
<td>Reference Number</td>
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<tr>
<td>Martinson, 2009[76]</td>
<td>South Africa</td>
<td>1994-2006</td>
<td>Retrospective cohort of children (&lt;15 years) recruited from 4 clinics over a 12 year period. Incidence determined for the period pre- and post-ART</td>
<td>281</td>
<td>1132</td>
<td>12.3 (9.8-12.6)</td>
<td>2 563</td>
<td>0-14</td>
<td>B/C</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Prasitsuebsai, 2014[77]</td>
<td>SE Asia</td>
<td>1993-2009</td>
<td>Retrospective and prospective cohort of HIV-infected children (≤18 years) from 14 clinics in 5 countries in SE Asia. Recruited over a 16 year period. Wide range of OIs assessed. Period covered before ART, during mono- or dual-therapy and on HAART</td>
<td>477</td>
<td>2280</td>
<td>21.5(19.4-23.7)</td>
<td>7</td>
<td>1136</td>
<td>0-18</td>
<td>C/C</td>
<td>na</td>
</tr>
<tr>
<td>Thomas, 2000[78]</td>
<td>USA (NYC)</td>
<td>1989-1995</td>
<td>Retrospective study in HIV-exposed and -infected children enrolled in a longitudinal study. TB cases determined by review of clinical records and by linkage to local TB registry. Registry data assessed for a 6 year period</td>
<td>45</td>
<td>1426</td>
<td>0.61 (0.44-0.82)</td>
<td>0</td>
<td>475</td>
<td>0-12</td>
<td>B/B</td>
<td>na</td>
</tr>
<tr>
<td>Walters, 2008[79]</td>
<td>South Africa</td>
<td>2003-2005</td>
<td>Chart review of all children (&lt;13 years) starting HAART at one hospital over a 3 year period and followed up until the end of the study period for incident TB. Cases defined as pre-HAART (if in the 9 months prior to HAART initiation) or post HAART</td>
<td>10</td>
<td>290</td>
<td>25.1(21.1-29.6)</td>
<td>0</td>
<td>142</td>
<td>0-14</td>
<td>C/A</td>
<td>na</td>
</tr>
<tr>
<td>Walters, 2014[80]</td>
<td>South Africa</td>
<td>2003-2010</td>
<td>Retrospective cohort of all children (&lt;2 years) starting HAART at one hospital over an 8 year period. Children divided into those developing TB-IRIS (developing TB with 3 months of starting HAART) and those with incident TB (developing TB after 3 months)</td>
<td>55</td>
<td>341</td>
<td>25.3(22.0-28.9)</td>
<td>0</td>
<td>161</td>
<td>&lt;2</td>
<td>B/C</td>
<td>na</td>
</tr>
<tr>
<td>Yirdaw, 2014[81]</td>
<td>Ethiopia</td>
<td>2007-2010</td>
<td>Retrospective cohort study of the electronic records of all patients (adults and children) starting ART over a three year period in 5 hospitals in one region of Ethiopia. Patients followed until the end of the study period and the interventions of ART and IPT evaluated. Incidence stratified by age enabling extraction children (&lt;15 years)</td>
<td>23</td>
<td>475</td>
<td>2.1(1.3-3.1)</td>
<td>ns</td>
<td>ns</td>
<td>0-15</td>
<td>B/C</td>
<td>na</td>
</tr>
<tr>
<td>Zar, 2007[20]</td>
<td>South Africa</td>
<td>2003-2004</td>
<td>Double blind RCT evaluating the impact of IPT on TB incidence in HIV-infected children (aged older than 8 weeks). Children recruited from two sites with the trial stopped after 17 months. Data on TB incidence taken from placebo arm.</td>
<td>13</td>
<td>131</td>
<td>56</td>
<td>23.4(12.4-50.0)</td>
<td>8</td>
<td>74</td>
<td>0-14</td>
<td>C/C</td>
</tr>
</tbody>
</table>
Quality assessment

TB cohorts were of low and moderate quality for our analysis (Table 1). Studies without controls could not be classed higher than moderate quality on selection and low quality on exposure. Controls were often drawn from clinic populations in the same context. In around half of studies, TB was defined only by a decision to treat.

