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Demographic and Clinical Characteristics of Patients With Hepatitis C and Hepatitis B Co-Infection, Georgia, 2017–2023

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Abstract

Persons co-infected with hepatitis C virus and hepatitis B virus (HCV-HBV) are at increased risk of developing liver disease compared with mono-infected individuals. In Georgia, all patients undergoing hepatitis C treatment are eligible for free testing for hepatitis B surface antigen (HBsAg). However, further hepatitis B evaluations and treatment are not free. We explored demographic and clinical characteristics associated with HCV-HBV co-infection among persons treated for HCV infection. Persons aged ≥ 18 years with HCV infection who initiated HCV treatment during 2017–2023 were included. Patients were grouped as HCV mono-infected, HCV-HBV co-infected (HBsAg positive), and HBV exposed (total HBV core antibody positive, HBsAg negative). We present descriptive analysis and adjusted prevalence ratios (aPR) with 95% confidence intervals (95% CI). Of 54,994 adults treated for hepatitis C, 68.1% had HCV mono-infection, 29.3% were previously exposed to HBV, and 2.6% had HCV-HBV co-infection. Persons who were aged 18–45 years (aPR: 1.75, 95% CI: 1.48–2.08), male (aPR: 1.38, 95% CI: 1.11–1.71), reported ever injecting drugs (aPR: 1.40, 95% CI: 1.19–1.66), had end-of-HCV treatment, alanine transaminase (ALT) levels > 80 IU/L (aPR: 2.14, 95% CI: 1.40–3.29) and did not achieve hepatitis C cure after treatment (aPR: 1.83, 95% CI: 1.13–2.95) were more likely to have HCV-HBV co-infection vs. HCV mono-infection. Patients who did not achieve cure and had persistently higher ALT levels after hepatitis C treatment were more likely to have HCV-HBV co-infection. Expanded access to hepatitis B care and treatment, and co-management of HBV infection along with HCV treatment in co-infected persons are needed to improve clinical outcomes.

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Conflicts of Interest

The authors declare no conflicts of interest.

Keywords

co-infection; Georgia; hepatitis B; hepatitis C

1 | Introduction

Persons with hepatitis C virus (HCV) and hepatitis B virus (HBV) co-infection are at an increased risk of developing liver cirrhosis and hepatocellular carcinoma compared to those having mono-infection of either virus. Hepatitis B surface antigen loss and hepatocellular carcinoma development in patients with dual hepatitis B and hepatitis C infection [1–5]. HBV and HCV share similar modes of transmission, and co-infection is not uncommon, but there are limited global or regional estimates of co-infection. Studies from Western Europe and East and Central Asian countries show that 2%–10% of HCV antibody reactive participants have chronic hepatitis B [4].

Currently, there are very effective medications for treating HCV infection, with 8- to 12-week pan-genotypic oral treatment regimens achieving sustained virologic response (SVR) in up to 94% of patients [6]. While there is no antiviral medication that leads to clearance of cccDNA in HBV infection, functional cure defined by the loss of HBsAg is possible. Furthermore, more than 90% of patients with chronic HBV infection who stay on treatment achieve viral suppression and observe a reduction in risk for the development of cirrhosis and liver cancer [7, 8]. According to current treatment guidelines, the majority of patients with chronic hepatitis B who start antiviral treatment will likely need to take medication for the rest of their lives [9]. Vaccination against HBV is highly effective and safe and provides long-term protection after three doses of the hepatitis B vaccine [9, 10].

Current evidence suggests that direct-acting antiviral (DAA) regimens are highly effective in treating HCV infection in patients co-infected with HBV, and treatment response is not different from that in those with HCV mono-infection [3, 11]. However, a major challenge in treating persons with HCV-HBV co-infection with DAAs is the possibility of reactivation of HBV infection and flares characterised by elevated HBV DNA and alanine transaminase (ALT) levels [12, 13]. A recent meta-analysis showed that the pooled HBV reactivation rate after HCV treatment was 14.1%, with the risk of reactivation highest during the treatment period, and 12% of patients with HBV reactivation experienced clinical signs of viral hepatitis and required HBV treatment [14].

There are different recommendations on how to approach treatment and prevention of HBV reactivation among persons co-infected with HCV [15]. According to the European Association for the Study of the Liver (EASL) guidelines, HCV-HBV co-infected patients who are HBV surface antigen (HBsAg) positive should be considered for prophylaxis with nucleoside or nucleotide analogues (NA) at the start of DAA therapy and for at least 12 weeks after the end of DAA therapy [13]. WHO guidelines recommend HBV treatment initiation for all adults and adolescents (aged ≥ 12 years) co-infected with HCV, irrespective of HBV DNA or ALT levels or of the aspartate aminotransferase (AST) to Platelet Ratio Index (APRI) score, with annual monitoring of treatment response [9]. On the other hand, the American Association for the Study of Liver Disease (AASLD) hepatitis B guidelines

take into consideration HBV DNA, fibrosis staging and ALT levels to determine hepatitis B treatment eligibility. All persons with detectable HBsAg who do not meet the AASLD hepatitis B treatment eligibility guidelines can receive prophylactic HBV treatment for the duration of DAA treatment until assessment for SVR 12 weeks after the end of treatment. HCV-HBV co-infected patients, irrespective of hepatitis B treatment eligibility, should be monitored for HBV DNA and ALT every 4–8 weeks during DAA treatment and for 3 months after the end of DAA treatment [13]. Georgia does not have unified national guidelines for treating HCV-HBV co-infected patients.

