Increased All-cause Mortality in People With HIV and Comorbidities: Hepatitis B and C Virus Seropositivity and Hyperglycemia in Myanmar, 2005–2017

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Background. Hepatitis C virus (HCV) and hepatitis B virus (HBV) coinfection are associated with increased mortality in people with HIV (PWH), and hyperglycemia is a common comorbidity in PWH. In this study, we used routinely collected clinical data to assess the associations between HBV and HCV seropositivity with all-cause mortality and whether this relationship differs by hyperglycemia status.

Methods. Eligible participants included adult PWH (≥15 years) who initiated antiretroviral therapy between May 2005 and June 2016 in Myanmar. HBV and HCV serostatus and hyperglycemia were measured at enrollment to HIV care using HBV surface antigen, HCV antibody tests, and random blood glucose (≥140 mg/dL), respectively.

Results. Among 27 722 PWH, 2260 (8%) were HBV seropositive, 2265 (9%) were HCV seropositive, 178 (0.6%) were HBV-HCV seropositive, and 1425 (5%) had hyperglycemia. During the median follow-up (interquartile range) of 3.1 (1.5–5.1) years, 3655 (13%) PWH died, and the overall mortality rate was 3.8 (95% CI, 3.7–3.9) per 100-person-years (PY). The mortality rate (per 100 PY) among PWH who were HBV seropositive was 4.6, among PWH who were HCV seropositive it was 5.1, and among PWH who were HBV-HCV seropositive it was 7.1. When stratified by glycemic status, the mortality rate was higher among patients with hyperglycemia compared with those with euglycemia (5.4 vs 4.0 per 100 PY), and the difference in mortality rate between patients with hyperglycemia and euglycemia was highest among those with HCV seropositivity (9.8 vs 5.0 per 100 PY).

Conclusions. Increased mortality rates associated with HBV and HCV seropositivity in PWH differed by their glycemic status. PWH with HCV seropositivity and hyperglycemia had the highest mortality rates.

Keywords. HIV; hepatitis; hyperglycemia.

People with HIV (PWH) are at higher risk of coinfection with hepatitis B virus (HBV) and hepatitis C virus (HCV) as all three infections can be transmitted through sexual contact, mother-to-child, exposure to contaminated blood and blood products, and sharing injection drug use equipment [1, 2]. Compared with patients with HIV mono-infection, PWH coinfected with HBV or HCV have higher mortality rates due to increased risk of chronic hepatitis, accelerated liver fibrosis and cirrhosis, and complications that occur in the management of multiple infections [3–6]. Previous studies have suggested that the risks of mortality among both PWH with HCV and those with HBV were higher compared with those with HIV mono-infection [5, 7]. However, to date there are limited data on mortality rates among PWH jointly infected with HCV and HBV, and most studies have come from high-income settings with limited follow-up time.

Patients with HCV also have an increased risk of type 2 diabetes mellitus (T2DM), although the mechanism for this relationship is unclear [8]. Extrahepatic effects of HCV viremia may disrupt endocrine function and glucose homeostasis, resulting in increased risk of insulin resistance, hyperglycemia, and T2DM [9–11]. T2DM is an important comorbidity in PWH, which is also associated with increased risk of mortality [12–14]. Hence, comorbidities with HBV or HCV and T2DM

together may negatively impact quality of life and survival in PWH. Preliminary studies suggest that insulin resistance, hyperglycemia, and T2DM are associated with accelerated liver fibrosis, which is the leading cause of liver death in patients with HCV infection [15, 16]. However, among PWH there is a lack of information on mortality associated with HBV and/or HCV in the context of hyperglycemia.

Among PWH, the clinical management of HCV or HBV with hyperglycemia presents a substantial challenge for health care systems and physicians [10]. Data that support the development of clinical guidelines to manage these comorbidities among PWH are urgently needed. The International Union Against Tuberculosis and Lung Disease operated the Integrated HIV Care program in Myanmar through 49 clinics providing antiretroviral therapy (ART) to more than one-third of the total PWH on treatment in Myanmar. In 2015, ~240 000 out of 52 million total population in Myanmar had HIV, and 106 320 were on ART [18]. The prevalence of HBV and HCV was 6.5% and 2.7%, respectively, in general population [19]. We therefore conducted a cohort study among PWH in the Integrated HIV Care program in Myanmar to (1) assess the association between HBV and HCV seropositivity with all-cause mortality and (2) determine whether the association between HBV and HCV seropositivity with all-cause mortality varied by baseline hyperglycemia status among PWH.

METHODS

Study Design, Setting, and Source of Data
We conducted a cohort study using routinely collected data from the Integrated HIV Care program in Myanmar. At enrollment to HIV care at the Integrated HIV Care Program's clinics, PWH received a clinical examination, tuberculosis (TB) disease screening, and baseline laboratory measures including HBV, HCV, CD4 count, hemoglobin, and random blood glucose. PWH received antiretroviral therapy (ART) and treatment for other opportunistic infections according to World Health Organization (WHO) HIV clinical guidelines [17]. Chronic HBV treatment (tenofovir disoproxil fumarate [TDF] and lamivudine) became available in 2011 as part of the preferred first-line ART. HCV RNA testing and chronic HCV treatment using direct-acting antivirals were not available during the study period. PWH were followed up routinely every 3 months. At every visit, medical officers recorded the patient's data on paper-based patient medical records, and data entry operators entered this into an electronic database, which was used for this study.

