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Sexual Transmission of Hepatitis B in Mwanza, Tanzania

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Background: **Hepatitis B virus (HBV) is endemic and poses a grave public health problem in Africa where it is mainly transmitted from mother to baby or during childhood. Sexual transmission has also been suggested to play a role in East Africa, but this has never been properly demonstrated. Additional preventive strategies may be proposed if sexual transmission of HBV occurred in this region where HIV and other STDs are highly prevalent.**

Goals: **To determine the prevalence of markers for hepatitis B virus (HBV)and other sexually transmitted diseases (STD) in routine blood samples taken from three populations in Mwanza, Tanzania, and to use the data collected to look at the association between hepatitis B and other STDs, including human immunodeficiency virus (HIV).**

Study Design: **Routine blood samples were collected from 1,025 patients attending a clinic for STDs, 253 voluntary blood donors from secondary schools, and 952 blood donors who gave blood in a hospital specifically for a relative who needed a blood transfusion. All samples were tested for HIV by double enzyme-linked immunosorbent assay (ELISA), and for syphilis using the *Treponema pallidum* hemagglutination (TPHA) and rapid plasma reagin (RPR) tests. Two markers for HBV were examined by the double ELISA method, the presence of the anti-hepatitis B core antigen (anti-HBc) and the hepatitis B surface antigen (HBsAg).**

Results: **There were high prevalences of HBV, syphilis, and HIV in relative donors and STD patients. Although HBV markers were more prevalent in men of increasing ages, syphilis and HIV markers were more prevalent in young women. Evidence of past infection with HBV (presence of anti-HBc) was associated with serologic markers of recent treponemal infection (both TPHA and RPR positive) in both sexes (men odds ratio [OR] = 1.91, $P < 0.011$; women OR = 2.34, $P < 0.02$) and with HIV in men (OR = 1.93, $P < 0.003$). Current infection with HBV (presence of HBsAg) was associated with recent syphilis in men (OR = 2.13, $P < 0.006$). In STD patients, current infection with HBV was associated with *Trichomonas vaginalis* in women (OR = 3.57, $P < 0.002$) and recent syphilis in men (OR = 3.46, $P < 0.001$). There was no further association between HBV markers and any other STD pathogen or any particular STD syndrome, nor was there any association between current HBV infection and HIV in both sexes. The population attributable fraction for sexual acquisition of hepatitis B is estimated at 7.2% in men and 3.0% in women, based on the association between hepatitis B and syphilis.**

Conclusions: **These findings suggest that sexual acquisition of hepatitis B occurs at low levels in Mwanza, and that HBV can be prevented through enhancement of the current HIV/STD control activities, in addition to improved vaccination strategies.**

HEPATITIS B POSES a grave public health problem worldwide because of the absence of simple treatment, the danger of chronic carriage of the virus, and the possibility of progression toward liver cirrhosis and hepatocellular carcinoma.[1]

In areas of low endemicity, infection with hepatitis B virus (HBV) is mainly confined to certain groups who are exposed either parenterally[2] or by sexual contact.[3,4] In Africa, where the virus is endemic, the general population is at risk for its acquisition, and HBV may be acquired through vertical transmission from the mother,[2] or during childhood from siblings or contacts.[5] In West Africa, prevalence of HBV markers peaks at an early age: 80% of children aged younger than 7 years in a study in Senegal displayed antibodies to the core antigen of the virus (anti-HBc).[6] Conversely, in East Africa, childhood prevalence is around 50% and postpuberty transmission occurs, and although sexual transmission has been suggested as a mechanism for this, it has not been clearly demonstrated.[7–10]

Current strategies for the prevention of HBV include screening of blood units, proper sterilization or disposal of injecting equipment, and vaccination of high-risk

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groups.[11] These interventions may not all be feasible or cost effective in Africa, and further research on the relative importance of different routes of transmission of HBV is thus warranted to direct preventive strategies more efficiently.

The natural history of HBV could be altered in places that also are highly endemic for human immunodeficiency virus (HIV). The latter could have an effect on the acquisition of HBV or on the course of both previously established chronic HBV infection and newly acquired HBV infection.[12]

To investigate the importance of sexual transmission of HBV in East Africa, we have undertaken a cross-sectional serosurvey from three populations with potentially different sexual exposure to the virus. The results of the laboratory tests on the blood samples collected included HBV and other serologic markers of sexual exposure (HIV and syphilis).