Georgia launched its national Hepatitis C Elimination Program in 2015 [16], which offers free diagnostics and treatment with DAAs to all persons aged ≥ 12 years with HCV infection. Since 2015, treatment regimens have evolved considerably from only using sofosbuvir in combination with ribavirin with or without interferon, based on HCV genotype and fibrosis level, to changes in 2016, when ledipasvir/sofosbuvir became available and was recommended for all patients, but was prescribed with or without ribavirin depending on genotype and fibrosis level [17]. Finally, in late 2018, the pangenotypic velpatasvir/sofosbuvir was introduced and by 2020 represented nearly all treatments prescribed [18]. The program also includes free screening for HBsAg and hepatitis B vaccination (for susceptible individuals) for all persons eligible for hepatitis C treatment. However, further hepatitis B management including HBV DNA testing and treatment is not covered by the program nor standard health insurance. The hepatitis B vaccine was introduced in Georgia's national immunisation program in 2001, with birth dose (HepB-BD) for all newborns introduced in 2003 [19]. Hepatitis B vaccination is not universally offered to adults in Georgia, but it is free for some high-risk groups, including patients with HCV infection and persons who inject drugs (PWID).

A better understanding of the burden of HCV and HBV co-infection in Georgia is necessary to inform hepatitis B management and elimination efforts. The aim of this evaluation was to assess the prevalence of HCV-HBV co-infection among all patients treated for HCV infection in Georgia during 2017–2023. In addition, we explore socio-demographic characteristics, behaviours and clinical and laboratory parameters associated with HCV-HBV co-infection.

2 | Materials and Methods

2.1 | Data Sources

Data for this analysis comes from Georgia's National Electronic Hepatitis C Elimination Program Treatment database, which collects data on basic demographics, hepatitis C and hepatitis B diagnostic testing, baseline and on-treatment liver function test results, and HCV treatment outcomes. All Georgian citizens with current HCV infection determined through HCV RNA or HCV core antigen testing are eligible for DAA treatment. Persons aged ≥ 18 years who initiated HCV treatment within the programme from January 1, 2017, to December 31, 2023, were included in this analysis. Patients with missing test results for HBsAg or total HBV core antibody (total anti-HBc) were excluded.

Patients were categorised at baseline prior to initiating HCV treatment as HCV mono-infected (HCV RNA or HCV core antigen positive and negative for total anti-HBc and HBsAg), HCV-HBV co-infected (HCV RNA or HCV core antigen positive and HBsAg positive), or HCV infection previously exposed to HBV (HCV RNA or HCV core antigen positive and total anti-HBc positive and HBsAg negative). Liver fibrosis stage was determined at baseline, with advanced fibrosis defined as a liver elastography score $\geq$ F3 or FIB-4 score > 3.25 [20]. Priority was given to liver elastography results if there was a discrepancy. Clinical variables included ALT, AST and platelet (PLT) counts recorded at baseline/pre-treatment, ALT levels at weeks four and eight after DAA treatment initiation, and at the end of treatment (EOT; week 12 or 24, depending on regimen duration), and SVR at least 12 weeks after EOT. The upper end of the normal range for ALT and AST was 40 IU/L. All patients were treated with DAAs using either 12- or 24-week regimens (Table 1). History of injection drug use (IDU) was self-reported at the time of enrolment in the treatment programme. Mortality estimates were derived using death dates in the hepatitis C treatment programme database, which is linked to the national vital statistics database.

2.2 | Statistical Analysis

We present descriptive analysis and adjusted prevalence ratios (aPR) with 95% confidence intervals (CI) for HCV-HBV co-infection compared to HCV mono-infection for demographic characteristics, risk behaviours, clinical variables and treatment outcomes (e.g., SVR). In a multivariable model, aPRs were adjusted for age, sex, body mass index (BMI), HCV genotype and history of IDU. Covariates were tested for interaction and effect modification by adding interaction terms to the model and included in the final model for any with $p < 0.10$. In a sensitivity analysis, inverse probability weighting was used to elucidate the effect of missing values for ALT results at weeks four, eight, and end of treatment, as well as SVR testing, which was compared to unweighted results to assess potential bias in missing results. Similarly, for mortality analysis, inverse probability weighting was used to account for missing values for injection drug use. The proportion of patients with co-infection was determined using the year of DAA treatment initiation. In addition, we present descriptive analysis and aPRs with 95% CIs comparing patients with different status of HCV-HBV co-infection and exposure.

Odds ratios (ORs) and 95% CIs were calculated for the likelihood of having died by the end of the analysis period for HCV-HBV co-infected and HCV infected-HBV exposed (HBsAg negative and anti-HBc positive) compared to HCV mono-infected patients. Adjusted ORs (aOR) were produced after controlling for age, sex, BMI, history of injecting drugs and year of treatment initiation. All analysis was performed in SAS version 9.4 (Cary, North Carolina, USA).

Data for this analysis comes from Georgia's Hepatitis C Elimination Program, which was determined by the Institutional Review Board at Georgia's National Center for Disease Control and Public Health (NCDC) to be a programme evaluation and deemed by NCDC and U.S. Centers for Disease Control and Prevention (CDC) to be a public health programme activity.

3 | Results

3.1 | Characteristics of the Patient Population

From January 1, 2017 to December 31, 2023, among 57,805 adults treated for HCV infection in Georgia, 56,798 (98.3%) were screened for HBsAg, 50,356 (87.1%) were screened for total anti-HBc, and 12,643 (21.9%) for anti-HBs. After excluding 2811 persons with missing test results that prevented classification, the final sample size was 54,994 adults (Table 1). Overall, 68.1% ($n = 37,454$) of patients had HCV mono-infection, 29.3% ($n = 16,102$) had HCV mono-infection and were previously exposed to HBV, and 2.6% ($n = 1438$) had HCV-HBV co-infection. The median age was 47 years (interquartile range 39–57 years), and 74.2% were male. Among 53,014 persons with BMI results, 20.2% were obese, and among 46,634 respondents, 39.8% reported past or current injection drug use. Of 54,525 persons with elastography and/or FIB-4 scores, 27.2% had advanced liver fibrosis.

Overall, 16.5% had pre-treatment PLT count below the normal level of $150 \times 10^9/L$, 20.4% had pre-treatment AST > 80 IU/L and 31.3% of patients had pre-treatment ALT > 80 IU/L. At weeks four, eight and at the end of HCV treatment, 1.7%, 1.4% and 1.3%, respectively, had ALT > 80 IU/L. Of the 54,994 patients included, 52,113 (94.8%) completed their treatment course, 37,776 (72.5%) of whom were tested for SVR, and of them, 98.6% achieved cure.

