International Journal of Infectious Diseases (2008) **12**, 51—56

http://intl.elsevierhealth.com/journals/ijid

Risk factors and algorithms to identify hepatitis C, hepatitis B, and HIV among Georgian tuberculosis patients

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Received 7 September 2006; received in revised form 3 April 2007; accepted 9 April 2007
Corresponding Editor: William Cameron, Ottawa, Canada

KEYWORDS
Hepatitis C;
HIV;
Hepatitis B;
Tuberculosis;
Hepatotoxicity;
Georgia;
Epidemiology

Summary
Objectives: To determine prevalence, risk factors, and simple identification algorithms for HIV, hepatitis B, and hepatitis C co-infection; factors that may predispose for anti-tuberculosis therapy-induced hepatotoxicity.
Methods: We recruited 300 individuals at in-patient tuberculosis hospitals in three cities in Georgia, administered a behavioral questionnaire, and tested for antibody to HIV, hepatitis C (HCV), hepatitis B core antigen (anti-HBc), and the hepatitis B surface antigen (HBsAg).
Results: Of the individuals tested, 0.7% were HIV positive, 4.3% were HBsAg positive, 8.7% were anti-HBc positive, and 12.0% were HCV positive. In multivariable analysis, a history of blood transfusion, injection drug use, and prison were significant independent risk factors for HCV, while a history of blood transfusion, injection drug use, younger age at sexual debut, and a high number of sex partners were significant risk factors for HBV. Three-questionnaire item algorithms predicted HCV serostatus 74.1% of the time and HBV serostatus 85.2% of the time.
Conclusions: Treatment of tuberculosis patients in resource-limited countries with concurrent epidemics of HCV, HBV, and HIV may be associated with significant hepatotoxicity. Serologic screening of tuberculosis patients for HBV, HCV, and HIV or using behavioral algorithms to identify patients in need of intensive monitoring during anti-tuberculosis therapy may reduce this risk.

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1201-9712/$32.00
doi:10.1016/j.ijid.2007.04.015

Introduction

Although roughly one third of the human population is chronically infected with *Mycobacterium tuberculosis*,[1] the distribution of infections is far from uniform. Sub-Saharan Africa, Asia, and Eastern Europe have the highest prevalence and incidence rates worldwide,[2] and are the areas where the World Health Organization (WHO) Directly Observed Therapy Short-Course (DOTS) program for tuberculosis control has been most vigorously implemented. Although highly effective,[3] several shortcomings have recently been identified in the DOTS program.[4] One of these identified shortcomings is the failure of first-line DOTS treatment regimens in difficult-to-treat populations, e.g., HIV co-infected patients, patients infected with multidrug-resistant *M. tuberculosis* strains, and other patients with special needs.

Patients with increased susceptibility to the hepatotoxic effects of first-line treatment regimens represent special populations and need to be identified prior to therapy initiation and monitored more carefully than the general population of *M. tuberculosis* infected patients. Unfortunately, although three of the first-line drugs, rifampin, pyrazinamide, and isoniazid, are known to be hepatotoxic,[5–9] the patient characteristics that confer greater risk of treatment-associated liver injury are poorly understood. Older age,[10,11] concurrent or chronic alcohol use,[12–15] hepatitis C,[16] hepatitis B,[17] and HIV[16] virus infections have been found to increase the risk of hepatotoxicity in some studies, but non-significant associations for all of these putative risk factors have also been reported.[5,14,15,18–23] Until definitive studies are conducted, caution suggests that patient populations should be screened for the above-mentioned characteristics and monitored carefully following initiation of therapy.

Many countries of the former Soviet Union have experienced major increases in tuberculosis incidence over the past fifteen years,[2,24] and are attempting to control epidemics of HIV, hepatitis B, and hepatitis C viruses with limited healthcare resources. Georgia is situated south of the Russian Federation in the Caucasus region between the Black and Caspian Seas (see Figure 1), and currently faces major concurrent epidemics of tuberculosis,[25–27] hepatitis B,[28,29] and hepatitis C.[28–31] WHO estimates suggest that tuberculosis incidence is 83 cases per 100 000 person-years, and 16% of new tuberculosis cases are multidrug-resistant in Georgia.[32] Research studies have also found multidrug-resistant *M. tuberculosis* strains to be common in Georgia,[27,33] and an evaluation of the Georgian DOTS program in the mid-1990s suggested that 25% of individuals who begin anti-tuberculosis therapy regimens will not complete them.[34] While this study did not evaluate the reasons for therapy interruption among the Georgian patients, a recent study from Russia has suggested that difficulty tolerating anti-tuberculosis therapy because of co-morbid illnesses such as HIV and viral hepatitis is common.[35]

