The impact of HIV on morbidity and mortality from tuberculosis in sub-Saharan Africa: a study in rural Malawi and review of the literature*

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Abstract

Since the mid-1980s tuberculosis (TB) case numbers and HIV seroprevalence have both risen sharply in sub-Saharan Africa. Estimates for the relative risk of TB in those infected with HIV have ranged from less than five to more than 20. The proportion of TB cases attributable to HIV (the population attributable fraction) has been calculated for several populations but is difficult to interpret if no account is taken of the age and sex distribution of the cases. In a rural area of Malawi we have studied the proportion of TB attributable to HIV over time. Nearly 40 per cent of smear-positive TB cases in this rural area of Malawi can now be attributed directly to HIV. The actual effect of HIV on TB is even greater than this because increased case numbers increase transmission of tuberculosis infection to both HIV-infected and non-infected sections of the population. We compare our findings with others from sub-Saharan Africa and discuss reasons for the differences, and methodological issues in interpretation.

In the presence of the HIV epidemic the number of cases of tuberculosis (TB) reported in sub-Saharan Africa has increased sharply (De Cock et al. 1992). Increases in TB of more than ten per cent per year have been reported from several countries (Cantwell and Binkin 1996). In Malawi notified cases of TB rose from 5334 in 1985 to 19,496 in 1994 (Harries et al. 1996). Increases in TB have also been reported in many other parts of the world, but the reasons for the increases are not the same in all populations. In Africa the increases are assumed to be due to HIV, but increases are also found in Eastern Europe, in areas relatively untouched by the HIV epidemic (Raviglione et al. 1994). Reasons for reported increases in TB other than through HIV include changes in ascertainment and reporting, and real increases in TB due to poverty, inadequate TB control programs and increasing drug resistance. These effects are not

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independent. For example, a good control program should mitigate the effect of HIV in increasing TB rates, and there is some evidence that it can do so (Cantwell and Binkin 1996). The first effect of an improved control program may be to improve case finding and notification so an increase in reported cases is expected although the actual number may start to go down.

In this paper we examine trends in TB and HIV in a rural area of Malawi. We estimate the impact of HIV on TB morbidity and mortality in this population and elsewhere in sub-Saharan Africa.

Methods

Karonga District, a rural area in Northern Malawi, has been the site of a large epidemiological study of mycobacteria (The LEPRA Evaluation Project/Karonga Prevention Study or KPS) since 1978. HIV infection probably reached the district in the early 1980s and seroprevalence levels between four and 25 per cent have been measured in antenatal clinics in different parts of the district in recent years.

House-to-house total population surveys were carried out in 1980-84 and 1986-89 to ascertain cases of TB and leprosy, the second survey forming the recruitment phase of a trial of repeat BCG and/or BCG plus killed \(M. leprae\) vaccination (Ponnighaus et al. 1993; Karonga Prevention Trial Group 1996). Since the end of the second survey KPS staff have been stationed in health centres and the district hospital outpatients department to assess all attenders for TB and leprosy. In addition, house-to-house case-finding surveys were conducted in selected areas of the district. In the surveys and health centres individuals were examined for leprosy and asked about cough. Sputum specimens were collected from those with cough of at least three weeks' duration, and biopsies were taken from those with suspected tuberculous lymphadenopathy or cutaneous TB. Throughout the period symptomatic patients could self-present at any time. No matter how they were originally identified, all TB patients treated in the hospital were seen by KPS staff and further specimens for confirmation of the diagnosis were taken if necessary. Since 1988 blood samples for HIV testing have been requested from all adult TB patients.

Sputum specimens were examined by fluorescence and light microscopy in the project headquarters in Malawi. Cultures were set up in Malawi, and those that macroscopically suggested \(M. tuberculosis\) were sent to the UK PHLS laboratory in Cardiff for species confirmation and drug sensitivity testing. Biopsy specimens were examined in London. Patients were classified as having 'certain or probable' tuberculosis if they had a positive culture or smear, excluding those who only had one smear with fewer than ten acid fast bacilli. Patients with a clinical diagnosis of TB lymphadenopathy, or with any form of extrapulmonary TB confirmed by biopsy or culture, were also included as 'certain or probable' TB (Karonga Prevention Trial Group 1996). Those who had previously been seen by the project without TB, and had no history of previous TB, were considered incident cases. Age-sex specific rates for smear-positive tuberculosis were estimated using the second survey population as the denominators.