The prevalence of HCV-HBV co-infection among persons treated for HCV infection ranged from 2.2% in 2018 and 2019 to 3.5% in 2023, with a year-to-year increase of 28% from 2020 to 2021 and 21% from 2022 to 2023 (Figure 1).

3.2 | Characteristics Associated With HCV-HBV Co-Infection

In a multivariable regression analysis, after adjusting for confounding, patients who were aged 18–45 years compared to those aged 46–60 years (aPR: 1.75, 95% CI: 1.48–2.08), male (aPR: 1.38, 95% CI: 1.11–1.71), reported a history of injection drug use (aPR: 1.40, 95% CI: 1.19–1.66), and were infected with HCV genotype 3 compared to genotype 1 (aPR: 1.33, 95% CI: 1.13–1.56) were more likely to have HCV-HBV co-infection compared to those having HCV-mono-infection (Table 2). In stratified analysis, HCV-HBV co-infection was more common among patients infected with HCV genotype 3 compared to genotype 1 if they reported never injecting (aPR 1.49; 95% CI: 1.16–1.90) or if they reported ever injecting drugs (aPR 1.24; 95% CI: 1.01–1.53).

Patients who, at the start of treatment, had a PLT count below the normal limit of 150×10^9 were more likely to have HCV-HBV co-infection (aPR: 1.29, 95% CI: 1.08–1.55), while patients who had advanced fibrosis stage (aPR: 1.11, 95% CI: 0.92–1.33), or elevated levels (> 80 IU/L) of ALT (aPR: 0.99, 95% CI: 0.82–1.19) or AST (aPR: 1.15, 95% CI: 0.95–1.39) were not more likely to have HCV-HBV co-infection compared to patients with HCV mono-infection.

Patients who, at week eight of the treatment, had elevated ALT (40–80 IU/L and > 80 IU/L compared to < 40 IU/L) were more likely to have HCV-HBV co-infection (aPR: 1.33, 95% CI: 1.06–1.67 and aPR: 2.60, 95% CI: 1.79–3.78, respectively). Having end-of-treatment

ALT levels of > 80 IU/L compared to < 40 IU/L was associated with HCV-HBV co-infection (aPR: 2.14, 95% CI: 1.40–3.29). Patients with a higher median value of ALT at week eight of treatment (aPR: 1.01, 95% CI: 1.01–1.01) and at the end of treatment (aPR: 1.01, 95% CI: 1.01–1.01) were more likely to have HCV-HBV co-infection. Patients with HCV-HBV co-infection had higher median values of ALT at pre-treatment, week 4, week 8 and at the end of treatment compared to patients with HCV mono-infection and those infected with HCV and exposed to HBV (Figure 2). Patients who did not achieve SVR were more likely to have HCV-HBV co-infection (aPR: 1.83, 95% CI: 1.13–2.95) compared to HCV mono-infection.

3.3 | Mortality Estimates for HCV Mono-Infection and HCV-HBV Co-Infection

Persons with HCV-HBV co-infection (aOR: 1.03; 95% CI: 0.78–1.34) and those infected with HCV and exposed to HBV (aOR: 1.07; 95% CI: 0.99–1.16) did not have significantly higher all-cause mortality compared to those with HCV mono-infection after adjusting for covariates in complete case analysis (Table 3). These findings did not change significantly after applying inverse probability weighting to assess the effect of missing values for injection drug use among those with HCV-HBV co-infection (aOR: 1.16; 95% CI: 0.87–1.54) or exposed to HBV (aOR: 1.06; 95% CI: 0.98–1.15).

3.4 | Characteristics Associated With HCV Infection and Exposure to HBV Infection

In a multivariable regression analysis, after adjusting for confounding, patients who were aged > 60 years compared to aged 46–60 years (aPR: 1.06, 95% CI: 1.01–1.11), male (aPR: 1.40, 95% CI: 1.34–1.47), reported a history of injection drug use (aPR: 1.21, 95% CI: 1.16–1.26) and were infected with HCV genotype 3 compared to genotype 1 (aPR: 1.12, 95% CI: 1.08–1.17) were more likely to have been previously exposed to HBV compared to those with HCV mono-infection (Table S1).

Patients who were aged 18–45 years compared to aged 46–60 years (aPR: 0.68, 95% CI: 0.65–0.71) who had elevated levels of ALT (between 40 and 80 IU/L) at weeks four and eight of treatment (aPR: 0.90, 95% CI: 0.85–0.95 and aPR: 0.92, 95% CI: 0.86–0.98, respectively), and EOT ALT between 40 and 80 IU/L (aPR: 0.92, 95% CI: 0.86–0.99), and did not achieve SVR (aPR: 0.74, 95% CI: 0.61–0.91) were less likely to have been exposed to HBV compared to those with HCV mono-infection in a complete case analysis.

3.5 | Sensitivity Analysis for Missing Values

Several of the variables used in our analysis had a high percentage of missing values (e.g., history of injection drug use [15% missing], end of treatment ALT [21% missing] and testing for SVR [31% missing]). After we conducted inverse probability weighting to assess the effect of missing values for these variables on the regression analysis results, the point estimates for prevalence ratios did not change meaningfully (Table S2). In sensitivity analysis, we observed that patients with higher ALT at week four of treatment (40–80 IU/L and > 80 IU/L compared to < 40 IU/L) were more likely to have HCV-HBV co-infection. Prior to inverse probability weighting, this association was not statistically significant.

4 | Discussion

Among 54,994 adults treated for HCV infection within the Hepatitis C Elimination Program in Georgia from 2017 to the end of 2023, who received testing for HBV infection, 2.6% had HCV-HBV co-infection. Compared to patients with HCV-mono-infection, patients who were aged 18–45 years (compared to aged 46–60 years), male, reported a history of injecting drugs, were infected with HCV genotype 3 versus genotype 1, had elevated ALT at week 8 of the treatment, and at the end of treatment and did not achieve SVR, were more likely to have HCV-HBV co-infection.

