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Elevated HIV seroprevalence and risk behavior among Ugandan TB suspects: implications for HIV testing and prevention

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SUMMARY

OBJECTIVES—Voluntary counseling and testing (VCT) for the human immunodeficiency virus (HIV) is recommended for persons treated for tuberculosis (TB). Opportunities to diagnose HIV may be missed by limiting HIV testing to only persons diagnosed with TB. Among TB suspects in Uganda, we determined HIV prevalence, risk behaviors, and willingness to refer family for VCT.

METHODS—Consenting adult patients presenting for evaluation at a referral TB clinic received same-day VCT. TB diagnosis data were abstracted from clinical records.

RESULTS—Among 665 eligible patients, 565 (85%) consented to VCT. Among these, 238 (42%) were HIV-positive. Of the HIV-infected patients, 37% had received a non-TB diagnosis. HIV seroprevalence was higher in patients with a non-TB diagnosis (49%) than those diagnosed with TB (39%) ($P = 0.02$). Fewer than 6% of HIV-infected patients reported always using condoms with sexual partners. The majority of patients (86%) reported being 'very willing' to refer family members for VCT.

CONCLUSIONS—Over 35% of HIV-infected cases in our population would have been undetected if HIV testing was limited to cases with diagnosed TB. The high HIV seroprevalence in both TB and non-TB cases merits HIV testing for all patients evaluated at TB clinics. HIV-infected TB suspects reporting high-risk behavior are at risk for HIV transmission, and should receive risk-reduction counseling.

Keywords

HIV testing; tuberculosis; Africa; VCT; prevention

IN SUB-SAHARAN AFRICAN COUNTRIES with advanced human immunodeficiency virus (HIV) epidemics, it is estimated that the majority of tuberculosis (TB) patients are also infected with HIV.[1–3] Because of this, HIV voluntary counseling and testing (VCT) is recommended for persons treated for TB.[4,5] Integrating HIV VCT into TB treatment services may be one of the most effective ways to identify patients with undiagnosed HIV who may be candidates for

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life-saving antiretroviral therapy (ART).6,7 However, TB clinics serve as a referral point for persons with both TB and a broad range of other pulmonary infections. TB suspects who receive an alternative diagnosis frequently report constitutional symptoms, including night sweats, fever, and weight loss, and may also be at increased risk for HIV infection.8 Significant opportunities to diagnose HIV may be missed by limiting HIV testing to only those persons diagnosed with TB.

We implemented HIV VCT at an urban TB referral clinic in Uganda, where the annual TB incidence is estimated to be 920 cases per 100 000 population.[9] Currently, HIV testing is not routinely offered at TB clinics in Uganda. Our goals were to determine the seroprevalence of HIV among patients presenting for evaluation of TB symptoms to compare HIV prevalence between patients diagnosed with TB and those given an alternative diagnosis. We also examined HIV risk behaviors and evaluated the willingness of TB suspects to refer household members for HIV testing.

METHODS

Setting and patient recruitment

The study was carried out in the National Tuberculosis and Leprosy Program (NTLP) referral TB clinic at Mulago Hospital in Kampala, Uganda. Patients may present to the clinic for evaluation, or are referred to the clinic by health care providers in Kampala and several neighboring districts. Approximately 100 new patients are seen at the TB clinic every week.

During our study period of October 2004 to October 2005, every third out-patient aged ≥18 years and being newly evaluated for TB at the NTLP clinic was invited to participate in the study. Trained study counselors provided information about study procedures and HIV pre-test counseling, and offered same-day rapid HIV VCT to patients who accepted the invitation.

HIV counseling and testing procedures

HIV VCT was performed according to the guidelines of the US Centers for Disease Control and Prevention.[10] Study counselors received special training on rapid testing counseling procedures and confidentiality requirements. Counselors also administered a standardized written questionnaire to gather basic demographic information and to assess HIV risk behaviors and testing practices, including willingness to refer family members for HIV VCT. Individualized post-test counseling services were provided for all patients. Patients who were diagnosed with HIV were referred to specialized HIV clinical care and support group services.