A case-control study of leprosy and HIV was started in the district in 1988; initial results have already been published (Ponnighaus et al. 1991). In 1990 a parallel study of TB was started and is continuing. Cases were certain or probable incident cases of TB (or leprosy) diagnosed in the district among people aged 14 years and above. Controls were selected randomly from the computer database from the second population survey. Controls were matched on sex, age group (within 5 years up to age 35 and within 10 years thereafter) and area of residence (living within the same square kilometre as the case, or adjacent square kilometre if insufficient eligible controls were available). This study will be reported fully elsewhere.
HIV testing was carried out in the project laboratory using a four-test protocol as previously described (Sterne et al. 1995). The total population of controls selected for both leprosy and TB studies, who had HIV results available, has been used to estimate HIV prevalence in the district at different times. It was possible for a control to be chosen more than once, but in this analysis each subject has been included only once, at the time of first selection.

The prevalence of HIV seropositivity in the general population over the age of 14 years was calculated using the age-sex-period specific estimates from the control population, and the age and sex structure of the population recorded in the second population survey (1986-89). The prevalence \( p \) in different time periods was used, together with the odds ratio calculated from the case-control study as an estimate of the relative risk (RR), to calculate the proportion of TB cases attributable to HIV (the population attributable fraction or PAF) according to the formula:

\[
\text{PAF} = \frac{p(\text{RR}-1)}{(p(\text{RR}-1)+1)}
\]

This formula has been used in many studies, but may not give the correct answer if, as is the case, both the HIV seroprevalence and the TB incidence vary in different sections of the population, for example, with age and sex. We have therefore also calculated PAF separately for each age-sex-period group and obtained an overall PAF for each time period by weighting these estimates by the number of cases of TB in each age-sex-period group (Schlesselman 1982).

**Results**

Between 1988 and 1995, 2334 individuals were seen as controls for leprosy or TB patients and had their HIV status recorded. HIV status by age, sex and year is shown in Figure 1. Since relatively few people were seen between 1992 and 1995 the data from this time period have been pooled. The prevalence of HIV has increased markedly except in men under 25 and in the oldest age groups. The infection has been identified in all areas, although Karonga township has been most affected.
Figure 1. HIV status of individuals blood-tested as controls for leprosy or TB patients in Karonga District, 1988-1995.

TB has increased in the district over the period of study, and the increase has been largest in women between 15 and 44, and men over 25 (Figure 2). The number of ‘certain or probable’ smear-positive cases diagnosed increased from 50 per year to over 100 per year between 1986 and 1994.
Preliminary results from the case-control study show that 101/255 TB cases and 59/558 controls were HIV positive (OR 7.41, 95% confidence interval (CI) 4.41-12.4). The analyses were repeated for the 212 smear-positive pulmonary cases and their controls, giving an odds ratio for HIV of 6.26 (95% CI 3.58-11.0).

PAF was calculated using the odds ratio of 6.26 for smear-positive TB by the two different methods discussed above. The results are shown in Table 1. The proportion of adult TB cases attributable to HIV rose from 17 per cent to 39 per cent over the period studied, after adjusting for age and sex. Figure 3 compares the observed and estimated TB cases without HIV.
Table 1.
The proportion of smear-positive pulmonary TB attributable to HIV (PAF) in the adult population of Karonga District by time period.

<table>
<thead>
<tr>
<th>Time period</th>
<th>HIV+ (%)</th>
<th>PAF (%) (crude)</th>
<th>PAF (%) (Age-sex adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988/89</td>
<td>2.96</td>
<td>13.6</td>
<td>17.0</td>
</tr>
<tr>
<td>1990/91</td>
<td>5.26</td>
<td>21.8</td>
<td>19.7</td>
</tr>
<tr>
<td>1992/95</td>
<td>10.78</td>
<td>36.4</td>
<td>38.5</td>
</tr>
</tbody>
</table>

Figure 3.
Smear-positive pulmonary TB in Karonga District: observed cases and numbers expected in the absence of HIV.
Discussion

Trends in TB and HIV

HIV seroprevalence has now reached more than 15 per cent in the age groups most at risk in Karonga District: women aged 15-45 and men aged 25-55. This may be an underestimate since the population controls on whom these figures are based were people who were present in the district during the second survey (1986-89) and were then found again in the same area of residence, and moreover agreed to be tested. The prevalence may be higher in more mobile sections of the population and among refusals.