Despite its potential effect on improving tuberculosis treatment completion rates (through careful monitoring and treatment adjustment when indicated), serologic screening for hepatitis B, hepatitis C, and HIV viruses is not routine practice among Georgian tuberculosis clinics because of limited resources and the scarcity of diagnostic capabilities within tuberculosis hospitals. In this study, we used behavioral and biomarker data collected between October 1997 and June 1998 in three Georgian in-patient tuberculosis hospitals to describe the prevalence and risk factors for three putative viral risk factors for anti-tuberculosis therapy-induced hepatotoxicity. We additionally assessed the ability of simple questionnaire algorithms to accurately predict infection with HCV and HBV to determine whether this screening mechanism could identify subsets of patients who are in need of intensive monitoring during anti-tuberculosis therapy.

Materials and methods

Study population

Between October 1997 and June 1998, we recruited individuals at in-patient tuberculosis hospitals as part of an HIV/AIDS surveillance project conducted by the Georgian AIDS and Clinical Immunology Research Center.[28] Recruited individuals were between the ages of 18 and 65 and were patients in hospitals in the Georgian cities of Tbilisi, Batumi, and Poti. Subjects were enrolled into the study if they gave their informed consent to answer a confidential questionnaire, be tested for HIV, HCV, and HBV, and receive the results of these tests along with appropriate counseling. The research protocol was reviewed and approved by institutional review boards at the AIDS and Clinical Immunology Research Center in Tbilisi, Georgia and the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA.

Behavioral questionnaire

Recruited individuals who agreed to participate in the study were interviewed confidentially by trained interviewers regarding their clinical and demographic characteristics, history of drug use, and sexual behaviors. After the interview data were collected they were transferred to a Microsoft Access database for archive and analysis.

Laboratory methods

Blood samples drawn from participating individuals were assayed for antibody to HIV-1 with the Abbott Recombinant

Figure 1 Republic of Georgia.

HIV-1 assay (Abbott Laboratories, Abbott Park, IL, USA). Blood samples reactive for HIV-1 were confirmed using a licensed Western blot assay (DuPont Co, Willmington, DE, USA). Antibody to HCV was assessed using the Ortho HCV Version 3.0 ELISA (Ortho Diagnostics Systems, Raritan, NJ, USA). Hepatitis B surface antigen (HBsAg) and core antibody (anti-HBcore) were assessed using Auszyme Monoclonal and Corzyme assays (Abbott Laboratories, Abbott Park, IL, USA). All laboratory testing was conducted at the AIDS and Clinical Immunology Research Center in Tbilisi, Georgia.

Statistical methods

We calculated descriptive statistics for laboratory results and questionnaire variables. We used bivariate and multivariable logistic regression models to evaluate the association of demographic, drug use history, and sexual history variables with HCV and HBV seropositivity. We defined individuals testing positive for either anti-HBcore or HBsAg to be HBV positive. We used bivariate analysis to evaluate city of residence and age-group associations, and multivariable analysis, with all evaluated variables in a single model, to evaluate all other associations. Too few individuals were infected with HIV to conduct a statistical assessment of HIV risk factors.

For our assessment of the ability of questionnaire combination algorithms to accurately predict viral infection status, we constructed two- and three-questionnaire item combinations and divided the number of individuals reporting yes to any of the questionnaire items in the combination by the number of individuals serologically diagnosed with HCV or HBV infection. This quotient then reflected the sensitivity of the questionnaire item combination compared to the gold standard of serology. All analyses were conducted using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Demographic, drug use history, and sexual history variables are listed in Table 1. Most patients were male and were recruited from hospitals in Tbilisi. Patients were most often in their thirties and most had completed secondary school. Histories of blood transfusion, prison, and injection drug use were relatively rare, although sexual activity in the past two years was not.

