Current Hepatology Reports (2019) 18:310–315
https://doi.org/10.1007/s11901-019-00479-9

HEPATITIS B (JK LIM, SECTION EDITOR)

# Chronic Hepatitis B in US Veterans

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Published online: 29 July 2019


## Abstract

**Purpose of Review** This review summarizes recent data on chronic hepatitis B virus (HBV) epidemiology, issues in special populations undergoing immunosuppressive and hepatitis C virus (HCV) direct-acting antiviral (DAA) therapy, and describes care delivery, adherence to guideline-recommended care, and barriers to access to care and high-quality care for chronic HBV.

**Recent Findings** Chronic HBV is present in up to 1% of veterans and is more than in the general US population. HBV is associated with more advanced liver disease in HCV, HIV, and delta hepatitis co-infection. Recent data on HBV reactivation show a substantial risk of reactivation with anti-CD20 antibodies, no documented cases of reactivation with anti-tumor necrosis factor (anti-TNF) therapy, and a low risk of reactivation with HCV DAA therapy. Adherence to guideline-recommended care for HBV is suboptimal for many quality indicators.

**Summary** Important studies in HBV epidemiology, long-term outcomes, and care delivery practices have been conducted in the VA. Future studies should prospectively investigate how to improve guideline-recommended care for HBV.

**Keywords** Hepatitis delta · Hepatocellular carcinoma · Cirrhosis · Hepatitis B epidemiology · Care quality · Hepatitis B reactivation

## Introduction

The Veterans Affairs (VA) is the largest single integrated health system in the USA and has a centralized database with detailed national clinical and administrative data. Veterans represent a high-risk population with an increased prevalence of comorbidities, including liver disease and chronic hepatitis B virus (HBV). This review summarizes recent research on the epidemiology and care delivery practices in HBV in the VA.

This article is part of the Topical Collection on *Hepatitis B*

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## HBV Screening, Prevalence of Chronic HBV, and HBV Exposure Among US Veterans

Several recent studies have reported on the prevalence of screening and positive chronic HBV in the VA population using the Corporate Data Warehouse (CDW), the VA national repository of clinical data. Backus et al. assessed screening measures for HBV during outpatient visits in a retrospective cohort study analyzing data from 1999 to 2013 [1]. Among 5,587,838 veterans in VA care in 2013, 22% were screened for HBV infection. Screening rates were highest among African-Americans (34%), Asians (27%), and Hispanics (34%). Among the 1,506,051 veterans tested, the prevalence of HBV infection was estimated at 0.84%; this was 0.96% if include patients with HBsAg+ status and negative HBV DNA. Particularly high prevalence was found among Asians (4.9%) and African-Americans (1.5%). As expected, the prevalence of HBsAg+ status was higher among high-risk groups such as among persons who inject drugs (1.4%), those with STDs (1.7%), hepatitis C virus (HCV) (1.2%) and HIV co-infection (5.1%), hemodialysis (1.4%), and immunosuppressive therapy (0.75%). The prevalence of chronic HBV among veterans was found to be triple the contemporary national average of 0.27%, an estimate from National Health and Nutrition Examination Survey and twice the 0.3 to 0.5%

national prevalence estimated by the Centers for Disease Control and Prevention (CDC) [2, 3]. Although, it should be noted that direct comparisons may not reflect true proportions due to the variability in the denominator of patients who were tested.

Homelessness is a known risk factor for viral hepatitis. Noska et al. investigated the prevalence of HBV, HIV, and HCV among veterans, and investigated whether homelessness was associated with increased risk for chronic HBV in 2015 [4•]. The percentage of homeless veterans who were tested for HBV was 52.8%, while 27.6% of the non-homeless veteran population were tested. HIV and HCV testing rates were both higher than testing rates for HBV, although HBV testing rates were higher in homeless veterans than in non-homeless veterans. Among all veterans, the prevalence of a single HBsAg+ test was 1.36% among those tested and 0.42% overall. The tested prevalence was 1.80% among homeless veterans and 1.30% among non-homeless veterans.