Study Population
Eligible participants included adult PWH defined as, according to HIV care program guidelines in Myanmar, aged ≥15 years who initiated ART between May 1, 2005, and June 31, 2016,

and who were tested for HBV and/or HCV coinfection at enrollment to HIV care. We excluded 11% of PWH whose HBV and HCV status were not measured.

Study Variables
The primary exposure variables were HBV and/or HCV seropositivity status at enrollment to HIV care. HBV infection was measured using hepatitis B surface antigen (HBsAg; Alere Determine), and HCV seropositivity was measured by HCV antibody testing (OraQuick immunoassay). We categorized PWH as having HIV mono-infection if the patient tested negative for both HBV and HCV; HBV coinfection if the patient tested positive for HBV only; HCV seropositive if the patient tested positive for HCV only; and HBV-HCV seropositive if the patient tested positive for both HBV and HCV. The secondary exposure of interest was hyperglycemia at enrollment, defined as random blood glucose ≥140 mg/dL using the WHO 2-hour postprandial blood glucose classification for diagnosis of prediabetes [18]. Random blood glucose was measured at enrollment to HIV care by glucometer using capillary blood.

The primary outcome was all-cause mortality, defined as death due to any cause between the date of ART initiation and June 30, 2017 (the end of follow-up). The patient outcome was recorded as death based on hospital records or a report from the patient's family. Date of death was recorded from hospital records if patients died at the hospital or as reported by families if the patient died at home. Other patient outcomes included regular follow-up (attending scheduled clinic appointments), loss to follow-up (not attending the clinic within 3 months after a scheduled appointment date), and transfer out (patient was transferred to another HIV care program).

Covariates included age, gender, alcohol use, body mass index (BMI), CD4 cell count, WHO HIV clinical staging, anemia, tuberculosis disease status at enrollment, and ART regimen at initiation. Alcohol use was categorized based on self-report (never, habitual [daily], or socially [occasionally]) at the time of enrollment. BMI was calculated from enrollment weight and height. Anemia was categorized based on hemoglobin (mg/dL) levels tested at enrollment: normal (male, ≥13 g/dL; female, ≥12 g/dL), mild (male, 11–12.9 g/dL; female, 11–11.9 g/dL), moderate (both sexes, 8.0–10.9 g/dL), and severe anemia (both sexes, <8.0 g/dL). TB disease status (yes/no) was defined by whether the patient had a diagnosed pulmonary or extrapulmonary tuberculosis at the time of enrollment to HIV care. ART regimen was categorized into 2 groups: PWH initiating treatment on a TDF and lamivudine–containing regimen and those initiating treatment on other regimens.

Analysis and Statistics
All-cause mortality rates (per 100 person-years [PY] of follow-up) were calculated by dividing the number of deaths by total

PY of follow-up for 4 exposure groups: HIV mono-infection, HBV coinfected, HCV seropositive, and HBV-HCV seropositive. Follow-up PY were calculated as the time between the date of ART initiation and date of all-cause mortality, loss to follow-up, or end of follow-up (June 30, 2017). Kaplan-Meier survival estimates were used to plot survival curves during the follow-up after ART initiation, stratified by HBV and/or HCV seropositive status. To determine the association between HBV and/or HCV seropositivity with rate of all-cause mortality, we used Cox proportional hazard models to estimate hazard ratios (HRs) with 95% CIs. Variables that did not satisfy proportional hazard assumptions were included as time-varying covariates in the regression model [19]. Final models were adjusted for potential confounders based on directed acyclic graph theory [20] and observed characteristics associated with exposure (HBV and/or HCV seropositive) and outcome (all-cause mortality) in bivariate analysis. We stratified the Cox proportional hazard models by hyperglycemia status to determine whether the association between HBV and HCV seropositivity with all-cause mortality in PWH varied by hyperglycemia status. Statistical interaction between HBV and/or HCV seropositivity and hyperglycemia status was assessed by including interaction terms (product terms between hepatitis and hyperglycemia) in multivariable models. All analyses were performed using STATA, version 14.2 (STATACorp, College Station, TX, USA).

Sensitivity Analyses

A sensitivity analysis was performed to account for bias due to outcome misclassification by estimating HRs using an alternate definition of all-cause mortality. In the sensitivity analysis, we classified PWH who were recorded as loss to follow-up as deaths because they may have died at home without reporting to the clinic. To account for missing data on hepatitis status and covariates, we performed multiple imputation using chained equations and estimated the hazard ratios.

Ethics Approval

The Ethics Advisory Group of The Union, Paris, France, the ethical review committee of the Department of Medical Research, Ministry of Health and Sports, Myanmar, and the Institutional Review Board at Georgia State University approved this study.

Patient Consent

The study used secondary programmatic data, and the need for informed patient consent was waived. The design of the work has been approved by our local ethical committee (Department of Medical Research, Ministry of Health and Sports, Myanmar).

