# A PRELIMINARY STUDY OF THE INFLUENCE OF HIV INFECTION IN THE TRANSMISSION OF TUBERCULOSIS

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**Abstract.** The human immunodeficiency virus (HIV) epidemic has had a profound influence on the epidemiology of tuberculosis (TB). The potential for HIV-associated TB cases to transmit *M. tuberculosis* and to produce a secondary increase in TB morbidity is unknown. A cross-sectional study was carried out to compare the prevalence of *M. tuberculosis* infection among the household contacts of HIV-positive and HIV-negative pulmonary tuberculosis (PTB) patients. Records of tuberculin (Mantoux) tests administered during routine contact investigations at the Chest Clinic, Hospital Kota Bharu, from 1999 to 2000 were reviewed. The HIV status of the patients was based on the results of ELISA tests while information on household contacts was gathered during visits to their houses. Ninety-four contacts of 39 HIV-negative patients and 44 contacts of 17 cases of HIV-positive patients were included in this preliminary study. 30% (12/40) of the contacts of HIV-positive PTB had a positive tuberculin compared with 52.8% (47/94) of the contacts of HIV-negative patients [OR = 0.41, 95% Confidence interval (CI) 0.17 - 0.97; p = 0.016]. The difference was still significant after performing multivariate logistic regression analysis to adjust for variables associated with infectiousness of TB (adjusted OR = 0.24, 95% CI 0.07 - 0.87; p = 0.03). This study has shown that HIV-infected PTB patients are less infectious to their contacts than HIV-negative patients. The presence of HIV in the community may not necessitate a change of the current policy of the management of contacts.

## INTRODUCTION

Tuberculosis (TB) is still a leading contender for the dubious distinction of being the most important plague of mankind. According to the World Health Organization (WHO), one third of the world's population is already infected with *Mycobacterium tuberculosis* which causes about 3 million deaths each year (Raviglione *et al*, 1995). Seven to eight million people develop tuberculosis each year. At the same time, the human immunodeficiency virus (HIV) pandemic is increasing rapidly in many communities worldwide; more than 30 million people are currently infected and 1.5 million deaths are estimated to have occurred in 1996. Nearly 14 million people were estimated to have both infections by the year 2000 (WHO, 1998). The effects of HIV on TB will be greatest where the two diseases overlap: in the developing world, at present principally in Africa countries (Colebunders *et al*, 1989; Elliot *et al* 1990).

With regards to Malaysia, the number of tuberculosis cases detected per year has not declined substantially either. Since 1989, an average of 11,500 to 12,000 cases anually has been recorded; the latest data showed that the number of new cases showed have increased in year 1999 with an incidence rate of 64.7 cases per 100,000 population. The trend of TB with HIV co-infection has continuously increased since 1990 and contributed about 4.0% to the total number of TB cases in the country (MOH, 2000). The annual number of reported cases of HIV infection has also shown an increasing pattern: cases increased from 200 in 1989 to 4,692 in 1999 (Anonymous, 2000).

The potential for HIV-associated TB patients to transmit *M. tuberculosis* and to

produce a secondary increase in TB morbidity is unknown. If alterations in the TB mediated by HIV infection result in more efficient transmission, or behavioral factors result in the exposure of more contacts, or if HIV infection is prevalent among the contacts themselves, then there is the potential for accelerated epidemic spread. Few reports have specifically investigated the rate of tuberculosis in the contacts of HIV-infected tuberculosis index cases. It is not clear whether these phenomena were due to the increased infectiousness of the index cases or enhanced susceptibility of the contacts, or both (Selwyn *et al*, 1989).

Therefore it is of considerable importance to public health to establish whether patients with HIV-associated pulmonary tuberculosis (PTB) are more or less infectious than those with PTB without HIV infection. The purpose of this study is to identify the influence of HIV on the epidemiological transmission of TB and to determine whether changes are required in the management of contacts of PTB cases in the era of the HIV epidemic, particularly in developing countries.