HIV testing was performed using whole blood finger-stick assays according to a parallel rapid testing algorithm. Whole blood was tested using two simultaneous rapid enzyme immunoassays (EIAs): Determine (Abbott Laboratories, Abbott Park, IL, USA) and Uni-Gold (Trinity Biotech, Wicklow, Ireland). Specimens that were concordantly positive or negative by the two rapid EIAs were considered positive or negative, respectively. Discordant results were evaluated using a third rapid EIA, Stat-Pak (Chembio, Medford, NY, USA). If the third rapid EIA was negative, the HIV test result was reported as negative. Likewise, if the third rapid EIA was positive, the HIV test result was reported as positive. The test characteristics of the three rapid EIA test kits used on whole blood have been validated previously in the field in Uganda and other sub-Saharan African countries.[11–13] Study counselors provided patients with HIV test results and post-test counseling within 30 minutes. The entire counseling and testing process was completed within 90 minutes.

TB diagnosis data

At the Mulago NTLP Clinic, TB is diagnosed on the basis of clinical, radiographic, or sputum acid-fast bacilli (AFB) smear results. Patients with positive AFB sputum smears are diagnosed with pulmonary TB. Patients for whom the sputum smear results are AFB-negative or not available are diagnosed with TB based on clinical and/or radiographic findings. AFB sputum cultures are not routinely performed for new TB suspects. Patients who are diagnosed with both pulmonary and extra-pulmonary TB are classified as having pulmonary TB in the TB register. Trained study staff abstracted information regarding diagnosis of TB, including AFB sputum smear results, TB disease classification, and initiation of TB therapy, from the Mulago NTLP TB register using a standardized form.

Ethics

All study subjects provided written informed consent for study participation and HIV testing. Ethics approval was obtained from the institutional review boards of the Uganda National Council on Science and Technology, the University of California San Francisco, and the Case Western Reserve University School of Medicine.

Statistical methods

Data were double-entered and stored in a Microsoft Access database (Microsoft Corporation, Redmond, WA) and analyzed using SAS version 9.0 (SAS Institute, Cary, NC). Categorical variables were compared using χ^2 or Fisher's exact tests, and matched observations were compared using McNemar's test. To determine independent predictors of HIV infection among TB suspects, a multivariable logistic regression model was constructed. Biologically plausible risk factors that were significant at a P value of ≤ 0.1 were included in the model. All reported P values were two-sided, and a P value of ≤ 0.05 was considered significant.

RESULTS

Patient characteristics

During the 12-month study period, 665 new patients attending the Mulago NTLP clinic for evaluation of TB symptoms met the eligibility criteria and were approached for enrollment in the study. Of these, 565 (85%) consented to study participation and HIV testing. The median age of the study participants was 30 years (range 18–81 years); 320 (57%) were male (Table 1). Fewer than half of the study patients reported receiving more than a primary level of education, and 40% said they were currently in a monogamous marriage. Among the 565 study patients, 35% reported previous testing for HIV and 36% reported concern that the symptoms prompting their visit to the Mulago TB clinic were actually due to HIV infection.

TB diagnosis status

Among the 554 TB suspects with available data, 378 (68%) were diagnosed with TB (Table 2). Of these, 323 (85%) received a diagnosis of pulmonary TB and 55 (15%) a diagnosis of extra-pulmonary TB. The majority of the pulmonary TB patients were AFB sputum smear-positive (63%), while the remainder was diagnosed on the basis of clinical and radiographic findings alone. TB disease classification did not vary by HIV serostatus ($P = 0.2$). Clinical symptoms among the 176 patients who received a non-TB diagnosis included cough (89%), weight loss (81%), night sweats (73%), fever (73%), difficulty breathing (63%), and diarrhea (14%), and did not differ significantly in comparison to patients who received a diagnosis of TB.

