HIV-associated Tuberculosis among a Cohort of Heterosexual Discordant Couples in Lusaka, Zambia

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ABSTRACT

The purpose of this study was to determine the association between human immunodeficiency virus (HIV) infection and tuberculosis (TB) among a cohort of heterosexual discordant couples (one partner HIV-positive and the other HIV-negative) enrolled at an HIV prevention and research centre in Lusaka, Zambia. All medical records identified from January 1994 to July 1998 were extensively reviewed. In addition, follow-up visits to local health department and chest clinics and to sputum analyses laboratories were conducted to validate the extracted medical data. The study used a nested approach based on a retrospective study design. The participants with HIV-associated tuberculosis (HAT), when compared with HIV-negative subjects with diagnosis of presumptive tuberculosis, were more likely to have presented with negative sputum analyses, to have been diagnosed with pulmonary tuberculous lesion, to have experienced relapse from tuberculosis, to have never been hospitalized for tuberculosis-related complications, and to have died due to tuberculosis. In addition, 9% of the urban heterosexual discordant couples enrolled in the primary cohort study were positive for presumptive tuberculosis. This study reports the first major impact of HIV infections on the outcomes of tuberculosis among heterosexual discordant couples. However, further research using vigorous methodological criteria is recommended to confirm the above findings.

Key words: HIV; Discordant couples; Acquired immunodeficiency syndrome; Tuberculosis; Zambia

INTRODUCTION

Several reports have documented that over 60% of African adults are infected with Mycobacterium tuberculosis (1-4) and that tuberculosis (TB) may account for up to 26% of the overall mortality among HIV-infected persons (1-2). Despite case detection by hospitals and TB programmes, the traditional approach to diagnosis (cardinal symptoms, physical findings, tuberculin tests, chest x-rays, and sputum analyses) can even be less reliable (3-11). Other diagnostic procedures, such as polymerase chain reaction, fluorescent microscopy, bronchoscopy, and/or tissue biopsy, are more reliable (5,7-8), but largely remain impractical for developing countries, especially in settings with seroprevalence of high HIV infections where health programmes have access to extremely-limited resources (3-4,6-10). Furthermore, despite advances in diagnosis of concurrent HIV and tuberculous infections in industrialized settings (3-5,8,11-16), diagnosis of HIV-associated tuberculosis remains a medical challenge for the healthcare delivery system in sub-Saharan Africa.

The impact of HIV on the incidence of TB is alarming in sub-Saharan Africa, considering that over 90% of newly-acquired HIV infections occur in developing nations (16-17). Research findings from regions as diverse as North America, Europe, and other areas of
Africa have established a strong association between HIV infections and tuberculosis (1-4,7-8,10,12-16), accounting for the fact that HIV infection continues to be one of the single most important determinants attributed to the increased incidence of TB (1,13,16).

In Zambia, the seroprevalence rate of HIV among adults is estimated to be 20-30%, with the urban rate being twice that in the rural areas (18-20). HIV-associated tuberculosis has been reported in adults and children, and co-infection rates above 70% are documented (4,10,12,14,16). However, extensive literature review and consultations with local key informants did not produce high-quality epidemiological data on tuberculosis in Zambia, except for reports published and distributed by the Central Board of Health (CBoH) in Lusaka, Zambia (21). In addition, the association between HIV infections and tuberculosis among heterosexual discordant couples (one partner HIV-positive and the other HIV-negative) in a longitudinal cohort study has not been previously reported.

This paper is the first report to document the negative health impact of HIV infections on TB among a cohort of heterosexual discordant couples at Project San Francisco (PSF), an HIV prevention and research centre in Zambia. The paper discusses the limitations in diagnosis of HIV-associated tuberculosis and the challenges associated with quality data collection and reporting procedures in the developing world.

**MATERIALS AND METHODS**

To be included in the study, subjects must have been enrolled in the heterosexual discordant couple cohort study at the PSF from its inception in Lusaka, Zambia, in January 1994 to the time of the proposed study—July 1998. Subjects enrolled in the primary cohort from September 1998 and beyond were excluded from the current study. Therefore, the medical records of all patients followed up at the PSF during the above study period were eligible for enrollment, and their medical and clinical records, approximately 3,000 charts, were extensively reviewed by two of the three authors. To minimize intra- and inter-person data extraction errors, about one-third of those medical charts were randomly selected by one of the PSF’s data analysts based on the consecutive numbering system of the medical charts, and those primary variables cross-checked for quality assurance and consistency in data extraction by the other author who did not participate in the initial data extraction.