## MATERIALS AND METHODS

A cross-sectional study was conducted to compare the prevalence of tuberculosis infection, based on a survey of the tuberculin reactivity and the incidence of tuberculosis among the household contacts, in HIV positive and negative index cases of PTB that registered and attended the Chest Clinic of Kota Bharu Hospital (HKB), Kelantan, from 1999 to 2000. All adult TB patients and their respective household contacts were eligible for enrolment in the study and give written consent. Index cases of PTB with known HIV status and their contacts aged above 12 that had records of tuberculin (Mantoux) tests were included in this study. HIV status was determined from enzyme-linked immunoassay (Abbott Diagnostics, USA®) conducted at the HKB laboratory. Mantoux testing of contacts used 10 TU in 0.1 ml tuberculin solution (Tuberculin PPD RT 23 SSI, Copenhagen, Denmark®); two experienced senior assistant nurses at the clinic read the Mantoux results after 72 hours. Information on the demographic, clinical, radiological and HIV status of index cases was gathered from their medical records and TB forms while house visits were undertaken to enable the interviewing of their household contacts.

### Statistical analysis

Descriptive statistics and cross-tabulations were used to explore all the data. Univariate analyses included a *t*-test for the comparison of the means of continuous variables while a chi-squared test was used to test the significance of association between categorical variables. For dichotomous variables with small cell sizes (expected count less than 5 is more than 20%), Fisher's exact test was used. The value of significance (p value) was taken as 0.05. Each contact was treated as an independent observation. The relationship between the positive tuberculin-test contacts (with induration $\geq$ 10 mm) and the HIV status and other variables related to the index patients, the household setting, and the contacts, was examined. Simple logistic regression was applied in univariate analysis to determine potential predictors. Variables that were found statistically significant in univariate analysis ($p < 0.25$) and also proven significant in other studies were included in multivariate modeling with logistic-binomial regression using the backward stepwise method of SPSS® version 9.0. The statistical significance, biological plausibility, clinical importance and variables found significant by previous studies were considered in the final model. Results were tabulated with crude and adjusted odds ratio, 95% confidence intervals and p-values.

## RESULTS

In this preliminary study, we identified and included 94 contacts of 39 index cases of HIV-negative and 44 contacts of 17 cases HIV-positive PTB that had records of a tuberculin test administered during routine contact investigations at the Chest Clinic, Kota Bharu Hospital.

Table 1 shows that HIV-positive patients were from younger age groups (82.4% from aged 25 - 44) while older age was a feature of HIV-negative cases ($p < 0.05$). None of the HIV-positive patients was female; most HIV-positive patients (52.9%) were single. There were no significant associations between the type of TB, the duration of cough or the sputum smear positivity, and the HIV status of index cases. Most of the HIV-positive cases presented with mild chest X-ray lesions (58.8%) with no cavity formation compared with HIV-

Table 1
Characteristics of pulmonary TB cases by HIV status according to demographic, clinical and radiological findings and behavioral risk factors of HIV, Chest Clinic, Hospital Kota Bharu, Kelantan, 1999 - 2000.

