



Significance and Management of Isolated Hepatitis B Core Antibody (Anti-HBc) in HIV and HCV: Strategies in the DAA Era

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Abstract

Purpose of Review The purpose of this review is to summarize the prevalence and clinical implications of the isolated anti-HBc serologic profile in HIV-infected individuals. We highlight the rare but important issue of HBV reactivation in the setting of HCV therapy and describe an approach to management.

Recent Findings The isolated anti-HBc pattern, a profile that most often indicates past exposure to HBV with waning anti-HBs immunity, is found commonly in HIV-infected individuals, particularly those with HCV. Some large cohort studies demonstrate an association with advanced liver disease, while others do not. Conversely, meta-analyses have found an association between occult HBV infection (a component of the isolated anti-HBc pattern) and advanced liver disease and hepatocellular carcinoma in HIV-uninfected individuals. In HIV-uninfected individuals with anti-HBc positivity, HBV reactivation has been reported in patients receiving HCV therapy. This phenomenon is likely the result of disinhibition of HBV with HCV eradication.

Summary In HIV-infected patients, the long-term liver outcomes associated with the isolated anti-HBc pattern remain to be fully elucidated, supporting the need for large cohort studies with longitudinal follow-up. HBV reactivation during HCV DAA therapy has been well-described in HIV-uninfected cohorts and can inform algorithms for the screening and management of the isolated anti-HBc pattern in this population.

Keywords DAA · HCV treatment · Isolated anti-HBc · Occult HBV · HIV/HCV · HIV infection

Introduction

The isolated hepatitis B core antibody serologic profile, defined as a positive anti-HBc with negative HBsAg and anti-HBs, occurs in up to 37% of HIV co-infected with hepatitis C virus (HCV) [1]. Isolated hepatitis B core antibodies (anti-HBc) in the absence of HBsAg and anti-HBs pose challenges in

interpretation and management for providers. Understanding the management of the isolated anti-HBc profile in the context of HBV prevention and HCV therapy is important given the ramifications for HBV susceptibility and HBV reactivation. The purpose of this review is to examine the prevalence, clinical implications, and management of the isolated anti-HBc profile, with special attention to direct-acting antiviral therapy for patients with chronic HCV infection.

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Hepatitis B Virus Life Cycle

Hepatitis B virus establishes itself in chronic infection by way of dynamic processes involving viral and host immunity defenses (see Fig. 1). Attachment entry of the HBV virus requires interaction between HBsAg and hepatocyte surface proteins. HBV-relaxed circular DNA (rcDNA) is converted to covalently closed circular DNA (cccDNA), which serves as a transcriptional template for subsequent viral mRNA production and pregenomic RNA (pgRNA). This matures into nucleocapsid with viral polymerase, for viral propagation in the forms of virions outside the hepatocyte, or return to the nucleus as

Table 1 Interpretation of hepatitis B serologies

HBsAg	Anti-HBc IgM	Anti-HBc	Anti-HBs	Interpretation
Negative	–	Negative	Negative	Susceptible
Negative	–	Positive	Positive	Immune due to previous infection
Negative	–	Negative	Positive	Immune due to hepatitis B vaccination
Positive	Positive	Positive	Negative	Acute infection
Positive	Negative	Positive	Negative	Chronic infection
Negative	–	Positive	Negative	Isolated anti-HBc pattern: 1. Resolved infection with waning immunity (most common) 2. False-positive anti-HBc 3. “Low-level” chronic infection, i.e., occult HBV viremia 4. Resolving acute infection

HBsAg hepatitis B surface antigen, *Anti-HBc IgM* antibody to hepatitis B core antigen, *Anti-HBs* antibody to HBsAg

downregulating DNA and subsequent mRNA expression, with subsequent quiescence of HBsAg production [8]. Other epigenetic factors such as downregulation of acetylation may also play important roles towards transcriptional suppression of cccDNA in hepatocytes to explain serological patterns noted in patients with the isolated anti-HBc profile.