RESULTS

Of the 27 722 PWH who were eligible for this study, 2260 (8%) were HBV positive, 2265 (8%) were HCV positive, and 178 (0.6%) were both HBV and HCV positive (Figure 1). The median age (interquartile range [IQR]) was 35 (30–42) years, 57% were male, 5% had hyperglycemia (random blood glucose ≥140 mg/dL), 36% had BMI <18.5, and 59% had CD4 <200 cell/mm³ (Table 1).

Association of HBV and/or HCV Seropositivity With All-Cause Mortality

A total of 27 722 PWH contributed to 96 994 person-years of follow-up in this analysis. During a median follow-up (IQR) of 3.1 (1.5–5.1) years, 3655 (13%) PWH died. The overall mortality rate was 3.8 (95% CI, 3.7–3.9) per 100 PY (Table 2). Demographic characteristics associated with all-cause mortality are reported in Supplementary Table 1. The mortality rate was highest among PWH with both HBV and HCV, at 7.7 per 100 PY, compared with HBV alone (4.6 deaths per 100 PY) and HCV alone (5.1 per 100 PY). Overall, cumulative survival at 8 years among those with HBV (77%) and HCV (73%) seropositivity was lower compared with those with HIV mono-infection (82%; log-rank P < .001) (Figure 2).

Compared with PWH with HIV mono-infection, the adjusted HR of all-cause mortality among PWH with HBV was 1.25 (95% CI, 1.11–1.40), among those who were HCV seropositive it was 1.52 (95% CI, 1.35–1.71), and among those who were both HBV and HCV seropositive it was 2.14 (95% CI, 1.51–3.02) (Table 2).

Association of HBV and/or HCV Seropositivity With All-Cause Mortality Stratified by Baseline Hyperglycemia Status

When stratified by glycemia status at enrollment to HIV care, the association between HCV seropositivity and mortality was greater among PWH with hyperglycemia. Overall, the mortality rate was higher among patients with hyperglycemia compared with those with euglycemia (5.4 vs 4.0 deaths per 100 PY), and the difference in mortality rate between patients with hyperglycemia and euglycemia was highest among those with HCV coinfection (9.8 vs 5.0 deaths per 100 PY) (Table 2). Among PWH with euglycemia, the adjusted HR for PWH with HCV coinfection was 1.44 (95% CI, 1.24–1.66), and for those who were both HBV and HCV seropositive it was 1.78 (95% CI, 1.14–2.77) compared with the HIV mono-infection group. Among PWH with hyperglycemia, the adjusted HR for PWH who were HCV seropositive was 1.85 (95% CI, 1.23–2.78), and for those who were both HBV and HCV seropositive it was 4.39 (95% CI, 1.51–12.76).

Sensitivity Analysis

In the sensitivity analyses that re-classified PWH who were lost to follow-up into the all-cause mortality group, the associations
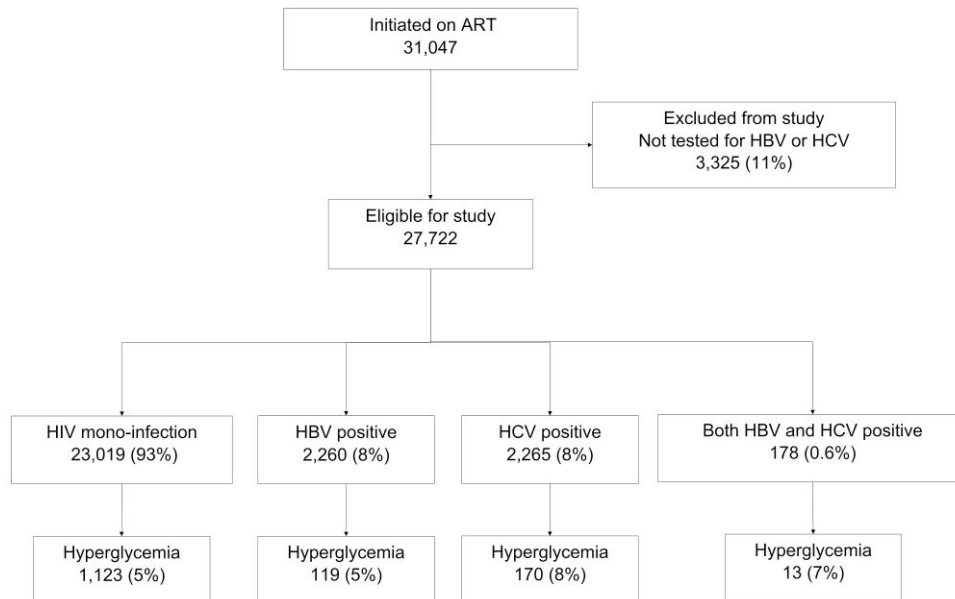
Figure 1. Flow diagram of the people with HIV initiated on ART stratified by their baseline HBV and/or HCV coinfection and hyperglycemia status, Myanmar, 2005–2017. Hyperglycemia: random blood glucose ≥140 mg/dL. Abbreviations: ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus.

between hepatitis seropositivity and all-cause mortality remained significant. For example, the adjusted hazard ratio (aHR) for all-cause mortality among PWH with HBV was 1.19 (95% CI, 1.09–1.32), for those with HCV it was 1.46 (95% CI, 1.32–1.60), and for those with HCV and HBV it was 2.36 (95% CI, 1.82–3.06), which remained similar compared with the primary analyses. After missing data were imputed (n = 31 704), the aHR for all-cause mortality among PWH with HBV was 1.11 (95% CI, 1.01–1.22), for those with HCV it was 1.20 (95% CI, 1.07–1.36), and for those with HCV and HBV it was 1.50 (95% CI, 1.07–2.12).

