High Incidence of Tuberculosis among HIV-Infected Infants: Evidence from a South African Population-Based Study Highlights the Need for Improved Tuberculosis Control Strategies

A. C. Hesseling,¹,M. F. Cotton,² T. Jennings,¹ A. Whitelaw,³ L. F. Johnson,² B. Eley,⁴ P. Roux,⁶ P. Godfrey-Faussett,⁸ and H. S. Schaaf¹

¹Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Health Sciences, and ²KidCru, Tygerberg Academic Hospital, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa, ³National Health Laboratory Service, ⁴Department of Medical Microbiology, ⁵Paediatric Infectious Diseases Unit, Red Cross Children’s Hospital and School of Child and Adolescent Health, ⁶Department of Paediatrics, Groot Schuur Hospital, and ⁷Centre for Actuarial Research, University of Cape Town, Cape Town, South Africa; and ⁸Clinical Research Unit, Department of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom

Background. There are limited population-based estimates of tuberculosis incidence among human immunodeficiency virus (HIV)–infected and HIV-uninfected infants aged ≤12 months. We aimed to estimate the population-based incidence of culture-confirmed tuberculosis among HIV-infected and HIV-uninfected infants in the Western Cape Province, South Africa.

Methods. The incidences of pulmonary, extrapulmonary, and disseminated tuberculosis were estimated over a 3-year period (2004–2006) with use of prospective representative hospital surveillance data of the annual number of culture-confirmed tuberculosis cases among infants. The total number of HIV-infected and HIV-uninfected infants was calculated using population-based estimates of the total number of live infants and the annual maternal HIV prevalence and vertical HIV transmission rates.

Results. There were 245 infants with culture-confirmed tuberculosis. The overall incidences of tuberculosis were 1596 cases per 100,000 population among HIV-infected infants (95% confidence interval [CI], 1151–2132 cases per 100,000 population) and 65.9 cases per 100,000 population among HIV-uninfected infants (95% CI, 56–75 cases per 100,000 population). The relative risk of culture-confirmed tuberculosis among HIV-infected infants was 24.2 (95% CI, 17–34). The incidences of disseminated tuberculosis were 240.9 cases per 100,000 population (95% CI, 89–433 cases per 100,000 population) among HIV-infected infants and 14.1 cases per 100,000 population (95% CI, 10–18 cases per 100,000 population) among HIV-uninfected infants (relative risk, 17.1; 95% CI, 6–34).

Conclusions. This study indicates the magnitude of the tuberculosis disease burden among HIV-infected infants and provides population-based comparative incidence rates of tuberculosis among HIV-infected infants. This high risk of tuberculosis among HIV-infected infants is of great concern and may be attributable to an increased risk of tuberculosis exposure, increased immune-mediated tuberculosis susceptibility, and/or possible limited protective effect of bacille Calmette-Guérin vaccination. Improved tuberculosis control strategies, including maternal tuberculosis screening, contact tracing of tuberculosis-exposed infants coupled with preventive chemotherapy, and effective vaccine strategies, are needed for infants in settings where HIV infection and tuberculosis are highly endemic.

Infants in settings where tuberculosis and HIV infection are highly endemic are at high-risk of tuberculosis-related morbidity and mortality [1]. Studies from the prechemotherapy era indicate that, in the absence of preventive chemotherapy, up to 40% of infants who were infected with Mycobacterium tuberculosis subsequently developed tuberculosis disease. Children aged <2 years were most at risk of developing disease, and...
disease progression occurred mostly in the first calendar year after primary infection [2–4]. The incidence of infant tuberculosis is an indicator of both control of infectious tuberculosis and the effectiveness of tuberculosis prevention strategies, such as neonatal bacille Calmette-Guérin (BCG) vaccination. The Joint United Nations Program on HIV/AIDS estimated that, in 2007, 390,000–470,000 children aged <15 years acquired HIV infection, mostly through mother-to-child (vertical) transmission [5]. There are few estimates comparing tuberculosis rates between HIV-uninfected and HIV-infected infants and children.