The pattern of increased incidence of TB since the late 1980s reflects the increase in HIV, with large increases being seen in all age groups except the youngest men and oldest women. Changes in ascertainment procedures during the study, from house-to-house surveys to health centre based, are also likely to have influenced the numbers of cases diagnosed in each time period.

HIV-infected TB patients have much higher mortality rates than do those without HIV, so the effect of HIV on TB mortality rates will be even more marked than its effect on incidence rates. In Karonga District, among smear-positive patients, 32/134 HIV-positive and 15/281 HIV-negative patients died during therapy (hazard ratio 5.6, 95% CI 3.0-10 in a Cox regression analysis: Karonga Prevention Study unpublished results). Similarly increased mortality rates have been reported in other studies (Perriens et al. 1991; Nunn et al. 1992; Elliott et al. 1995; Ackah et al. 1995). The mortality rate in HIV-positive patients depends on the degree of immune deficiency (Ackah et al. 1995). Many of the deaths are not directly attributable to TB (Nunn et al. 1992; Elliott et al. 1995) and there is some evidence that TB may accelerate the progression of HIV disease (Goletti et al. 1996).

Relative risk of TB in HIV-positive and HIV-negative persons

The results of the current case control study are similar to those of a previous study: odds ratio for the association of HIV and TB of 7.4 (95% CI 3.3-16.7) for the period 1988-89 in Karonga District (Ponnighaus et al. 1991). Several previous studies in Africa have also estimated relative risks for the association between HIV and TB, and are summarized in Figure 4. The studies have varied in the certainty of diagnosis of cases of TB, whether they include all types of TB or only pulmonary cases, and in their choice of control groups. These factors are likely to bias the measurements of relative risk in various ways.

Since several HIV-related diseases can be difficult to distinguish clinically from TB, studies which include all diagnosed TB cases rather than bacteriologically confirmed cases are likely to overestimate the relative risk. Several studies have shown higher rates of HIV positivity in patients with extra-pulmonary TB than in those with pulmonary TB (Elliott, Halwiindi et al. 1993), so lower relative risks would be expected in studies which include only pulmonary TB cases. In our preliminary results, and in two other studies from sub-Saharan Africa in which data have been presented separately for all diagnosed TB and bacteriologically confirmed pulmonary TB, lower relative risks were found for confirmed pulmonary TB (Figure 4). In a cohort study in Zaire of HIV-positive and HIV-negative women of childbearing age in which regular follow-up visits were made, the rate ratio was 10

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(95% CI 1.5-47) for smear-positive pulmonary TB and 26 (95% CI 5-125) for all diagnosed TB (Braun et al. 1991). In southern Tanzania, in a study with blood donor controls, the odds ratio was 8.1 (95% CI 4.4-16.3) for smear-positive TB and 11.8 (95% CI 7.9-18.3) for all TB (Van Cleeff and Chum 1995).

Figure 4
Summary of studies of the association between HIV and TB in Africa.

Notes: Studies are presented in groups by study type and comparison group used. For each study the country, years of data collection, and confounders adjusted for are given. Studies referring to all diagnosed TB and those restricted to microbiologically confirmed pulmonary TB are distinguished. For the studies in the Ivory Coast and Guinea Bissau cases and controls infected only with HIV-2 have been excluded. Rate ratios are presented for the cohort studies and odds ratios for the case-control studies, except for the study in Tanzania 91/93 (Chum et al. 1996) in which the risk ratio was given and it was not possible to calculate an odds ratio from the information given.

Blood donors have often been used as controls, but they are not a random sample of the community, and the section of the community they represent will vary from place to place and according to whether they are paid or not. Since donors are likely to be healthy, and in some populations are prescreened for risk factors for HIV, studies which use blood donor controls may overestimate the relative risk. In some populations potential donors with perceived risk factors for HIV infection are excluded from blood donation. On the other hand blood donors may be more likely to be urban dwellers and have higher HIV rates than the general population. Hospital patients are sometimes used as controls, but are likely to have high rates of HIV unless carefully chosen to exclude patients seen for HIV-related conditions, so their use will tend to underestimate the relative risk. Hospital workers have been used as controls, but they may come from a different section of society than do the TB patients and they may
be occupationally exposed to HIV, so they are also unlikely to be a suitable comparison group.