HIV seroprevalence

Among the 565 TB suspects tested, 238 (42%) were HIV-seropositive (Table 3). Of these, 87 (37%) had received a non-TB diagnosis. When stratified by TB diagnosis status, patients who received a non-TB diagnosis were significantly more likely to be HIV-seropositive than those who were diagnosed with TB (49% vs. 39%; odds ratio [OR] 1.6, 95% confidence interval [CI] 1.1–2.2, $P = 0.02$). Other characteristics associated with HIV infection on univariate analysis were female sex (OR 1.5, 95%CI 1.1–2.2, $P = 0.02$), age >25 years (OR 4.4, 95%CI 2.7–7.2, $P < 0.001$), and having received less than primary school education (OR 1.6, 95%CI 1.1–2.3, $P = 0.009$). When controlling for these and other demographic variables in a logistic regression model, female sex and age >25 years remained independent predictors of HIV infection. Receiving a non-TB diagnosis remained marginally associated with HIV infection ($P = 0.06$) in the multivariable model.

HIV risk behaviors

The majority of patients (59%) reported having at least one sexual partner in the 6 months before study enrollment. Among 238 HIV-infected TB suspects, 108 (45%) reported one sexual partner, and 33 (14%) reported two or more sexual partners in the previous 6 months (Table 4). Very few HIV-infected patients reported always using a condom with sexual partners: 5% did so with regular sexual partners and 4% with casual sexual partners.

Household referral for VCT

The vast majority of study patients (86%) stated they were ‘very willing’ to refer household members for HIV VCT (Table 5). Among those patients who reported having a spouse, 87% stated they were ‘very willing’ to refer their spouse for HIV VCT. Individual patient responses did not change significantly when they were requestioned after disclosure of HIV test results ($P = 0.1$). Willingness to refer family members for HIV testing did not differ by HIV serostatus (83% HIV-positive vs. 87% HIV-negative, $P = 0.3$). Patients were more willing to refer household members for clinic-based VCT in comparison to home-based VCT ($P = 0.008$).

DISCUSSION

In the present era of scaling up ART programs, key priorities in battling the African HIV epidemic are to identify persons who are HIV-infected and link them to care.[14,15] Our study demonstrates that HIV testing for all patients presenting for evaluation of TB symptoms in a high HIV seroprevalence setting is a highly effective and acceptable mode of detecting persons with undiagnosed HIV infection. Among all the TB suspects approached in our study, 85% accepted HIV testing, and over 40% of those tested were diagnosed with HIV. Notably, TB suspects who received an alternative, non-TB diagnosis in our study were at high risk for HIV infection; almost 50% were diagnosed with HIV.

Under current international guidelines, HIV testing is recommended for persons treated for TB.[4,5] Although there has been discussion of expanding HIV testing in TB clinic settings, testing of all TB suspects in resource-limited settings is currently not standard practice. As a result, over 35% of the persons diagnosed with HIV in our study may not have been offered HIV testing, and their HIV infection would likely have remained undiagnosed. Once linked to HIV care, co-infected patients who receive ART have a greatly reduced risk of AIDS events and mortality.[16,17] Even HIV-infected TB suspects who may not be eligible or do not yet have access to ART experience survival gains from cotrimoxazole prophylaxis[18,19] and benefit from counseling and care services.[20] The effective interventions available for all HIV-infected persons in even the most resource-constrained settings, coupled with the very high frequency of HIV among both TB and non-TB cases, merit the implementation of HIV testing for all patients evaluated at TB clinics in countries with a high HIV seroprevalence.

TB clinic-based VCT can also serve as a gateway to expand HIV testing to the households of TB suspects. Household members of TB clinic patients, especially spouses and young children, have a greatly elevated HIV seroprevalence in comparison to the general population.[21,22] The vast majority of patients in our study reported being 'very willing' to refer household members for HIV testing. While patients in our study reported a mild preference for clinic-based HIV testing of household members, home-based HIV testing has also been effectively implemented in Uganda and other resource-limited settings,[23,24] and may be useful in overcoming several logistical barriers faced by patients face in accessing HIV testing services.[25] Expansion of HIV VCT services to the household can also be coupled with screening for TB among family members in contact with TB suspects, who are at elevated risk for developing secondary TB.[22,23]