DISCUSSION

In this study, we found a high prevalence of HBV or HCV seropositivity among a cohort of PWH: Nearly 1 in 10 patients had HBV- or HCV-positive serology at enrollment to HIV care. We observed that being HBV and/or HCV seropositive greatly increased the all-cause mortality rate among PWH on HIV treatment. The relative all-cause mortality rate in PWH with HBV coinfection was 20% higher, and for those who were HCV seropositive it was 50% higher at any given point in time compared with patients with HIV mono-infection. Among PWH with dual HBV and HCV seropositivity, the hazard of mortality was 2 times higher compared with those who were seronegative. Importantly, our results suggest that the relationship between HBV and/or HCV seropositivity and mortality varies by the patient's hyperglycemia status. The mortality

rate of HCV-seropositive PWH with hyperglycemia was twice the mortality rate of those who were HCV seropositive and euglycemic.

Our finding that PWH with HBV and/or HCV had higher mortality rates is commensurate with data from other settings where treatment for HBV or HCV coinfection was not available [3, 5, 21–25]. Previous studies have suggested that PWH with HBV or HCV coinfection were more likely to progress to chronic hepatitis, have a high HBV or HCV replication rate, and experience rapid progression to liver fibrosis—contributing to higher mortality compared with those with individual infection [26–28]. A meta-analysis conducted in 2009 estimated that mortality rates in PWH with HCV were 1.35 (95% CI, 1.11–1.63) times the rate observed in those with HIV mono-infection [5]. TREAT Asia, which was a multicenter cohort study conducted among 7455 PWH followed for 10 years on ART in Asian Pacific countries, showed similar results, although Myanmar was not one of the study sites [29]. The aHR of mortality among PWH with HCV compared with HIV mono-infection was 1.81 (95% CI, 1.21–2.72) in the TREAT Asia study and 1.52 (95% CI, 1.35–1.71) in our study. The same study also reported that PWH with HBV had higher mortality rates than those with HIV mono-infection (aHR, 1.33; 95% CI, 0.90–1.98), which is similar to our findings (aHR, 1.25; 95% CI, 1.11–1.40). The TREAT Asia study did not estimate aHR among PWH with both HBV and HCV infections. Another large cohort study (n = 25 486) with a long follow-up time conducted in the United Kingdom in 2014 reported that

Table 1. Demographic, Clinical, and Treatment Characteristics of People With HIV at Antiretroviral Therapy Initiation by HBV and/or HCV Coinfection Status, Myanmar, 2005–2017 (n = 27 722)

Characteristics	Total No.	Total Col %	HIV Mono-infection (n = 23 019) No.	HIV Mono-infection Row %	HBV (n = 2260) No.	HBV Row %	HCV (n = 2265) No.	HCV Row %	HBV and HCV (n = 178) No.	HBV and HCV Row %
Age	…	…	…	…	…	…	…	…	…	…
Median (IQR), y	35 (30–42)		35 (30–41)		35 (30–41)		35 (30–43)		35 (30–40)	
15–24 y	1838	7	1537	84	135	7	156	8	10	1
25–45 y	21 887	79	18 207	83	1851	8	1686	8	143	1
>45 y	3997	14	3275	82	274	7	423	11	25	1
Gender	…	…	…	…	…	…	…	…	…	…
Male	15 764	57	12 385	79	1538	10	1699	11	142	1
Female	11 958	43	10 634	89	722	6	566	5	36	0
Random blood glucose	…	…	…	…	…	…	…	…	…	…
Median (IQR), mg/dL	90 (76 106)		88 (75–106)		90 (76–107)		94 (77–114)		95 (79–118)	
Euglycemia (<140 mg/dL)	20 428	74	16 959	83	1676	8	1659	8	134	1
Hyperglycemia (≥140 mg/dL)	1425	5	1123	79	119	8	170	12	13	1
Not recorded	5869	21	4937	84	465	8	436	7	31	1
Alcohol drinking	…	…	…	…	…	…	…	…	…	…
Never	18 386	66	15 863	86	1299	7	1140	6	84	0
Habitual (daily)	2370	9	1834	77	278	12	242	10	16	1
Social (occasionally)	6145	22	4627	75	623	10	821	13	74	1
Not recorded	821	3	695	85	60	7	62	8	4	0
BMI	…	…	…	…	…	…	…	…	…	…
Median (IQR), kg/m^2	19 (17–22)		19 (1722)		19 (1721)		19 (1822)		21 (18–22)	
<18.5 kg/m^2	9970	36	8342	84	858	9	725	7	45	0
18.5–22.9 kg/m^2	9853	36	7920	80	829	8	1018	10	86	1
23.0–27.5 kg/m^2	3363	12	2821	84	245	7	273	8	26	1
>27.5 kg/m^2	1599	6	1421	89	113	7	63	4	2	0
Not recorded	2933	11	2515	86	215	7	186	6	19	1
WHO clinical staging	…	…	…	…	…	…	…	…	…	…
1 or 2	11 192	40	9342	83	820	7	954	9	76	1
3 or 4	16 519	60	13 667	83	1440	9	1310	8	102	1
Not recorded	11	0	10	91	0	0	1	9	0	0
CD4 count	…	…	…	…	…	…	…	…	…	…
Median (IQR), cells/mm^3	158 (72–287)		154 (70–284)		149 (70–274)		201 (104–329)		209 (116–337)	
>350 cells/mm^3	4668	17	3816	82	335	7	476	10	41	1
200–349 cells/mm^3	6522	24	5289	81	523	8	657	10	53	1
<200 cells/mm^3	16 323	59	13 741	84	1380	8	1120	7	81	0
Not recorded	210	1	173	82	22	10	12	6	3	1
Anemia	…	…	…	…	…	…	…	…	…	…
No anemia	8566	31	6879	80	686	8	925	11	76	1
Mild to moderate	16 610	60	13 964	84	1375	8	1184	7	87	1
Severe	2088	8	1798	86	155	7	123	6	12	1
Not recorded	458	2	378	83	44	10	33	7	3	1
Tuberculosis disease[a]	…	…	…	…	…	…	…	…	…	…
No	19 452	70	16 171	83	1516	8	1634	8	131	1
Yes	8270	30	6848	83	744	9	631	8	47	1
Initiated on TDF and lamivudine	…	…	…	…	…	…	…	…	…	…
No	14 100	51	12 344	88	725	5	992	7	39	0
Yes	13 622	49	10 675	78	1535	11	1273	9	139	1

