Seroprevalence of Hepatitis B, Hepatitis C, and Human T-Cell Lymphotropic Virus Infections in HIV-Infected Patients in Sierra Leone

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Abstract. HIV coinfection with hepatitis B virus (HBV), hepatitis C virus (HCV), and human T-cell lymphotropic viruses 1 and 2 (HTLV-1 and HTLV-2) is common because of shared transmission routes. There is no published data on the prevalence of these infections in people living with HIV in Sierra Leone. We conducted a cross-sectional study of 211 HIV-positive patients aged ≥ 18 years in Freetown, Sierra Leone, in November 2017. Plasma samples were analyzed using the chemiluminescent microparticle immunoassay (Architect System, Abbott ARCHITECT Analyzer, Abbott Park, IL). The majority were female (63.5%), with median age 36 years (interquartile range [IQR]: 32–44) and median CD4 count of 396 cells/ μ L (IQR: 214–534). Sixty patients (28.4%) were newly diagnosed and antiretroviral therapy (ART) naive; 151 patients (71.6%) were ART experienced. The prevalence of the hepatitis B surface antigen (HBsAg), total anti-hepatitis B core antibody, and anti-HCV was 21.7%, 82.9%, and 4.3%, respectively. No cases of HTLV-1 or HTLV-2 were detected. Male gender ($P = 0.004$) and CD4 < 350 cells/ μ L ($P = 0.017$) were associated with the HBsAg positive status.

Coinfection with HIV and viral hepatitis—that is, hepatitis B virus (HBV) and hepatitis C virus (HCV)—leads to significant morbidity and mortality, through bidirectional effects that result from their shared transmission dynamics.¹ These include early progression to AIDS,^{2,3} accelerated decompensation of cirrhosis, and increased incidence of hepatocellular carcinoma.⁴ HIV/human T-cell lymphotropic virus 1 (HTLV-1) coinfection is linked to adult T-cell leukemia-lymphoma and neurologic complications (tropical spastic paraparesis),⁵ whereas HIV/human T-cell lymphotropic virus 2 (HTLV-2) coinfection has been implicated in long-term nonprogressor phenotype expression.⁶

The WHO 2017 Global Hepatitis report estimated that there were 257 million HBV- and 71 million HCV-infected individuals globally in 2015, with both infections accounting for 1.34 million deaths, which surpassed deaths caused by HIV.⁷ Of the 36.7 million people living with HIV (PLHIV) globally, an estimated 2.7 million are coinfecting with HBV, whereas 2.3 million are coinfecting with HCV.⁷ Although they are not routinely screened for, there are an estimated 10–20 million people infected with HTLV-1 or HTLV-2 worldwide.^{8,9} In recognition of its growing public health importance, the WHO announced an ambitious global agenda to eliminate viral hepatitis as a public health threat by 2030.⁷ However, routine testing and treatment availability unfortunately remain limited, especially in Sierra Leone and many of the high-burden countries in sub-Saharan Africa. Hepatitis B virus infection is vaccine preventable and treatable by antiviral agents; furthermore, the recent development of direct-acting agents offers unprecedented opportunity for HCV treatment, with sustained viral response achieved in up to 98% of HIV/HCV-coinfecting individuals.¹⁰ Knowledge of the HIV coinfection status with these viruses is therefore critical in the clinical

management of patients and in shaping public health policy in endemic countries.

Sierra Leone is a West African country with a multitude of endemic viruses co-circulating with HIV in the general population. The latest countrywide HIV prevalence rate was estimated at 1.7%, representing 67,000 PLHIV, with less than 30% on antiretroviral therapy (ART) in 2016.¹¹ Only a handful of studies have assessed the prevalence of viral hepatitis in select demographics in Sierra Leone. The seroprevalence of the hepatitis B surface antigen (HBsAg) has been reported at 8.7% among health-care workers,¹² 9.7% in blood donors countrywide,¹³ 11.3% in pregnant women,¹⁴ and 13.7% among febrile patients in Bo District.¹⁵ On the other hand, HCV infection appears to be much less prevalent, ranging from 1% in blood donors nationally¹³ to 7.5% in a northern Sierra Leonean hospital.¹⁶ However, the prevalence of viral hepatitis and HTLV infection in PLHIV in Sierra Leone has not been studied before, and in the face of an escalating HIV epidemic fueled by past political instability and a recent Ebola epidemic (2014–2016) in the country,¹⁷ this relevant public health information is urgently needed.