The variation in relative risk seen between the different studies may be due to bias and the lack of adjustment for confounding in many of the studies. On the other hand the confidence intervals on many of the estimates are wide. Most studies are compatible with a ‘true’ relative risk of about 7, but there may not be a single, constant relative risk in all situations.

There is some suggestion that the relative risk varies with age. The highest relative risks have been reported from three cohort studies of women of childbearing age, one in Zaire (Braun et al. 1991) and two in Rwanda. In Rwanda the rate ratio for all TB was 21.8 (95% CI 5.1-92.9) in one study (Allen et al. 1992) and 18.2 (95% CI 2.4-137) in the other (Leroy et al. 1995).

A case-control study in Mwanza, Tanzania, based on all TB cases, and controls selected from a population database, found an odds ratio of 8.3 (95% CI 6.4-11.0) overall, but a higher odds ratio for the 25-34 year age group (13.4, 95% CI 8.9-20.7) and lower odds ratio for those aged 45-54 (2.9, 95% CI 1.0-7.9) (Van den Broek et al. 1993). Two other Tanzanian studies, which used blood donor controls and did not adjust for any possible confounders, found a similar pattern of higher odds ratios in the 25-34 year age group and lower ones in those over 45 years (Chum et al. 1996; Van Cleeff and Chum 1995). In Harare, Zimbabwe, a study with hospital controls also found the lowest odds ratios in the oldest age group (recalculated as 3.0, 95% CI 1.5-6.1 in those over 45), but the highest was in those aged 35-44 (recalculated as 8.3, 95% CI 4.3-16.3) (Houston et al. 1994). A study of bacteriologically proven TB cases in Kenya using neighbourhood controls found an overall odds ratio of 4.9 (2.6-6.8), with no clear pattern by age group (Orege et al. 1993). And there was no clear trend with age in Abidjan, Ivory Coast, in a study which compared pulmonary TB cases with blood donors, considered HIV-1 and HIV-2 infection, and found an overall odds ratio (recalculated) of 5.1 (95% CI 4.1-6.7) (De Cock et al. 1991).

The true odds ratio may change with time, as the HIV epidemic matures, since the proportions of people with HIV who have different levels of immunosuppression will change. There may also be variation as segments of the population with different underlying risks of TB are affected by HIV. HIV may affect the relative risk of developing primary disease, reactivation disease and reinfection disease differently, so the overall odds ratio would depend on the proportion of the population at risk for the various types of disease. Older people are more likely to have been previously infected with TB so differences in relative risk at different ages may be a reflection of the different influence of HIV on the different pathways to TB disease.

Population attributable fraction

Using a constant relative risk we have calculated the proportion of TB cases attributable to HIV infection in the adult population. Since neither the population prevalence of HIV nor the relative risks were accurately measured, this is inevitably a rough estimate both in our study and in others. The PAFs calculated overall and those adjusted for age and sex are similar. This will not always be the case, if other populations such as children are included in the calculations. For instance, data from the Malawi AIDS program for the first six months of 1996 found that 12.8 per cent of reported AIDS cases in the country were children aged less than 15 years. Using this to estimate the proportion of children HIV-positive in our population and including the (few) smear-positive TB cases seen in children we can recalculate the PAF for the period 1992-95 by the two methods. The all-age population prevalence of HIV is estimated at 6.7 per cent, giving a PAF of 25.9 per cent by the crude method. Using separate PAFs for different age and sex groups gives an age-sex adjusted PAF of 37.7 per cent.
It is often unclear in published studies which age groups have been included in estimating HIV prevalence and PAF. Blood donors, presumably young adults, were used to calculate a PAF of 35 per cent for all adult TB in Abidjan in 1989, for HIV-I and HIV-II combined (De Cock et al. 1991). Estimates based on blood donors and antenatal clinic attenders were used together with census data, TB registers and seroprevalence data among TB patients to calculate PAFs of 36 per cent in 1989 and 40 per cent in 1991 in separate studies in Abidjan (Richards et al. 1995). In Mwanza a PAF of 29 per cent was calculated for those aged 15-54 years with all types of TB (Van den Broek et al. 1993). In a study from southern Tanzania with blood donor controls the estimated PAF rose from 19 per cent to 31 per cent between 1987 and 1990, but it is not clear to what age group the population HIV prevalence figures used refer (Van Cleeff and Chum 1995).