At the start of DAA treatment, we observe that more than two-thirds of all patients have elevated ALT levels (> 40 IU/L); however, we do not find that patients with elevated ALT levels are more likely to be co-infected. After 8 weeks of treatment and at the end of the treatment, approximately 1 in 10 patients still have elevated ALT levels, but at this point, those with elevated ALT are more likely to be co-infected. These findings suggest that some patients who were treated for HCV infection for more than 8 weeks still had signs of worsening liver disease. One potential explanation for this finding is worsening of liver disease due to HBV reactivation after receiving DAA treatment. Other studies have shown that compared to untreated HBV mono-infected controls, HCV-HBV co-infected patients receiving DAAs had a significantly higher risk of HBV reactivation, especially once HCV infection had been successfully cured [11]. HBV reactivation can have serious clinical consequences, and this has prompted the US Food and Drug Administration to include a boxed warning on all DAAs regarding the risk of HBV reactivation in individuals with HCV-HBV co-infection [11, 12, 21]. In this study, we did not have access to HBV DNA results, which are necessary to determine whether the worsening of liver status is due to HBV reactivation or another reason. To reduce the complications of HBV reactivation among co-infected patients, all patients undergoing HCV treatment should be tested for HBsAg and HBV DNA, monitored throughout the treatment process, evaluated for eligibility for HBV treatment, and offered treatment if eligible.

After conducting inverse probability weighting to assess the effect of missing values for ALT and other variables, we observed that patients with higher ALT levels at week 4 of treatment were more likely to have been co-infected. In contrast, the unweighted analysis did not reveal a statistically significant association at week 4 of treatment. This finding suggests that for some patients, HBV reactivation could start much earlier in the DAA treatment, and co-infected patients should be closely monitored from the start of the DAA treatment [14].

Several reviews showed that, especially in low and middle-income countries, testing for HBV is inaccessible mainly due to high costs or a lack of trained personnel, resulting in poor linkage to care and treatment and an increase in HBV transmission [22, 23]. The Hepatitis C Elimination Program in Georgia includes one free screening for HBsAg, but HBV DNA testing and further management and treatment for hepatitis B must be paid out of pocket by patients. These additional costs could be a substantial barrier for many patients to get evaluated for HBV treatment in Georgia, and this is one of the reasons we did not have access to HBV DNA results that would help us better understand the reasons for elevated ALT levels among some patients after starting DAA treatment. Ensuring that hepatitis B

testing, management and treatment are accessible to all patients would improve the clinical management of those co-infected with HCV and HBV, as well as all patients with HBV infection.

While almost one in four persons in our patient cohort had advanced liver fibrosis, they were not more likely to be co-infected. Several studies have shown that patients with advanced liver fibrosis and HCV-HBV co-infection had a higher risk of developing cirrhosis and liver cancer [1–3]. These studies indicated that co-infected patients with elevated pre-treatment FIB-4 or liver elastography score were more susceptible to liver disease progression and should be regularly monitored after HCV cure. Recent analysis from Georgia demonstrated a substantial reduction in overall and liver-related mortality for patients treated for HCV infection [24]. We did not find a significant difference in the adjusted odds of all-cause mortality among patients with HCV-HBV co-infection compared to those with HCV infection and exposure to HBV and HCV mono-infected patients. However, a more in-depth analysis of mortality among these two groups is recommended due to the smaller numbers of deaths in both groups and wide confidence intervals in our analysis. Given the increased risk for liver disease progression among HCV-HBV co-infected patients with advanced liver fibrosis, regular follow-up visits and HBV treatment should be considered in Georgia [11].

While the vast majority of patients who were tested for SVR achieved HCV cure (98.6%), patients who did not achieve SVR were almost twice as likely to have HCV-HBV co-infection compared to patients who were HCV mono-infected. Our findings differ from recent meta-analysis and the large longitudinal study of HCV-HBV co-infected patients, which did not find a significant reduction in SVR rates among co-infected patients who were treated with DAAs and were not treated for HBV infection [3, 14]. Although a higher percentage of co-infected patients were found to have HCV genotype 3 –likely through exposure by injecting drug use [25], which can be more challenging to treat – this finding remained significant after adjusting for genotype in the multivariable model. Further, previous analyses have shown similarly high rates of SVR for all genotypes in Georgia [17], even before the program began transitioning to pangenotypic regimens in December of 2018 [26].

Another interesting finding in our study is the higher probability of achieving SVR among patients with HCV infection and previous exposure to HBV compared to HCV mono-infected patients, which is different from other studies [3]. While not reaching SVR among patients treated with DAAs is rare in Georgia, when it happens, HCV-HBV co-infection could be an important reason for the treatment failure. This could happen because patients with co-infection had more frequent side effects or experienced acute flares of hepatitis related to HBV reactivation, which could impact adherence to DAAs and their effectiveness. However, reasons for not achieving SVR among HCV-HBV co-infected patients in Georgia were unavailable; future clinical studies should explore this area. In the meantime, all patients who do not achieve SVR in Georgia should be re-tested for HBsAg and HBV DNA and evaluated for hepatitis B treatment.

Our analysis showed that patients with a history of injection drug use were more likely to be co-infected with HBV or to have been previously exposed to HBV, which is similar to

the results of several recent reviews [27, 28]. Significant strides have been made in Georgia to reduce the HCV prevalence among PWID. In a 2021 serosurvey, 18% of persons who ever injected drugs had HCV infection, which was a substantial drop from 51% in 2015 [29]. However, results from a 2022 integrated bio-behavioural survey among PWID in six Georgian cities reported that 13% of PWID who were cured of HCV had HCV re-infection, 2.5% were positive for HBsAg, only 7% reported being vaccinated against HBV, and only 28% of non-vaccinated individuals were willing to be vaccinated against HBV [30]. Given the high burden of HCV and HBV infections among PWID in Georgia, testing for HBsAg and evaluation for HBV treatment for those found to have chronic HBV should be added to the current set of harm reduction services available for PWID in Georgia (e.g., syringe service programs and opioid substitution treatment) [31, 32].