HIV cohorts were typically of low quality for our analyses (Table 2). Most studies were clinic-based and not necessarily community-representative; prevalent TB was not always ruled out at baseline; there were often shortcomings in follow-up or case definitions for TB.

Meta-Analyses for TB cohorts

The random-effects meta-analysis of TB cohorts for the odds of having HIV in TB cases included 8 case-control studies (Figure 2). In total, 1,215 TB cases and 1,232 non-TB controls were included. The pooled estimate for the OR was 7.9 (95% confidence interval [CI]: 4.5 - 13.7), and the I-squared heterogeneity statistic was $I^2 = 69.8\%$ (see Figure 2). A funnel plot corresponding to this analysis is presented in Appendix p.8.

The Bayesian meta-analysis included 35 studies (including all 8 with controls) and produced a pooled estimate of the OR for HIV among children with TB of 7.0 (95% credible interval [CrI]: 5.7 – 8.5), see Figure 3. This analysis also found the paediatric HIV prevalence in controls to be substantially higher than national UNAIDS estimates of HIV prevalence in the <15 year age group, with an odds ratio of 7.3 (95%CrI: 5.9 – 8.8). For studies that lacked explicit control groups (indicated in red in Figure 3), this analysis also predicted what the odds ratios would have been for HIV prevalence in TB cases versus HIV prevalence in a putative control group of comparable children without TB. The pooled estimates of effect for the analyses with and without the UNAIDS data were similar (Appendix p.11).

Meta-analyses for HIV cohorts

For HIV cohorts, the random effects meta-analysis of TB incidence in children with severe compared to non-significant immunosuppression according to WHO categorisation gave an IRR of 5.0 (95%: 4.0 – 6.0) with I-squared heterogeneity statistic $I^2 = 87.1\%$ (see Figure 4). The Bayesian meta-analysis of the gradient of the logarithmic IRR with respect to CD4% yielded a pooled estimate of -0.063 (95%CrI: -0.188 – +0.063), corresponding to a reduction in IRR of 0.94 (95%CrI: 0.83 – 1.07) per one percentage-point increase in CD4% (see Figure 5). This point estimate implies a mean IRR of 7.1 over CD4 percentages ranging between 0% and 50%. The random effects meta-analysis of protection from ART yielded a pooled hazard ratio estimate of 0.30 (95%CI: 0.21 - 0.39) with I-squared heterogeneity statistic $I^2 = 79\%$ (see Figure 6).

The non-linear mixed effects regression for the protection from ART by time-since-initiation estimated a rapid initial decline in incidence over the first year, reaching a
plateau as protection from ART fully establishes over around two years at a pooled asymptotic hazard ratio of 0.10 (95% CI: 0.04 - 0.25), giving a mean hazard ratio over the first 30 months on ART of approximately 0.25 (see Figure 7).
DISCUSSION

In this systematic review, we identified cohorts of children with TB and cohorts of children with HIV. We observed a high but variable prevalence of HIV infection in the TB cohorts, and a very high TB incidence in the HIV cohorts. Accounting for background risk of TB, we found, as in adults, HIV was important risk factor for TB and that TB risk increases with immunosuppression. ART was strongly protective against TB, but took two years for full potential of protection against TB to be realized.

In adults, IRRs for TB given HIV around 6 have been estimated for populations with generalized HIV epidemics,[7] corresponding to most newly diagnosed adult TB cases having HIV infection. Our IRR for children is comparable, but lower HIV prevalence is seen in children with TB due to a lower overall paediatric HIV prevalence. In adults, meta-analyses of cohorts of HIV patients suggest exponentially increasing IRR for TB with declining CD4 cell count,[9] and current CD4 cell counts on ART strongly predict TB incidence.[82] A systematic review and meta-analysis of the protective effect of ART against TB found a hazard ratio of 0.35 (0.28-0.44) across all baseline CD4 cell counts,[10] comparable to our result for children. Long-term follow-up of adults on ART suggests 4-5 years for protection against TB to become fully established.[83] Our analysis suggests that protection against TB in children on ART establishes more rapidly (1-2 years), consistent with faster CD4 reconstitution among children[84] compared to adults.[85 86]