Abbreviations: BMI, body mass index; IQR, interquartile range; TB, tuberculosis; TDF, tenofovir disoproxil fumarate.

[a]Patients who received TB treatment at enrollment to HIV care or started TB treatment within 90 days of enrollment to HIV care.

dual HBV-HCV coinfection substantially increased the mortality rate in PWH (adjusted risk ratio, 2.97; 95% CI, 2.12–4.14) compared with HIV mono-infection, although mortality rates for all groups were lower in the UK study compared with our study [25]. The mortality rate among people with HIV mono-infection and dual HBV-HCV coinfection in the UK study was 7.4 and 8.7 per 1000 PY, while the mortality rate in our study was 36 and 77 per 1000 PY.

Table 2. Association Between HBV and/or HCV Coinfection and All-Cause Mortality Among People With HIV, Overall and Stratified by Their Glycemia Level, Myanmar, 2005–2017 (n = 27 722)

	Total		All-Cause Mortality									
	No.	Person-Years	No.	Rate[a]	[95% CI]	HR[b]	[95% CI]		aHR[b,c]	[95% CI]	
All patients	27 722	96 994	3655	3.8	[3.7–3.9]	…	…	…	…	…	…
HIV mono-infection	23 019	82 184	2932	3.6	[3.4–3.7]	Ref	…	…	Ref	…	…
HBV	2260	7885	358	4.6	[4.1–5.1]	1.37	[1.23–1.54]		1.25	[1.11–1.40]	
HCV	2265	6498	332	5.1	[4.6–5.7]	1.50	[1.33–1.69]		1.52	[1.35–1.71]	
HBV and HCV	178	428	33	7.7	[5.5–10.9]	2.27	[1.61–3.21]		2.14	[1.51–3.02]	
Patients with euglycemia	20 428[d]	66 841	2681	4.0	[3.9–4.2]	…	…	…	…	…	…
HIV mono-infection	16 959	56 557	2160	3.8	[3.7–4.0]	Ref	…	…	Ref	…	…
HBV	1676	5444	274	5.0	[4.5–5.7]	1.43	[1.26–1.62]		1.28	[1.12–1.46]	
HCV	1659	4512	227	5.0	[4.4–5.7]	1.39	[1.21–1.61]		1.44	[1.24–1.66]	
HBV and HCV	134	328	20	6.1	[3.9–9.5]	1.72	[1.11–2.69]		1.78	[1.14–2.77]	
Patients with hyperglycemia	1425[d]	4464	241	5.4	[4.8–6.1]	…	…	…	…	…	…
HIV mono-infection	1123	3706	181	4.9	[4.2–5.7]	Ref	…	…	Ref	…	…
HBV	119	387	21	5.3	[3.5–8.3]	1.16	[0.73–1.83]		0.95	[0.59–1.51]	
HCV	170	356	35	9.8	[7.1–13.7]	1.79	[1.19–2.67]		1.85	[1.23–2.78]	
HBV and HCV	13	16	4	25.6	[9.6–68.3]	4.22	[1.50–11.93]		4.39	[1.51–12.76]	

Likelihood ratio *P* value for statistical interaction term between HBV and/or HCV coinfection and hyperglycemia status = .09. Euglycemia = random blood glucose <140 mg/dL; Hyperglycemia = random blood glucose ≥140 mg/dL.

Abbreviations: aHR, adjusted hazard ratio; HR, hazard ratio; HBV, hepatitis B virus; HCV, hepatitis C virus.

[a]Rate per 100 person-years of follow-up.

[b]Proportional hazard assumption did not hold for the exposure variable and was included as a time-varying covariate in the model.