In addition to investigating HBV testing and chronic HBV prevalence, Bhattacharya et al. conducted a study to characterize previous HBV exposure defined in this study as the prevalence of isolated hepatitis B virus core antibody (HBcAb+, HBsAg−, HBsAb−) and resolved HBV infection HBcAb+, HBsAg−, HBsAb+) in a VA national cohort of HIV-infected patients in the Veterans Aging Cohort Study (VACS-VC) from 1996 to 2010 [5]. In a cross-sectional study of 12,196 HIV-infected veterans, the presence of isolated HBcAb+ was 1504 (12.3%) among HIV mono-infected patients and was in 2707 of 7290 (37%) HIV/HCV co-infected patients. The prevalence or resolved HBV was 35% for HIV mono-infected and 19% for HIV/HCV co-infected patients. Isolated HBcAb+ status was associated with advanced hepatic fibrosis in HIV/HCV co-infected veterans, but not in HIV-mono-infected veterans. In multivariable analyses, HIV/HCV co-infection with isolated HBcAb+ had higher odds of advanced fibrosis (assessed by Fibrosis 4 score > 3.25, AST-to-platelet ratio index (APRI) > 2.0, or platelet count < 140,000 per microliter).

## Summary

Recent studies found that the prevalence of chronic HBV infection among veterans is up to 1% and is probably higher among veterans compared to the general population where estimates range from 0.3 to 0.5%. It should be noted that accurate general US population-based estimates remain suboptimal given the unknown denominator of patients tested. Veterans with homelessness, HCV, and HIV co-infection, Asians, African-Americans, persons who inject drugs, and dialysis patients are at elevated risk for HBV infection. The prevalence of HBV exposure is high among patients co-infected with HIV and HCV and appears to be associated with advanced fibrosis.

## Cirrhosis and Hepatocellular Carcinoma in US Veterans with Hepatitis B

HBV is a known risk factor for cirrhosis as well as hepatocellular carcinoma (HCC) in the presence or absence of cirrhosis. Using data from the VA Corporate Data Warehouse, Beste et al. retrospectively investigated the trends of cirrhosis and HCC from 2001 to 2013 in a population of 5,720,614 veterans, of whom 60,553 (1.06%) had cirrhosis and 7670 (0.13%) had HCC [6••]. Of the patients with cirrhosis, 2.1% had HBV infection compared to 78% attributed to HCV and alcohol-related liver disease. Among the patients with HCC, 79% had HCV or alcohol-related liver disease compared to only 2.3% having HBV infection. However, the overall prevalence of HBV among veterans with cirrhosis increased from 1.4% in 2001 to 2.1% in 2013. The incidence of cirrhosis with HBV increased from 2.84 cases per 100,000 veterans in 2002 to 3.32 per 100,000 in 2012 and a similar increase was noted in HCC incidence from 2.3 cases per 100,000 in 2003 to 2.8 cases per 100,000 in 2012.

The impact of HCV/HBV co-infection on adverse outcomes has been studied in US Veterans. Kruse et al. investigated the effect of HCV/HBV co-infection on cirrhosis, HCC, and death compared to HCV mono-infection and utilized the National Veterans Affairs HCV Clinical Case Registry to identify patients with HCV viremia and HBV co-infection from 1997 to 2005. A total of 99,548 patients with HCV infection were identified and 1730 patients (1.4%) were found to be HCV/HBV co-infected [7]. The subsequent incidence of cirrhosis, HCC, and death was significantly higher in the HCV/HBV/HBV DNA+ co-infected cohort compared to the HCV-mono-infected cohort: cirrhosis (HR 2.15, 95% CI 1.66–2.79), HCC (HR 1.97, 95% CI 1.16–3.33), and death (HR 1.37, 95% CI 1.12–1.67).