5 | Limitations

We reported the strength of the associations between multiple socio-demographic characteristics, behaviours and clinical parameters and HCV-HBV co-infection. However, given that this is a cross-sectional study, we can only report associations between variables and cannot claim causality. We hypothesise that increased ALT during and at the end of DAA treatment among some of the patients treated for HCV could be due to HBV reactivation. However, HBV DNA levels at the start or end of DAA treatment were not available, and we did not have clinical measures that could confirm HBV reactivation or eligibility for HBV treatment. Our dataset also lacked information about HBV treatment for patients with HBV-HCV co-infection. Patients who did not achieve SVR were more likely to have HCV-HBV co-infection, but future clinical outcomes for these patients and if they received HBV treatment after the treatment with DAAs are unknown. Several variables used in our analysis had high percentages of missing values. To address this issue, we used inverse probability weighting to estimate the impact of missing data on regression analysis. Some self-reported variables, like history of injecting drugs, may be underreported due to social desirability bias. Despite these limitations, we believe our evaluation includes a well-defined, robust cohort of patients with HCV-HBV co-infection treated for HCV infection using DAAs, and containing clinical parameters and treatment outcomes.

In conclusion, our analysis found that patients with HCV-HBV co-infection were more likely to have elevated ALT at the end of DAA treatment and less likely to achieve SVR for hepatitis C. Ensuring that hepatitis B testing, management and treatment are accessible for patients co-infected with HCV and HBV, as well as all patients with HBV infection, may prevent disease progression and HBV reactivation. Studies are needed to better understand the reasons for lower SVR after DAA treatment among patients with HCV-HBV co-infection in Georgia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

Research data are not shared.

Abbreviations:

AASLD	American Association for the Study of Liver Disease
ALT	alanine transaminase
aPR	adjusted prevalence ratio
anti-HBc	HBV core antibody
aOR	adjusted odds ratio
APRI	AST to Platelet Ratio Index
AST	aspartate aminotransferase
BMI	body mass index
CDC	US Centers for Disease Control and Prevention
95% CI	95% confidence interval
DAA	direct-acting antiviral
EASL	European Association for the Study of the Liver
EOT	end of treatment
GEL	Georgian Lari
HBsAg	HBV surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
IDU	injection drug use
NA	nucleotide analogues
NCDC	National Center for Disease Control and Public Health
OR	odds ratio
PLT	platelet

PWID	persons who inject drugs
SVR	sustained virologic response
TDF	tenofovir disoproxil fumarate

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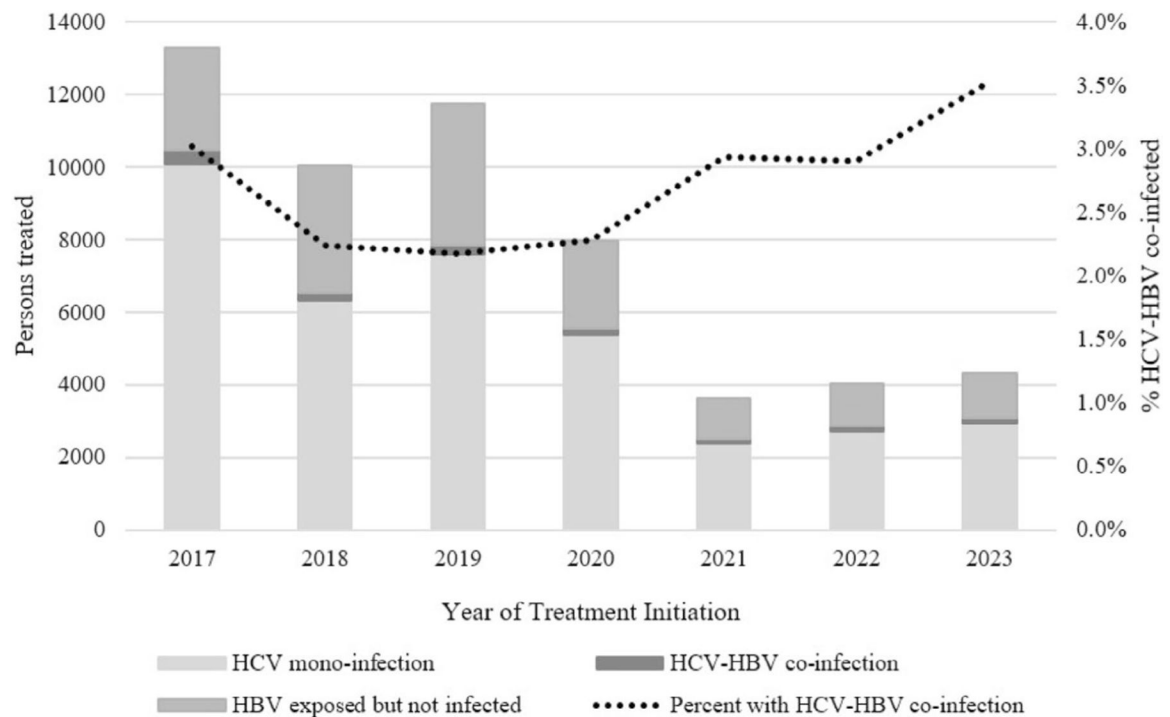


FIGURE 1 |.

Number of persons with HCV mono-infection, HCV-HBV co-infection and HCV infection-previous HBV exposure and percentage of HCV-HBV co-infection per year, Georgia, 2017–2023. HBV, hepatitis B virus; HCV, hepatitis C virus; HCV mono-infection—HCV RNA or HCV core antigen positive (HCVcAg); HB surface antigen (HBsAg) negative, anti-HBc negative; HBV exposed—HCV RNA or HCV core antigen positive; HBsAg negative, and anti-HBc positive; HCV-HBV co-infection—HCV RNA or HCVcAg positive and HBsAg positive.