| | | HIV +ve (n = 17) | HIV-ve (n = 39) | p |
|---|---|---|---|---|
| **Age group (yrs)** | 15 - 24 | 2 (11.8%) | 1 (2.6%) | 0.001[a] |
| | 25 - 34 | 6 (35.3%) | 4 (10.3%) | |
| | 35 - 44 | 8 (47.1%) | 6 (15.4%) | |
| | 45 - 54 | 1 (5.9%) | 3 (7.7%) | |
| | > 55 | 0 | 25 (64.1%) | |
| **Sex** | male | 17 (100%) | 30 (76.9%) | 0.031[b] |
| | female | 0 | 9 (23.1%) | |
| **Race** | Malay | 16 (94.1%) | 37 (94.9%) | |
| | Chinese | 1 (5.9%) | 2 (5.1%) | 0.908[b] |
| **Educational status** | primary | 1 (5.9%) | 12 (31.6%) | |
| | secondary | 16 (94.1%) | 10 (26.3%) | |
| | tertiary | 0 | 2 (5.3%) | |
| | others (no formal education) | 0 | 14 (36.8%) | 0.000[a] |
| **Marital status** | married | 4 (23.5%) | 34 (89.5%) | |
| | single | 9 (52.9%) | 1 (2.6%) | |
| | others | 4 (23.5%) | 3 (7.9%) | 0.000[a] |
| **Type of TB** | pulmonary | 12 (70.6%) | 34 (87.2%) | |
| | both | 5 (29.4%) | 5 (12.8%) | 0.152[b] |
| **Cough duration** | < 2 weeks | 2 (11.8%) | 12 (20.5%) | |
| | 2 - 4 weeks | 4 (23.5%) | 16 (41.0%) | |
| | > 4 weeks | 11 (64.7%) | 15 (38.5%) | 0.194[a] |
| **Initial CXR classification** | mild | 10 (58.8%) | 14 (35.9%) | |
| | moderately advanced | 2 (11.8%) | 18 (46.1%) | |
| | severely advanced | 2 (11.8%) | 6 (15.4%) | |
| | no lesion | 3 (17.6%) | 1 (2.6%) | 0.026[a] |
| **CXR findings** | cavitation/s | 0 | 16 (41.0%) | |
| | infiltrates/opacity | 13 (76.5%) | 19 (48.7%) | |
| | pleural disease | 1 (5.9%) | 1 (2.6%) | |
| | hilar and/or med nodes | 1 (5.9%) | 0 | |
| | clear/no lesion | 2 (11.8%) | 3 (7.7%) | 0.030[a] |
| **Sputum smear AFB** | positive | 9 (52.9%) | 28 (71.8%) | |
| | negative | 8 (47.1%) | 11 (28.2%) | 0.288[c] |
| **Behavioral risk for HIV** | Intravenous drugs users | 15 (88.2%) | 1 (2.6%) | |
| | Promiscuity/Homosexual | 2 (11.8%) | 1 (2.6%) | |
| | Not determined | 0 | 37 (94.9%) | 0.000[a] |

p-value of $< 0.05$ is significant, test for [a]chi-square for trend, [b]Fisher's exact test , [c]Yate's corrected.

Table 2
Relationship between Mantoux positivity[a] and household contacts, index cases and household setting.

| Risk factors | No. (% +ve) | Odd ratios (OR) crude | p | adjusted (95% CI)[b] | p-value |
|---|---|---|---|---|---|
| **Age groups of contacts (yrs)** | | | | | |
| < 14 | 3/11 (21.4) | 3.67 | 0.014 | 2.72 (0.29-24.78) | 0.055 |
| 15-24 | 14/34 (41.2) | 1.43 | | 0.87 (0.13-5.89) | |
| 25 -34 | 20/29 (69.0) | 0.45 | | 0.24 (0.03-1.78) | |
| 35-44 | 4/17 (23.5) | 3.25 | | 2.09 (0.25-17.41) | |
| 45-54 | 6/16 (37.5) | 1.67 | | 0.98 (0.14-7.00) | |
| 55-64 | 6/9 (66.7) | 0.50 | | 0.32 (0.04-2.96) | |
| > 65 | 4/8 (50.0) | 1.00 | | | |
| **Sex of contacts** | | | | | |
| female | 23/55 (41.8) | 1.00 | | 1.00 | |
| male | 36/74 (48.6) | 1.32 | 0.441 | 1.08 (0.39-2.99) | 0.441 |
| **BCG scar of contacts** | | | | | |
| absent | 49/112 (43.8) | 1.00 | | 1.00 | |
| present | 10/17 (58.8) | 1.84 | 0.245 | 0.96 (0.16-5.73) | 0.962 |
| **Relationship to index cases** | | | | | |
| others | 16/29 (55.2) | 1.00 | | | |
| son/daughter | 15/39 (38.5) | 1.97 | | 1.69 (0.51-5.71) | |
| siblings | 8/23 (34.8) | 2.31 | | 2.66 (0.35-19.96) | |
| parents | 4/10 (40.0) | 1.85 | | 1.61 (0.36-7.13) | |
| spouse | 16/28 (57.1) | 0.92 | 0.329 | 3.89 (1.22-12.39) | 0.499 |
| **Intimacy to index cases** | | | | | |
| share a bed 1 | 4/25 (56.0) | 1.00 | | | |
| share bedroom | 4/4 (100.0) | 0.01 | | 0.01 (0.01-1.91) | |
| share living room | 41/100 (41.0) | 1.83 | 0.016 | 1.36 (0.41-4.50) | 0.811 |
| **Crowding of house** | | | | | |
| < 2 persons/room | 27/61 (44.3) | 1.00 | | | |
| > 2 persons/room | 26/50 (52.0) | 0.73 | 0.417 | 1.54 (0.59-3.97) | 0.377 |
| **Sputum smear AFB** | | | | | |
| negative | 16/44 (36.4) | 1.00 | | | |
| positive | 43/85 (50.6) | 1.79 | 0.124 | 0.67 (0.22-2.11) | 0.494 |
| **Cavitations on CXR** | | | | | |
| no cavity | 41/95 (43.2) | 1.00 | | | |
| cavity | 18/34 (52.9) | 1.48 | 0.326 | 0.67 (0.22-2.11) | 0.500 |
| **Duration of cough** | | | | | |
| < 2 weeks | 11/20 (55.0) | 1.00 | | | |
| 2-4 weeks | 18/38 (47.4) | 1.36 | | 1.65 (0.41-6.62) | |
| > 4 weeks | 30/71 (42.3) | 1.67 | 0.583 | 0.96 (0.25-3.09) | 0.624 |
| **HIV status of cases** | | | | | |
| negative | 47/89 (52.8) | 1.00 | | | |
| positive | 12/40 (30.0) | 0.41 | 0.016 | 0.24 (0.07-0.87) | 0.029 |