Our findings have implications for patient care, guidelines, TB programmes, and mathematical modelling. For clinicians, TB risk with HIV and ART informs patient treatment and appropriate family counseling. For TB programme officers, understanding risks informs resource allocation, and service configuration for HIV testing and treatment. These findings can inform evidence-based guideline development; timely given the recent revision of WHO ART guidelines advocating universal treatment for children with HIV, irrespective of clinical and immunological stage. Finally, these data inform models of burden estimates and for evaluating the impact of interventions, in relation to HIV and ART.

Our review has limitations. Although our search strategy was comprehensive, studies were excluded if not representative of children with TB in that context. The cohorts identified were generally of low quality for our analyses, the most common shortcomings being around population representativeness and TB case-definitions. The majority of studies were from sub-Saharan Africa, where 90% of all HIV-infected children live, and the findings may not generalize to other regions. The studies spanned a long time period, and may not be representative of the current era. Statistical heterogeneity was high for summary statistics from both TB cohorts and especially HIV cohorts, reflecting diverse study settings and dates, and unreported clinical and methodological heterogeneity. However, measures of heterogeneity were comparable with those from similar studies.[87] There were a number of limitations of our meta-analyses of TB cohort data. Controls were often not from the general population. This may partially explain the differences between HIV prevalence in study controls and UNAIDS paediatric HIV prevalence estimates. However, UNAIDS reports country-level estimates for children aged <15 years, which are not likely to reflect the HIV prevalence in younger children local to these studies. Difficulties in
diagnosing TB in children with HIV may have led to differential detection of cases by HIV status, affecting the IRR from case-control TB cohorts. Moreover, estimates of the increased risk of TB progression will be confounded by higher exposure due to sharing households with HIV-infected parents, themselves at increased risk of TB. This makes it difficult to differentiate the direct biological impact of HIV from indirect effects. Implicitly, our analyses assume the same relationship between HIV, ART and TB holds regardless of population TB or HIV prevalence, which may not be the case across the very wide range of prevalences in the studies included.

A number of limitations apply to our meta-analyses of HIV data. CD4 percentage categories were disparately reported, and we used category mid-points for analyses of CD4% and time-on-ART. Many studies allowed for unmasking of prevalent TB at ART initiation by excluding a certain period after initiation from comparisons, but this varied between studies. However, excluding all children diagnosed with TB soon after initiating ART may underestimate early incident TB in children who are still highly immunosuppressed. Only three HIV cohorts reported co-trimoxazole use,[14 19 20] but as guidelines have varied over time and by setting, co-trimoxazole use may have been under-reported. Confounding by indication was not considered in estimates of ART protection (except for Edmonds et al.[72]), and choice of covariates varied between studies. Our direct meta-analysis of the protective effect of ART was not able to include how long children had been on ART, and will average over the different distribution of treatment durations between studies.

We were not able to analyse age effects on TB, as data were seldom reported with multiple age stratifications. Our analysis of protection by time-on-ART may be confounded by age. Young children have particularly high TB progression risk, in part due to immature cell-mediated immune responses.[1] The impact of age on efficacy of ART is also complex, as early ART initiation, at a better baseline immune status, leads to better immune reconstitution (although adherence can be challenging at the youngest ages due to a paucity of palatable formulations).[84 88 89] The studies in our review were conducted over years when ART treatment guidelines, availability and formulations were evolving. The relevance of our findings to current universal treatment recommendations needs careful consideration; individual patient data meta-analysis would be highly informative on the impact of host characteristics on risk of TB, in particular the age of the child and age at which ART was initiated. As children are started on ART at higher CD4 values, the protective benefit of ART against TB may be lower.