Prevalence and Predictors of the Anti-HBc Serologic Profile and Occult HBV Infection in HIV Infection

Wide variation exists on the prevalence of isolated anti-HBc findings. In HIV+ cohorts, 7 to 40% of patients have been reported to have the isolated anti-HBc [1, 5, 6, 9–23], owing to similar routes of transmission for HIV and HBV. Predictors of the isolated anti-HBc pattern include HIV infection [5, 24, 25], HCV infection [5], and specifically HCV viremia [25], older age [24], IDU, multiple sexual partners, and elevated HIV RNA levels [25]. The isolated anti-HBc pattern is particularly common in HIV/HCV co-infection, likely due to shared routes of transmission and viral interplay (see below). Estimates of prevalence of isolated anti-HBc may be limited due to differences in geography, as well as sensitivities of different immunoassays used in each study. This is in contrast to HIV-negative cohorts, where the prevalence of the isolated anti-HBc ranges from 5.3 to 31.6% [5, 14].

The definition of occult HBV varies across studies; some define occult HBV infection as HBV DNA positivity with HBsAg negativity, regardless of anti-HBc status, while other studies define occult HBV as HBV viremia only in the setting of the isolated anti-HBc profile. Several studies have assessed the prevalence of occult HBV infection among patients with HIV and isolated anti-HBc, which has been reported to range from 0.6 [11] to 2.5% noted in the BHOI study [9], to as high

as > 89.5% in a Swiss cohort study [23]. In the Women’s Interagency Cohort Study (WICS), 2% of women with HIV and a pattern of isolated HBcAb were found to have detectable HBV DNA [14]. Occult HBV viremia was associated with severe immunosuppression with CD4 < 200 cells/mm³ in the WIHS cohort.

Association With Advanced Liver Disease and Its Complications

The association with the isolated anti-HBc pattern and advanced liver disease is difficult to ascertain, in part, because studies have assessed the association of advanced liver disease with both the isolated anti-HBc pattern and occult HBV infection, which is a component of the isolated anti-HBc pattern but not its sole etiology. When assessing the isolated anti-HBc pattern overall, varying liver progression outcomes have been observed in HIV-infected cohorts (Table 2). One study of 344 HIV+ women suggested that the isolated anti-HBc pattern was not associated with accelerated liver progression over a median 9.5 years [25]. In contrast, a large American cross-sectional analysis in the Veterans Aging Cohort Study (VACS) found that isolated anti-HBc in patients with HIV/HCV co-infection was associated with more advanced hepatic fibrosis, as defined by APRI and FIB-4 scores [1]. These differences may lie in differences in study design (cross-sectional vs longitudinal), and study populations as women are less likely to have liver disease progression, compared to men.

When specifically evaluating occult HBV infection in HIV infection, again varying associations are reported. In one cross-sectional analysis of HIV-infected women, there was no association with elevated transaminases [14]. In the setting of antiretroviral therapy initiation, two studies have demonstrated no impact on subsequent ALT elevation with ART

Table 2 Prevalence of, and association with, liver disease outcomes in patients with the isolated anti-HBc serologic profile and/or occult HBV infection in HIV-infected cohorts