The protective effect of BCG vaccination against pulmonary tuberculosis in childhood is inconsistent [6], and there is limited epidemiological evidence of any BCG-induced protective effect in HIV-infected children [7, 8]. However, there is considerable evidence for the protective efficacy of BCG vaccination against disseminated tuberculosis in HIV-uninfected infants [9]. Recent data indicate that HIV-infected infants have a substantially increased risk of serious BCG-associated complications, including disseminated BCG disease [10], with a reported incidence of 110–1300 cases per 100,000 population [11, 12]. We aimed to determine the population incidence of culture-confirmed tuberculosis among HIV-infected and HIV-uninfected infants in a setting where HIV infection and tuberculosis are highly endemic, where BCG vaccine is routinely administered at birth.

METHODS

Study setting. This study was conducted using prospective laboratory-based surveillance data collected from 1 January 2004 through 31 December 2006 among infants aged ≤12 months in 3 provincial pediatric referral hospitals that serve the entire Western Cape Province: Tygerberg Children’s Hospital, Red Cross Children’s Hospital, and Groote Schuur Hospital (Cape Town, South Africa).

In the Western Cape Province, the vast majority of infants are born in health care facilities. Intradermal BCG vaccination (Danish 1331 strain; Statens Serum Institute) is routinely administered to infants at birth; the rate of neonatal BCG vaccine coverage was 98% in 2005 [13]. The province reported an adult tuberculosis incidence of 1037 cases per 100,000 population in 2006 [14]. Routine surveillance from the province indicates a tuberculosis notification rate of 620 cases per 100,000 population among children (ages, 0–14 years) in 2007 (Western Cape Department of Health, unpublished data); routine notification data are not available for infants. The reported incidence of disseminated tuberculosis (probable and confirmed cases) among HIV-uninfected infants in the province, from a study conducted in the period 1999–2002, was 40.3 cases per 100,000 population [15]. Although isoniazid preventive therapy (IPT) is recommended by the South African TB Control Programme in children ≤5 years of age with documented sputum-positive household contact or with proof of M. tuberculosis infection, this is not routinely implemented.

The prevalence of HIV infection among pregnant women in the public health sector was 15.1% (95% CI, 11.6%–18.7%) in 2006, determined by antenatal HIV surveys [16]. There is a well-established provincial prevention of mother-to-child HIV transmission (PMTCT) program with recommended universal antenatal HIV testing in the public health sector. In the period 2004–2005, dual therapy for PMTCT was provided to mothers and infants; the mother received zidovudine treatment starting at ≥34 weeks of pregnancy then the newborn received zidovudine for 7 days, and both mother and newborn received a single dose of nevirapine. This regimen was revised in 2006 to adjust zidovudine treatment to begin at ≥28 weeks of gestation, in conjunction with exclusive feeding options.

Data collection. HIV testing and mycobacterial cultures were performed on the basis of routine clinical indications at the discretion of attending physicians at the 3 hospitals. Mycobacterial cultures were routinely performed using the automated Middlebrook 7H9 broth–based Mycobacterial Growth Indicator Tube culture system (Becton-Dickinson). The date recorded on the sample obtained for mycobacterial culture was used to define the infant’s age at determination of tuberculosis diagnosis. Isolates were confirmed to be M. tuberculosis with use of a multiplex PCR assay that distinguishes M. tuberculosis from Mycobacterium bovis BCG [17]; all isolates were tested in one central laboratory. Infant HIV infection status was confirmed with use of HIV DNA PCR (Amplicor; Roche). If the HIV status was unknown, the infant was classified as HIV uninfected for the purpose of incidence calculations.

The tuberculosis disease classification was made on the basis of the mycobacterial culture source in conjunction with a review of clinical data, chest radiographs, and other imaging, including brain CT. Medical folders were reviewed and chest radiographs were read by a single pediatric tuberculosis expert (H.S.S.), who was blinded to patient clinical information.