We conducted a cross-sectional study of 211 HIV-positive adults aged ≥ 18 years selected consecutively at the HIV Clinic at Connaught Hospital in Freetown, Sierra Leone, during November 2017 to assess the prevalence of HBV, HCV, and HTLV infection in this population. The clinic is the largest HIV treatment facility in Sierra Leone providing services to more than 4,000 adult PLHIV. After obtaining written informed consent from study participants, demographic and clinical data were recorded. The HIV status was determined using the fourth-generation rapid test SD Bioline HIV-1/2 3.0 (Standard Diagnostics, Inc., Kyonggi-do, South Korea). The Alere Pima™ Analyzer (Abbott Laboratories) was used to determine the CD4 cell count. Plasma samples collected from patients were stored at -20°C in Sierra Leone before shipping on dry ice to Spain, where they were preserved at -80°C before analysis. The HBV, HCV, and HTLV serostatus was determined using the chemiluminescent microparticle immunoassay by an Architect System

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immunoassay analyzer (Abbott Laboratories). Statistical analysis was performed using the SPSS Version 19.0 (IBM Corp., Armonk, NY). $P < 0.05$ was considered statistically significant. Ethics approval was obtained from the Sierra Leone Ethics Scientific and Research Committee and the Institution Board Review committee at Case Western Reserve University/University Hospitals Cleveland Medical Center.

Table 1 shows the baseline characteristics and serostatus of the 211 study participants. The majority were female (63.5%), with a median age of 36 years (interquartile range [IQR]: 32–44). The median CD4 count was 396 cells/ μ L (IQR: 214–540). Sixty patients (28.4%) were newly diagnosed (within 1 month of the study) and ART naive; 151 patients (71.6%) were ART experienced (defined as currently on ART or having previously been exposed to ART for any length of time),¹⁸ with a median time from diagnosis of 48 months (IQR: 15–79). The prevalence of HBsAg was 21.7% (38/175), and the total hepatitis B core antibody (anti-HBc) was 82.9% (175/211). All 38 participants who were HBsAg positive also tested anti-HBc positive, leaving 65.0% (137/211) of participants who were anti-HBc positive and HBsAg negative. Nine participants, that is, 4.3% (9/211) were positive for the anti-hepatitis C antibody (anti-HCV Ab), whereas none were positive for either of anti-HTLV-1 or anti-HTLV-2 antibody (Ab).

Table 2 shows the characteristics of HBsAg positive ($n = 38$) compared with participants who were HBsAg negative ($n = 173$). Among HBsAg-positive patients, the majority were male (57.9%, 22/38), with median age of 37 years (IQR: 32–43) and median CD4 count of 324 cells/ μ L (IQR: 171–427). Within this subgroup, 26.3% (10/38) of participants were newly diagnosed and ART naive, whereas 73.7% (28/38) were on ART. The proportion of participants who were on an ART regimen

containing one active anti-HBV agent (i.e., zidovudine/lamivudine/nevirapine) or two active anti-HBV agents (i.e., tenofovir/lamivudine/efavirenz) was 13.2% (5/38) and 60.5% (23/38), respectively. Male gender ($P = 0.004$) and late-stage HIV disease, defined as CD4 < 350 cells/ μ L and/or the presence of an AIDS-defining illness regardless of CD4 cell count,¹⁹ (60.5% versus 39.5%; $P = 0.017$) were significantly associated with the HBsAg positive status. No association was observed based on age ($P = 0.812$) or ART exposure ($P = 0.851$).