The medical and clinical screening forms in those charts were similar and standardized, basically containing information on personal identifiers, past and present medical history, clinical examination, laboratory requests and results, and medication and treatment records. Twenty variables were previously identified as relevant to the goals of the study. Based on those variables, data were extracted from the medical record of a subject only if any characteristics were consistent with the diagnosis of presumed TB, as described later. No data were extracted from the charts of subjects who did not meet the criteria for presumed TB. In addition, chest radiographs ordered for TB investigations were interpreted by one senior-level internal medicine resident and another infectious disease fellow ([one from PSF and the other from the University Teaching Hospital (UTH), University of Zambia], blinded to the study, as either being radiologically consistent for the diagnoses of TB, not radiologically consistent for the diagnoses of TB, or radiologically indeterminate for the diagnoses of TB. Both the doctors had had senior medical residency-level training in radiograph interpretations. Standard radiological features (4,22), in the absence of medical history and clinical examination, were the criteria used in classifying the radiographs as being radiologically consistent for the diagnoses of TB. A consultant radiologist from the UTH, also blinded to the study and the findings of the two senior doctors, was contacted to minimize the radiological differences that may have occurred from the interpretation of chest radiographs. Lastly, follow-up visits to local health centres, chest clinics, and sputum analyses laboratories were implemented as quality assurance procedures.

Because of the limitations in epidemiological information and the diagnostic challenge posed by TB, especially in sub-Saharan Africa, presumptive TB for the purpose of this study was based on the presence of one or more of the following six indicators: (i) self-reported past medical history and/or hospital records for TB; (ii) current or previous history of anti-tuberculosis treatment based on TB treatment card; (iii) detailed medical history, clinical signs, and radiological features consistent with TB; (iv) positive sputum smear for acid-fast bacilli; (v) documented clinical response to empirical anti-tuberculosis treatment; and (vi) results of lymph node biopsy with histological features suggestive of TB. The above criteria have been previously reported and subsequently found to be relatively effective in the diagnosis of presumptive TB in resource-limited settings (1-2,14-15). Lastly, despite limitations in self-reporting
and under-reporting associated with stigmatized medical conditions, such as TB, the TB-positive subjects identified in this study were based on the above indicators.

The study methods and protocols for enrollment of subjects at the PSF have been extensively described and previously reported elsewhere (23-24). In addition, the study has been approved by the appropriate ethical committees of UTH, Ministry of Health (MoH) of Zambia, and University of Alabama at Birmingham (UAB). Lastly, readers interested in obtaining additional information on the primary study protocols, procedures, and findings may review the referenced publications (25-27).

Briefly, the PSF—a National Institutes of Health (NIH)-funded HIV prevention and research centre in Lusaka, Zambia—aims at studying the impact of heterosexual transmission of HIV and preventive practices by prospectively following discordant couples. Previously, outreach workers selected from among the study participants and trained in voluntary testing and counselling (VTC) recruited couples by randomly distributing door-to-door invitations in their respective communities. Interested couples gathered at a common point and were transported to the PSF. At the PSF, there was a half-hour group video show and interactive educational session on HIV, followed by confidential pretest counselling with trained counsellors. Couples requesting rapid HIV and serology tests provided written informed consents, and coded blood samples were collected. The samples were tested for HIV with both Dipstick HIV 1+2 (dot-immunoblot, developed by Appropriate Technology and Health, Seattle, Washington, USA) and Capillus HIV-1/HIV-2 (Latex Agglutination; Cambridge Biotech Ltd, Galway, Ireland), and for syphilis with Rapid Plasma Reagin (Macro-vue, Becton-Dickinson Europe, Meylon, France). Client-centred post-test counselling was followed and results provided.

