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Hepatitis B virus infection and factors associated with its acquisition among adults in a Lake Victoria HIV hyperendemic fishing community in Kyotera district, Uganda: a cross-sectional observation

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ABSTRACT

Objective To investigate hepatitis B virus (HBV) prevalence and factors associated with viral acquisition in a HIV-hyperendemic fishing community, we tested sera for anti-hepatitis B core (HBc) and hepatitis B surface antigen (HBsAg).

Design Observational cross-sectional study.

Setting Large fishing village on Lake Victoria, one of the HIV-hyperendemic Rakai Community Cohort Study (RCCS) sites (HIV prevalence ~40%).

Participants Sample of 460 RCCS participants aged 15–49 years from survey conducted from 5 December 2016 to 13 February 2017. These proportionately included HIV-negative, HIV-positive antiretroviral therapy (ART)-naïve and HIV positive on ART participants.

Results Of the 460 participants, 49.6% (95% CI 45.0% to 54.1%) had evidence of prior HBV infection and 3.7% (95% CI 2.3% to 5.9%) were either acutely or chronically infected. HBV risk increased with age, number of lifetime sex partners and HIV seropositivity. HBV risk decreased with HIV ART use among HIV-positive participants. Prevalence of prior HBV infection was 17.1% in participants aged 15–19 years, 43.2%, 55.3% and 70.1% in participants aged 20–39, 30–39 and 40–49 years, respectively (p<0.001). Additionally, the prevalence of prior HBV infection was 23.8% in participants with 0–1 lifetime sex partners, 43.2% and 54.8% in participants with 2–3 lifetime sex partners and 4+ lifetime sex partners, respectively (p<0.001).

Conclusions Findings from this fishing community suggest the need to provide HBV vaccination to adults at risk of sexual transmission who have not been previously immunised.

Strengths and limitations of this study

- The study presents the prevalence of hepatitis B virus (HBV) infections across age groups of a population with documented sexual partner history to allow for estimating HBV transmission after sexual debut.
- The study provides stratified sampling by HIV status and antiretroviral therapy (ART) use, which allowed for estimating differences in HBV infection risk by HIV status and ART use.
- This is however a cross-sectional study which is limited in assessing a cohort effect to HBV infection and transmission.

INTRODUCTION

Hepatitis B virus (HBV) and its resulting viral hepatitis are a major public health concern. Globally, over 2 billion people have serological evidence of previous exposure to HBV, and >350 million are chronically infected.[1] Chronic infection is associated with a 15%–40% risk of developing cirrhosis, liver failure or hepatocellular carcinoma and a 15%–25% risk of dying from HBV-related liver diseases.[2]

The global burden of HBV is borne primarily by the African and Western Pacific regions, accounting for 68% of worldwide cases in 2017.[1] Sub-Saharan Africa has high incidence of hepatocellular carcinoma (41.2 per 100 000 people per year), with 80% of cases due to HBV infection.[3] Unfortunately, 92% of patients diagnosed with hepatocellular carcinoma in sub-Saharan Africa die within 1 year of symptom onset because most countries lack surveillance programmes for small tumours.[3] WHO estimated that HBV accounts for 87 890 deaths annually in the sub-Saharan Africa region.[1]

In Uganda, the national prevalence of HBV is 10%, although the burden varies across regions.[4] However, serological evidence of

prior infection occurs in up to 66% of the population.[5] Most HBV acquisition in sub-Saharan Africa is thought to occur prior to sexual debut, either perinatally or through close household contacts and/or playmates.[6] Routine use of the neonatal HBV vaccine was introduced in Uganda in 2002 as part of the Expanded Programme on Immunisation.[4] However, cases of HBV community acquisition after sexual debut are increasingly being recognised, suggesting sexual transmission and raising the opportunity for HBV prevention through immunisation of at-risk adult populations. Fishing communities in Uganda, which often have high risk sexual behaviours and HIV burden, may have particularly large at-risk populations.[7] HIV anti-retroviral therapy (ART) guidelines in Uganda have consistently recommended use of adult regimens containing at least one drug active against HBV, such as lamivudine (3TC) and tenofovir disoproxil fumarate (TDF).[8]

We investigated the prevalence of HBV and factors associated with its acquisition in a HIV hyperendemic fishing community in Kyotera district in rural south-central Uganda.