To the best of our knowledge, this is the first study that has specifically assessed the prevalence of viral hepatitis in HIV-infected patients in Sierra Leone. A recent study by Yambasu et al.¹³ using nationally representative data that included nearly 17,000 asymptomatic blood donors at five blood banks across all four geographic regions of Sierra Leone during January–December 2016 reported a prevalence rate of 9.7% for HBsAg and 1.0% for HCV. In comparison, the prevalence of HBsAg and anti-HCV Ab in our cohort of HIV-infected individuals was 2-fold and 4-fold higher, respectively, than in the general population, suggesting that HIV patients are a high-risk demographic group for viral hepatitis coinfection in Sierra Leone. These results are in concordance with recent findings from Cameroon, Nigeria, Ghana, and elsewhere in sub-Saharan Africa where the prevalence rates of HBV and HCV were found to be significantly higher in HIV patients than in the general population.^{20–22} In Sierra Leone and other endemic countries in sub-Saharan Africa, HBV infection is likely acquired early in life through mother-to-child transmission, the risk being greatest in HIV/HBV-coinfecting mothers.²³ However, there is currently no national public health strategy in Sierra Leone for HBV control targeted at newborns; pregnant women; and other at-risk demographic groups, such as HIV-infected individuals, health-care workers, and injection drug users. Of note, HBV vaccination for infants was only introduced in Sierra Leone in 2009, but because of low population coverage, the risk of perinatal HBV transmission remains high. Therefore, allocation of resources toward the implementation of specific evidence-led interventions targeting PLHIV and other high-risk demographics for screening, treatment, and prevention of HBV infection through vaccination could yield public health dividends in Sierra Leone and other endemic countries in the region.

The median CD4 count of HBsAg-positive participants was 324 cells/ μ L, which fulfills the criteria for late-stage HIV disease, that is, CD4 < 350 cells/ μ L and/or the presence of an AIDS-defining illness.¹⁸ Late-stage HIV presentation remains a major obstacle to efforts seeking to bring the global HIV epidemic under control.²⁴ In a recent study, we observed a high prevalence of late-stage HIV disease, that is, CD4 < 350 cells/ μ L (75.4%); AIDS, that is, CD4 < 200 cells/ μ L (49.0%); and severe immunosuppression, that is, CD4 < 100 cells/ μ L (23.2%) in a cohort of 155 newly diagnosed HIV-infected individuals in Sierra Leone.²⁵ Severe immunosuppression itself has been linked to spontaneous reactivating of HBV infection and chronic coinfection in HIV-infected individuals.²⁶ In the present study, the HBsAg positive status was associated with late-stage HIV presentation ($P = 0.017$), thus putting these patients at significant risk of accelerated progression to AIDS and overall poor clinical outcomes.^{2,3}

Our study had several limitations including the small number of patients enrolled at a single tertiary health-care center in an urban setting, making it difficult to generalize our findings at

TABLE 1

Baseline characteristics and serostatus of study participants

Characteristics	Frequency (%), $N = 211$
Gender	
Male	73 (34.5)
Female	138 (63.5)
Median age (years)	36 (32–44)
CD4 count (cells/ μ L), IQR	
Median	396 (214–534)
ART naive	225 (168–282)
ART experienced	476 (442–510)
ART exposure	
Naive	60 (28.4)
Experienced	151 (71.6)
TDF/3TC/EFV	99 (47.0)
AZT/3TC/EFV	8 (3.8)
AZT/3TC/NVP	41 (19.4)
TDF/3TC/NVP	3 (1.4)
Median duration of ART exposure (months), IQR	48 (15–79)
Serologic markers	
HBV	
HBsAg	38 (21.70)
Anti-HBc	175 (82.9)
HCV	
Anti-HCV	9 (4.3)
HTLV	
Anti-HTLV-1	0 (0)
Anti-HTLV-2	0 (0)

ART = antiretroviral therapy; AZT = zidovudine; EFV = efavirenz; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV-1 and HTLV-2 = human T-cell lymphotropic viruses 1 and 2; IQR = interquartile range; NVP = nevirapine; TDF = tenofovir disoproxil fumarate; 3TC = lamivudine.