Two (0.7%) of the 300 surveyed individuals were HIV positive, 13 (4.3%) were HBsAg positive, 26 (8.7%) were anti-HBcore positive, and 27 (9.0%) were positive for either HBsAg or anti-HBcore. Thirty-six (12.0%) were HCV positive. One of the two HIV positive individuals was HCV co-infected, and six individuals were positive for both HCV and HBV. The two HIV positive individuals were both male, one had received a blood transfusion and the other had injected illicit drugs.

Risk factors for HCV and HBV seropositivity are listed in Table 2. In bivariate analysis, neither HCV nor HBV seroprevalence differed significantly by city of recruitment or gender. In multivariable adjusted analysis, having a university-level education was protective against the presence of HCV, but not against the presence of HBV. Both a history of blood transfusion and a history of injection drug use were highly significant risk factors for both HCV and HBV. Having been in prison was a significant risk factor for HCV, but not for HBV.

Table 1 Characteristics of the study population ($N = 300$)

Characteristic	Number	%
City of residence		
Tbilisi	245	81.7
Poti	32	10.7
Batumi	23	7.7
Gender		
Male	242	80.7
Female	58	19.3
Age		
18—27 years	95	31.7
28—37 years	126	42.0
≥38 years	79	26.3
Education		
Primary	38	12.7
Secondary	173	57.7
University	89	29.7
Blood transfusion		
No	287	95.7
Yes	13	4.3
Ever injection drug use		
No	277	92.3
Yes	23	7.7
Ever prison		
No	278	92.7
Yes	22	7.3
Ever male homosexual contact		
No	281	93.7
Yes	19	6.3
Age at first sexual contact		
≤18 years	85	28.3
19—21 years	120	40.0
≥22 years	95	31.7
Number of sex partners in last 2 years		
0—1 partners	113	37.7
2—3 partners	150	50.0
≥4 partners	37	12.3

Older age at first sexual contact was significantly protective against the presence of HBV, while having four or more sexual partners in the past two years was a significant risk factor for HBV.

Table 3 shows the sensitivity of two-questionnaire item combinations to predict HCV and HBV status as diagnosed by serology. As seen in the first part of Table 3 (HCV), three two-questionnaire item combinations predicted HCV status 61.1% of the time. Inclusion of a third questionnaire item to form the algorithm "Did you ever inject drugs?; Did you have your first sexual contact at ≤18 years of age?; Did you ever have a blood transfusion?" increased the ability to predict HCV serostatus to 72.2%.

As seen in the second part of Table 3 (HBV), one two-questionnaire item combination predicted HBV status 74.1% of the time. Inclusion of a third questionnaire item to form

Table 2 Risk factors for HCV and HBV seropositivity ($N = 300$)

Variable	HCV		HBV	
	OR*	95% CI	OR*	95% CI
City of residence				
Tbilisi	1.0		1.0	
Poti	0.71	0.21, 2.49	1.61	0.51, 5.04
Batumi	0.66	0.15, 2.94	1.69	0.46, 6.17
Gender				
Male	1.0		1.0	
Female	0.82	0.35, 1.90	0.82	0.32, 2.14
Age				
18–27 years	1.0		1.0	
28–37 years	1.11	0.49, 2.52	1.04	0.40, 2.70
≥38 years	0.98	0.39, 2.50	1.23	0.44, 3.43
Education				
Primary	1.0		1.0	
Secondary	0.46	0.13, 1.66	1.09	0.13, 9.20
University	0.04	0.00, 0.55	0.84	0.20, 3.66
Blood transfusion				
No	1.0		1.0	
Yes	12.37	2.52, 60.56	14.02	2.51, 78.29
Ever injection drug use				
No	1.0		1.0	
Yes	18.26	5.37, 62.12	12.72	3.57, 45.29
Ever prison				
No	1.0		1.0	
Yes	4.83	1.23, 18.97	1.28	0.29, 5.79
Ever male homosexual contact				
No	1.0		1.0	
Yes	0.62	0.11, 3.43	4.16	0.91, 18.96
Age at first sexual contact				
≤18 years	1.0		1.0	
19–21 years	1.39	0.49, 3.94	0.54	0.17, 1.72
≥22 years	0.54	0.13, 2.20	0.11	0.02, 0.65
Number of sex partners in last 2 years				
0–1 partners	1.0		1.0	
2–3 partners	0.45	0.14, 1.49	0.55	0.14, 2.12
≥4 partners	1.61	0.43, 6.00	4.45	1.19, 16.70

HCV, hepatitis C virus; HBV, hepatitis B virus; OR, odds ratio; CI, confidence interval.
* ORs are adjusted for: city, gender, age group, education, blood transfusion, injection drug use, prison, male homosexual contact, age at first sexual contact, and number of sex partner variables.

the algorithm "Did you ever inject drugs?; Did you have your first sexual contact at ≤18 years of age?; Have you had ≥4 sex partners in the past two years?" increased the ability to predict HBV status to 85.2%.