METHODS

Study population

We conducted a cross-sectional study of the 17th Rakai Community Cohort Study (RCCS) survey that was conducted from 5 December 2016 to 13 February 2017 among residents in a large fishing village on Lake Victoria, one of the HIV-hyperendemic RCCS study sites (HIV prevalence ~40%).[7] RCCS study is a community cluster randomised study that was established in 1995 to study sexually transmitted diseases among residents of Rakai and Kyotera districts. To date, participants are residents aged 15–49 years at the time of enrolment. RCCS surveys are conducted approximately every 12–18 months where demographic data, behavioural data including age, gender and number of lifetime sex partners, and biological specimens including blood and/or swabs are collected. HIV testing, risk behaviour counselling for HIV prevention and ART treatment for HIV infection are routinely provided as part of the RCCS.

Study sample selection

Overall, 2732 RCCS participants were surveyed, including 1755 (64%) HIV-negative, 192 (7%) HIV-positives/ART-naïve and 785 (29%) HIV-positive on ART. We performed a proportionate stratified random sampling to select a sample representative to the HIV status and ART use distribution of the RCCS survey population based on a previous study conducted in predominantly agrarian study communities of the RCCS, that observed the HBV prevalence to range from 40% in HIV-negative and 53% in HIV-positive participants.[9] Therefore, we assumed the expected HBV prevalence to approximately range from 40% to 60%, at 5% level of significance and power of 90%, and computed an equivalent random sample size of 460/2732 (17%) participants. Given that ART use was highly scaled up, we proportionately sampled 296/1755 (17%) HIV-negative participants, 32/192 (17%) HIV-positive/ART-naïve and 132/785 (17%) HIV-positive on ART study participants.

Laboratory testing

Sera were tested for anti-HBc using the Murex anti-HBc (total) test kit, with subsequent positive samples tested for hepatitis B surface antigen (HBsAg) using Murex HBsAg V.3 and confirmed using Murex HBsAg Confirmatory V.3 test kit (Diasorin, Italy). HIV testing had prior been conducted following the Uganda Ministry of Health HIV parallel rapid-testing algorithm using Determine HIV-1/HIV-2 (Alere Medical, Chiba, Japan), HIV-1/HIV-2 Stat-Pak Dipstick (Chembio Diagnostic Systems, Medford, New York, USA) and Uni-Gold HIV (Trinity Biotech, Bray, Ireland) as a tiebreaker for discordant Determine/Stat-Pak results.

Statistical analysis

The primary outcome was evidence of prior HBV infection, defined as testing positive for anti-HBc and/or HBsAg. The study population was described using proportions, and statistical significance was estimated using χ^2 tests. Log binomial regressions were performed to estimate prevalence risk ratios (PRR) with 95% CIs. Where collinearity was observed between age and number of lifetime sex partners, we performed independent multivariate analyses adjusted for gender and HIV status. We estimated the population attributable fraction (PAF) of prior HBV infection due to reporting multiple (1+) lifetime sex partner as the difference in the prevalence of prior HBV infection observed in the study and the prevalence of prior HBV infection had all participants reported a maximum of one (0 or 1) lifetime sexual partner. Corresponding CIs were calculated using normalising and variance-stabilising transformation methods. Analyses were performed using STATA/IC V.15.1 (STATA, Texas, USA).

Patient and public involvement

The RCCS is monitored by a Community Advisory Board that meets regularly to ensure the interests of the study communities are incorporated into study design and conduct. Board members are selected to represent different groups in the community including study participants, civil servants, mass media, religious and political leaders as well as special interest groups such as youths, key populations and people living with HIV. It has representation from each of the different super clusters that make up the RCCS study area, one of which is Kasensero. Findings from this and other studies conducted in the RCCS are used to develop health communication messages that are disseminated at community meetings and shared with local and national authority to inform policy guidelines. In addition, study findings will be disseminated to the public through publication in peer-reviewed journals.

RESULTS

Characteristics of the study participants

Of the 460 participants, majority were men (60.4%). The mean age was 30.3 years (range: 15–49 years), with the largest proportion in the 20–29 years age group (40%). Most participants (82%) reported three or more sex partners in their lifetime.