Cohort	Number of HIV + patients	Prevalence of isolated anti-HBc and/or occult HBV infection	Liver outcomes	Reference
HIV-infected				
HIV-infected, USA, VACS cohort, cross-sectional	19,486	Isolated anti-HBc 1504 (12.3%) OBI not reported	Isolated anti-HBc associated with advanced fibrosis (FIB-4, platelets) in HIV/HCV, when compared to resolved anti-HBs (OR, 1.65; 95% CI, 1.20–2.28) No association with baseline-elevated transaminases	Bhattacharya JAIDS 2017 Palacios HIV Clin Trials 2008
HIV-infected individuals, Spain, cross-sectional	3030	Isolated anti-HBc 202 (6.6%) OBI of anti-HBc 5 (2.5%)	No association with HBV perinatal transmission	Khamduang CID 2013
HIV-infected HBsAg negative pregnant women, Thailand, PHPT-2	1682	Isolated anti-HBc 229 (13.6%) OBI of anti-HBc 47 (2.8%)	–	Witt Clin Infect Dis 2012
HIV-infected, USA, MACS Cohort, longitudinal	1169	Isolated anti-HBc 259 (22.2%) OBI not reported	–	Neau CID 2005
HIV-infected, France, Aquitaine Cohort, cross-sectional	1123	Isolated anti-HBc 160 (14.2%) OBI of anti-HBc 1 (0.63%)	–	Firmhaber Int J Infect Dis 2009
HIV-infected, South Africa, cross-sectional	502	Isolated anti-HBc 53 (10.6%) OBI 38/43 (88.4%) OBI 28/441 (6.3%)	–	Saha PLOS One 2017
HIV-infected, India, cross-sectional	441	OBI of anti-HBc 8 (2%)	No association between ALT levels and OBI status	Tsui Clin Infect Dis 2007
HIV-infected, USA, WIHS Cohort, cross-sectional	400 with isolated anti-HBc	OBI 35 (1%)	Increased proportion (65%) with elevated transaminases after ART initiation at 1 month, but not 6 and 12 months	Chadwick AIDS 2013
HIV-infected, Ghana, cross-sectional	385	Isolated anti-HBc 132 (38.3%) OBI	No difference in change of ELF over time b/w anti-HBc and other serologies (<i>p</i> = 0.64)	French JAIDS 2016
HIV-infected women, USA, WIHS cohort, longitudinal	344 HIV/HCV median 9.5 years f/u	Isolated anti-HBc 42 (17.5%) OBI 13 (5.4%)	No association between isolated anti-HBc and acute LEE	Piroth J Hepatol 2002
HIV-infected, France	240	Isolated anti-HBc 38 (15.8%) OBI 4 (10.5%)	No association between ALT levels and HBV DNA positivity	Shire JAIDS 2004 Shire JAIDS 2007
HIV-infected, USA, ACTG, cross-sectional	209	Isolated anti-HBc 40 (19.1%) OBI 7 (7.5%)	–	Karaosmanoglu HIV Clin Trials 2013
HIV-infected, Turkey, cross-sectional	209	Isolated anti-HBc 40 (19.1%) OBI 7 (7.5%)	–	Lukhwareni J Med Virol 2009
HIV-infected, South Africa	192	Isolated anti-HBc 29 (15.1%) OBI 11 (37.9%)	–	Filippini AIDS 2006
Multicenter prospective study HIV-infected, HBsAg negative, ART naïve, Italy	115	Isolated anti-HBc 42 (36.5%) OBI 17/86 (19.8%)	32.5% (28/86) patients experienced hepatic flare (more frequent in OBI, 64.7% of OBI vs 24.6% HBV DNA negative)	
HIV-infected HBsAg–	97 anti-HBc+	OBI 13 (13%)	No difference in transaminitis following ART initiation	Lo Re V J Clin Virology 2008
HIV-infected anti-HBc+, Switzerland, Swiss HIV Cohort Study	57	Isolated anti-HBc 57 (100%) OBI 51 (89.5%)	In anti-HCV negative and HBV DNA positive individuals 8/22 (36.4%) had ALT elevation for 6 or more months Significantly higher ALT values in 12/29 (41.4%) of HBV DNA and anti-HCV-positive individuals	Hofer Eur. J. Clin. Microbiol. Infect. Dis. 1998

initiation in those with occult HBV infection [22, 26], while another demonstrated elevated aminotransferases in those with HIV and OBI during ART initiation or change [21]. With regard to HBV perinatal transmission, there was no HBV perinatal transmission in a cohort of HIV-infected Thai women with occult HBV infection [10].

In non-HIV-infected populations, however, the association between occult HBV infection and adverse outcomes seems clearer. Two large meta-analyses have found an association with occult HBV infection and chronic liver disease and hepatocellular carcinoma [27, 28] with varying prevalence and impact depending on geography and endemicity of HBV [29]. In one study, patients with chronic hepatitis C with concomitant occult hepatitis B infection had a higher risk of death related to liver disease as compared to patients without evidence of occult HBV infection over a median of 11 years of follow-up [30]. It is notable that another small study demonstrated no association between isolated anti-HBc and increased hepatocellular carcinoma risk [31] but this may have been limited by sample size. Other studies have demonstrated reduced responses to IFN-containing regimens in HCV-infected patients [32–36] although there has thus far been no association between occult HBV infection and HCV therapy response rates in the all oral direct-acting antiviral (DAA) era.