Pulmonary tuberculosis was defined as M. tuberculosis cultured from respiratory secretions (gastric, tracheal or nasopharyngeal aspirates, bronchoalveolar lavage, or induced sputum) in the presence of chest radiological abnormalities suggestive of tuberculosis [18]. Extrapulmonary disease was defined on the basis of a culture positive for M. tuberculosis for a specimen obtained from the anatomical source in conjunction with a clinical profile compatible with disease that included tuberculous meningitis, peripheral lymphadenitis, pleural effusion, osteoarticular disease, abdominal disease, and miliary tuberculosis. Miliary tuberculosis was defined as a culture positive for M. tuberculosis in the presence of chest radiographic features compatible with miliary disease [18]. Miliary disease, tuberculous meningitis, or disease confirmed through...
blood and bone marrow culture in combination with systemic signs and symptoms were classified as disseminated tuberculosis. Tuberculosis meningitis was defined as a \textit{M. tuberculosis}–positive culture of a specimen of CSF or another source in conjunction with clinical features and typical brain CT changes, including obstructive hydrocephalus and basal enhancement [19]. Infants with disease caused by \textit{M. bovis} BCG and nontuberculous mycobacteria were excluded.

We report the following clinical data: age, HIV exposure and infection status, \textit{CD4}+ T lymphocyte count in HIV-infected infants, reported household tuberculosis contact currently receiving treatment, and tuberculosis disease classification. We do not report information regarding the treatment, detailed clinical and HIV disease characteristics, outcome and drug susceptibility results (authors’ unpublished data). This study was approved by the Research Ethics Committees of Stellenbosch University and the University of Cape Town.

\textbf{Estimation of incidence.} Tuberculosis incidence was calculated over the total 3-year study period for each disease entity. New cases all involved infants who received a diagnosis of culture-confirmed tuberculosis during the study period at the 3 referral hospitals. Several data sources were used to estimate the denominators that were used to calculate the incidence of tuberculosis—the total number of HIV-infected and HIV-uninfected infants in the province at risk of developing tuberculosis. The total number of person-years of observation for all infants were taken from estimates from the Actuarial Society of South Africa 2003 AIDS and Demographic Model for the Western Cape [20, 21]. The proportion of the total person-years of observation for HIV-infected infants was estimated from the maternal HIV prevalence rate multiplied by the vertical HIV transmission rates, on the basis of data from the provincial PMTCT program. The total number of HIV-infected infants was then subtracted from the total infant population to calculate the total number of HIV-uninfected infants. We conducted a sensitivity analysis to assess the effect of infants with unknown HIV status on our estimates by excluding infants with unknown HIV status from the analysis.

Statistical analyses were performed using Excel (Microsoft) and SPSS, version 16 (SPSS). We used a bootstrap percentile method to determine conservative 95% CIs around estimates, treating the key parameters in the incidence rate calculation as independent random variables [22]. The number of tuberculosis cases was sampled from Poisson distributions with the mean number equal to the observed number of tuberculosis cases; the HIV prevalence rates were sampled from \( \beta \) distributions with means and standard deviations from published antenatal prevalence estimates and 95% CIs (rounded to the closest decimal), and the mother-to-child transmission rates were sampled from \( \beta \) distributions with use of reported transmission rates and sample sizes. The sampling procedure was repeated 10,000 times for each incidence estimate.

\textbf{RESULTS}

\textbf{Clinical data.} In the 3-year study period, there were 245 infants who received a diagnosis of culture-confirmed tuberculosis (median age, 6 months; range, 0–12 months); 133 (54.3%) were male. Fifty-three (21.6%) were HIV infected, 122 (49.8%) were HIV uninfected, and 70 (28.6%) had no documented HIV testing performed. The median age at tuberculosis diagnosis was similar between HIV-infected and HIV-uninfected infants (6 vs. 5 months). The mean CD4+ T lymphocyte percentage (\( \pm SD \)) among HIV-infected infants was 20.94\% \( \pm 10.76\% \).

There were 232 cases (94.7\%) of pulmonary disease, of which 70 (30.2\%) involved both pulmonary and extrapulmonary disease; the remaining 13 cases (5.3\%) involved extrapulmonary tuberculosis only. A total of 49 infants (20.0\%) had disseminated tuberculosis (based on the presence of miliary disease) or tuberculous meningitis or had a positive blood or bone marrow culture result; 27 (11.0\%) had tuberculous meningitis, and 22 (9.0\%) had miliary tuberculosis; 10 infants (4.1\%) had both tuberculous meningitis and miliary disease. The source for \textit{M. tuberculosis} isolation was gastric aspirate in the majority (187 infants [76.3\%]) of infants. Only 1 infant had a blood culture positive for \textit{M. tuberculosis}.