HBV prevalence

Overall, 228 (49.6%) had prior HBV infection, including 17 (3.7%) who were either acutely or chronically infected (positive HBsAg). The prevalence of prior HBV infection was 43.9% (95% CI 38.3% to 49.7%) among the HIV-negative, 74.2% (95% CI 55.9% to 86.7%) among the HIV-positive and ART-naïve participants and 56.4% (95% CI 47.8% to 64.6%) among the HIV-positive on ART. Of those with prior HBV, the median age was 32.0 years (IQR 27–39), 139 (61%) were men and 202 (89%) had 3 or more sex partners in their lifetime at the time of the survey. Prevalence of prior HBV infection was 17.1% in participants aged 15–19 years, 43.2%, 55.3% and 70.1% in participants aged 20–39, 30–39 and 40–49 years, respectively (p<0.001). Additionally, the prevalence of prior HBV infection was 23.8% in participants with 0–1 lifetime sex partners, 43.2% and 54.8% in participants with 2–3 lifetime sex partners and 4+ lifetime sex partners, respectively (p<0.001).

Factors associated with prior HBV infection

Prevalence of HBV increased both with age and number of sex partners, with a correlation of 0.42 (figure 1). In univariate analysis, prior HBV infection was significantly associated with older age, number of lifetime sex partners and HIV positivity. In multivariate analysis, age and number of lifetime sex partners had a collinear relationship to HBV infection. Therefore, we separately performed an age-adjusted multivariate model (age-model) and another multivariate model adjusted for number of sex partners (partner-model).

In the age-model, after adjusting for gender and HIV status in multivariate analysis, age remained significantly associated with HBV positivity: the rates of prior HBV infection increased progressively with age group (15–19 years as the reference; 20–29 years: PRR=2.48, 95% CI 1.24 to 4.97; 30–39 years: PRR=3.09, 95% CI 1.54 to 6.19 and 40–49 years: PRR=3.89, 95% CI 1.93 to 7.85).

In the partner-model, after adjusting for gender and HIV status in multivariate analysis, prior HBV infection rates significantly increased with number of lifetime sex partners. Compared with participants who reported 0–1 lifetime sex partners, the prevalence of HBV positivity was greater among those reporting 2–3 lifetime sex partners (PRR=1.68, 95% CI 0.93 to 3.04) and those reporting 4+ lifetime sex partners (PRR=2.11, 95% CI 1.20 to 3.70). HIV positivity was significantly associated with HBV infection in the partner-model (PRR=1.23, 95% CI 1.02 to 1.48).

After accounting for ART use, HIV-negative participants and HIV-positive on ART participants had equivalent prevalence of HBV infection (PRR=0.86, 95% CI 0.71 to 1.06), while HIV-positive/ART-naïve participants had 34% higher prevalence of prior HBV infection than HIV-positive participants on ART (PRR=1.34, 95% CI 1.05 to 1.73).

After controlling for the effect of gender and HIV status, the PAF of prior HBV infections associated with having 2+ lifetime sex partners were 48.1% (95% CI 11.7% to 69.5%), and having 1+ lifetime sex partners was 87.1% (95% CI 14.1% to 98.1%).

Lastly, we compared HBV infection among virally suppressed and non-suppressed HIV-positive participants and found no significant differences (56% of virally suppressed HIV-positive participants, and 56% non-suppressed participants (p=0.99) had HBV infection).

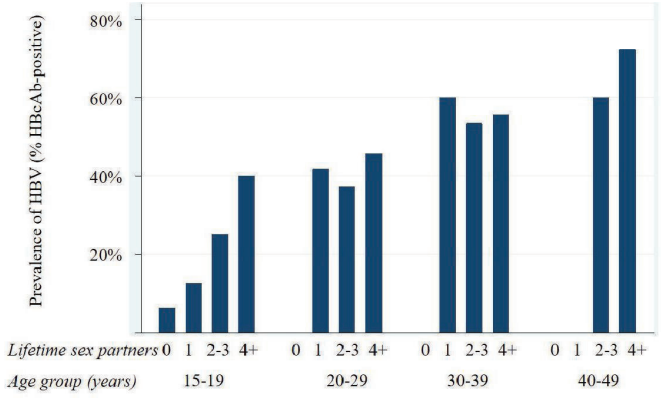

Figure 1 Prevalence of hepatitis B virus by number of lifetime sex partners and age group.