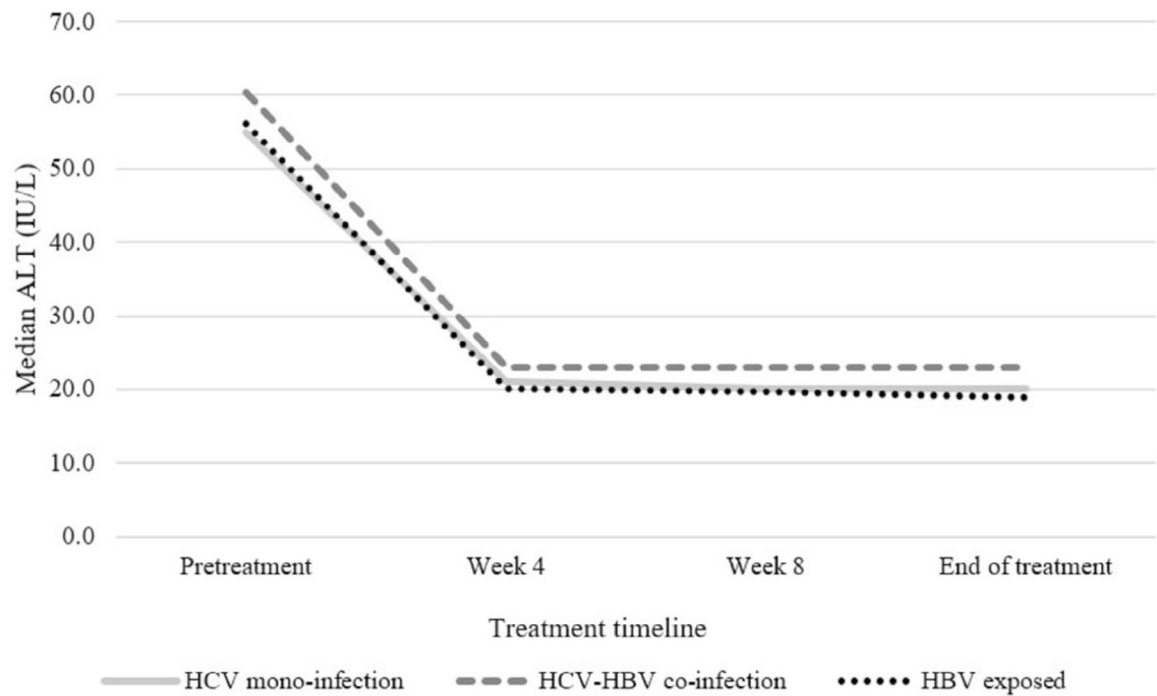


FIGURE 2 |.

Alanine transaminase (ALT) levels among persons with HCV mono-infection, HCV-HBV co-infection, and HCV infection-previous HBV exposure over time, Georgia, 2017–2023. ALT, alanine transaminase; HBV, hepatitis B virus; HCV, hepatitis C virus.

TABLE 1 |

Demographic and clinical characteristics of persons treated for hepatitis C and screened for hepatitis B in the Georgian Hepatitis C Elimination Program, 2017–2023.

	Total N (%)	HCV mono-infection (HBsAg negative and anti-HBc negative) n (%)	HCV-HBV co-infection (HBsAg positive) n (%)	HCV infection and exposed to HBV (total anti-HBc positive, HBsAg negative) n (%)
Overall (row percentage)	54,994	37,454 (68.1)	1438 (2.6)	16,102 (29.3)
Age				
18–45	24,457 (44.5)	17,771 (47.4)	905 (62.9)	5781 (35.9)
46–60	21,073 (38.3)	13,362 (35.7)	413 (28.7)	7298 (45.3)
61+	9464 (17.2)	6321 (16.9)	120 (8.3)	3023 (18.8)
Sex				
Female	14,214 (25.8)	10,720 (28.6)	244 (17.0)	3250 (20.2)
Male	40,780 (74.2)	26,734 (71.4)	1194 (83.0)	12,852 (79.8)
Body mass index ^d				
< 25.0	22,369 (42.2)	15,148 (42.1)	611 (45.3)	6610 (42.2)
25.0–29.9	19,946 (37.6)	13,580 (37.7)	507 (37.6)	5859 (37.4)
≥ 30.0	10,699 (20.2)	7266 (20.2)	232 (17.2)	3201 (20.4)
History of IDU ^b				
Yes	18,541 (39.8)	11,784 (37.0)	619 (52.5)	6138 (45.0)
HCV genotype ^c				
1	18,215 (48.8)	12,737 (49.9)	371 (39.7)	5107 (46.9)
2	6101 (16.3)	4207 (16.5)	144 (15.4)	1750 (16.1)
3	11,872 (31.8)	7788 (30.5)	391 (41.9)	3693 (33.9)
Other	1163 (3.1)	807 (3.2)	28 (3.0)	328 (3.0)
Liver fibrosis stage ^{d,e}				
Not advanced	39,688 (72.8)	27,726 (74.6)	1061 (74.7)	10,901 (68.4)
Advanced	14,837 (27.2)	9442 (25.4)	359 (25.3)	5036 (31.6)
Treatment regimen				
SOF + RBV	176 (0.3)	148 (0.4)	9 (0.6)	19 (0.1)
LED/SOF	17,068 (31.0)	11,933 (31.9)	350 (24.3)	4785 (29.7)
LED/SOF + RBV	12,266 (22.3)	8431 (22.5)	382 (26.6)	3453 (21.4)
SOF/VEL	24,984 (45.4)	16,673 (44.5)	682 (47.4)	7629 (47.4)