Of the 49 infants with disseminated tuberculosis, 8 (16.3\%) were HIV infected, 31 (63.3\%) were HIV uninfected, and 10 (20.4\%) had no documented HIV status. Maternal HIV status was recorded as negative for 26 infants (10.6\%), and 70 (28.6\%) had a known HIV-infected mother (HIV-exposed infants); however, in most infants (149 [60.8\%] of 245 infants), the maternal HIV status was not recorded in the hospital folder.

There was a reported household tuberculosis contact for 135 infants (55.1\%); 96 (39.2\%) had no reported contact and 14 (5.7\%) did not have this information recorded. Of the 49 infants with disseminated tuberculosis, 32 (65.3\%) had a reported household tuberculosis contact. Infants that were known to have a documented HIV-infected mother were more likely to have a tuberculosis contact, compared with infants for whom maternal HIV status was negative or unknown (OR, 1.76; 95\% CI, 1.12–2.77; \( P = .033 \)). There was documentation of a referral for IPT for only 14 (10.4\%) of 135 infants.

\textbf{Incidence rates.} The estimated total numbers of HIV-infected and HIV-uninfected infants in the province during the study period and the number of tuberculosis cases are indicated in table 1. The estimated incidence rates for pulmonary, extrapulmonary, and disseminated tuberculosis in HIV-infected and HIV-uninfected infants are indicated in table 2. HIV-infected infants were at a 24.1-fold (95\% CI, 17–34-fold) higher risk of pulmonary tuberculosis and a 17.1-fold (95\% CI, 6–34-
infected infants may be attributable to several factors, including neonatal tuberculosis [25, 26]. A substantial increase in maternal HIV-related tuberculosis and infected infants [24], recent data from South Africa indicate a significant increase in the incidence of tuberculosis among HIV-infected children. The extent of this problem has not been previously documented.

**DISCUSSION**

We demonstrate a high overall population incidence of culture-confirmed tuberculosis among infants; the incidence was substantially higher among HIV-infected infants than among HIV-uninfected infants. Our population estimates indicate 24.2-fold (95% CI, 17–34-fold) higher rates for any form of tuberculosis and 17.1-fold (95% CI, 6–34-fold) higher rates of disseminated tuberculosis among HIV-infected infants. The extent of this problem has not been previously documented.

The observed incidence of 1595 cases of tuberculosis per 100,000 population among HIV-infected infants is high, compared with the reported incidence of culture-confirmed tuberculosis from other studies. Elenga et al. [23] have reported that the cumulative incidence of probable and confirmed tuberculosis cases among HIV-infected children from Côte d’Ivoire was 2060 cases per 100,000 population at 12 months follow-up, 3390 cases per 100,000 population at 2 years follow-up, and 5930 cases per 100,000 population at 3 years follow-up (median enrollment age, 5.3 years; range, 1.4–15.8 years). Our data could be extrapolated to bacteriologically confirmed disease incidence rates of 3192 cases per 100,000 population at 2 years of age and 4788 cases per 100,000 population at 3 years of age. Although an earlier review did not confirm an overall significant increase in the incidence of tuberculosis among HIV-infected infants [24], recent data from South Africa indicate a substantial increase in maternal HIV-related tuberculosis and neonatal tuberculosis [25, 26].

The observed excess incidence of tuberculosis among HIV-infected infants may be attributable to several factors, including HIV-related cellular immune suppression, the high level of *M. tuberculosis* exposure, and potentially reduced BCG vaccine protection. In Côte d’Ivoire, the tuberculosis incidence among HIV-infected children was significantly increased among children with a CD4 + T cell percentage <15%, compared with children with a CD4 + T cell percentage ≥15% [23]. Although the impact of HAART on tuberculosis incidence among HIV-infected children is not well documented through controlled studies, Kouakoussui et al. [27] have documented that, among HIV-infected children in Africa, the incidence of respiratory disease, including tuberculosis, was significantly reduced after the initiation of HAART. This reduction is likely attributable to a partial restoration of cellular immunity.