In addition to identifying persons with undiagnosed HIV infection, it is equally critical to identify those who are at increased risk of transmitting or acquiring HIV infection to target prevention efforts. While elevated HIV transmission risk and high-risk sexual behaviors are commonly associated with persons attending STD (sexually transmitted disease) clinics,[26] acutely ill individuals such as TB suspects may be perceived as less likely to engage in risk behaviors. However, the majority of HIV-infected patients in our study reported being sexually active in the 6 months before study enrollment, and fewer than 5% reported always using condoms with regular or casual sexual partners. Although 'be faithful' remains an important component of Uganda's 'ABC' HIV prevention strategy, the risks associated with not using a condom with regular partners of unknown or discordant HIV serostatus have been recognized, and are now also included in Uganda's HIV prevention messages.27 Furthermore, our findings are based on self-reported sexual behavior, and may thus be an underestimation of the true frequency of high-risk behavior among TB suspects.28 The implementation of VCT thus presents an important opportunity for risk-reduction counseling of these HIV-infected persons, who may have an elevated HIV viral load in the setting of active TB or another infection,[29,30] and as such are at particularly increased risk of transmitting HIV.[31] Numerous studies have also demonstrated that VCT can promote behavior change among HIV-infected individuals and result in reduced sexual risk behavior.[20,32,33]

Although we have been discussing our study results in the context of HIV VCT, our recommendations for expanded HIV testing in TB clinics are operationally closer to the concept of provider-initiated routine counseling and testing (RCT).[34] Under RCT, all individuals are informed that they will be tested for HIV in addition to their other diagnostic tests unless they specifically 'opt out'. TB clinic-based RCT can also help normalize HIV testing, which in turn may reduce the stigma surrounding HIV testing and lead to fewer individuals opting out. As our study results indicate, HIV RCT for all TB suspects would lead to the identification of a significant number of undiagnosed HIV infections and provide opportunities for linkage to care and treatment.

There were several limitations to our study. Diagnostic assessment for TB among patients in our study was restricted to clinical, radiographic, and AFB sputum smear studies. The lack of sputum AFB culture limits the sensitivity of TB evaluation; a proportion of patients who received a non-TB diagnosis may have undetected TB. However, the criteria used at the Mulago NTLP clinic to diagnose TB reflect the real-world diagnostic challenges faced by the majority of physicians evaluating TB suspects in resource-limited settings. Causes of illness among patients who were given a non-TB diagnosis may include a host of possibilities, including undiagnosed *Mycobacterium tuberculosis*, another opportunistic infection, or even advanced HIV disease itself. Implementing HIV testing for all TB suspects in high seroprevalence, resource-limited settings can prompt a more comprehensive work-up for TB,[35] as well as evaluation of other HIV-related causes of pulmonary infection among HIV-infected persons who initially receive a non-TB diagnosis. A recent Ugandan study of hospitalized HIV-infected

TB suspects with negative sputum AFB smears revealed that 24% had undiagnosed TB, while another 38% had *Pneumocystis jirovecii* pneumonia on bronchoscopy.[36] Knowledge of HIV serostatus can thus guide the diagnostic work-up of a TB suspect, allow for detection of additional TB cases with the use of additional diagnostic tests, and impact therapy choices.

Determining the optimal approaches to providing HIV testing in resource-limited settings is essential to effectively link HIV-infected persons to care and treatment services. Our findings support arguments for the implementation of routine HIV testing for all clinically symptomatic patients attending health care facilities in Africa.[37] In particular, our results provide evidence for the expansion of routine HIV testing services in high HIV seroprevalence areas to all patients presenting with TB symptoms, and not just those who are diagnosed with TB. While these efforts may require additional resources and personnel, such testing may be one of the most efficient ways to identify thousands of persons with undiagnosed HIV who may be candidates for ART. In these regions, TB clinics can serve as a highly effective entry point for testing TB suspects and their at-risk household members for HIV, initiating prevention efforts to reduce HIV transmission among serodiscordant partners, and linking eligible patients to life-saving antiretroviral therapy.