Subjects and Methods

Subjects

All subjects were recruited from January to December, 1992 in the town of Mwanza, the second largest town in Tanzania, located on the southern shores of Lake Victoria.

Voluntary blood donors were enrolled from secondary schools. During the recruitment lectures for voluntary donations, people were urged to exclude themselves if they had unprotected sex with several partners, or if they had a history of sexually transmitted diseases (STD). Potential donors were also excused from blood donation if donation would have been detrimental to their health, based on their age, body weight, blood pressure levels, pulse rate, and hemoglobin concentration.

Relative blood donors were relatives or friends who donated a blood unit for patients requiring a blood transfusion in the referral hospital in Mwanza. There were no self-exclusion criteria for this group, but they were excused from blood donation if this would have been detrimental to their own health, as for voluntary donors.

Patients with STDs were recruited from the referral clinic for STDs at Sekou Toure Hospital, Mwanza. These had a full clinical examination, and samples were taken for laboratory tests. Clinical classification was based on the World Health Organization definition of STD syndromes.[13]

Laboratory Methods

A 5- to 10-ml venous blood sample was taken from each subject and screened for antibodies against HIV-1 (Vironostika anti HTLV-III; Organon Teknika, Boxtel, The Netherlands). All sera testing positive or indeterminate by the initial enzyme-linked immunosorbent assay (ELISA) method were subjected to a second ELISA (Wellcozyme HIV 1/2 GACELISA; Murex Diagnostics, Dartford, United Kingdom) for confirmation.

All sera were screened for the presence of hepatitis B surface antigen (HBsAg) and anti-HBc by ELISA (Hepanostika; Organon Teknika). Sera testing positive or within 10% of the cut-off value were retested with the same test, and were declared positive only when the optical density was greater than the cut-off value plus 10%.

Antibodies to *Treponema pallidum* were determined by hemagglutination assay (TPHA-Nosticon; Organon Teknika). All sera testing positive were further tested by the rapid plasma reagin test (RPR-Nosticon; Organon Teknika) to differentiate past syphilis (TPHA positive and RPR negative) and untreated or recently treated syphilis infection (both TPHA and RPR positive)—which we refer to as "recent syphilis" in this text.

In addition to these serologic tests, the STD patients had specific investigations done as part of the routine management of STDs in this clinic. Genital samples were collected for the following:

1. *Neisseria gonorrhoeae* culture on modified Thayer-Martin media from men and women with genital discharge syndrome or pelvic inflammatory disease. Samples from these patients were not routinely tested for *Chlamydia trachomatis* in this clinic.
2. Wet preparations for the diagnosis of *Trichomonas vaginalis* and *Candida albicans*, for women with genital discharge syndrome or pelvic inflammatory disease.
3. *Hemophilus ducreyi* culture on gonococcal- and Mueller–Hinton-based agar plates, herpes simplex virus antigen-detection ELISA (Wellcozyme) and dark-field microscopy (*T. pallidum*) for patients with genital ulcer syndrome. These tests for *H. ducreyi* and herpes simplex were taken as part of a cross-sectional survey of genital ulcer disease.

Statistical Analysis

Three age groups were used in the analysis, 15 to 19 years, 20 to 24 years, and 25 years and older. The prevalences were calculated within each age group and the proportions compared using the chi-square test. Logistic regression was used to assess the correlation between HBV markers and other variables across the age and sex groups. Odds ratios (OR) and their associated *P*-values are presented to show the size of the correlation found.

Results

Two hundred sixty-seven voluntary blood donors, 961 relative blood donors, and 1,105 patients with STDs

were recruited in this study. The number of potential blood donors who refused or were excluded has not been recorded. No STD patient refused or was excluded from participation in the study. There were only five male voluntary donors older than 25 years of age and one female voluntary donor older than 20 years of age; they have been excluded from this analysis. A total of 253 voluntary blood donors (183 men and 70 women), 952 relative blood donors (891 men and 61 women), and 1,025 patients with STDs (515 men and 510 women) had the full range of serologic tests performed and have been included in the analysis.

Prevalence of Serologic Markers

The prevalences of HIV, HBsAg, anti-HBc, and *T. pallidum* by TPHA and RPR are shown in Table 1. The overall prevalence of HIV, anti-HBc, TPHA, and recent syphilis was significantly lower in voluntary blood donors than in the other populations for both sexes. Adjusting for age, the HIV prevalence in STD patients was higher than among the relative donors for men (18% vs. 8%, OR = 2.61, $P < 0.001$) and for women (26% vs. 15%, OR = 2.04, $P < 0.08$). There were no significant differences in the prevalences of TPHA between STD patients and relative donors, or between men and women.

