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Gender and HIV-associated pulmonary tuberculosis: presentation and outcome at one year after beginning antituberculosis treatment in Uganda

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Abstract

Background: Tuberculosis is responsible for more female deaths around the earth than any other infectious disease. Reports have suggested that responses to tuberculosis may differ between men and women. We investigated gender related differences in the presentation and one year outcomes of HIV-infected adults with initial episodes of pulmonary tuberculosis in Uganda.

Methods: We enrolled and followed up a cohort of 105 male and 109 female HIV-infected adults on treatment for initial episodes of culture-confirmed pulmonary tuberculosis between March 1993 and March 1995. A favorable outcome was defined as being cured and alive at one year while an unfavorable outcome was not being cured or dead. Subjects were followed-up by serial medical examinations, complete blood counts, serum β_2 microglobulin, CD4+ cell counts, sputum examinations, and chest x-rays.

Results: Male patients were older, had higher body mass indices, and lower serum β_2 microglobulin levels than female patients at presentation. At one year, there was no difference between male and female patients in the likelihood of experiencing a favorable outcome (RR 1.02, 95% CI 0.89–1.17). This effect persisted after controlling for symptoms, serum β_2 microglobulin, CD4+ cell count, and severity of disease on chest x-ray (OR 1.07, 95% CI 0.54–2.13) with a repeated measures model.

Conclusions: While differences existed between males and females with HIV-associated pulmonary tuberculosis at presentation, the outcomes at one year after the initiation of tuberculosis treatment were similar in Uganda. Women in areas with a high HIV and tuberculosis prevalence should be encouraged to present for screening at the first sign of tuberculosis symptoms.

Background

Tuberculosis is estimated to cause at least three million deaths per year worldwide [1] and also accounts for more than one-quarter of all preventable adult deaths in developing countries [2]. Infection with the human immunodeficiency virus (HIV) is thought to be the single most important factor that has contributed to the increased incidence of tuberculosis globally in the last decade [2]. Tuberculosis is now the leading cause of death among HIV-infected individuals worldwide and accounts for at least 40% of deaths among HIV-infected persons in Africa [3]. Furthermore, tuberculosis kills more women than any other infectious disease, including malaria and AIDS [4].

Reports have suggested that responses to tuberculosis differ between men and women, and that barriers to early detection and treatment of tuberculosis may be greater for women than for men [5]. A 10-year study performed among Ethiopian Jews who immigrated to Israel found that women had an incidence rate of tuberculosis that was twice that of men (120 versus 69 cases per 100,000 population per year) [6]. In addition, studies have suggested that progression from tuberculosis infection to disease may be faster in women of reproductive age than men of the same age [7,8]. Nonetheless, there is an estimated 2:1 male to female ratio in the number of tuberculosis cases notified to public health authorities [9], indicating that any increase in the risk of development of tuberculosis that reproductive stress may confer upon women is transient. Despite this disparity in case notifications, mortality from tuberculosis is similar among young males and females in Africa [10].

The literature lacks information on the relationship between gender, tuberculosis, HIV-infection, and the outcome of tuberculosis in Africa. Studies that have examined gender relationships in tuberculosis patients found a similar proportion of HIV infection among males and females in Tanzania [11], Zambia [12] and Kenya [13]. Among younger age groups, female tuberculosis patients were more likely to be HIV-infected than males whereas the opposite was found in older age groups.

In 1992, almost 1.5 million (8.8%) of the 17 million people in Uganda were estimated to have been infected with HIV. Of these, 50% were estimated to have tuberculosis co-infection [14]. The total number of notifications of tuberculosis cases of all forms has been steadily rising in Uganda, from 14,740 in 1990 to 27,196 in 1996 (an increase of over 90%), even with an estimated case detection rate of about 44% [15].

This report describes an investigation of the relationship between gender and the baseline presentation and one-year outcome in a cohort of HIV-infected pulmonary tuberculosis patients in on tuberculosis treatment in Uganda.

Methods

Study population

Between March 1993 and March 1995, 18 to 50 year old HIV-infected patients with initial episodes of sputum acid-fast bacilli (AFB) smear-positive, culture-confirmed pulmonary tuberculosis were enrolled at the National Tuberculosis Treatment Center, Kampala, Uganda in a prospective cohort study. All patients received anti-tuberculosis treatment consisting of two months of daily self-administered isoniazid (INH), rifampicin, ethambutol, and pyrazinamide, followed by six months of daily INH and rifampicin, which was the recommended first line treatment by the World Health Organization (WHO).