Eligible couples, based on the study requirements, were asked to voluntarily return to the PSF, if they were interested in the study, to obtain information on the purpose of the study and recruitment procedures. Each eligible participant, prior to enrollment, signed a written informed consent form. Lastly, if enrolled, free medical evaluation (consisting of a self-administered questionnaire, clinical examination, and general laboratory investigations) and treatment based on the local standard of care were provided to all actively-enrolled subjects at a three-monthly interval and unscheduled sick visits, including free referral, transport, and consultation at the UTH.

Statistical analyses

The abstracted demographic and medical characteristics were entered into a customized Statistical Analytical Software (SAS Institute, Cary, NC, USA) dataset. The co-author verified data for accuracy, and the data were then analyzed using both SAS version 6.12 and Stata 3 (Computer Resource Center, Santa Monica, CA, USA) statistical software packages respectively. Most importantly, TB-positive individuals, and not discordant couples were the units of analyses.

Odds ratios (OR), using a subset of each variable as a reference, 95% confidence interval (CI), and statistical significance (p value) were subsequently determined by the Cochran-Mantel-Haenszel (CMH) methods from the table scores with TB-positive HIV-negative individuals as the controls. This method was also employed to the clinical case definition for AIDS (28-29) of the World Health Organization (WHO) to determine the relationships among the variables for both HIV-positive and HIV-negative subjects and its specificity and sensitivity as a relatively useful epidemiological tool in sub-Saharan Africa. In addition, the prevalence of tuberculosis and HIV-associated tuberculosis and the case-fatality rate for tuberculosis were computed, with the denominator being the total number of tuberculosis cases that were identified from the extensive review of the medical and clinical records of subjects enrolled in the study of discordant couple, who met the inclusion criteria. Finally, kappa (κ) coefficient (30) was calculated to determine the degree of chance or variability in the interpretations of the radiographs.

RESULTS

The medical and clinical records of approximately 3,000 enrolled subjects who met the inclusion criteria were extensively reviewed. As previously mentioned, 20 variables were extracted with individual-level data as the unit of analyses. Since data extractions were based on the presence of TB, no further data were extracted from the medical records of subjects who were not TB-positive. As such, no comparison of TB-positive versus TB-negative subjects was made. Furthermore, the specificity and sensitivity of TB indicators were also not ascertained for the purpose of this study because we believe that such methodological considerations are beyond the scope of this study.
Overall, 258 cases of presumptive TB were identified for this study, based on the diagnostic criteria previously described. The males (57%) accounted for a slightly greater proportion of those cases than the females (43%). Sixty percent of the TB-positive cases were identified from among the subjects aged 25-40 years, with a mean age of 32 years (range: 17-61 years). Most of the tuberculous lesions were localized in the pulmonary (87%) than in the extra-pulmonary (12%) regions. Thirty-nine percent of the subjects had previously been hospitalized for TB-related medical conditions, and 23% had experienced TB-related relapse, while 88% were still alive during the implementation of this study. For TB-related medications, it was observed that 14 (5%) subjects with prior or current history of taking anti-tuberculosis therapy reportedly developed complications from one or more of those medications. Of those complications, 6 (43%) were attributed to amenorrhoea, 5 (36%) to polynuropathy, and 2 (14%) to cutaneous reactions. While supportive therapy was administered to minimize cutaneous reactions, no information was provided on specific anti-tuberculosis medications that may have been responsible for the complications. Lastly, the prevalence of TB among the heterosexual discordant couples enrolled in the primary longitudinal cohort study at the PSF was 9%.