The main protective mechanism that is attributed to BCG vaccination is the limiting of the hematogenous spread of *M. tuberculosis* after primary infection, which is consistent with the observed efficacy of the BCG vaccine against disseminated tuberculosis. It is possible that, when specific T cell–mediated responses are required, HIV-related T cell suppression may compromise this defense, thus leading to reduced BCG-induced immune responses and reduced cell-mediated protective immunity in HIV-infected infants. Limited evidence from available epidemiological studies does not indicate a substantial BCG-induced protective effect in HIV-infected children. In a retrospective case-control study from Zambia, no protective BCG effect was observed among 116 HIV-infected children with tuberculosis and 154 control children without tuberculosis (OR, 1.0; 95% CI, 0.2–4.6); HIV-infected children had 6–8-fold higher odds of acquiring tuberculosis, compared with HIV-uninfected children [7].

Opportunities for chemoprophylaxis through IPT were missed for a large proportion (>50%) of infants in our study, who were documented to have been exposed to household tuberculosis contacts. Despite existing guidelines, tracing of children’s tuberculosis contacts and IPT are not routinely implemented in this setting, because of a programmatic emphasis.
on adult patients with smear-negative tuberculosis and inadequate and overburdened health systems that do not prioritize patients who are perceived to be healthy. Strengthening health systems to improve access to IPT for HIV-infected and other at-risk children is imperative. A clear distinction should be made between IPT for children with defined tuberculosis contacts and primary IPT in the absence of documented exposure or infection. A multicenter trial assessing the effect of IPT on HIV-exposed but uninfected infants and HIV-infected infants in Africa was recently halted, because of interim analyses that showed no benefit of primary isoniazid treatment (M.F.C., unpublished data; National Institutes of Health IMPAACT P1041); 10.1% of infants (mean age at enrollment, 3 months) were excluded at baseline, because of reported *M. tuberculosis* exposure [28]. In contrast, IPT has been shown to reduce both the incidence of tuberculosis disease and all-cause mortality among older HIV-infected children with symptomatic HIV disease [29].

Because our study only assessed infants who were examined for tuberculosis in the 3 provincial referral hospitals, results may have been biased toward the detection of infants with more-severe disease and a greater number of HIV-infected infants. Infants with tuberculosis meningitis may, in particular, be more likely to be hospitalized because of their clinical presentation [30]. HIV-infected infants could have been more readily investigated for tuberculosis because of the perceived increased risk. Of the total number of infants with tuberculosis, a high proportion (20.1%) had disseminated disease; 15.1% of HIV-infected infants and 21.4% of HIV-uninfected infants had disseminated tuberculosis. These rates may be attributable to the pattern of hospital referral, which tends to select more severely ill infants, but reflect findings from large infant cohort studies performed in the prechemotherapy era [31].

In our study, HIV-infected infants were at increased risk of all types of tuberculosis without a disproportionate increase in disseminated tuberculosis. This is consistent with a recent report about 596 children with culture-confirmed tuberculosis in South Africa, among whom 14.3% of HIV-infected children versus 15.75% of HIV-uninfected children (age, 0–13 years) had miliary tuberculosis and in which HIV-infected children were less likely to have extrapulmonary tuberculosis (36.8% vs. 55.5%; OR, 2.12; 95% CI, 1.36–3.32) [32]. It is also possible that tuberculosis meningitis may have been underdiagnosed, and therefore, the incidence may have been underestimated among HIV-infected infants, because classic CT signs of tuberculous meningitis may be less common among HIV-infected children [30].

The incidence rates of tuberculosis among HIV-infected and HIV-uninfected infants in our study are likely to considerably underestimate the true rates. First, we only assessed culture-confirmed cases of tuberculosis that were diagnosed at all provincial referral hospitals; in general, approximately 30%–40% of childhood tuberculosis in the study setting is culture-confirmed [33], and we expect that some cases may have been missed because of lack of referral. The lower incidence of disseminated tuberculosis among HIV-uninfected infants observed in our study, compared with data from a recent surveillance study [34], may be explained by the fact that, in the latter study, all notified cases reported from all levels of health care, including both culture-confirmed and clinically diagnosed tuberculosis cases, were included. We also excluded cases of infection due to nontuberculous mycobacteria and BCG, because our case definition was limited to culture-confirmed tuberculosis disease. An advantage of the stringent case definitions is that these conservative estimates allow direct comparison with recent estimates of disseminated BCG disease in HIV-infected infants who were admitted to the same 3 hospitals over the identical study period [35]. Although the World Health Organization recommended in 2007 that BCG vaccine should not be given to HIV-infected infants [36], BCG vaccine continues to be administered to infants in most high HIV-burden settings, because of the difficulty of implementing selectively deferred BCG vaccination. Epidemiological data are needed on both the incidence of severe adverse events attributable to BCG and tuberculosis incidence among HIV-infected infants.