It is well accepted that chronic HBV is a risk factor for HCC in the absence of cirrhosis. Chayanupatkul et al. examined the extent to which HCC occurs in chronic HBV in the absence cirrhosis [8]. In a national cohort of 8539 patients with chronic HBV, 317 developed HCC. Of the HCC patients, a total of 30 (9.5%) had no evidence of cirrhosis at the time of HCC diagnosis. Factors associated with HCC in the absence of cirrhosis were race (African-American, OR 6.78; 95% CI 2.05–22.4; Asian, OR 11.6, 95% CI 2.63–50.8 compared to White) and family history (OR 32.9, 95% CI 3.76–288). Interestingly, patients without cirrhosis had larger tumors compared to those with cirrhosis (mean tumor size 7.5 cm without cirrhosis, 4.5 cm with cirrhosis, $P < 0.001$). Median survival was similar among HBV patients with HCC and cirrhosis (13.0 months) and without cirrhosis (14.5 months).

The impact of HBV on outcomes among patients with diabetes has been examined in a few studies. El-Serag et al. retrospectively examined the relationship between diabetes and the risk for hepatocellular carcinoma (HCC) in a cohort

of US Veterans while controlling for several known risk factors of HCC including HBV [9]. Compared to patients without viral hepatitis, those with HBV were more likely to have HCC (adjusted OR 9.22, 95% CI 4.52–18.80). Diabetes modestly increased the risk of HCC among patients with HBV (adjusted OR for diabetes 1.27, 95% CI 1.02–1.57).

An additional risk factor for adverse outcomes in HBV is hepatitis delta virus (HDV) co-infection. HDV is a human RNA virus that requires HBV co-infection for replication and has been associated in previous studies with accelerated fibrosis progression and HCC compared to HBV mono-infection. Generally, patients co-infected with HDV have suppressed HBV DNA. A recent VA study reported results of national data on HDV testing prevalence and HBV/HCV co-infection [10•]. Among 8159 veterans with chronic HBV infection, only 2008 (7.8%) were subsequently tested for HDV and 73 of those 2008 (3.6%) were HDV+. Some of the factors associated with HDV testing among chronic HBV-infected veterans were White race, concurrent HCV and HIV testing, cirrhosis, substance abuse, and specialty care (gastroenterology, hepatology, infectious disease). Having a "high-risk profile" for HDV defined as having alanine aminotransferase (ALT) levels greater than two times the upper limit of normal and HBV DNA < 2000 international units/mL increased the odds of HDV+ status (OR 4.2, 95% CI 1.4–7.5). HDV+ status was also associated with HCV Ab+, alcohol abuse, cirrhosis, substance abuse, and interferon therapy. HDV co-infection was associated with increased risk of HCC (IRR 2.9, 95% CI 1.4–5.4).

### Summary

Among veterans with HCC, about 2% have chronic HBV infection. The incidence of cirrhosis and HCC related to HBV has increased among veterans from 2002 to 2012. HCV/HBV co-infection, HDV+ status, Asian and African-America race, and family history of HCC are associated with increased risk of HCC. HBV co-infection appears to be associated with accelerated fibrosis progression in HCV. Diabetes is modestly, but independently associated with increased risk of HCC among veterans with HBV.

## Adverse Events and HBV Reactivation in Veterans Requiring Immunosuppressive Therapy and HCV Direct-Acting Antiviral Therapy

### Anti-CD20 Antibody Therapy

Hunt et al. investigated adverse liver-related outcomes among patients receiving anti-CD20 antibody therapy. In a cohort of 18,464, there were 16 (0.09%) cases of de novo acute HBV among HBV patients. Among patients with chronic HBV, 13/30 (43%) had hepatitis defined as ALT > 2 times the upper limit of normal, and 1/30 (3%) had liver failure defined as hepatitis in the presence of INR > 1.5. Hepatitis was noted in 30–36% of patients with prior HBV exposure and the incidence of hepatitis and INR > 1.5 was 1%. The mean time to adverse events was 210–278 days after anti-CD20 therapy initiation. It was not clear how HBV antiviral prophylaxis impacted adverse event rates. All-cause mortality was > 30%; however, it was not ascertained what was the proportion of death attributable to liver disease versus to underlying malignancy or rheumatologic disease [11].

