In both adults and children, the increased risk of tuberculosis as a result of advancing human immunodeficiency virus (HIV) infection is a major contributor to HIV-associated morbidity and mortality. This is especially so in African settings,

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where the background risk of tuberculosis is already high.

It is predictable that anti-retroviral therapy (ART), through allowing recovery of immune function, should reduce this increased risk in patients with HIV, and a number of studies in adults have indeed demonstrated such reductions.\(^1\)\(^-\)\(^3\) Quantifying this reduction is complicated by the fact that the same clinical parameters that determine tuberculosis risk are also determinants of who starts ART and are themselves affected by ART, leading to potential time-varying confounding. Statistical methods appropriate to causal questions of this nature are increasingly being used in observational clinical studies.\(^4\)

In this issue, Edmonds and colleagues describe the impact of ART on tuberculosis risk in a cohort of HIV-infected children, based on a Cox proportional hazards marginal structural model.\(^5\) The only other quantification of tuberculosis risk reduction due to ART that has, to date, employed such an approach was a study in South African children, in which the risk reduction due to ART was 39%.\(^6\) In the present study, the equivalent estimate is 49%. These estimates are much lower than many would have anticipated and than some of the prior estimates in adults and children. A recent study in HIV-infected South Africa children, which did not adjust for time-varying confounding, estimated the risk reduction on ART to be 70% for all tuberculosis cases as well as for microbiologically confirmed cases.\(^7\)

There are a number of potential limitations to the observational nature of these studies, as discussed by the authors of the current analysis. The high proportion of events on ART, which occur in the first few months of therapy, may represent disease that preceded ART initiation, but only became clinically apparent due to ART. This unmasking might underestimate the effect of ART, especially in expanding programmes with progressive enrolment. Similarly, clinical programmes typically go to great lengths to exclude tuberculosis before ART initiation, or are referred sick patients who have a higher risk of tuberculosis diagnosis, both potentially overestimating the effect of ART. What then is the contribution of these findings to our understanding of approaches for managing HIV-associated tuberculosis in children in HIV and tuberculosis endemic settings?

First, the risk reduction is nonetheless substantial, and confirms that ART is an important component of any strategy to reduce the tuberculosis risk in HIV-infected children, especially where treatment can be optimally provided as soon as children have failed prevention of mother-to-child transmission interventions.\(^8\) Secondly, there is considerable room for further risk reduction. There remains insufficient evidence regarding isoniazid prophylaxis in HIV-infected children prior to or during ART\(^9\)—two studies on isoniazid preventive therapy (IPT) for children with or exposed to HIV have been stopped by data safety monitoring boards, one due to the effectiveness of the intervention\(^10\) and another due to the lack of effectiveness.\(^11\) In the latter study, two-thirds of children were on ART by the time of the interim analysis. In adults, where the effectiveness of isoniazid in selected patients with HIV is well established, there is strong observational evidence that this will also be the case in patients on ART, although the additional benefit of IPT in ART-treated adults has yet to be quantified in controlled trials.\(^12\)\(^-\)\(^13\)

Finally, the absolute incidence of tuberculosis in this study of 13.6 per 100 person-years highlights the burden of disease due to tuberculosis in HIV-infected children, and the associated difficulties clinicians face in making and confirming this diagnosis. The use of a clinical scoring system in this study demonstrates the challenges for diagnosing tuberculosis in children in the context of HIV. Scoring systems have been incompletely validated in paediatric practice and perform poorly in HIV-infected children, compromising diagnostic certainty.\(^14\) Culture for Mycobacterium tuberculosis is seldom available in Africa, and even where available, as in the South African study, the majority of the tuberculosis diagnoses in children are not microbiologically confirmed. These limitations draw attention to the inadequacy of current TB diagnostics in the setting of paediatric HIV clinical practice.

Conflict of interest: None declared.

References


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