	Total N (%)	HCV mono-infection (HBsAg negative and anti-HBc negative) n (%)	HCV-HBV co-infection (HBsAg positive) (%)	HCV infection and exposed to HBV (total anti-HBc positive, HBsAg negative) n (%)
SOF/VEL + RBV	480 (0.9)	258 (0.7)	15 (1.0)	207 (1.3)
ELB/GRZ	20 (0.0)	11 (0.0)	0 (0.0)	9 (0.1)
Regimen duration				
12 weeks	53,331 (97.0)	36,531 (97.5)	1388 (96.5)	15,412 (95.7)
24 weeks	1663 (3.0)	923 (2.5)	50 (3.5)	690 (4.3)
Completed treatment				
Yes	52,113 (94.8)	35,547 (94.9)	1359 (94.5)	15,207 (94.4)
No	2881 (5.2)	1907 (5.1)	79 (5.5)	895 (5.6)
Pretreatment PLT×(10 ⁹ /L) ^e				
≤ 150	9081 (16.5)	5816 (15.5)	267 (18.6)	2998 (18.6)
> 150	45,871 (83.5)	31,611 (84.5)	1170 (81.4)	13,090 (81.4)
Pretreatment AST (IU/L) ^e				
< 40	23,844 (43.4)	16,620 (44.4)	558 (38.9)	6666 (41.4)
40–80	19,920 (36.2)	13,478 (36.0)	558 (38.9)	5884 (36.6)
> 80	11,189 (20.4)	7330 (19.6)	320 (22.3)	3539 (22.0)
Pretreatment ALT (IU/L) ^e				
< 40	17,581 (32.0)	12,097 (32.3)	397 (27.6)	5087 (31.6)
40–80	20,198 (36.8)	13,789 (36.8)	536 (37.3)	5873 (36.5)
> 80	17,174 (31.3)	11,542 (30.8)	503 (35.0)	5129 (31.9)
Week 4 ALT (IU/L) ^f				
< 40	43,751 (87.8)	29,826 (87.6)	1061 (83.0)	12,864 (88.7)
40–80	5234 (10.5)	3661 (10.8)	175 (13.7)	1398 (9.6)
> 80	830 (1.7)	551 (1.6)	42 (3.3)	237 (1.6)
Week 8 ALT (IU/L) ^g				
< 40	42,078 (89.4)	28,772 (89.4)	994 (82.3)	12,312 (90.1)
40–80	4327 (9.2)	2991 (9.3)	157 (13.0)	1179 (8.6)
> 80	673 (1.4)	438 (1.4)	57 (4.7)	178 (1.3)
EOT ALT (IU/L) ^h				
< 40	38,933 (90.0)	26,597 (90.1)	899 (83.4)	11,437 (90.5)
40–80	3740 (8.6)	2559 (8.7)	133 (12.3)	1048 (8.3)

	Total N (%)	HCV mono-infection (HBsAg negative and anti-HBc negative) n (%)	HCV-HBV co-infection (HBsAg positive) n (%)	HCV infection and exposed to HBV (total anti-HBc positive, HBsAg negative) n (%)
> 80	573 (1.3)	379 (1.3)	46 (4.3)	148 (1.2)
SVR result ⁱ				
Achieved	37,259 (98.6)	25,728 (98.5)	917 (97.6)	10,614 (98.9)
Not achieved	517 (1.4)	379 (1.5)	23 (2.4)	115 (1.1)

Abbreviations: ALT, alanine transaminase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; AST, aspartate aminotransferase; ELB, elbasvir; EOT, end of treatment; FIB, fibrosis; GRZ, grazoprevir; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injection drug use; LED, ledipasvir; PLT, platelet; RBV, ribavirin; SVR, sustained virologic response; SOF, sofosbuvir; VEL, velpatasvir.

^aMissing values range (for all three subgroups): 3%–6%.

^bMissing value range: 15%–18%.

^cMissing value range: 32%–35%.

^dAdvanced fibrosis is defined as a liver elastography score $\geq$ F3 or FIB-4 score > 3.25 . Not advanced is defined as liver elastography $<$ F3 or FIB-4 score < 1.45 . Priority is given to elastography results for all determinations.

^eMissing value range: $< 2\%$.

^fMissing value range: 9%–11%.

^gMissing value range: 14%–16%.

^hMissing value range: 21%–25%.

ⁱMissing value range: 30%–35%.

TABLE 2 |

Comparison of demographic and clinical characteristics of patients with HCV-HBV co-infection with those having HCV mono-infection, Georgia 2017–2023.

	HCV mono-infection (HBsAg negative, anti-HBc negative)	HCV-HBV co-infection (HBsAg positive)	PR for HCV-HBV co-versus HCV mono-infection (95% CI)	p	aPR ^a (95% CI)	p
Age						
18–45	17,771 (95.2)	905 (4.8)	1.62 (1.44, 1.81)	< 0.001	1.75 (1.48, 2.08)	< 0.001
46–60	13,362 (97.0)	413 (3.0)	1	1	1	1
61+	6321 (98.1)	120 (1.9)	0.62 (0.51, 0.76)	< 0.001	0.73 (0.53, 1.00)	0.05
Sex						
Female	10,720 (97.8)	244 (2.2)	1	1	1	1
Male	26,734 (95.7)	1194 (4.3)	1.92 (1.68, 2.20)	< 0.001	1.38 (1.11, 1.71)	0.003
Body mass index						
< 25.0	15,148 (96.1)	611 (3.9)	1	1	1	1
25.0–29.9	13,580 (96.4)	507 (3.6)	0.93 (0.83, 1.04)	0.21	0.94 (0.80, 1.10)	0.44
≥ 30.0	7266 (96.9)	232 (3.1)	0.80 (0.69, 0.93)	0.003	0.93 (0.76, 1.14)	0.50
History of IDU						
No	20,028 (97.3)	560 (2.7)	1	1	1	1
Yes	11,784 (95.0)	619 (5.0)	1.83 (1.64, 2.05)	< 0.001	1.40 (1.19, 1.66)	< 0.001
HCV genotype						
1	12,737 (97.2)	371 (2.8)	1	1	1	1
2	4207 (96.7)	144 (3.3)	1.17 (0.97, 1.41)	0.11	1.00 (0.80, 1.24)	1.00
3	7788 (95.2)	391 (4.8)	1.69 (1.47, 1.94)	< 0.001	1.33 (1.13, 1.56)	< 0.001
Other	807 (96.6)	28 (3.4)	1.18 (0.81, 1.73)	0.38	1.02 (0.68, 1.53)	0.93
Liver fibrosis stage ^b						
Not advanced	27,726 (96.3)	1061 (3.7)	1	1	1	1
Advanced	9442 (96.3)	359 (3.7)	0.99 (0.88, 1.12)	0.92	1.11 (0.92, 1.33)	0.28
Pretreatment PLT×(10 ⁹ /L)						
≤ 150	5816 (95.6)	267 (4.4)	1.23 (1.08, 1.40)	0.002	1.29 (1.08, 1.55)	0.01
> 150	31,611 (96.4)	1170 (3.6)	1	1	1	1
Pretreatment AST (IU/L)						
< 40	16,620 (96.8)	558 (3.2)	1	1	1	1