The overall prevalence of HBsAg was 9.9% in voluntary donors, 11.2% in relative donors, and 8.1% in STD patients. The HBsAg prevalence for all populations combined was higher in men than in women, with a 2.2 : 1 carrier rate of men to women. Allowing for the age and sex differences, there were no further significant differences between the three populations for HBsAg. The prevalence of anti-HBc was lower among female STD patients (66%) than among relative donors (82%) after adjusting for age (OR = 0.434, $P < 0.02$), but there was no difference among men in these populations.

Association Between Hepatitis B and Other Serologic Markers

Twenty-four of the 121 men (20%) with recent syphilis (TPHA+/RPR+) had a current infection with hepatitis B (HBsAg), compared with 153 of 1,403 men (11%) without evidence of syphilis (TPHA-) and 5 of 65 men (8%) with evidence of past syphilis (TPHA+/RPR-). After allowing for the effect of age and population, the association between recent syphilis and HBsAg in men (OR = 2.13, $P < 0.002$) implies an attributable risk of 9% (the difference between 20% and 11%) for sexually acquired HBsAg in these populations. There was no such association between HIV infection and hepatitis B in men.

TABLE 1. The Prevalence and Number of Markers for HIV, Hepatitis B Surface Antigen, Hepatitis Core Antibodies, TPHA, and Recent Syphilis by Sex and Age Group in Blood Donors and STD Patients in Mwanza, Tanzania

	N	HIV	HBsAg	Anti-HBc	TPHA	Active Syphilis
Men						
VD						
15–19 years	121	1 (1)	16 (13)	62 (51)	1 (1)	0
20–24 years	62	2 (3)	4 (6)	41 (66)	2 (3)	1 (2)
RD						
15–19 years	50	1 (2)	9 (18)	34 (68)	3 (6)	2 (4)
20–24 years	203	9 (4)	23 (11)	141 (69)	17 (8)	11 (5)
25+ years	638	62 (10)	70 (11)	485 (76)	91 (14)	65 (10)
STDP						
15–19 years	68	8 (12)	6 (9)	49 (72)	6 (9)	2 (3)
20–24 years	173	18 (10)	28 (16)	121 (70)	20 (12)	15 (9)
25+ years	274	70 (26)	26 (9)	201 (73)	46 (17)	25 (9)
Women						
VD						
15–19 years	70	3 (4)	5 (7)	25 (36)	1 (1)	0
RD						
15–19 years	14	0	2 (14)	11 (79)	1 (7)	1 (7)
20–24 years	18	4 (22)	2 (11)	14 (78)	1 (6)	0
25+ years	29	5 (17)	1 (3)	25 (86)	7 (24)	6 (21)
STDP						
15–19 years	116	22 (19)	11 (9)	72 (62)	18 (16)	14 (12)
20–24 years	170	56 (33)	5 (3)	111 (65)	34 (20)	19 (11)
25+ years	224	55 (25)	7 (3)	155 (69)	28 (12)	16 (7)

HIV = human immunodeficiency virus; TPHA = *Treponema pallidum* hemagglutination; STD = sexually transmitted diseases; VD = voluntary blood donors; RD = relative blood donors; STDP = patients attending an STD clinic; HBsAg = hepatitis B surface antigen; anti-HBc = hepatitis B core antibodies. Values are no. (%). Recent active syphilis as defined by both TPHA and RPR tests positive.

In women, there was no significant association between current infection with hepatitis B as indicated by HBsAg and other serologic markers of sexual exposure (HIV and syphilis, data not shown).

Evidence of past infection with hepatitis B as seen by the anti-HBc marker was associated with both serologic markers for HIV and syphilis in men and with syphilis in women (Table 2). After allowing for age and population, the association between HIV and the anti-HBc marker was OR = 1.93, $P < 0.003$ for men. The association between recent syphilis and the anti-HBc marker was OR = 1.91, $P < 0.011$ for men and OR = 2.34, $P < 0.02$ for women.