Of the 258 TB-positive cases, HIV serostatus data were unavailable for three subjects. For the comparison based on HIV serostatus, those three subjects were excluded from the analyses. Of the 255 TB-positive subjects with identifiable HIV serostatus results, 80% were HIV-positive, while the remaining 20% were HIV-negative. Compared to the HIV-negative subjects with TB, the HIV-positive subjects with TB were slightly more likely to be females (44% vs 39%, OR 1.2, 95% CI 0.6-2.3, p<0.5), aged less than 25 (20% vs 16%) and greater than 40 (19% vs 16%, OR 1.0, 95% CI 0.9-1.0, p=0.9) years, diagnosed with pulmonary tuberculous lesions (89% vs 84% OR 0.6, 95% CI 0.3-1.5, p<0.3) and HIV-positive based on the WHO clinical criteria (46% vs 22%, OR 3.0, 95% CI 1.4-6.0, p=0.003), and also diagnosed to have suffered from TB-related relapse (24% vs 18%, OR 1.4, 95% CI 0.6-3.0, p<0.4) and died of TB-related complications (13% vs 4%, OR 0.3, 95% CI 0.1-1.2, p<0.09). In addition, these HIV-positive subjects were less likely to have presented with positive sputum analyses for acid-fast bacilli (83% vs 88%, OR 0.7, 95% CI 0.1-8.0, p=0.7) or even hospitalized for TB-related complications (57% vs 62%, OR 0.8, 95% CI 0.4-1.6, p<0.6) than their corresponding HIV-negative subjects. Furthermore, unlike reports from other studies (1-2,5-7) that had also examined the radiographic features among HIV-positive and negative subjects with TB, those HIV-positive subjects in this study, compared to their HIV-negative subjects, presented with a slightly increased proportion of radiological findings that were relatively consistent with the diagnoses of TB (68% vs 67%, OR 1.0, 95% CI 0.2-7.0, p<0.97). Unlike the findings of WHO clinical criteria for the diagnosis of HIV/AIDS, which was statistically significant (p<0.003), other findings comparing HIV-positive and -negative subjects were relatively less significant (Table). Of those 14 complications attributed to anti-tuberculosis drugs, HIV-negative subjects (57%) accounted for a slightly greater proportion than HIV-positive subjects (43%). Polyneuropathy was the most commonly-reported complication among the HIV-negative subjects; it was observed among 10% of all HIV-negative subjects. Among the HIV-positive subjects, amenorrhoea was the most commonly-reported complication; it was observed among 3% of all HIV-positive subjects and 7% of the HIV-positive females.

Data for a significant proportion of the chest radiographs (83%) and sputum samples (87%) for both HIV-positive and -negative subjects were unavailable. Of the TB-positive subjects examined based on HIV serostatus, surprisingly, only 43 (17%) were referred for chest radiographs and 32 (12%) for sputum analyses to investigate for tuberculous infections. Of those 43 radiographs, 37 (86%) were requested for HIV-positive subjects compared to 6 (14%) for HIV-negative subjects. In addition, of the 32 sputum samples collected for acid-fast bacilli analyses, 26 (81%) were requested for HIV-positive subjects and 6 (19%) for HIV-negative subjects.

As part of this study, we also assessed the WHO clinical case definition in predicting infectivity of HIV (28-29). We report that the sensitivity of the WHO criteria in predicting TB-positive HIV-positive individuals was computed as 45% and the specificity of eliminated TB-positive HIV-negative subjects to be 78%. The positive predictive (PPV) and negative predictive values (NPV) were subsequently calculated to be 0.90 and 0.25 respectively [data not shown].

Lastly, the inter-observer agreement for the interpretations of the 43 radiographs by the two independent senior doctors was approximately 55%, resulting in a kappa (k) of 0.35.
DISCUSSION

The above findings clearly point to HIV infection as one of the major determinants attributed to increased morbidity and mortality observed among the TB-positive for the greatest burden of HIV infections and TB worldwide (16-17). In the primary study which is basically geared at better understanding of the heterosexual mode of HIV transmission, the association