DISCUSSION

We found evidence of prior HBV infection in half of the population surveyed in a HIV hyperendemic Lake Victoria population in Uganda. Prior HBV infection was associated with both older age and greater numbers of lifetime sexual partners, which suggests ongoing sexual transmission in adulthood and challenges the belief that most HBV transmission occurs in early childhood prior to sexual debut.

ART use was associated with reduced risk of HBV infection among HIV-positive participants. This may be due to use of regimens containing drugs active against HBV in this population. At the time of the survey, all HIV-positive participants on ART were on regimens containing an anti-HBV drug: 3TC, TDF or both.[8] These were the preferred regimens for at least the prior 3 years.[10]

Our lifetime HBV exposure estimate of 50% is higher than the 41% previously reported by a 2011 study in the general agrarian/trading communities in Rakai.[9] This difference may be due to risky sexual behaviours which are more common in fishing communities compared with agrarian and trading communities in rural Uganda.[11] The prevalence of HBV (acute/chronic) infection (3.7%) in our study is lower than the national estimate (10%),[4]

possibly explained by timing of HBV transmission: adult transmission of HBV confers less risk of HBV chronicity than perinatal transmission.[12]

In sub-Saharan Africa, exposure to HBV was traditionally thought to occur before sexual debut.[13] However, there is increasing evidence of HBV acquisition among adults in recent years.[9] Possible acquisition modes in this category include unprotected sex with an infected person, injecting drug use, body piercing, scarification procedures and blood transfusion.[14] Most of these practices are rare in Africa and almost non-existent in Uganda. Blood for transfusion is carefully screened for HBV in Uganda, and transmission through this means is unlikely. Scarification is not practised in the study communities and therefore transmissions are not attributable to this practice.[9] Our study's estimate of 48% PAF for multiple lifetime sex partners suggests that the prevalence of HBV would have been as low as 24% if multiple lifetime sex partners were eliminated in our study population. This is evidence of sexual transmission of HBV, and aligns with findings from other African countries, including a Tanzania study which estimated the PAF for sexual acquisition of hepatitis B to be 7.2% in men and 3.0% in women.[15]

Introduction of a neonatal HBV vaccine in Uganda's Expanded Programme on Immunization in 2002 was thought to eliminate the infection through provision of early childhood protection.[4] However, a large pool of older Ugandans remain at risk for sexual transmission of HBV, not having benefited from this programme as infants and lacking access to the HBV vaccine due to cost. Among HIV-positive individuals at risk for hepatitis B, our group has shown a strong protective effect of HIV ART on the risk of HBV acquisition.[16] The current universal ART coverage goal for sub-Saharan Africa could have additional indirect benefits on reducing HBV sexual transmission in HIV-infected undervaccinated populations. Findings from this fishing community suggest the need to provide HBV vaccination to adults at risk of sexual transmission who have not been previously immunised.

The study had the following limitations: this cross-sectional study is limited in assessing a cohort effect to HBV infection and factors associated with its acquisition. We did not establish the HBV immunisation status of participants at survey time, with this having a potential confounding effect. While we ensured representativeness of the RCCS survey population in the fishing villages by proportionately sampling from strata of HIV negatives, HIV positives that were ART-naïve and HIV positives that had initiated ART, these results may not be generalisable to the non-fishing communities of the RCCS study area. We lacked enough power in the study to conduct an analysis among participants with active infection (HBsAg) to isolate risk factors for active HBV infections. We could not differentiate between chronic and acute infections, this being a cross-sectional survey.

We therefore advocate for longitudinal designs to study this relationship in greater detail.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the 'Methods' section for further details.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from the Uganda Virus Research Institute's Research Ethics Committee (No: GC/127/19/11/137), the Uganda National Council for Science and Technology (HS 540) and from the Committee for Human Research at the Johns Hopkins University School of Public Health and School of Medicine (JHU NA_00069085), and Western Institutional Review Board. All participants provided written informed consent.

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Data availability statement Data are available on reasonable request. Data access will require authorisation by the study site for clearly documented objectives.

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