[a]Mantoux (tuberculin) positive taken as induration of 10 mm or more.
[b]Adjusted for all listed risk factors that are significant on univariate analysis and variables that biologically significant on the infectivity of tuberculosis, based on multivariate logistic regression analysis.

negative cases and these findings were statistically significant. As expected, the majority (88.2%) of HIV-positive patients were intravenous drug users. None of the contacts of either of the HIV-positive or negative patients had developed active TB at the time of the study. It was also found that no contact had a known history of illness or other possible factors, such as recent infection or immunization, which may have influenced susceptibility to TB infection or the tuberculin response.

Table 2 shows the relationship between the HIV-status of index cases and tuberculin response in household contacts. Observed prevalence of infection, showed by Mantoux positivity of 10 mm induration, in contacts of HIV-positive patient was significantly lower than of HIV-negative patient (30.0 % *vs* 52.8%) (OR = 0.41 with 95% CI = 0.173 - 0.971; p = 0.016). The association was still significant after adjustment for other variables that influence the infectiousness of TB (adjusted OR = 0.24, 95% CI 0.07 - 0.87).

The influence of variables related to the index cases, household contacts and household overcrowding on the tuberculin response were also examined and are shown in Table 2. In the univariate analysis, apart from the HIV-status of the index cases, there were two other variables that had significant associations to the positive tuberculin of the contacts. There were significant associations between the age group of contacts (p = 0.014) and their intimacy to the index cases (p = 0.016) and the tuberculin positivity of the contacts. Besides the younger age group (<14 years old), the 35 - 44 age group was also at higher risk of tuberculin positivity. Those sharing living rooms were more likely to be tuberculin positive than those sharing the same bed or bedroom; however these two variables were no more significant after being adjusted for other variables.

Household contacts, who were male and had a BCG scar, had a higher likelihood of a tuberculin positivity. The siblings, parents and sons and daughters of the index cases were more likely to be tuberculin positive than the spouses. For the household contacts of an index case with positive sputum smear, cavitation on X-ray or a longer duration of cough was associated with a greater likelihood of having a positive tuberculin response. However, those findings were not significant even after applying multivariate analysis to adjust for other related variables.

## DISCUSSION

The main finding of the study was a much lower prevalence of positive tuberculin (Mantoux) response among contacts of HIV-positive pulmonary TB patients than among contacts of HIV-negative patients. The similarity in risk factors for tuberculin response between household contacts of HIV-positive and HIV-negative index cases in this study and those documented in other similar studies suggested that HIV infection may not influence the infectivity of index pulmonary TB patients to their contacts (Elliot *et al*, 1990; Klausner *et al*, 1993; Nunn *et al*, 1994; Cauthen *et al*, 1996; Espinal *et al*, 2000).