### Table. Demographic and medical characteristics among 255 tuberculosis (TB)-positive subjects categorized by HIV serostatus*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>TB-positive</th>
<th>HIV-positive subject</th>
<th>HIV-negative subject</th>
<th>Odds ratio†</th>
<th>95% confidence interval†</th>
<th>p value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Female</td>
<td>90</td>
<td>44</td>
<td>19</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>116</td>
<td>56</td>
<td>30</td>
<td>61</td>
<td>1.225</td>
<td>0.647-2.318</td>
</tr>
<tr>
<td>Age (years)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt; 25</td>
<td>41</td>
<td>20</td>
<td>8</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-40</td>
<td>123</td>
<td>61</td>
<td>33</td>
<td>67</td>
<td>1.002</td>
<td>0.967-1.039</td>
</tr>
<tr>
<td>&gt;40</td>
<td>39</td>
<td>19</td>
<td>8</td>
<td>16</td>
<td>1.002</td>
<td>0.967-1.039</td>
</tr>
<tr>
<td>Site of tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pulmonary</td>
<td>184</td>
<td>89</td>
<td>41</td>
<td>84</td>
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<tr>
<td>Extrapulmonary</td>
<td>22</td>
<td>11</td>
<td>8</td>
<td>16</td>
<td>0.613</td>
<td>0.256-1.466</td>
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<tr>
<td>Sputum analyses*,‡</td>
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<tr>
<td>Negative</td>
<td>23</td>
<td>88</td>
<td>5</td>
<td>83</td>
<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>3</td>
<td>12</td>
<td>1</td>
<td>17</td>
<td>0.652</td>
<td>0.054-7.836</td>
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<td>Chest radiographs*,¶</td>
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<tr>
<td>Not suggestive</td>
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<td>32</td>
<td>2</td>
<td>33</td>
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<td></td>
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<tr>
<td>Suggestive</td>
<td>25</td>
<td>68</td>
<td>4</td>
<td>67</td>
<td>1.042</td>
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<td>Hospitalization</td>
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<tr>
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<td>79</td>
<td>38</td>
<td>21</td>
<td>43</td>
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<tr>
<td>No</td>
<td>127</td>
<td>62</td>
<td>28</td>
<td>57</td>
<td>0.829</td>
<td>0.441-1.561</td>
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<td>Relapse</td>
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<td></td>
<td></td>
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<td>24</td>
<td>9</td>
<td>18</td>
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<td></td>
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<td>76</td>
<td>40</td>
<td>82</td>
<td>1.425</td>
<td>0.647-3.135</td>
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<td>WHO criteria/AIDS§</td>
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<tr>
<td>Negative</td>
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<td>54</td>
<td>38</td>
<td>78</td>
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<tr>
<td>Positive</td>
<td>94</td>
<td>46</td>
<td>11</td>
<td>22</td>
<td>2.899</td>
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<td></td>
<td></td>
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<tr>
<td>Dead</td>
<td>26</td>
<td>13</td>
<td>2</td>
<td>4</td>
<td>0.295</td>
<td>0.073-1.191</td>
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<tr>
<td>Alive</td>
<td>180</td>
<td>87</td>
<td>47</td>
<td>96</td>
<td></td>
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</table>

*Missing HIV serostatus data for three subjects were omitted from calculations, resulting in 255 instead of 258 subjects being classified by HIV serostatus. In addition, other cells for the ages in years, sputum analyses, and chest radiograph had missing and/or unavailable data. Therefore, the calculations were based on the combined total (n) per medical/demographic characteristic per cell to make relative comparison between HIV-positive and -negative subjects. As such, the denominator used for calculation of each of the proportions is the total number of presumed tuberculosis cases per characteristic per cell

†p values less than 0.05 were considered statistically significant. A reference level of 1 was used for calculating odds ratios, 95% confidence interval

‡The sputum microscopy for acid-fast bacilli was based on the Ziehl-Neelsen technique (8)

¶Chest radiographs were assessed based on standard radiological features for TB (4,22)

§WHO provisional clinical case definition for diagnosis of HIV/AIDS (28-29)

individuals enrolled in this study on the urban heterosexual discordant couples in Lusaka, Zambia. Moreover, the above findings are also alarming considering the premise that sub-Saharan Africa accounts between HIV infection and TB was clearly established, especially the significant impact of HIV on its prevalence, diagnosis and treatment, decreased frequency of hospitalizations and complications, and
increased frequency of relapses and mortality among those individuals with TB (Table).

Tuberculosis is a major public-health concern that discriminately affects the socially-marginalized populations at disproportional rates. The WHO estimates that there will be one billion new infections, with morbidity escalating to 200 million and mortality of 70 million between 1998 and 2020 (12). Most importantly, there is no referenced information on the prevalence of tuberculosis in Zambia; therefore, this study provides a baseline prevalence estimate that can be used by planners, policy-makers, and researchers to formulate local health policies until a more rigorous study could be conducted to obtain a more generalizable finding.