Clinical Implications and the Management of the Isolated Anti-HBc Serologic Profile in HIV Infection

Susceptibility to HBV Infection

In HIV infection, the presence of the isolated anti-HBc pattern does not necessarily indicate immunity to HBV infection. Indeed, varying anamnestic responses to a single dose of HBV vaccine have been reported, ranging from as low as 7 [37] to 32% [38], with higher levels of response to multiple doses of HBV vaccine administered. A prospective study conducted by Piroth and colleagues demonstrated that in 54 HIV-infected patients with the isolated anti-HBc profile, a single dose of 20 µg HBV vaccine resulted in a 46% response rate, defined as anti-HBs > 10 mIU/ml; in those who did not respond to a single dose, a three-dose series of double-dose 40 µg HBV vaccine resulted in 89% of remaining patients developing anti-HBs titers of > 10 mIU/mL at 28 weeks following vaccination [39]. Based on the results of this study, the current DHHS guidelines recommend that HIV-infected patients with the isolated anti-HBc profile receive one standard dose of HBV vaccine followed by anti-HBs assessment 1–2 months post-dose. If anti-HBs is < 100 IU/mL, then the individual should receive the full series of either single- or

double-dose HBV vaccine, with subsequent anti-HBs testing 1–2 months after completion of the vaccine series [40].

HBV Reactivation During DAA-Therapy in HCV-Infected Patients

With the advent of direct-acting antiviral (DAA) therapy for the treatment and eradication of hepatitis C, a number of cases of hepatitis B reactivation have been reported in post-marketing treatment outcomes. To date, at least 29 cases have been reported to the US Food and Drug Administration (FDA) Adverse Event Reporting System [41], including all serologic profiles. Where HBsAg baseline data was available, 76% of reactivation cases (13/17) occurred in patients with positive HBsAg prior to treatment. Few cases have reported baseline HBcAb testing, and it is difficult to assess how prevalent HBV reactivation is amongst patients with isolated HBcAb to date, though emerging reports on cohorts indicate that HBsAg positivity in the absence of suppressive therapy for HBV is a strong risk factor for HBV reactivation (Table 3) [41–55].

Smaller cohorts such as those described in one Taiwanese and Korean cohort ($n = 173$) have failed to show evidence of HBV reactivation [45] during HCV treatment with ledipasvir-sofosbuvir. In a larger observational cohort in China ($n = 327$), of which 124 patients were defined as having occult HBV infection, three cases of HBV reactivation have been noted [44] associated with HCV DAA treatment. A large, retrospective evaluation of 62,920 veterans treated for hepatitis C identified nine patients (0.01%) with evidence of HBV reactivation during DAA therapy; one of these nine patients tested positive for isolated HBcAb [42]. Though HBV reactivation would seem in this large retrospective cohort to be an infrequent event, a meta-analysis by Chen and colleagues [43] found more clinical severe reports of hepatitis due to HBV reactivation in patients treated with HCV DAA therapy than interferon-based treatment, as well as an earlier onset of hepatitis in the DAA-treated populations. In general, HBV reactivation occurred 4–8 weeks after initiation of DAA-based therapy, whereas HBV reactivation occurred after cessation of IFN-based HCV therapy [43]. Another retrospective study examined the prevalence of HBV reactivation comparing interferon-era vs interferon-free therapies and found a significant proportion of patients (6/85) experienced HBV viremia during or after DAA treatment, and no cases of reactivation in the interferon based group (0/72) [55]. Together, these findings underscore the importance of screening for chronic or occult hepatitis B infection prior to treatment of HCV with DAAs.