[c]Adjusted for age, gender, alcohol drinking history, body mass index, CD4+ T-cell count, anemia, and tuberculosis disease at enrollment and initiated on TDF plus lamivudine regimen or not.

[d]These numbers do not add up to the total because 5869 (21%) PWH had missing random blood glucose measurements. The overall mortality rate among those with missing random blood glucose measurements was 2.85 (95% CI, 2.65–3.07).

Growing evidence suggests that PWH with HCV coinfection are at increased risk of metabolic syndromes including hyperglycemia and T2DM. Together, HCV coinfection and T2DM are likely to increase metabolic complications, which contribute to increased mortality rates in PWH [30–32]. A 2018 cohort study from Italy included 15 571 PWH and reported a significant association between the prevalence of HCV coinfection and T2DM (adjusted odds ratio, 3.35; 95% CI, 2.38–4.71) [9]. In this same study, PWH with HCV coinfection and T2DM had a 3-fold higher risk of liver-related death compared with those without T2DM. In our study, HCV-coinfected PWH with hyperglycemia had a nearly 2-fold higher risk of all-cause mortality compared with those without hyperglycemia. Emerging evidence suggests that treatment of HCV may improve metabolic complications in PWH with HCV and T2DM [33, 34]. A large cohort study (n = 1411) conducted in Taiwan in 2014 found that PWH with HCV and T2DM who received HCV treatment had a significantly lower rate of metabolic complications, such as end-stage renal disease, ischemic stroke, and acute coronary syndrome, compared with those without HCV treatment (HR, 0.16, 0.53, and 0.64, respectively) [33]. At the time of our study, HCV treatment was unavailable in Myanmar, which likely contributed to the increased mortality among HCV-seropositive PWH with hyperglycemia. Although HCV treatment in PWH has become available in Myanmar and other settings, access to HCV treatment for

PWH remains challenging in low- and middle-income countries including Myanmar [35]. Even in a high-income country like the United States, only an estimated 56% of insured PWH who have HCV infection received HCV RNA testing and only 27% received treatment in 2014–2019 [36]. Additional studies should assess the impacts of HCV treatment on metabolic, hepatic, and survival outcomes among PWH to advocate for increased HCV treatment coverage among PWH.

Our study has 4 main limitations. First, our results cannot differentiate whether increased mortality rates were associated with acute or chronic HBV-HCV infections because the serology tests used in this study only measured acute HBV or previous HCV infection status (an estimated 90% of acute HBV and 50% of acute HCV infection naturally resolves) [37, 38]. In addition, our data did not capture those who acquired coinfection during follow-up and those who may have had their infection resolved with hepatitis treatment from private clinics. Second, there is potential misclassification of hyperglycemic status given that our measure of blood glucose was limited to one-time measurement of random blood glucose, which cannot be used for diagnosis of diabetes or prediabetes and does not capture long-term glycemic status: This requires measurement of glycated hemoglobin, which was not available during our study. However, in many resource-limited settings, a single measure of hyperglycemia by random blood glucose is often used as an indicator for further testing. It is also possible that
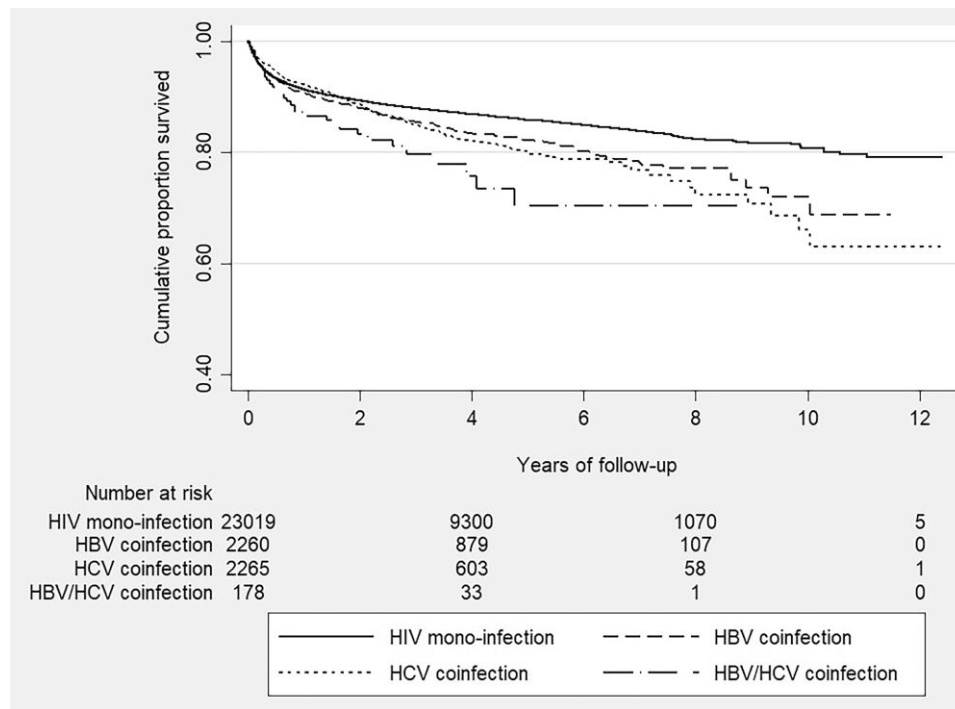
Figure 2. Kaplan-Meier survival curve of all-cause mortality during follow-up HIV care after antiretroviral therapy stratified by hepatitis B and/or C coinfection status, Myanmar, 2005–2017. Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus.