### Anti-TNF Therapy

Shah et al. investigated clinical outcomes of HBV reactivation (HBVr) following anti-TNF therapy in a veteran cohort from 2003 to 2011 [12•]. A total of 3357 inflammatory bowel disease (IBD) patients filled their prescriptions for anti-TNF medications. The HBV testing rate for these patients, prior to anti-TNF initiation, increased by 23.7% between 2003 and 2011 (8.1% in 2003 and 43.2% in 2011). African-American race, volume of IBD patients, and academically affiliated facilities were factors associated with higher HBV screening rates. Chronic HBV was very rare in the IBD cohort with only 6 patients with documented HBsAg+ status; 22 additional patients had HBV antiviral prescriptions prior to initiation of anti-TNF therapy but their HBsAg status was not reported. No cases of HBVr were noted after anti-TNF initiation.

### HCV DAA Therapy

In 2016, the United States Food and Drug Administration issued a warning recommending screening of all HCV-infected patients for current or previous HBV infection. As HBsAg+ patients were specifically excluded from HCV direct-acting antiviral (DAA) registration trials, this warning was initially based on a few case reports of severe HBVr, one of which resulted in liver transplantation and two that resulted in death [13]. A retrospective study by Serper et al. investigated HBVr among 134 HBsAg+ patients who were on treatment with HBV antiviral at the time of HCV DAA initiation from 2014 to 2016 [14••]. A total of 30% of HBsAg+ patients not on HBV therapy developed possible HBVr as defined by two-fold increase in ALT; this was higher among patients with cirrhosis (44%). While less common, 15% developed hepatitis with a fourfold increase in ALT. Definite HBVr (where HBV DNA was available) defined as at least a 1 log IU/mL increase in HBV DNA occurred in at least 7% of cases. Among patients with evidence of prior HBV exposure (HBsAg −/HBcAb+), HBVr occurred in < 1% of patients. HBsAb status did not predict HBVr or hepatitis events. In a VA study

conducted during a similar timeframe and with slightly different definitions of adverse events, Belperio et al. found that among 62,290 HCV-infected veterans completing DAA therapy, HBVr occurred only in 0.01% of patients (9 total, 8 HBsAg+, 1 HBsAg−, HBcAb+) [15••]. Only 3 of the HBVr patients had ALT > 2 times the upper limit of normal.

### Summary

HBV testing remains suboptimal among patients undergoing immunosuppressive therapy and HCV DAA antiviral therapy. Anti-CD20 therapy is associated with the highest risk of HBVr, clinically significant hepatitis, and adverse events, more commonly among HBsAg+ and HBsAg−/HBcAb+ patients. HBVr has not been documented among veterans treated with anti-TNF therapy for IBD and the risk of HBVr among HBsAg+ patients treated with HCV DAA antivirals is very low.