**Effect of HIV on TB**

The PAF measures only the direct effect of HIV on TB cases. As the HIV epidemic progresses and the number of TB cases including smear-positive TB cases rises, transmission to both the HIV-positive and HIV-negative population must increase. Lienhardt and Rodrigues (1997) have calculated a factor $f$ by which the number of cases of TB increases in a population as a direct effect of HIV:

$$f = \frac{\text{risk of TB in general population} (r_t)}{\text{risk of TB in HIV-negative part of population} (r_o)}$$

$$= \frac{1}{1-\text{PAF}}$$

They go on to argue that, if HIV-infected TB cases are as infectious as HIV-negative TB cases and there is random population mixing, then the annual risk of infection in the short term would be expected to increase by the same factor $f$ due to the infections caused by these ‘extra’ cases. In the longer term there would be a further increase due to transmission from second-generation cases in the HIV-negative population. Based on the above formula, PAFs of between 30 per cent and 40 per cent translate into expected increases in the annual risk of infection of between 40 per cent and 70 per cent above what they would have been in the absence of HIV. This should ultimately increase the number of cases of TB in both HIV-positive and HIV-negative individuals, through infection or reinfection.

More complex models for estimating the effect of HIV on TB have also been developed (Heymann 1993; Schulzer et al. 1994). Models are inevitably constrained by assumptions made in defining their parameters, and in both of these models transmission is also apparently assumed to be the same from HIV-positive and HIV-negative TB cases. The relative infectiousness of HIV-infected TB cases is uncertain, however, making this indirect effect of HIV on TB difficult to quantify.

Three studies in Africa have compared infection with *M. tuberculosis* (as assessed by tuberculin responses) and disease rates in contacts of HIV-positive and HIV-negative index patients with pulmonary TB. In Kinshasa (Klausner et al. 1993) and Nairobi (Nunn et al. 1994) infection rates were similar in the two sets of contacts, and in Lusaka they were lower in the contacts of the HIV-positive group even after adjusting for degree of sputum smear positivity (Elliott, Hayes et al. 1993). In all three studies, BCG vaccination coverage and background TB infection rates were high which will have led to probably non-differential misclassification of tuberculous infection, and is likely to have biased the relative risks towards 1. The rates of TB disease were similar in contacts of HIV-positive and HIV-negative index cases in all the studies, but the numbers were small. In a study in Florida, where BCG is
not used and background TB infection rates are low, lower tuberculin positivity rates were found in contacts of HIV-positive patients than in those of HIV-negative patients (Cauthen et al. 1996). Lower infectiousness of HIV-positive patients may be partly explained by lower degrees of smear positivity (Elliott, Hayes et al. 1993), and, in some places, by closer monitoring of HIV-positive patients leading to earlier diagnosis.

Studies of transmission among contacts inevitably rely on diagnosed patients, who should become non-infectious soon after the start of treatment, but many TB patients go undiagnosed. Since HIV-positive TB patients have a higher mortality rate and are likely to die earlier than do HIV-negative TB patients, transmission from undiagnosed TB cases is likely to be less from the HIV-positive than from the HIV-negative individuals, mainly because the former would have less time during which to transmit.

Conclusions

HIV has led to an increase in TB cases in sub-Saharan Africa, with 30-40 per cent of TB cases, and an even higher proportion of TB deaths, now being directly attributable to HIV in many areas. The indirect effect of this increase in terms of the annual risk of infection and subsequent generations of cases may be less than some have predicted, since HIV-positive TB patients may transmit infection to fewer people than do HIV-negative patients, but some increase in infection and subsequently in disease rates would still be expected. It remains to be seen whether the projected increase in TB can be contained by TB control programs, and whether the increase is sufficient to reverse the long-term downward trend in the annual risk of infection recorded in many populations (Murray, Styblo and Rouillon 1990).

References