the misclassification of hyperglycemia status was differential with respect to mortality because severely ill patients who were at risk of higher mortality may have either very low (poor nutrition) or very high (stress related) blood glucose levels. Similarly, we were unable to access information on whether patients had a previous T2DM diagnosis or used medications to manage hyperglycemia. Third, we excluded 11% of PWH with no information on HBV or HCV status who may have had different clinical characteristics compared with those included in the study. To assess the impact of missing HBV-HCV status on our inference, we performed multiple imputation using chained equations and estimated hazard ratios assuming missingness at random. The results from the imputation analysis reported HRs for all the models with similar results, suggesting that the missing results did not importantly impact generalizability. Fourth, there may have been data recording and data entry errors, as our analysis was based on routinely collected paper-based program data transcribed into electronic data.

Despite limitations, this large cohort study included nearly 100 000 PY of follow-up data from one-third of Myanmar's PWH, and the key public health and clinical implications are broadly generalizable. First, high HBV and HCV seroprevalence in PWH suggests the need for strengthening of public health prevention interventions such as HBV vaccination programs and harm reduction approaches for HCV, specifically for

PWH and those at high risk of HIV [7, 26, 39]. Second, as HCV coinfection significantly increased mortality among PWH, HCV treatment with direct-acting antiviral agents for HCV that are effective in HIV/HCV-coinfected patients should be accessible for this population to decrease mortality [40, 41]. Third, although a single measure of glycemic status by random blood glucose is not sufficient to diagnosis hyperglycemia (ie, diabetes or prediabetes), the association between HCV seropositivity and mortality was higher in PWH with hyperglycemia. A single measure of random blood glucose may have clinical utility to identify PWH who (1) need to be referred for additional metabolic screening and hyperglycemia management and (2) have increased mortality risk regardless of underlying hyperglycemia. Future studies among PWH designed to formally evaluate the effectiveness of screening by random blood glucose for diabetes and mortality prevention should be prioritized in resource-limited settings.

CONCLUSIONS

The seroprevalence of HBV and HCV was high in this group of PWH from Myanmar. Mortality rates were increased among PWH with either HBV or HCV, and the mortality rates were even higher among those with hyperglycemia. Prevention, management, and treatment of HBV and HCV would be beneficial to reduce mortality among PWH. Management of blood

glucose levels among PWH with HBV and/or HCV needs to be evaluated.