## Quality of Care Delivered to US Veterans for Hepatitis B

HBV is a less well recognized cause of liver disease among US Veterans. Studies have been conducted to identify care delivery patterns and adherence to guideline-recommended care in the veteran population and have found sizable gaps in care. Serper et al. conducted a national retrospective cohort study to investigate process outcomes such as appropriate laboratory testing, hepatitis A vaccinations, HCC surveillance among those meeting surveillance criteria, HBV antiviral therapy initiation with nucleoside/nucleotide analogues, and receipt of specialty care with gastroenterology, hepatology, or infectious disease [16••]. The study identified 21,419 veterans with at least one HBsAg+ result between 1999 and 2013. Of these patients, 58% had unconfirmed HBV infection and 42% had confirmed chronic HBV infection. The HBV care cascade from 2010 to 2012 is shown in Fig. 1. Of the veterans with HBsAg+, only 54% had follow-up HBsAg testing within 6 months to confirm chronic infection and HBV was entered into the electronic medical record's problem list 55% of the time. One half of the patients were seen by specialists and among those who met the criteria for an antiviral, 38% were actually prescribed it. Receipt of specialty care was associated with higher adherence to guideline-recommended care in all domains from appropriate laboratory testing, to hepatitis A vaccination, HCC surveillance, and appropriate prescription of antiviral therapy. Although receipt of specialty care was associated with higher all-cause mortality (HR 1.11, 95% CI 1.02–1.21) and hepatic decompensation (HR 4.51, 95% CI 3.94–5.17), the authors hypothesized that this was secondary to referral practice patterns and because patients were typically referred to specialists in more advanced stages of liver disease. Importantly, receipt of antiviral therapy (HR 0.85, 95% CI 0.76–0.95) and liver imaging (HR 0.84, 95% CI 0.76–0.91) were associated with reduced all-cause mortality. A study investigating the prevalence of HDV co-infection in veterans showed that HDV testing of HBsAg+ patients occurred only 8% of the time and only in 19% of cases with clinically significant hepatitis without HBV viremia where HDV co-infection should have been suspected [10•]. Gaps in HBV care are not unique to the VA population and have been previously reported [17].

Another by Kushner et al. investigated barriers to appropriate follow-up laboratory testing and clinical care among patients with chronic HBV at 3 diverse VA medical centers [18•]. Of the 517 veterans with chronic HBV, 25% (112/517) did not receive any VA follow-up care within 2 years of initial diagnosis and 26% were seen by a specialist. There were significant baseline differences noted between the veterans that received follow-up care and those that did not including drug abuse (36% vs. 59%, $P < 0.05$) and alcohol misuse (33% vs. 48%, $P < 0.05$). Factors which were positively correlated with appropriate laboratory testing included cirrhosis (OR 3.20, 95% CI, 1.86–5.51) and HCV (OR 2.36, 95% CI, 1.61–3.46). Additional factors that increased the odds of appropriate laboratory testing were having at least 2 primary care visits

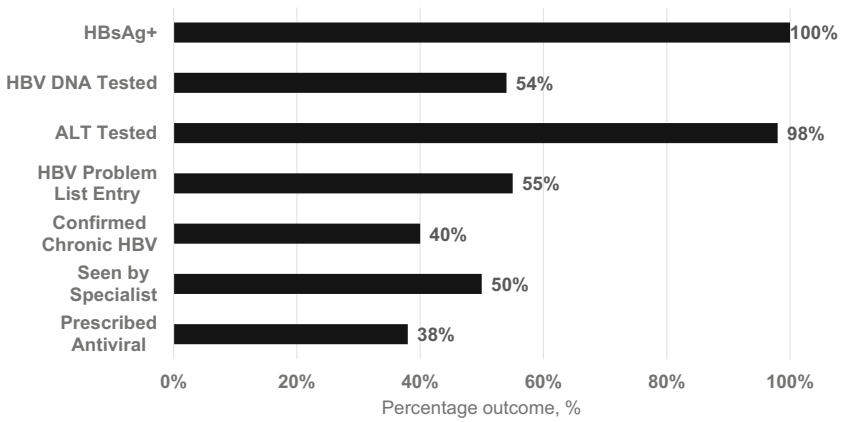


**Fig. 1** Cascade of hepatitis B care in the Veterans Affairs. X axis label: percentage outcome, %. HBsAg hepatitis B surface antigen, HBV hepatitis B virus, ALT alanine aminotransferase. (Reproduced from Marina Serper, Gina Choi, Kimberly A. Forde, et al., Hepatology, 2016, Volume 63, Issue 6, with permission from John Wiley and Sons. https://aasldpubs.onlinelibrary.wiley.com/doi/full/10.1002/hep.28340)

(OR 3.06; 95% CI, 2.04–4.65), having non-VA health insurance coverage (OR 1.67, 95% CI 1.18–2.38), and the presence of psychiatric disorder (OR 1.43; 95% CI 1.00–2.04).