Discussion

Hepatotoxicity is a common side effect associated with the use of many therapeutic agents.[8,35] Drug-related hepatotoxicity

Table 3 Sensitivity (%) of two-item questionnaire combinations to detect serologically confirmed HCV and HBV infections

	Primary education	Blood transfusion	Injection drug use	Prison	≤18 years at first sex
HCV					
Blood transfusion	52.8				
Injection drug use	55.6	58.3			
Prison	44.4	41.7	52.8		
≤18 years at first sex	52.8	55.7	61.1	61.1	
≥4 sex partners	44.4	38.9	61.1	41.7	58.3
HBV					
Blood transfusion	33.3				
Injection drug use	55.6	48.2			
Prison	44.4	33.3	44.4		
≤18 years at first sex	63.0	63.0	74.1	63.0	
≥4 sex partners	55.6	55.6	63.0	59.3	70.4

HCV, hepatitis C virus; HBV, hepatitis B virus.

of antiretroviral therapy for HIV infection is more frequent among patients who are co-infected with hepatitis viruses.[36] Although some studies examining the role of viral hepatitis co-infection on adverse events following anti-tuberculosis therapy have produced conflicting results, countries of the former Soviet Union, which are facing serious epidemics of both tuberculosis and viral hepatitis, should exercise caution and carefully monitor their patients for drug-associated hepatotoxicity.

Our study found that HIV infection was rare but HBV and HCV infections were common among Georgian tuberculosis patients. High and increasing prevalence of HCV has been reported among both tuberculosis patients and blood donors in Georgia between 1998 and 2001,[25,29,30] but this study is the first to indicate that HBV is a significant problem among patients with tuberculosis in Georgia.

This study indicates that injection drug use and blood transfusions were major risk factors for both HCV and HBV, and that spread of HCV was additionally common among prisoners, even after adjusting for injection drug use. These results are consistent with those of Richards et al.[25] with regard to the spread of HCV in prisons but differ in finding that a history of blood transfusion and injection drug use were both associated with HCV infection. Routine screening of the Georgian blood supply for HCV was initiated in 1997,[28,29] so current blood transfusions may be less likely to transmit HCV than those conducted prior to this time. Our results also suggest that younger age of sexual initiation and multiple sex partners are significant risk factors for the acquisition of HBV.

Our evaluations of simple two- and three-question behavioral algorithms suggest that HBV can be predicted in many patients who respond in the affirmative to any one of three simple questions. These data should be of interest to tuberculosis clinicians, since they represent a simple and inexpensive screening tool to identify patients who may be at increased risk of hepatotoxic side effects to anti-tuberculosis drugs. The three-questionnaire item algorithm to predict HCV status was less sensitive than that of the HBV algorithm, and additionally was dependent on receipt of blood transfusion, a risk factor that may currently be of less significance in Georgia. It is important to note however that the proposed algorithms, while valid for Georgia and countries with similarly propagated HCV and HBV epidemics, may not be valid for countries with epidemiologically distinct epidemics.

Georgia is just one of many countries in the former Soviet Union struggling to control its burgeoning tuberculosis problem. Successful treatment of tuberculosis patients with viral hepatitis and HIV co-infection will be a challenging task. However, it may be useful to utilize behavioral algorithms to identify which patients are at highest risk of drug toxicity in conjunction with serologic screening of high risk tuberculosis patients for HCV, HBV, and HIV infection. Careful clinical and laboratory monitoring, and treatment adjustment as needed, will also be necessary to avert serious hepatotoxicity in these patients.

Acknowledgements

Supported in part by the NIH/AIDS International Training and Research Program of Emory University (D43 TW01042) and the Civilian Research and Development Foundation (CRDF Grant #7213 and GB1-2013).

Conflict of interest: The authors have no conflicts of interest concerning the work reported in this paper.

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