A limitation of our study is that the HIV status was not

<table>
<thead>
<tr>
<th>Indicator</th>
<th>All infants</th>
<th>HIV-uninfected infants</th>
<th>HIV-infected infants</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis incidence</td>
<td>83.1(73–94)</td>
<td>65.9(57–75)</td>
<td>1596(115–2132)</td>
<td>24.2(17–34)</td>
</tr>
<tr>
<td>Pulmonary tuberculosis incidence</td>
<td>78.7(69–89)</td>
<td>62.5(53–72)</td>
<td>1505.6(1075–2023)</td>
<td>24.1(17–34)</td>
</tr>
<tr>
<td>Extrapulmonary tuberculosis incidence</td>
<td>28.2(22–34)</td>
<td>22.9(18–29)</td>
<td>481.8(257–751)</td>
<td>21.0(11–35)</td>
</tr>
<tr>
<td>Disseminated tuberculosis incidence*</td>
<td>16.6(12–21)</td>
<td>14.1(10–18)</td>
<td>240.9(87–432)</td>
<td>17.1 (6–34)</td>
</tr>
<tr>
<td>Miliary tuberculosis incidence</td>
<td>10.9(7–15)</td>
<td>9.3(6–13)</td>
<td>150.6(31–301)</td>
<td>16.2(3–37)</td>
</tr>
<tr>
<td>Tuberculosis meningitis incidence</td>
<td>9.2(6–13)</td>
<td>7.9(5–11)</td>
<td>120.1(28–258)</td>
<td>15.2(3–39)</td>
</tr>
</tbody>
</table>

* Disseminated tuberculosis was defined as miliary tuberculosis, tuberculosis meningitis, or disseminated disease, diagnosed on the basis of positive culture results of isolates from blood culture and/or bone marrow.

Table 2. Estimated incidence of culture-confirmed tuberculosis (TB) among HIV-infected and HIV-uninfected infants.
known for all infants; those with unknown status were classified as HIV uninfected, resulting in potential misclassification. We assessed this potential effect in a sensitivity analysis. Misclassification of infant HIV infection status implies an underestimation of the tuberculosis incidence rate among HIV-infected infants, and an overestimation of the incidence of tuberculosis among HIV-uninfected infants results in a potential underestimation of the relative risk. We did not investigate the efficacy of BCG vaccination, and infants were assumed to have received BCG vaccination on the basis of the routine provincial coverage rates.

On the basis of the high observed risk of tuberculosis among HIV-infected infants, we recommend the following strategies to improve tuberculosis control in this vulnerable population. Infants with suspected tuberculosis should be routinely tested for HIV infection. Maternal tuberculosis screening should be incorporated into antenatal and postnatal PMTCT programs, and infant screening should be incorporated into postnatal programs. In the case of documented M. tuberculosis exposure, IPT may be a critically important preventive strategy in HIV-exposed and HIV-infected infants. Improved access to and early initiation of antiretroviral therapy for HIV-infected infants may also reduce the incidence of tuberculosis; HIV-exposed infants should be tested for HIV infection at the earliest opportunity. Finally, improved tuberculosis vaccine strategies are required. New vaccine candidates should be tested among HIV-infected and HIV-exposed infants in settings where tuberculosis and HIV infection are highly endemic. More data are needed regarding the protective effect of BCG vaccination among HIV-exposed and HIV-infected infants; ideally these data will be obtained through controlled trials.

Acknowledgments

We thank Wendy Brittle, for mycobacterial culture and Tippi K. Mak and Robert P. Gie, for helpful critical comments.

Financial support. Harry Crossley Trust (to A.C.H.) and South African Medical Research Council for funding (to H.S.S.).

Potential conflicts of interest. All authors: no conflicts.

References