Supplementary Data

Acknowledgments

References

1. World Health Organization. Hepatitis B factsheet. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed December 31, 2019.
2. World Health Organization. Hepatitis C factsheet. Available at: https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed December 31, 2019.
3. Anderson KB, Guest JL, Rimland D. Hepatitis C virus coinfection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA Cohort Study. Clin Infect Dis 2004; 39:1507–13.
4. Teira R, Study Group VACH. Hepatitis-B virus infection predicts mortality of HIV and hepatitis C virus coinfected patients. AIDS Lond Engl 2013; 27:845–8.
5. Chen T-Y, Ding EL, Seage GR, Kim AY. Meta-analysis: increased mortality associated with HCV in HIV-infected persons is not related to HIV disease progression. Clin Infect Dis 2009; 49:1605–15.
6. Kovari H, Rauch A, Kouyos R, et al. Hepatitis C infection and the risk of non-liver-related morbidity and mortality in HIV-positive persons in the Swiss HIV Cohort Study. Clin Infect Dis 2016; 64:490–7.
7. Chun HM, Roediger MP, Hullsiek KH, et al. Hepatitis B virus coinfection negatively impacts HIV outcomes in HIV seroconverters. J Infect Dis 2012; 205: 185–93.
8. White DL, Ratziu V, El-Serag HB. Hepatitis C infection and risk of diabetes: a systematic review and meta-analysis. J Hepatol 2008; 49:831–44.
9. Leone S, Lorenzini P, Cozzi-Lepri A, et al. Impact of diabetes on the risk of serious liver events and liver-related deaths in people living with HIV and hepatitis C co-infection: data from the ICONA Foundation Cohort Study. Eur J Clin Microbiol Infect Dis 2019; 38:1857–65.
10. Collins LF, Adekunle RO, Cartwright EJ. Metabolic syndrome in HIV/HCV co-infected patients. Curr Treat Options Infect Dis 2019; 11:351–71.
11. Negro F, Forton D, Craxì A, Sulkowski MS, Feld JJ, Manns MP. Extrahepatic morbidity and mortality of chronic hepatitis C. Gastroenterology 2015; 149:1345–60.
12. Moreira RC, Pacheco AG, Paula A, et al. Diabetes mellitus is associated with increased death rates among HIV-infected patients in Rio de Janeiro, Brazil. AIDS Res Hum Retroviruses 2016; 32:1210–8.
13. Suligoi B, Virdone S, Taborelli M, et al. Excess mortality related to circulatory system diseases and diabetes mellitus among Italian AIDS patients vs. non-AIDS population: a population-based cohort study using the multiple causes-of-death approach. BMC Infect Dis 2018; 18:428.
14. Serraino D, Bruzzone S, Zucchetto A, et al. Elevated risks of death for diabetes mellitus and cardiovascular diseases in Italian AIDS cases. AIDS Res Ther 2010; 7:11.
15. Desbois A-C, Cacoub P. Diabetes mellitus, insulin resistance and hepatitis C virus infection: a contemporary review. World J Gastroenterol 2017; 23:1697–711.
16. Li X, Gao Y, Xu H, Hou J, Gao P. Diabetes mellitus is a significant risk factor for the development of liver cirrhosis in chronic hepatitis C patients. Sci Rep 2017; 7: 9087.
17. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. 2016. Available at: http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf. Accessed August 17, 2019.
18. World Health Organization. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia. 2006. Available at: http://www.who.int/diabetes/publications/diagnosis_diabetes2006/en/. Accessed June 27, 2018.
19. Kleinbaum DG, Klein M. Survival Analysis: A Self-Learning Text. Springer; 2006.
20. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology 1999; 10:37–48.
21. Tsuchiya N, Pathipvanich P, Rojanawiwat A, et al. Chronic hepatitis B and C co-infection increased all-cause mortality in HAART-naive HIV patients in Northern Thailand. Epidemiol Infect 2013; 141:1840–8.
22. van Griensven J, Phirum L, Choun K, Thai S, Weggheleire AD, Lynen L. Hepatitis B and C co-infection among HIV-infected adults while on antiretroviral treatment: long-term survival, CD4 cell count recovery and antiretroviral toxicity in Cambodia. PLoS One 2014; 9:e88552.
23. Branch AD, Van Natta ML, Vachon M-L, et al. Mortality in hepatitis C virus-infected patients with a diagnosis of AIDS in the era of combination antiretroviral therapy. Clin Infect Dis 2012; 55:137–44.
24. Hernando V, Perez-Cachafeiro S, Lewden C, et al. All-cause and liver-related mortality in HIV positive subjects compared to the general population: differences by HCV co-infection. J Hepatol 2012; 57:743–51.
25. Thornton AC, Jose S, Bhagani S, et al. Hepatitis B, hepatitis C, and mortality among HIV-positive individuals. AIDS Lond Engl 2017; 31:2525–32.
26. Kourtis AP, Bulterys M, Hu DJ, Jamieson DJ. Hiv–HBV coinfection—a global challenge. N Engl J Med 2012; 366:1749–52.
27. Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. Lancet Infect Dis 2007; 7:402–9.
28. Debes JD, Bohjanen PR, Boonstra A. Mechanisms of accelerated liver fibrosis progression during HIV infection. J Clin Transl Hepatol 2016; 4:328–35.
29. Chen M, Wong W-W, Law MG, et al. Hepatitis B and C co-infection in HIV patients from the TREAT Asia HIV observational database: analysis of risk factors and survival. PLoS One 2016; 11:e0150512.
30. Bedimo R, Abodunde O. Metabolic and cardiovascular complications in HIV/HCV-co-infected patients. Curr HIV/AIDS Rep 2016; 13:328–39.
31. Reid M, Ma Y, Scherzer R, et al. Higher CD163 levels are associated with insulin resistance in hepatitis C virus-infected and HIV-infected adults. AIDS Lond Engl 2017; 31:385–93.
32. Slama L, Le Camus C, Serfaty L, Pialoux G, Capeau J, Gharakhanian S. Metabolic disorders and chronic viral disease: the case of HIV and HCV. Diabetes Metab 2009; 35:1–11.
33. Hsu Y-C, Lin J-T, Ho HJ, et al. Antiviral treatment for hepatitis C virus infection is associated with improved renal and cardiovascular outcomes in diabetic patients. Hepatol Baltim Md 2014; 59:1293–302.
34. Hsu Y-C, Ho HJ, Huang Y-T, et al. Association between antiviral treatment and extrahepatic outcomes in patients with hepatitis C virus infection. Gut 2015; 64: 495–503.
35. Rupasinghe D, Choi JY, Kumarasamy N, et al. Viral hepatitis and the cascade of care among people living with HIV in the Asia-Pacific. HIV Med 2022; 23:959–68.
36. Ferrante ND, Newcomb CW, Forde KA, et al. The hepatitis C care cascade during the direct-acting antiviral era in a United States commercially insured population. Open Forum Infect Dis 2022; 9:XXX–XX.
37. Fattovich G. Natural history of hepatitis B. J Hepatol 2003; 39(Suppl 1):S50–8.
38. Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol 2014; 61: S58–68.
39. National Hepatitis Control Program. Myanmar national strategic plan on viral hepatitis 2016–2020. 2017. Available at: https://www.aidsdatahub.org/resource/myanmar-national-strategic-plan-viral-hepatitis-2016-2020. Accessed December 30, 2019.
40. Breskin A, Westreich D, Cole SR, et al. The effects of hepatitis C infection and treatment on all-cause mortality among people living with human immunodeficiency virus. Clin Infect Dis 2019; 68:1152–9.
41. Kronfli N, Bhatnagar SR, Hull MW, et al. Trends in cause-specific mortality in HIV–hepatitis C coinfection following hepatitis C treatment scale-up. AIDS Lond Engl 2019; 33:1013–22.