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Table 1

Patient characteristics of TB suspects evaluated at Mulago TB Clinic, Kampala, October 2004–October 2005 (n = 565)

Patient characteristics	*n* (%)
Demographics	
Age, years*	
18–25	157 (28)
26–35	217 (38)
36–45	95 (17)
≥46	91 (16)
Male sex	320 (57)
Marital status	
Never married	158 (28)
Monogamous marriage	226 (40)
Polygamous marriage	42 (7)
Divorced	95 (17)
Widowed	43 (8)
Monthly income†	
No income	199 (35)
1–50 000 Ugandan Shillings (28 USD)	178 (32)
>50 000 Ugandan Shillings	173 (31)
Formal education	
None	55 (10)
Primary school	269 (48)
Secondary school or higher	236 (42)
HIV testing practices and attitudes	
Previously tested for HIV	195 (35)
Worried that symptoms prompting TB clinic visit are actually due to HIV	202 (36)
Concerned about having HIV and TB co-infection	179 (32)

*Ages not reported for five subjects.

†Monthly income not reported for 15 subjects.

TB = tuberculosis; HIV = human immunodeficiency virus.

Table 2

TB diagnosis status among patients evaluated at Mulago TB Clinic, Kampala, October 2004–October 2005 (*n* = 554)

TB status	***n/N* (%)**
TB diagnosis	378/554 (68)
Pulmonary TB	323/378 (85)
Sputum AFB smear positive	202/323 (63)
Sputum AFB smear negative	50/323 (15)
Sputum smear not done	71/323 (22)
Extra-pulmonary TB*	55/378 (15)
Non-TB diagnosis	176/554 (32)

* Patients diagnosed with both pulmonary and extra-pulmonary TB are classified in the TB register as pulmonary TB.

TB = tuberculosis; AFB = acid-fast bacilli.

Table 3

HIV seroprevalence among TB suspects at Mulago TB Clinic, Kampala (n = 565)

Patient group	HIV seropositive *n/N* (%)	Univariate analysis OR (95%CI)	*P* value	Multivariate analysis AOR* (95%CI)	*P* value
All patients	238/565 (42)	—		—	
By TB diagnosis status					
Received TB diagnosis	147/378 (39)	Referent		Referent	
Received non-TB diagnosis	87/176 (49)	1.6 (1.1–2.1)	0.02	1.5 (1.0–2.1)	0.06
Sex					
Male	120/317 (38)	Referent		Referent	
Female	117/242 (48)	1.5 (1.1–2.2)	0.02	1.8 (1.3–2.6)	0.002
Age, years					
<25	23/126 (18)	Referent		Referent	
≥25	213/430 (50)	4.4 (2.7–7.2)	<0.001	4.7 (2.8–7.7)	<0.001
Education					
≥Secondary school	84/234 (36)	Referent			
≤Primary school	152/322 (47)	1.6 (1.1–2.3)	0.009	NS	
Monthly income					
0–50 000 Ugandan Shillings	165/377 (44)	Referent			
>50 000 Ugandan Shillings	68/169 (40)	1.2 (0.8–1.7)	0.5	NS	
6-month sexual partners					
≤1 partner	205/495 (41)	Referent			
≥2 partners	33/67 (49)	1.4 (0.8–2.3)	0.2	NS	

HIV = human immunodeficiency virus; TB = tuberculosis; AOR = adjusted odds ratio; CI = confidence interval; NS = non-significant.

Table 4

HIV risk behaviors among HIV-positive TB suspects at Mulago TB Clinic, Kampala (*n* = 238)

Characteristic	*n* (%)
Number of sexual partners in previous 6 months	
None	97 (41)
One	108 (45)
2–5	29 (12)
≥6	4 (2)
Always use condoms with regular sexual partner	11 (5)
Always use condoms with casual sexual partners	10 (4)

HIV = human immunodeficiency virus; TB = tuberculosis.

Table 5

Willingness to refer household members for HIV VCT among TB suspects at Mulago TB Clinic, Kampala

Characteristic	*n/N* (%)	*P* value
Very willing to refer household member for HIV VCT	429/502 (86)	
HIV-positive	179/215 (83)	} 0.3*
HIV-negative	247/284 (87)	
Very willing to refer household member for clinic-based VCT	364/498 (73)	} 0.008†
Very willing to refer household member for home-based VCT	328/492 (67)	

*Fisher's exact test.

†McNemar's test.

HIV = human immunodeficiency virus; VCT = voluntary counseling and testing; TB = tuberculosis.