Receipt of anti-CD20 antibodies such as Rituximab is associated with HBV reactivation and adverse outcomes in the absence of appropriate prophylaxis. Hunt et al. performed a retrospective national VA study to identify the use of HBV serologic testing, vaccination, antiviral prophylaxis, and potential HBV-related complications among patients prescribed anti-CD20 antibodies from 2002 to 2014 [11]. Of the 18,464 veterans treated with anti-CD20 antibodies, 86% were treated for leukemia and lymphoma and 14% for rheumatologic conditions. Pre-anti-CD20 antibody treatment HBV serologic testing occurred up to 49% of the time. Only 37% (10/30) of patients with definite chronic HBV (persistent HBsAg+ for > 6 months) received HBV antiviral prophylaxis during the "high-risk period" defined as the 12 months following the initial anti-CD20 antibody prescription. Among patients with prior HBV exposure (HBsAg−, HBcAb+, HBsAb+/−), about one-fifth received HBV antiviral prophylaxis.

### Summary

Notable gaps exist in the quality of care provided to veterans with hepatitis B that parallel national practices outside of the VA healthcare system. Access to care (both primary care and subspecialty) are associated with improved adherence to guideline-recommended care. Receipt of HBV antiviral therapy and HCC surveillance are associated with reduced all-cause mortality among veterans with HBV.

## Conclusions

The VA has been the setting for multiple studies, which have led to important insights into HBV epidemiology, long-term sequelae, as well as its recognition, and care quality. HBV affects US Veterans at about three times the national average. Veterans with homelessness, HCV and HIV co-infection, Asians, African-Americans, persons who inject drugs, and dialysis patients are at elevated risk for HBV infection. HBV is an important factor in fibrosis acceleration among patients with HCV and HIV co-infection. HDV co-infection is rare; however, it is difficult to estimate with infrequent testing. HDV co-infection is associated with a nearly threefold increase in HCC risk. HBV reactivation has been studied and is associated with significant adverse events among HBsAg+ and HBsAg−/HBcAb+ veterans receiving anti-CD20 antibodies. Reactivation has not been reported in the VA with anti-TNF therapy and is extremely rare with HCV all-oral DAAs. Future research is needed to improve prognostication of the long-term risks of cirrhosis and HCC associated with chronic HBV infection in a setting of predominantly non-vertically transmitted infection as well as the impact of HBV antiviral therapy on mitigating these risks.

Recognition of HBV and subsequent appropriate testing and follow-up remain suboptimal. Based on available evidence to date, access to primary care and specialty care are associated with improved linkage to HBV care as well as higher adherence to evidence-based guidelines. The VA has recognized that important gaps in HBV care exist and internal efforts are underway by experts in the HIV, Hepatitis, and Related Conditions Programs of the Office of Specialty Care Services to improve the care for HBV at a national level. Future studies should investigate how to leverage the electronic health records (EHRs) and a centralized system of care to enhance HBV care. Tangible examples that may be investigated include automated EHR prompts for HBV testing among high-risk subgroups, the designation of HBsAg+ result as a critical lab value that requires a specialty care consultation, and automated reminders to patients about upcoming ultrasound appointments for those that require HCC surveillance. These prompts can also be used to increase follow-up testing after a single HBsAg+ result to confirm chronic infection that may subsequent treatment versus resolution of an acute infection. Additional efforts should include engaging patients at the point of care such as in mental health clinics or those on opioid substitution therapy and expanding collaborative care between primary care providers and specialists through telemedicine or other modalities to improve care coordination.

### Compliance with Ethical Standards

**Conflict of Interest** Patrik Garren declares no potential conflicts of interest. Marina Serper reports consulting fees from BioVie, Inc. outside the submitted work.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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