Of significant concern is the low proportion of individuals in this study, who were referred for clinical investigation despite the limitations associated with diagnosis of TB in resource-poor settings, like Zambia. There are several possible explanations for such low referrals for both chest radiographs and sputum analyses, especially when these two ancillary investigations are considered critical, in addition to thorough history and physical examinations for the diagnosis of TB. Although all reasons that followed do not consistently apply to the project site, some of those barriers include: (i) unavailability of functioning radiological machines and supplies, (ii) unavailability of reagents and laboratory devices for sputum analyses, (iii) cost to perform those investigations, (iv) inadequate or non-standardized record-keeping system, (v) unavailability of computers and constant electrical supplies, and lack of trained data-entry staff to develop a paperless record-keeping system, (vi) lack of any unified referral and/or diagnostic criteria for healthcare workers, (vii) over-burdened healthcare delivery system, and (viii) lack of sufficient trained medical doctors to institute effective medical and/or clinical decisions. Furthermore, the low-moderate agreement observed between the two senior doctors from their assessments of the radiographs for features consistent with TB, based on the kappa score, also creates another major concern for the healthcare delivery system.

Complications resulting from anti-tuberculosis treatment among individuals with HIV-associated tuberculosis have been previously reported (4,10,14,16,20,31-32), but not among heterosexual discordant couples. Unlike other reports that have described the complications resulting from anti-tuberculosis therapy as primarily those of cutaneous reactions to thiacetazone among individuals with HIV-associated tuberculosis (4,10,14,16,20), the occurrence of amenorrhoea for less than three months following the commencement of anti-tuberculosis treatment is uncommon. Although clinical investigations were not instituted to ascertain the cause and/or medications associated with the complications, those findings could have been a casual relationship or possibly attributed to HIV infections since these were documented only among HIV-positive women. Clearly, more research is warranted to substantiate our findings.

Due to the unavailability of resources and infrastructure for the diagnoses of HIV in resource-poor settings, the WHO developed a clinical case definition to predict the infectivity of HIV (28). This diagnostic model was based on a combination of major and minor medical and/or clinical diagnostic criteria, such as weight loss, prolonged diarrhoea, persistent fever of unknown origin, and persistent cough, among other indicators (28-29). Another important finding of this study was the relatively increased likelihood that those criteria could positively predict HIV serostatus among TB-positive subjects. With advances in rapid serology of HIV, we recommend that well-defined country-specific guidelines be developed for diagnosis of HIV-associated tuberculosis and incorporated into national tuberculosis programmes, especially in the developing world with limited resources to help relieve the over-burdened healthcare delivery system.

Strikingly, some of the most distressing findings observed in the study were: (i) difficulties encountered with diagnosis of HIV-associated tuberculosis; (ii) alarming impact of HIV on the health outcomes of individuals with tuberculosis; (iii) significant reduction in years of productive life from increased morbidity attributed to HIV-associated tuberculosis which also affects human resources, national development, and family stability, and (iv) consequences of HIV-associated tuberculosis on referral institutions, especially taking into account the added burden for competing hospital beds, human resources and training, and depleting resources. These findings re-echo WHO global emergency warning that the diagnosis of HIV remains a medical challenge in sub-Saharan Africa (12-13,31-32), and clearly, more research is required to develop a readily available, simple, and highly-sensitive diagnostic intervention model. If the WHO goal of detecting 70% and adequately treating 85% of TB cases by 2010 should be accomplished (12), significant paradigm shift in global health resources, policy, prioritization, and mobilization
is warranted, primarily targeting sub-Saharan Africa. Lastly, while we acknowledge limitations associated with self-reporting, standardization in data-collection procedures, and bias of clinicians due to the absence of unified diagnostic criteria for TB (1,13-14,31-32), it is apparent that further research is warranted to corroborate our findings.

ACKNOWLEDGMENTS

This research was supported by fund from the National Institutes of Health (NIH) grant no. T37-TW00077 provided to the Minority International Research Training Program, Department of International Health, University of Alabama at Birmingham School of Public Health.

We would like to acknowledge the staff of Project San Francisco in Lusaka, Zambia and the Minority International Research Training Program staff at the University of Alabama at Birmingham School of Public Health for their contributions in the successful implementation of this project. Lastly, we would like to also acknowledge Mr. Bernard Malanda for the assistance with data analyses and Dr. Richard Crosby of Emory University School of Public Health in Atlanta, GA, for editorial review.

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