Despite these limitations, internal consistency between results from different analyses increases the confidence in our conclusions. Our IRR from TB cohorts is comparable with the estimate of ‘Severe’ compared with ‘Not Significant’ immune staging, recognising that HIV may confer an increased risk of TB even before immunosuppression is clinically evident. The mean IRR over a range of CD4 percentages between 0% and 50% was 7.1 using the risk gradient point-estimate from our CD4 analysis – close to our IRR estimate for all HIV from TB cohorts. The mean protection against TB over the first 30 months on ART was 0.25 – comparable to our meta-analysis of estimates of protection (although these analyses ultimately stem from the same data). The decline in TB rates by time-on-ART occurred on a similar timescale to the analysis presented in Li et al.,[75] although to a lower final value. Comparing our HIV and ART risk results suggests that children commencing ART
are at higher risk of TB than HIV-uninfected children initially, but our results are too uncertain to specify whether long-term TB risks ART return to those of an HIV-uninfected child. For adults, TB risks established on long-term ART remain elevated over those of HIV-uninfected individuals.[83]

It is important to place ART in the context of other public health interventions. Our results suggest early diagnosis of infants and young children with HIV, followed by immediate ART, will reduce the pool of highly susceptible children and consequent progression to TB disease, providing further impetus to scale-up coverage among paediatric ART programmes. High HIV prevalence in the TB cohorts and high TB incidence in the HIV cohorts suggest that all children diagnosed with TB should be tested for HIV infection and all children with HIV should be regularly screened for TB disease. Scale-up of PMTCT will lead to fewer children becoming infected with HIV and is likely to be one of the most effective public health strategies to reduce paediatric HIV/TB; similarly, prompt diagnosis of TB in HIV-infected adults will reduce the risk of TB transmission to their HIV-infected children. TB control in adults more generally,[90] and infection control measures, will reduce the risk of TB transmission to vulnerable children. Isoniazid preventive therapy appears similarly effective at reducing TB incidence in HIV-infected children (around 70% reduction in incidence),[20 73] and evidence suggests that use in conjunction with ART is more protective than either intervention alone.[91] Evidence for the benefit of co-trimoxazole in preventing incident TB in children is emerging,[14] since it is now recommended long-term, co-trimoxazole prophylaxis may also help to reduce TB incidence among HIV-infected children on ART. Improving nutritional status among HIV-infected children may also be beneficial, as there is a high risk of TB in the context of malnutrition. Although individually these interventions are likely less effective than ART, their combination can be expected to protect the biggest number of children from developing TB.

Conclusions

Our results indicate that HIV infection is a potent risk factor for TB in children, with a gradient of risk by indices of immunosuppression. ART is strongly protective against TB in children with HIV infection, taking up to two years for protection to become fully established, underscoring the importance of prompt ART initiation.

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FIGURE CAPTIONS

Figure 1: PRISMA flow chart for systematic review (*One study included both a TB and HIV cohort[18])

Figure 2: Forest plot for meta-analysis of HIV risk in children aged <15 years with prevalent tuberculosis – studies with controls. ($I^2 = 69.8\%$)

Figure 3: Forest plot for Bayesian meta-analysis of HIV risk in children aged <15 years with prevalent tuberculosis. Where studies lacked their own controls, UNAIDS national HIV prevalence data were used to model HIV prevalence in controls based on those studies with both controls and UNAIDS estimates (red). Meta-analysis for studies with controls only are shown in blue; meta-analysis for studies using UNAIDS estimates of paediatric HIV prevalence are shown in red.

Figure 4: Relative tuberculosis incidence in children aged <15 years with HIV by WHO immunological staging. ($I^2 = 87.1\%$)

Figure 5: Forest plot for meta-analysis of relation between incidence rate ratio for tuberculosis incidence and CD4 percentage in children aged <15 years.

Figure 6: Forest plot of protection on ART against tuberculosis incidence in children <15 years with HIV infection. ($I^2 = 79.0\%$)

Figure 7: Meta-regression of protection from tuberculosis incidence in children <15 years by time-on-ART, and re-aligned incidence estimates from studies.
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