Few data of HBV reactivation exist in HIV-infected populations with respect to interferon-based or DAA-treated cohorts. To date, there has been one case report of HBV reactivation in HIV/HCV co-infection. The patient was anti-HBc

Table 3 HBV reactivation in HCV-infected patients receiving DAA therapy

Cohort	DAAs	N	Cohort	Other outcomes: ALT elevation, clinical illness, HBsAg appearance	HBV DNA elevation	Hepatic decompensation, liver transplant, death	Reference
Retrospective evaluation of veterans receiving DAAs from VA	SOF/SIM LDV/SOF OBV/PTV/r + DSV	N = 62,290	HBsAg+ (n = 377) Isolated anti-HBc+ (n = 7295)	HBsAg+ 6/8 with HBV DNA elevation with ALT elevation Isolated anti-HBc 0 of 390 tested had appearance of HBsAg	HBsAg+ n = 8 with HBV DNA > 1000 IU/ml from BL Isolated anti-HBc 4 of 173 tested had elevated HBV DNA, 1 with HBV DNA > 1000 IU/ml from baseline	Not reported	Belpert Hepatol 2017
Meta-analysis of HCV patients receiving DAA vs IFN containing therapy*	EBR/GRZ SOF/VEL DAAs IFN	28 studies (chronic HCV patients N = 779)	HBsAg+ HBsAg(-) and HBV DNA+	ALT elevation: HBsAg+ 12.2% DAA 0% IFN HBsAg(-) and HBV DNA+ 2 case reports DAA 0 IFN	HBsAg+ 12.2% DAA 14.5% IFN HBsAg(-) and HBV DNA+ 3 case reports DAA 0 IFN	Not reported	Chen Hepatol 2017
Prospective observational cohort study, China	LDV/SOF DAC/SOF Viekira Pak	N = 327	HBsAg+ (n = 10) Occult HBV (n = 124)	HBsAg+ 30% with hepatitis associated with HBV reactivation	Not reported	N = 2 with jaundice or liver failure	Wang CGH 2017
Retrospective cohort study; Taiwan/Korea	SOF/LDV	N = 173	Anti-HBc+ (n = 103)	Occult HBV 0% 1 had grade 3 ALT elevation at week 3 (up from grade 2 at BL)	2 with HBV DNA detectable		Sulkowski CID 2016
Prospective cohort study (Taiwan)	IFN-free DAAs	N = 93	Anti-HBc+ •HBsAg+ (n = 12) •HBsAg- (n = 81)		16.7% HBsAg+ 0 HBsAg-		Liu Open Forum Infect Dis 2017
Reported cases to FDA FAERS	Viekira Pak/RBV DCV/ASV SIM/SOF SIM/SOF/RBV SOF/RBV LDV/SOF SIM/PEG/RBV DCV/ASV	N = 29	HBsAg+ (n = 13) Anti-HBc+ (n = 6) HBV DNA+ (n = 9)	8/29 (29%) with clinical illness	% not reported	Decompensated liver failure in 3 patients • 2 deaths • 1 liver transplant	Bersoff-Matcha Ann Intern Med 2017
Prospective observational study, New Zealand	DCV/SOF/R-BV LDV/SOF/RBV SOF/LDV	N = 8	HBsAg+	0 with clinical flare	7/8 with HBV DNA elevation	None	Gane Antivir Ther 2016
Case study	SOF/SIM	1	NA	ALT increased from 62 IU/L before DAAs to 1495 IU/L	Increased HBV DNA from 2.3 IU/mL before DAAs to 22 million after	Hepatic decompensation (jaundice)	Collins Clin Infect Dis 2015

Table 3 (continued)

Cohort	DAA	N	Cohort	Other outcomes: ALT elevation, clinical illness, HBsAg appearance	HBV DNA elevation	Hepatic decompensation, liver transplant, death	Reference
Case study	LDV/SOF	1	NA	ALT elevation	From undetectable before DAAs to 8.9 log IU/mL after DAAs	Hepatic decompensation	De Monte J Clin Virol 2016
Case report	LDV/SOF	1	NA	ALT elevation/hepatitis after DAA termination	Increased HBV DNA	NA	Fabbri BMC Infect Dis 2017
Case report	Prev IFN/RBV SIM/SOF/RBV	1	NA	ALT elevation after DAA initiation	Increased HBV DNA	Fulminant hepatic failure requiring liver transplant	Ende J Med Case Rep 2015
Case study	DCV/ASV	1	NA	ALT elevation after DAA initiation	Increased HBV DNA	Acute liver failure (treated with entecavir), recovered	Hayashi Clin J Gastroenterol 2016
Case study	SOF/RBV	1	NA	ALT elevation after DAA initiation	Increased HBV DNA	Hepatic flare then treated with tenofovir	Madonia Liver Int 2016