Other inclusion criteria included residence within 20 kilometers of the Tuberculosis Treatment Center, ambulatory performance status (assessed by a Karnofsky performance score of greater than 50%) [16], and ability to provide informed consent. Exclusion criteria included previous tuberculosis or tuberculosis treatment, serious co-morbidity such as diabetes mellitus or hypertension, steroid or antiretroviral use (since there was no consistent policy in Uganda on the use of antiretroviral treatment between 1992 and 1995), pregnancy, and WHO clinical stage IV AIDS [17].

At baseline and monthly follow-up visits, patients had a full medical history and physical examination, a complete blood count (Coulter Electronics, Hialeah, Florida, USA), sputum AFB microscopy and culture, chest radiography, and serum β_2-microglobulin measurement (β_2-microglobulin enzyme immunoassay (EIA); Coulter, Miami, Florida, USA). The upper limit of normal for serum β_2 microglobulin for healthy HIV-seronegative Ugandan adults is 3.5 mg/L [18]. HIV-infection was determined by HIV-1 EIA (Recombigen HIV-1 env + gag EIA; Cambridge Bioscience, Worcester, Massachusetts, USA). Consistency of the HIV-EIA results was maintained by confirmatory testing according to a protocol that was in use at the study center – one of 10 HIV-1 EIA positive and one of 25 HIV-1 negative sera underwent confirmatory testing by HIV-1 Western immunoblotting (BioRad Novapath, Hercules, California, USA). All study subjects received pre- and post-HIV test counseling from trained counselors and received the standard management for HIV-1 infection available in Uganda at the time of the study, which included treatment of oral thrush, herpes simplex, herpes zoster, and recurrent bacterial infections. Antiretroviral therapy was not the standard of practice in Uganda during the study and was not given to the study subjects.

Table 1: Baseline characteristics of 214 HIV-1-infected adults with pulmonary tuberculosis, Uganda, 1993–1995

Characteristic Categorical variables:	Male (N = 105) n (%)	Female (N = 109) n (%)	P value
Demographic			
Educated	100(95.2)	102(93.6)	0.60
Married	85(80.1)	87(79.8)	0.83
Past Medical History			
Fever	62(59.1)	74(67.9)	0.18
Cough	104(99.1)	106(97.3)	0.33
Sweats	72(68.6)	67(61.5)	0.28
Hemoptysis	10(9.5)	14(12.8)	0.44
Diarrhea	15(14.3)	11(10.1)	0.35
Herpes zoster	4(3.8)	5(4.6)	0.78
Genital ulcers	21(20.0)	22(20.1)	0.97
Thrush	8(7.6)	9(8.3)	0.86
BCG scar	57(54.3)	61(56.0)	0.80
Chest radiography			
Cavitary disease	69(65.7)	57(53.3)	0.05
Fibrosis	20(19.0)	20(18.3)	0.90
Upper lung disease	85(80.9)	88(80.7)	0.97
Continuous variables:	**Mean (SD)**	**Mean (SD)**	
Age (years)	30.2(5.9)	28.2(6.5)	0.02
Weight (Kg)	53.8(6.6)	48.9(8.0)	<0.005
Body mass index (Kg/m^2)	18.8(2.1)	19.9(3.1)	<0.005
Tuberculin skin test result (mm)	14.3(6.6)	15.1(6.9)	0.44
Serum β_2 microglobulin (mg/L)	6.0(2.3)	6.8(3.5)	0.04
Absolute CD4 cell count (cells/μl)	404(309)	360(325)	0.32
Hemoglobin (g/dl)	10.9(2.5)	9.8(2.0)	0.001
WBC (cells × 1000/ μl)	7.7(2.9)	7.3(2.8)	0.30
Duration of symptoms (months)			
Fever	2.8(3.4)	2.6(2.3)	0.71
Sweats	2.3(2.6)	2.9(2.5)	0.17
Diarrhea	1.5(1.8)	1.2(1.4)	0.69
Signs			
Temperature (° Celsius)	37.0(1.0)	37.0(2.2)	0.55
Karnofsky score (%)	82.5(6.3)	82(6.8)	0.61
Extent of disease on x-ray	2.5(0.6)	2.4(0.7)	0.16