The characteristics of HIV-positive patients in this study may represent the actual situation in Malaysia: the majority of them are males from younger age groups; those involved in intravenous drug abuse and Malays are the predominant groups. Latest data from Ministry of Health of Malaysia show that injecting drug users remain the largest group (76.8%) of which 72.8% were Malays; 95.4% were males and a majority (77.9%) were from the 13 - 40 year age group (Anonymous, 2000).

Apart from HIV-status of index cases, the age groups of contacts and intimacy to the patients were found to influence tuberculin positivity. Those sharing living rooms with the patients had higher risk, especially siblings and children, than those sharing the same bed or bedroom; though findings were mixed in other similar studies (Elliot *et al*, 1990; Nunn *et al*, 1994; Espinal *et al*, 2000). The most probable explanation is that this is due to the longer duration of, and more opportunity for, expo-

sure to tubercle bacilli during the index patients' symptomatic illness.

This study showed that there were no associations between clinical features findings, for example the type of TB and cough duration, and sputum smear positivity. However, these findings may not represent the exact trends concerning the features of TB in HIV-infected individuals because the clinical presentation of TB is dependent on the immune status of the individual infected (Sepkowitz, 1995). The chest X-ray findings in the HIV-positive group, mild lesions with no cavitation, may explain the lower infectiousness of tubercle bacilli to their contacts but these findings may be obscured by the degree of immunosuppression of the patients, which was not stratified in this study (Daley, 1995).

The inclusion of sputum smear negatvie patients in both groups was necessary since positive acid-fast smears are present in only 31% - 82% with HIV infection who have pulmonary TB (Kramer *et al*, 1990; Barnes *et al*, 1991). The absence of active TB disease among the contacts at the time of the study might have been expected but probably is underestimated because only those who had a tuberculin response of 15 mm or more or those having TB symptoms during contact investigations would have been investigated radiologically at this center. In addition, the development of active TB may happen at later stages and a prospective cohort study may address this.

Some limitations were noted in this preliminary study. Apart from the small sample that may affect the power of the study and its generalization to reference populations, the estimation of secondary transmission rates in this cross-sectional study may bias the results and conclusions. Tuberculin reactivity may represent prior exposure to mycobacteria (*M. tuberculosis* or non-tuberculosis mycobacterium), or BCG vaccination as well as exposure to the index cases. We have assumed that the index pulmonary TB cases is the first case presenting in the family, and since all contacts were sputum smear negative and none had history of exposure to TB patients other than the index cases, the assumption of infection passing from the index to the contacts was reasonable. Furthermore, the study showed an absence of association between BCG scars among the contacts (which was also adjusted by statistical analysis) and the presence of tuberculin positivity in higher age groups, indicating that BCG vaccination during childhood may not greatly influence the outcome of tuberculin reactions.

HIV infection, depending on the degree of immunosuppression, may lead to anergy to tuberculin or alter the infectiousness of TB (CDC, 1991). Therefore, unrecognized HIV-positivity among contacts, who were not HIV-tested in this study due to limited resources and ethical constraints, could result in the underestimation of prevalence of TB infection among them.

**Conclusions and recommendations**

This study will be continued and extended as multi-centered study until an adequate sample size has been obtained. At this stage of the study, the data presented support the hypotheses that HIV-positive TB are less likely than HIV-negative patients to transmit TB to their contacts based on tuberculin reaction. The current contact management policy of TB disease in developing countries may not need to be revised in the face of rising HIV prevalence.

Future similar studies may need to determine HIV status among the higher risk groups, especially among the spouses or children of the patients. The CD4 count and AIDS status of the patients should also be included in order to stratify the clinical findings and infectivity of TB. We think that studies using DNA 'fingerprints' of isolates *M. tuberculosis* will at least be able to show that index case and contact are infected with same strain (Daley *et al*, 1992). Qualitative studies to determine sociocultural and behavioral factors that influence transmission of TB in HIV patients and contacts may also need to be conducted.

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