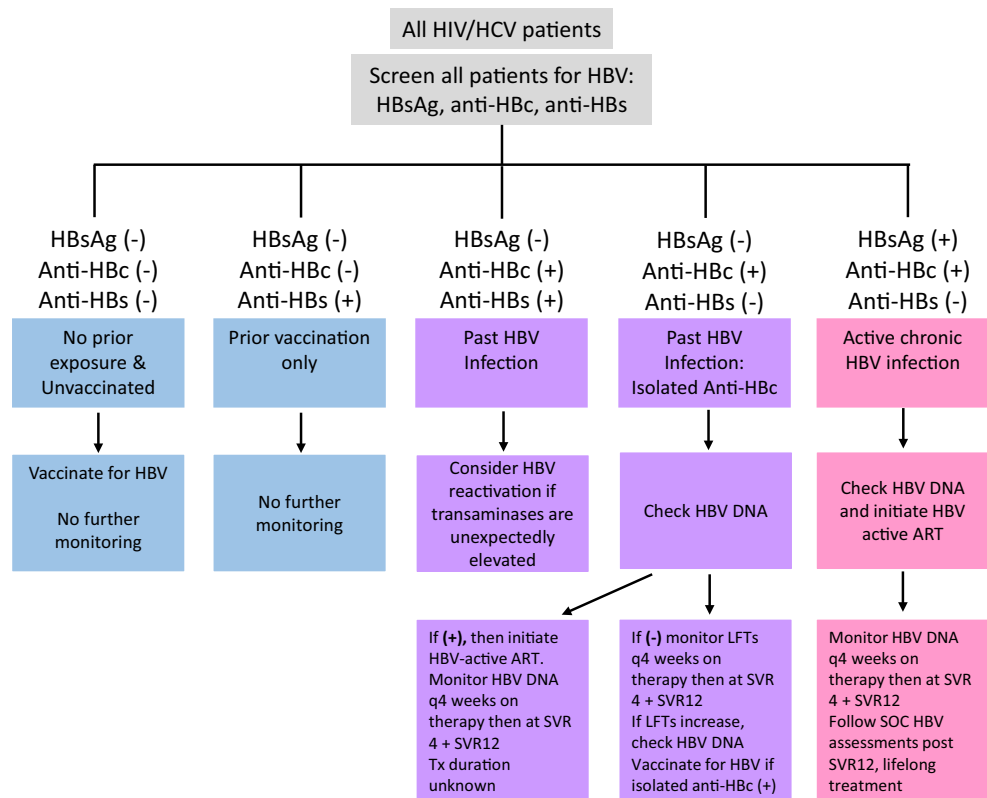
*11 studies included in meta-analysis did not have a clear definition for HBV reactivation but are included under HBV DNA elevation

and anti-HBs positive who had an acute hepatitis and HBV DNA elevation 4 weeks after completion of SOF/LDV therapy for HCV. She was successfully treated with entecavir with liver enzyme normalization [50].

Mechanism of HBV Reactivation in HCV Infection HBV and HCV have a unique viral interplay when infection with both viruses exists in one host. In general, HCV exerts an inhibitory effect on HBV, as evidenced by studies finding lower HBV viral loads in co-infection when compared with HBV mono-infected individuals [56]. Presence of HBeAg and levels of HBV DNA have been shown to be significantly lower in patients with HBV/HCV co-infection [57]. Mouse models in vivo have shown that HCV core protein has the capacity to inhibit HBV virus replication [58]. In addition, HBV and HCV may exert varying dominance over the course of each infection [59]. Interferon-based therapy can lead to HBsAg clearance [60, 61] in 30% of dual-infected patients. It is hypothesized that with DAA agents, as there is no inhibitory effect on HBV as with interferon, the ability of HBV to assume viral dominance and replication in the context of HCV clearance may be responsible for cases of HBV reactivation [43].