	HCV mono-infection (HBsAg negative, anti-HBc negative)		HCV-HBV co-infection (HBsAg positive)		PR for HCV-HBV co-versus HCV mono-infection (95% CI)		aPR (95% CI)		p	
40–80	13,478 (96.0)	558 (4.0)			1.22 (1.09, 1.37)		1.06 (0.90, 1.24)		< 0.001	0.48
> 80	7330 (95.8)	320 (4.2)			1.29 (1.13, 1.47)		1.15 (0.95, 1.39)		< 0.001	0.15
Pretreatment ALT cont. (IU/L)										
Median (IQR)	54.9 (34.3, 93.0)	60.3 (38.0, 103.4)			1.00 (1.00, 1.00)		1.00 (1.00, 1.00)		0.01	0.67
Pretreatment ALT (IU/L)										
< 40	12,097 (96.8)	397 (3.2)			1		1		1	1
40–80	13,789 (96.3)	536 (3.7)			1.18 (1.04, 1.34)		1.02 (0.85, 1.21)		0.01	0.84
> 80	11,542 (95.8)	503 (4.2)			1.31 (1.16, 1.50)		0.99 (0.82, 1.19)		< 0.001	0.87
Week 4 ALT cont. (IU/L)										
Median (IQR)	21.0 (15.3, 30.0)	23.0 (16.4, 33.0)			1.00 (1.00, 1.00)		1.00 (1.00, 1.00)		0.96	0.97
Week 4 ALT (IU/L)										
< 40	29,826 (96.6)	1061 (3.4)			1		1		1	1
40–80	3661 (95.4)	175 (4.6)			1.33 (1.14, 1.55)		1.13 (0.91, 1.41)		< 0.001	0.27
> 80	551 (92.9)	42 (7.1)			2.06 (1.53, 2.78)		1.44 (0.92, 2.28)		< 0.001	0.11
Week 8 ALT cont. (IU/L)										
Median (IQR)	20.1 (15.0, 29.0)	23.0 (16.6, 33.0)			1.00 (1.00, 1.00)		1.01 (1.01, 1.01)		0.97	< 0.001
Week 8 ALT (IU/L)										
< 40	28,772 (96.7)	994 (3.3)			1		1		1	1
40–80	2991 (95.0)	157 (5.0)			1.49 (1.27, 1.76)		1.33 (1.06, 1.67)		< 0.001	0.01
> 80	438 (88.5)	57 (11.5)			3.45 (2.68, 4.44)		2.60 (1.79, 3.78)		< 0.001	< 0.001
EOT ALT cont. (IU/L)										
Median (IQR)	20.0 (14.7, 28.0)	22.9 (16.0–32.0)			1.01 (1.01, 1.01)		1.01 (1.01, 1.01)		< 0.001	< 0.001
EOT ALT (IU/L)										
< 40	26,597 (96.7)	899 (3.3)			1		1		1	1
40–80	2559 (95.1)	133 (4.9)			1.51 (1.27, 1.81)		1.26 (0.98, 1.62)		< 0.001	0.08
> 80	379 (89.2)	46 (10.8)			3.31 (2.50, 4.38)		2.14 (1.40, 3.29)		< 0.001	< 0.001
SVR result										
Achieved	25,728 (96.6)	917 (3.4)			1		1		1	1
Not achieved	379 (94.3)	23 (5.7)			1.66 (1.11, 2.48)		1.83 (1.13, 2.95)		0.01	0.01

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Abbreviations: ALT, alanine transaminase; aPR, adjusted prevalence ratio; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to hepatitis B surface antigen; AST, aspartate aminotransferase; EOT, end of treatment; FIB, fibrosis; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IDU, injection drug use; PLT, platelet; PR, prevalence ratio; SVR, sustained virologic response.

^aPrevalence ratios adjusted for age, sex, body mass index, genotype and injection drug use. EOT, ALT and SVR results were also adjusted for treatment duration.

^bAdvanced fibrosis defined as liver elastography score $\geq$ F3 or FIB-4 score > 3.25 . Not advanced defined as liver elastography $<$ F3 or FIB-4 score < 1.45 . Priority is given to elastography results for all determinations.

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TABLE 3 |
Odds ratios for all-cause mortality among persons with hepatitis C, adjusted for age, sex, body mass index, injection drug use and year of treatment initiation stratified by HBV co-infection, Georgia, 2017–2023.

	Alive <i>n</i> (%)	Deceased <i>n</i> (%)	OR (95% CI)	Adjusted OR (95% CI)
HCV mono-infection	35,013 (93.5)	2441 (6.5)	1	1
HCV-HBV co-infection (HCV RNA and HBsAg positive)	1358 (94.4)	80 (5.6)	0.85 (0.67, 1.06)	1.03 (0.78, 1.34)
HCV infection and previously exposed to HBV (anti-HBc positive, HBsAg negative)	14,754 (91.6)	1348 (8.4)	1.31 (1.22, 1.41)	1.07 (0.99, 1.16)

Abbreviations: CI, confidence interval; OR, odds ratio.