1 = Minimal 2 = Moderate 3 = Advanced

Peripheral blood CD4+ lymphocyte counts were measured by flow cytometry (Becton-Dickinson, Santa Rosa, CA) at baseline and one, two, six, nine, and 12 months after the onset of anti-TB chemotherapy. Tuberculin skin tests were performed at baseline and one year follow-up by the Mantoux method using purified protein derivative (5 tuberculin units of Tubersol PPD, Connaught, Swiftwater, Pennsylvania, USA) [19]. Home health-visitors contacted patients who defaulted on clinic appointments. The study protocol was reviewed and approved by the Ugandan National AIDS Research Subcommittee and the institutional review boards of Case Western Reserve University and University Hospitals of Cleveland. All patients gave informed consent for study participation.

Statistical analyses

We investigated the influence of gender on the likelihood that a study patient achieved a favorable outcome (i.e., alive and cured of tuberculosis) or an unfavorable outcome (i.e., dead or not cured of tuberculosis) after one-year from the initiation of anti-tuberculosis treatment. Vital status was determined through interviews of family members. Study subjects who were acid-fast bacilli sputum smear and culture negative at the one-year follow-up sputum examination were considered cured. Only subjects whose status could be assigned into either of the two outcome groups were included in the analysis. We evaluated the bivariate relationships between gender and outcome with selected baseline covariates, and constructed a time-series repeated measures regression model [20,21] to

Table 2: Baseline characteristics of study subjects by one-year outcome status among HIV-1-infected pulmonary tuberculosis patients, Uganda, 1993–1995

Characteristic Categorical variables:	Favorable Outcome (Alive and cured at 1-year) (N = 169) n (%)	Unfavorable Outcome (Dead or not cured at 1-year) (N = 45) n (%)	p value
Demographic			
Educated	157 (92.9)	45(100)	0.02
Married	135(79.9)	37(82.2)	0.72
Past Medical History			
Fever	102(60.4)	34(75.6)	0.06
Cough	165(97.6)	45(100)	0.30
Sweats	109(64.5)	30(66.7)	0.79
Hemoptysis	20(11.8)	4(8.9)	0.58
Diarrhea	17(10.1)	9(20.0)	0.07
Herpes zoster	6(3.6)	3(6.7)	0.36
Genital ulcers	32(18.9)	11(24.4)	0.41
Thrush	5(3.0)	12(26.7)	<0.005
BCG scar	93(55.0)	25(55.6)	0.95
Chest radiography			
Cavitary disease	104(61.5)	22(48.9)	0.12
Fibrosis	37(21.9)	3(6.7)	0.02
Upper lung disease	140(82.8)	33(73.3)	0.15
Continuous variables:	**Means (SD)**	**Means (SD)**	
Age (years)	29.1(6.2)	29.5(6.4)	0.69
Weight (Kg)	51.9(7.5)	49.0(8.1)	<0.005
Body mass index (Kg/m^2)	19.5(2.7)	18.4(2.6)	<0.005
Tuberculin skin test result (mm)	15.7(6.2)	10.8(7.2)	<0.005
β_2 microglobulin (g)	6.2(2.5)	6.9(4.3)	<0.005
Absolute CD4 cell count (cells/μl)	428(313)	207(273)	<0.005
Hemoglobin (g/dl)	10.6(2.2)	9.6(2.5)	0.01
WBC (cells × 1000/ μl)	7.6(2.6)	7.1(3.4)	0.41
Duration of symptoms (months)			
Fever	2.5(2.5)	3.1(3.7)	0.39
Sweats	2.8(2.7)	2.0(1.9)	0.09
Diarrhea	1.3(1.7)	1.4(1.6)	0.89
Signs			
Temperature (° Celsius)	37.0(1.9)	37.0(1.0)	0.95
Karnofsky score (%)	83.1(6.1)	79.1(7.3)	<0.005
Extent of disease on x-ray	2.5(0.7)	2.3 (0.7)	0.15

1 = Minimal 2 = Moderate 3 = Advanced

describe the influence of gender on the outcome using data at baseline and two, six, nine and 12 months. We chose the time-series model because it accounts for the variations of covariates within the study patients with time. A proportional-hazards regression model was used to assess the influence of gender on one-year survival. All analyses were performed using the SAS/STAT® (version 6.12, SAS Institute, Cary, North Carolina, USA) module.