TABLE 2
Characteristics of HIV/HBV-infected individuals

Characteristics	HBsAg positive, N = 38 (100%)	HBsAg negative, N = 173 (100%)	P-value
Gender			
Male	22 (57.9)	59 (34.1)	0.004
Age (years)			
Median (IQR)	37 (32–43)	36 (32–44)	0.812
< 20	–	2 (1.2)	
21–30	8 (21.1)	39 (22.5)	
31–40	15 (39.5)	74 (42.8)	
41–50	10 (26.3)	32 (18.5)	
> 50	5 (13.2)	26 (15)	
CD4 count (cells/ μ L)			
Median (IQR)	324 (171–427)	396 (223–559)	0.017
< 350	23 (60.5)	75 (43.4)	
$\geq$ 350	15 (39.5)	98 (56.6)	
Anti-HBV agents in ART			
0 (ART naive)	10 (26.3)	37 (21.4)	0.851
1 (3TC)	5 (13.2)	40 (23.1)	
2 (TDF/3TC)	23 (60.5)	96 (55.5)	

ART = antiretroviral therapy; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; IQR = interquartile range; TDF = tenofovir disoproxil fumarate; 3TC = lamivudine.

the wider population level. Furthermore, most study participants were female and ART experienced with median ART exposure duration of 48 months, suggesting that the study participants are more likely to be patients who remain engaged in care. We recognize that this may not be representative of the broader cohort of the 4,000 patients enrolled in HIV care in the clinic, potentially resulting in selection bias. Another major limitation was that the anti-HCV positive status was not confirmed with HCV RNA testing, which may have resulted in overestimation of the true prevalence of HCV infection. Furthermore, no assiduous attempts were made to access for specific risk factors for viral hepatitis infection, such as intravenous drug use, prior vaccination against HBV infection, or levels of acquired natural immunity on exposure. A more rigorous investigation is therefore needed to determine the characteristics of HIV and viral hepatitis coinfection in Sierra Leone, including risk factors, modes of transmission, clinical presentation, prevalence of liver disease, and clinical outcomes.

In summary, a high seroprevalence of HBsAg (21.7%) and high levels of prior HBV exposure (65.0%) were observed in a cohort of 211 HIV-infected patients in Freetown, Sierra Leone. On the other hand, a relatively low seroprevalence of HCV (4.3%) and no cases of HTLV-1/2 were detected, the latter finding suggesting that routine screening for HTLV infection may be of limited utility in Sierra Leone. Currently, Sierra Leone has no national policy for the diagnosis, prevention, and control of viral hepatitis in the general population or one specifically aimed at PLHIV. This underscores the need to further investigate the extent of the problem and to implement specific measures targeting HIV/HBV- and HIV/HCV-coinfecting individuals and other at-risk demographic groups in the country.

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REFERENCES

- Chun HM, Carpenter RJ, Macalino GE, Crum-Cianflone NF, 2013. The role of sexually transmitted infections in HIV-1 progression: a comprehensive review of the literature. *J Sex Transm Dis* 2013: 176459.
- Eskild A, Magnus P, Petersen G, Sohlberg C, Jensen F, Kittelsen P, Skaug K, 1992. Hepatitis B antibodies in HIV-infected homosexual men are associated with more rapid progression to AIDS. *AIDS* 6: 571–574.
- Kovacs A et al., 2010. Activation of CD8 T cells predicts progression of HIV infection in women coinfecting with hepatitis C virus. *J Infect Dis* 201: 823–834.
- Thio CL, Seaberg EC, Skolasky R Jr., Phair J, Visscher B, Muñoz A, Thomas DL; Multicenter AIDS Cohort Study, 2002. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study. *Lancet* 360: 1921–1926.
- Beilke MA, Theall KP, O'Brien M, Clayton JL, Benjamin SM, Winsor EL, Kissinger PJ, 2004. Clinical outcomes and disease progression among patients coinfecting with HIV and human T lymphotropic virus types 1 and 2. *Clin Infect Dis* 39: 256–263.
- Giacomo M, Franco EG, Claudio C, Carlo C, Anna DA, Anna D, Franco F, 1995. Human T-cell leukemia virus type II infection among high risk groups and its influence on HIV-1 disease progression. *Eur J Epidemiol* 11: 527–533.
- WHO, 2018. *Global Hepatitis Report 2017*. Geneva, Switzerland: World Health Organization.
- Gessain A, Cassar O, 2012. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol* 3: 388.
- Murphy EL, Cassar O, Gessain A, 2015. Estimating the number of HTLV-2 infected persons in the world. *Retrovirology* 12: O5.
- Naggie S et al.; ION-4 Investigators, 2015. Ledipasvir and sofosbuvir for HCV in patients coinfecting with HIV-1. *N Engl J Med* 373: 705–713.