Hepatitis B Markers Among Patients With Sexually Transmitted Diseases

There was no significant association between *N. gonorrhoeae* and either hepatitis B marker for men or women (Table 3). Syphilis identified at the STD clinic by TPHA/RPR serology and by dark-field microscopy was not associated with a higher prevalence of anti-HBc in men or women; however, it was associated with a higher prevalence of HBsAg in men (OR = 3.46, $P < 0.001$), as was *T. vaginalis* infection for women (OR = 3.57, $P < 0.002$). No other STD pathogens were associated with anti-HBc or HBsAg. The broad clinical diagnoses made at the STD clinic of genital discharge syndrome, genital ulcer syndrome, and other STD syndromes were not significantly associated with serologic hepatitis markers.

Discussion

Heterosexual transmission has been suggested as one of the modes of transmission of hepatitis B in the Western world.[2–4] Seroepidemiologic surveys have found that heterosexuals with syphilis have a higher prevalence of HBV markers, and several studies have documented the association between past history of STDs, high number of sexual partners, or history of prostitution and infection with HBV.[3,4,14,15] Studies of sex partners or spouses of patients with acute hepatitis B or chronic carriage of HBsAg have documented that between one third to one half of both female and male sexual partners show evidence of past or present infection.[4]

In Africa, however, where there are fewer susceptible individuals beyond the prepuberty period, the demonstration would seem more arduous. Nevertheless, serologic studies in Somalia, Uganda, Rwanda, Tanzania, and South Africa have suggested that sexual transmission may occur.[7–10,16] In all these studies, the relative importance of sexual transmission of hepatitis B was not quantified, and the authors all failed to detect an effect among men, perhaps because men acquire HBV at a younger age than women, and any association will be masked if age groups are not analyzed separately.

In the current study, we compared three populations with potentially varying exposure to sexually acquired pathogens within comparable age groups. Voluntary blood donors recruited among secondary school students are known to present a low prevalence of HIV and syphilis in Mwanza,[17] and thus may represent a

TABLE 2. Prevalence of Anti-HBc in 1,589 Men and 641 Women by Serostatus for HIV and Syphilis (Measured by TPHA) by Sex and Age Group

	HIV Negative	HIV Positive	TPHA Negative	TPHA Positive
Men (N = 1,589)				
VD				
15–19 years	61/120 (51)	1/1 (100)	62/120 (52)	0/1
20–24 years	40/60 (67)	1/2 (50)	39/60 (65)	2/2 (100)
RD				
15–19 years	33/49 (67)	1/1 (100)	31/47 (66)	3/3 (100)
20–24 years	133/194 (69)	8/9 (89)	129/186 (69)	12/17 (71)
25+ years	431/576 (75)	54/62 (87)	408/547 (75)	77/91 (85)
STDP				
15–19 years	41/60 (68)	8/8 (100)	43/62 (69)	6/6 (100)
20–24 years	108/155 (70)	13/18 (72)	106/153 (69)	15/20 (75)
25+ years	145/204 (71)	56/70 (80)	165/228 (72)	36/46 (78)
Women (N = 641)				
VD				
15–19 years	24/67 (36)	1/3 (33)	24/69 (35)	1/1 (100)
RD				
15–19 years	11/14 (79)	0/0	10/13 (77)	1/1 (100)
20–24 years	11/14 (79)	3/4 (75)	13/17 (77)	1/1 (100)
25+ years	21/24 (88)	4/5 (80)	19/22 (86)	6/7 (86)
STDP				
15–19 years	56/94 (60)	16/22 (73)	57/98 (58)	15/18 (83)
20–24 years	74/114 (65)	37/56 (66)	86/136 (63)	25/34 (74)
25+ years	118/169 (70)	37/55 (67)	134/196 (68)	21/28 (75)

Values are no. (%).

TABLE 3. The Prevalence of Hepatitis B Serological Markers Among 515 Male and 510 Female STD Patients by Laboratory Test Results and by Clinical Diagnosis

Category	Men (N = 515)			Women (N = 510)		
	No. of Patients*	Hepatitis B Surface Antigen	Hepatitis B Core Antibodies	No. of Patients*	Hepatitis B Surface Antigen	Hepatitis B Core Antibodies
Laboratory pathogen						
No pathogen	261	27 (10)	182 (70)	270	8 (3.0)	182 (67)
N. gonorrhoeae	170	17 (10)	122 (72)	62	2 (3.2)	40 (60)
Syphilis†	55	15 (27)‡	43 (78)	56	4 (7.1)	43 (77)
T. vaginalis	—	—	—	126	12 (9.5)‡	80 (63)
Other agent	33	2 (6)	19 (58)	34	2 (5.9)	22 (65)
Clinical diagnosis (using World Health Organization syndrome classifications)						
Genital discharge syndrome	336	36 (10.7)	241 (72)	453	20 (4.4)	296 (69)
Genital ulcer syndrome	143	20 (14.0)	106 (74)	29	3 (10.3)	20 (69)
Other STD syndrome	37	4 (10.8)	24 (65)	31	1 (3.2)	25 (81)

*Patients may have more than one pathogen identified or clinical diagnosis.
†At the STD clinic a positive syphilis diagnosis is either by darkfield microscopy, or both TPHA and RPR serological tests being positive.
‡Significant association at $P < 0.05$.
Values are no. (%).