Results

Of 251 HIV-infected patients with pulmonary tuberculosis who were enrolled into the cohort study, 214 (86%) whose outcome status was known as either favorable (i.e., alive and cured of tuberculosis) or unfavorable (i.e., dead or not cured of tuberculosis) after one-year of initiation of anti-tuberculosis treatment formed the sample for this analysis. The majority of patients whose status could not be determined had withdrawn from the study before completion of treatment.

Of the 214 patients, 105 (49%) were male and 109 (52%) were female (table 1). At baseline, male patients were significantly older and had higher body mass indices (BMI) than female patients. Both male and female patients had

similar educational levels and marital status. There was no statistically significant difference between males and females in the frequency and previous duration of symptoms of tuberculosis (cough, fevers, hemoptysis and sweats) and other HIV-infection-associated conditions (herpes zoster, diarrhea, genital ulcers and thrush), and Karnofsky performance scores at baseline. However, female patients had significantly higher mean serum β_2-microglobulin levels, while male patients had significantly higher hemoglobin levels. There was no difference in baseline CD4+ cell counts and PPD skin test reactivity between males and females.

At one-year from the time of initiation of anti-tuberculosis treatment, 169 (79%) of the 214 study patients had experienced a favorable outcome (table 2). In a comparison of baseline characteristics, patients who developed a favorable outcome were similar in age to those with an unfavorable outcome but they had higher BMI and had more years of education. Both groups had similar tuberculosis and HIV-infection-associated symptoms though the subjects with an unfavorable outcome were more likely to have presented with a past history of fever, diarrhea, and thrush. In addition, patients with a favorable outcome had larger PPD skin test reactions, higher absolute CD4+ cell counts, lower serum β_2 microglobulin levels, and were more likely to have fibrotic changes on their initial chest x-ray, than subjects with an unfavorable outcome. Furthermore, patients who experienced a favorable outcome had significantly higher baseline Karnofsky performance status than those with an unfavorable outcome.

In an unadjusted comparison between gender and outcome, 87 (80%) of the 109 female patients compared to 82 (78%) of the 105 male patients had experienced a favorable outcome at one-year (relative risk 1.0, 95% CI 0.9–1.2). From the repeated measures model, female subjects were more likely to have a favorable outcome at one-year although the effect was not statistically significant (OR 1.1, 95% CI 0.5–2.1), after controlling for CD4+ cell count, serum β_2 microglobulin, hemoglobin, BMI, symptoms and radiology (table 3). Additionally increasing CD4+ cell count (OR 1.002, $p < 0.005$), increasing hemoglobin (OR 1.1, $p = 0.07$), increasing BMI (OR 1.1, $p = 0.06$) and decreasing serum β_2 microglobulin (OR 0.97, $p = 0.07$) were associated with a favorable outcome.

Among the 45 subjects with an unfavorable outcome 1-year after the beginning of anti-TB treatment, 38 had died. Of the 38 dead patients, 18 (47%) were female and 20 (53%) were male. The majority of the patients died with the first two months of TB treatment and we did not conduct autopsies, additionally the majority of the patients in the study were sputum culture negative at 2 months of treatment. Because of this difference we created a proportional-hazards model to investigate the influence of gender on survival, controlling for baseline presentation of fever, diarrhea, serum β_2 microglobulin, CD4+ cell count, hemoglobin, BMI, cavitary disease, and extent of disease on chest x-ray. Female patients were less likely to have died than male patients (relative hazard [RH] for death 0.60 [95%CI 0.30–1.21]) but this protective effect was not statistically significant. Higher baseline CD4+ cell count (RH 0.995, 95%CI 0.992–0.997), hemoglobin (RH 0.81, 95%CI 0.68–0.96), and lesser extent of disease on chest x-ray (RH 0.52, 95% CI 0.28–0.98) were each significantly associated with better survival. Baseline serum β_2 microglobulin levels had no effect on survival (RH 1.03, 95%CI 0.93–1.13).