11. UNAIDS, 2016. *Country Sierra Leone 2016*. Geneva, Switzerland: United Nations Joint Programme on HIV and AIDS.
12. Massaquoi TA et al., 2018. Cross sectional study of chronic hepatitis B prevalence among healthcare workers in an urban setting, Sierra Leone. *PLoS One* 13: e0201820.
13. Yambasu EE, Reid A, Owiti P, Manzi M, Murray MJS, Edwin AK, 2018. Hidden dangers-prevalence of blood borne pathogens, hepatitis B, C, HIV and syphilis, among blood donors in Sierra Leone in 2016: opportunities for improvement: a retrospective, cross-sectional study. *Pan Afr Med J* 30: 44.
14. Torlesse H, Wurie IM, Hodges M, 1997. The use of immuno-chromatography test cards in the diagnosis of hepatitis B surface antigen among pregnant women in West Africa. *Br J Biomed Sci* 54: 256–259.
15. Ansumana R et al., 2018. Seroprevalence of hepatitis B surface antigen (HBsAg) in Bo, Sierra Leone, 2012–2013. *BMC Res Notes* 11: 113.
16. García-Tardón N, Gresnigt TM, Fofanah AB, Grobusch MP, 2017. Hepatitis B and C in Tonkolili Province, Sierra Leone. *Lancet* 390: 1485.
17. Yendewa GA, Poveda E, Yendewa SA, Sahr F, Quiñones-Mateu ME, Salata RA, 2018. HIV/AIDS in Sierra Leone: characterizing the hidden epidemic. *AIDS Rev* 20: 105–114.
18. Antinori A et al.; European Late Presenter Consensus Working Group, 2011. Late presentation of HIV infection: a consensus definition. *HIV Med* 12: 61–64.
19. WHO, 2016. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*, 2nd Edition. Geneva, Switzerland: World Health Organization.
20. Noubiap JJN, Aka PV, Nanfack AJ, Agyingi LA, Ngai JN, Nyambi PN, 2015. Hepatitis B and C co-infections in some HIV-positive populations in Cameroon, west central Africa: analysis of samples collected over more than a decade. *PLoS One* 10: e0137375.
21. Ladep NG et al., 2013. Rates and impact of hepatitis on human immunodeficiency virus infection in a large African cohort. *World J Gastroenterol* 19: 1602–1610.
22. Agyeman AA, Ofori-Asenso R, 2016. Prevalence of HIV and hepatitis B coinfection in Ghana: a systematic review and meta-analysis. *AIDS Res Ther* 13: 23.
23. Maynard JE, 1990. Hepatitis B: global importance and need for control. *Vaccine* 8: S18–S20.
24. Yendewa GA, 2018. Hot news: new insights from leDEA and COHERE on global trends in CD4 counts at ART initiation. *AIDS Rev* 20: 174–175.
25. Yendewa GA, Poveda E, Lakoh S, Yendewa SA, Sahr F, Jiba DF, Salgado-Barreira A, Salata RA, 2018. High prevalence of late-stage disease in newly diagnosed human immunodeficiency virus patients in Sierra Leone. *Open Forum Infect Dis* 5: ofy208.
26. Hønge BL et al., 2014. Hepatitis B and Delta virus are prevalent but often subclinical co-infections among HIV infected patients in Guinea-Bissau, West Africa: a cross-sectional study. *PLoS One* 9: e99971.