"low-risk" population for sexual acquisition of HBV. Relative donors, however, are more likely to represent the general population in Mwanza,[18] and thus they may constitute the "medium-risk" population for HBV, whereas STD patients clearly represent the "high-risk" population.

Human immunodeficiency virus and syphilis serologies were chosen as markers of sexual exposure, and indeed we observed a gradient of exposure with these sexually acquired pathogens across the age groups among the three populations. We also detected a substantial increase in HBV infection in the individuals most infected with other sexually acquired pathogens. The most significant association was that individuals with a past history of syphilis were more likely to have had hepatitis B (anti-HBc) in both sexes and across all age groups.

We also noted an increase in HBsAg prevalence among men with recent syphilis, and among women with *T. vaginalis* infection. This could possibly indicate that infection with HBV and the STD pathogens may have occurred either concomitantly or separated by a short interval, through sexual transmission. This would be plausible because both syphilis and trichomoniasis determine a degree of mix between blood and genital fluids, which are both efficient "vehicles" for HBV transmission. Other studies have found very strong association between HBV and syphilis.[2,8–10,15] We could not, however, distinguish between recently acquired infection and prolonged carriage of HBsAg because we did not test for immunoglobulin M directed against core antibodies,[19] thus failing to differentiate between a cofactor effect and a marker of sexual activity.

Although we did control for the effect of age in our study, we did not control for the effect of other exposures to HBV. Percutaneous exposure to HBV probably occurs: injection equipment is often reused and not always properly sterilized in Mwanza[20]; many STD patients receive such injections before presentation at the STD clinic; scarification probably plays a minimal role (Jacobs, unpublished data); and blood transfusions have been screened for HBV in Mwanza only since 1992. Socioeconomic status could be another confounding factor, as demonstrated by a Nigerian study.[21] Voluntary donors, who were secondary school pupils, are likely to be members of the more affluent part of the society, and their exposure to the virus may have been different from that of the general population, either through environmental, medical, or cultural factors or through the choice of sexual partners.

From our data, it can be inferred that sexual acquisition of HBV occurs in Mwanza and it may be facilitated in the presence of other STDs. For example, with a prevalence of HBsAg of 20% in men with active syphilis and 11% in men without active syphilis, the attributable risk is 9%. This would mean that in the population of relative donors in Mwanza, where 8.8% of the men have active syphilis, the population attributable fraction (PAF) is (9% × 8.8%)/11% = 7.2%. In women, the prevalence of HBsAg was 7.1% in those with active syphilis and 5.3% in those with no evidence of syphilis infection, giving a PAF of 3.0%. The small PAF found in our study may include a combination of prolonged carriage and increased infection; thus, sexually acquired HBV may not add much to the overall burden of disease.

Public Health Implications

The fact that between 5% and 10% of women of reproductive age in Mwanza are carriers of HBV is of concern. The risk for chronic carriage in the newborn is greatly increased (up to 90%), and the consequences (cirrhosis and rapid onset of hepatocellular carcinoma) are serious.[22]

For other patients, the consequences of postpuberty acquisition of HBV should be less dramatic. Acute HBV infection is usually mild, and the risk of chronic infection in immunocompetent adults is less than 5%. Moreover, many chronic HBsAg carriers are asymptomatic and can be referred to as "healthy carriers," and even those with chronic hepatitis often have minimal liver disease.[22,23]

Efforts to control HBV should be enhanced, and proposed strategies, including the vaccination of high-risk populations[11] and universal vaccination of infants,[11,24] should be encouraged, although they may be logistically and financially difficult to undertake in parts of Africa. Acquired immunodeficiency syndrome control programs aiming at reducing the risk of HIV transmission through adherence to proper sterilization and injecting practices will enhance the control of HBV.[25] STD/HIV control that emphasizes the detection and early treatment of syphilis and other STD pathogens and the delivery of appropriate information aimed at sexual behavior modification will also have an increased preventive effect on HBV transmission.

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