Table 3: Repeated measures analysis of the relationship between gender and outcome

Variable	Odds Ratio	95% CI	p value
Fever	0.99	0.80, 1.23	0.95
Cough	0.98	0.81, 1.18	0.83
Diarrhea	0.82	0.54, 1.25	0.35
β_2 microglobulin	0.97	0.93, 1.003	0.07
CD4+ cell count	1.002	1.001, 1.003	0.002
Hemoglobin	1.06	0.99, 1.14	0.07
Body mass index	1.12	0.99, 1.27	0.06
Cavitary disease	1.12	0.80, 1.56	0.52
Extent of disease on x-ray	0.95	0.82, 1.1	0.48
Gender (Female)	1.07	0.54, 2.13	0.85
Male	1.00		

Discussion

We identified differences in the presentation of HIV-associated tuberculosis between men and women in Uganda; however, there were no differences in outcomes or survival at one year. HIV-infected women with pulmonary tuberculosis were younger, had lower body mass indices, and were more anemic than men at the time of presentation. This is consistent with observations in other settings where tuberculosis has been shown to occur more among younger females than males, and in persons of lower body mass indices [22]. However, in our study cohort, female patients had higher serum β_2 microglobulin levels at the time of diagnosis with tuberculosis, suggesting a possibly higher HIV burden [23,24], than male patients despite comparable CD4 lymphocyte counts. In spite of their comparative disadvantage at presentation, female patients had a similar likelihood of a favorable one-year treatment outcome.

Studies have suggested that tuberculosis and HIV may have a particularly severe impact on young women in a low-income setting [25]. We did not find that HIV-infected women fared any worse from tuberculosis than men. Hudelson has suggested that delays in care seeking for tuberculosis among women may be compounded by stigma associated with HIV infection [25]. We found no gender difference in the duration of symptoms of tuberculosis and HIV prior to the diagnosis of tuberculosis in our study cohort.

Differences in compliance with anti-tuberculous chemotherapy have been postulated to exist between female and male tuberculosis patients [26]. Women have less access to funds for transport and personal health-care than men do in Africa. We were unable to evaluate compliance because all patients were encouraged to come back to the treatment center by home health-visitors and those who defaulted on their treatment were often brought to the clinic.

Biologically there may be differences in immune responses to tuberculosis between males and females. It has been suggested that the immune response in tuberculosis may be closely related to differences between females and males in type and concentration of non-sex steroid and sex steroid hormones secreted [27], the direction of this response difference is, however, unclear. Cell mediated immune responses are depressed by protein-calorie malnutrition [28], and this could account for differences in the response to tuberculosis in males and females since females had significantly lower body mass indices. However, females would have experienced more unfavorable outcomes than males, which is not what we observed.

This study is subject to at least possible three limitations: first, the relatively small sample size, could have contributed to our inability to detect clear gender differences in this study. To detect the observed crude relative risk of 1.02 given the frequency of favorable outcomes at one-year in males of 78% and in females of 80%, with 95% confidence and 80% power, the study would have needed to enroll about 9000 males and 9300 females. However, the modest gender differences in the presentation and the similarity in the one-year outcome that this study suggests could provide impetus for larger and longer studies in this area, or studies with a different design e.g., case-control studies. Using the repeated measures model methodology [20,21] allowed us to use more data points, since each covariate was updated at the different time points, and it gave us more power and a more robust estimation of the effect of gender on outcome than using baseline covariates would have done. The second possible limitation could be a differential follow-up rate between male and female patients, leading to the apparent trend towards better one-year outcomes in the female patients. Nonetheless, we do not believe that there was a systematic difference in the follow-up rate by gender, and as indicated, home health visitors followed up all patients similarly. The third potential limitation is that serum β_2 microglobulin levels have not been shown to be associated with survival in HIV-infected patients on antiretroviral treatment, although high levels generally imply a higher burden of HIV infection. This restricts generalization of our results in terms of survival.

Conclusions

We conclude that female HIV-infected tuberculosis patients have a similar one-year outcome to males in Uganda, even though they have lower body mass indices, lower hemoglobin levels, and higher β_2 microglobulin levels at presentation, which may indicate more advanced HIV disease than the males. Because tuberculosis is the number one infectious disease killer of women, it is imperative that public health workers in areas of high HIV and tuberculosis prevalence should encourage women to present for screening as soon as they experience the first signs of tuberculosis.

Competing interests

We certify that we have participated sufficiently in the conception and design of this work, as well as its execution and the analyses of the data. Further we have collaboratively written the manuscript and take public responsibility for it. We have reviewed the final version of the submitted manuscript and approve it for publication. Neither this manuscript nor one with substantially similar content has been published or is being published elsewhere.

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter or materials discussed in the manuscript. Dr. Nsubuga will serve as the corresponding author.

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List of abbreviations

AIDS: Acquired Immune Deficiency Syndrome

BMI: Body Mass Index

HIV: Human immuno-deficiency virus

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