Management of Isolated Anti-HBc Pattern Prior to Treatment in HIV/HCV Infection Management of isolated anti-HBc profile in HIV/HCV co-infection remains a subject of discussion, given the risk of HBV reactivation during HCV DAA treatment. In the USA, both the AASLD/IDSA Treatment Guidance and the Veterans' Affairs centers have proposed management algorithms [62, 63]. Our proposed management strategy for addressing isolated anti-HBc serologic profile based on the studies above is shown in Fig. 2. Using our algorithm, all HIV/HCV co-infected patients should be screened for HBsAg, anti-HBc, and anti-HBs. If the patient is negative for all three markers, it can be concluded that they have had no prior exposure to HBV and are unvaccinated. These patients should then be vaccinated for HBV and do not require further monitoring. HBsAg and anti-HBc negativity with concurrent positive anti-HBs only indicate that the patient has been previously vaccinated with HBV, and therefore requires no further monitoring. If the individual is negative for HBsAg but is positive for both anti-HBc and anti-HBs (demonstrating past HBV infection) or the patient is negative for HBsAg and anti-HBs and is positive for anti-HBc (signifying isolated anti-HBc), we recommend assessment of baseline HBV DNA levels. The presence of HBV DNA requires HBV-active ART initiation. If positive at baseline, HBV DNA should be monitored every 4 weeks during therapy and sustained virologic response 4 and 12 (SVR4 + SVR12) weeks after completion of therapy should also be tested. The optimal treatment duration is unknown. If lifelong therapy is not preferred, HBV active ART should be continued for at

Fig. 2 HBsAg hepatitis B surface antigen; Anti-HBc antibody to hepatitis B core antigen; Anti-HBs antibody to HBsAg; HBV-active ART regimens containing TDF/FTC, TAF/FTC, TDF/3TC, and TAF/3TC, entecavir but note that entecavir should not be used in patients with HIV viremia. SVR4 sustained virologic response 4 weeks after end of therapy (EOT), SVR12 sustained virologic response 12 weeks after EOT, LFTs liver function tests, SOC standard of care. Modified from [36]



least 6 to 12 months after HCV end of treatment with monitoring of HBV DNA and LFTs with subsequent HBV active ART cessation. If the patient is negative for HBV DNA, their liver function tests (LFT) should be monitored every 4 weeks during therapy and at SVR12 weeks after HCV treatment cessation. An increase in LFTs would require that HBV DNA levels be checked again. Chronic HBV infection is determined by positive HBsAg and anti-HBc tests with negative anti-HBs. These patients should have their HBV DNA levels assessed and should initiate an HBV-active ART. Every 4 weeks during therapy and again at SVR4 and SVR12, the patient’s HBV DNA should be monitored. Standard of care HBV assessments should be followed post-SVR12 for lifelong treatment.

Summary/Conclusions

The isolated anti-HBc pattern (HBsAg(-)/anti-HBc(+)/anti-HBs (-)) occurs in 7–40% of HIV-infected individuals [1, 5, 6, 9–23] and in most cases represents a waning host immune response to HBV infection. The presence of anti-HBc denotes a transcriptionally active reservoir that can result in HBV reactivation. Whether the isolated anti-HBc pattern is associated with greater morbidity in HIV-infected patients is unclear, but large meta-analyses have demonstrated an association with

occult HBV infection (one part of the isolated anti-HBc pattern) with chronic liver disease and HCC in non-HIV-infected individuals. The isolated anti-HBc pattern is particularly relevant in HIV/HCV co-infected patients, both with respects to susceptibility to HBV infection and during DAA therapy. HBV reactivation has emerged in the era of DAA treatment of HCV infection, with varying consequences in morbidity ranging from asymptomatic infection to elevations in transaminases and/or resultant liver transplantation. Current guidelines recommended by the American Association for the Study of Liver Diseases (AASLD), and the Veterans’ Affairs recommend screening for HBsAg, HBsAb, and anti-HBc prior to consideration of treatment of HCV infection. Adherence to these recommendations and management of occult or isolated anti-HBc, as outlined here, may be essential in the prevention of HBV reactivation and subsequent morbidity that was less appreciated in the interferon era of HCV treatment.

Compliance with Ethical Standards

Conflict of Interest Debika Bhattacharya collaborated on an NIH sponsored protocol involving Merck, BMS, Abbvie, and Sanofi.

Jennifer J. Chang and Neaka Mohtashemi declare that they have no competing interests.

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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