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# Hepatitis B virus (HBV) reactivation—The potential role of direct-acting agents for hepatitis C virus (HCV)

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## Summary

Hepatitis C virus (HCV) is known to inhibit hepatitis B virus (HBV) replication in patients with HBV/HCV coinfection. Reactivation of HBV in patients treated for HCV with direct-acting agents (DAAs) has emerged recently as an important clinical consideration. A growing number of case reports and case series support the association between new HCV treatments and HBV reactivation. Yet, very little is known about the specific viral characteristics that facilitate reactivation as functional characterization of the reactivated HBV has been conducted only rarely. This review provides the most recent data on HBV reactivation in the context of DAA initiation and highlights the existing viral genomic data from reactivating viruses. Current functional studies of HBV reactivation are largely limited by the retrospective identification of cases, no standardization of genomic regions that are studied with respect to HBV reactivation, and the lack of inclusion of nonreactivating controls to establish specific viral mutations that are associated with HBV reactivation. Importantly, none of these sequencing studies included cases of HBV reactivation after initiation of DAAs.

While new HCV treatments have revolutionized care for HCV infected patients, HBV reactivation will likely increase in frequency, as DAAs are more commonly prescribed. Pretreatment determination of HBV status and thoughtful management of HBV coinfections will be necessary and lead to improved patient safety and yield optimal treatment results.

### Keywords

chemotherapy; direct-acting agents (DAA); hepatitis B virus (HBV); reactivation; hepatitis C virus (HCV)

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CONFLICT OF INTEREST

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# 1 | INTRODUCTION

## 1.1 | Defining hepatitis B virus reactivation

Approximately 240 million people are infected chronically with hepatitis B virus (HBV)—the world's leading cause of cirrhosis and hepatocellular carcinoma (HCC).[1,2] Initial infection frequently leads to clearance, but even in those who fail to completely eliminate the virus, the immune system is able to control replication. Unfortunately, loss of immunologic control is still possible and leads to reactivation of HBV replication.

No prevailing definition of HBV reactivation exists. Experts often define reactivation as de novo detection of HBV DNA in individuals without previously detectable HBV DNA or a 1 to 2 log IU/mL rise in serum HBV DNA levels. Hepatitis B surface antigen (HBsAg) seroreversion in HBsAg-negative individuals with antibodies to the HBV core antigen (hepatitis B core antigen [anti-HBc]) may also identify HBV reactivation (reviewed in Gonzalez and Perrillo[3]). It occurs most commonly during undiagnosed chronic infection when immunosuppressive agents are initiated. Multiple clinical interventions are associated with HBV reactivation including antimetabolites, tumor necrosis factor alpha inhibitors, transarterial chemoembolization, corticosteroids, systemic chemotherapy, and stem cell and solid organ transplantation (reviewed in other studies[3,4]). Despite recent guidelines from the American Gastroenterological Association highlighting the critical need for patient identification and management,[5] screening for HBV remains low in patients receiving immunosuppressive therapies in the US[6–8] and is rarely conducted in low and middle-income countries.

## 1.2 | Populations at risk for HBV reactivation

Even among individuals with "resolved" HBV infection, the risk of HBV reactivation remains when receiving immunosuppressive therapies and/or chemotherapy. For instance, a meta-analysis of individuals with resolved HBV infection receiving chemotherapy for hematologic malignancies observed reactivation in 14% of those with anti-HBc antibodies and 5% of those with anti-HBc and Hepatitis B surface antigen (anti-HBs) antibodies.[9] HBV reactivation occurred in 24.8% of patients with HBV-related HCC treated with radiotherapy.[10] A systematic review of individuals receiving anticancer drugs concluded that most agents utilized to treat solid tumors can lead to HBV reactivation and that HBV screening should be performed prior to drug treatment.[11] Similarly, HBV reactivation has been reported in individuals treated for autoimmune disorders or those undergoing transplantation.[12–17] Among HBsAg-negative patients, the risk of reactivation remains, as reactivation of occult infection (defined as HBsAg negative but HBV DNA positive infection) has been reported.[18–20] Similarly, HBV reactivation in HIV-positive individuals that initiate or terminate antiretroviral therapy has been described.[21–28] Nonetheless, large population-based studies of HBV reactivation in HIV-positive individuals have not been performed to date.

## 1.3 | Virus interactions and direct-acting agents

Recently, reactivation of HBV in patients treated for hepatitis C virus (HCV) with direct-acting agents (DAAs) has emerged as an important clinical consideration. Hepatitis C virus infection inhibits HBV replication in patients with HBV/HCV coinfection[29] and is mediated

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by several HCV proteins, including core, NS2, and NS5A.[30–35] Thus, DAA suppression of HCV could result in increased HBV replication and protein expression. A growing body of evidence supports this hypothesis (Table 1). For instance, De Monte et al[37] reported a case of HBV reactivation in an HCV-positive individual treated with the DAAs ledipasvir and sofosbuvir who had resolved HBV infection previously. Others reported HBV reactivation in an HCV-positive individual with inactive HBV treated with daclatasvir and asunaprevir[42] and elevated HBV DNA levels after triple therapy with Pegylated interferon (PEG-IFN), ribavirin, and simeprevir.[51] Two cases of reactivation during treatment with sofosbuvir and simeprevir have been reported as well.[36] Similarly, HBV reactivation occurred during treatment with sofosbuvir, simeprevir, and ribavirin in an individual with isolated HBV core antibody.[38] Additional cases of HBV reactivation after treatment with daclatasvir and asunaprevir have been reported.[39,41] As mentioned above, reactivation of occult HBV infection is also possible as described in an HIV/HCV coinfected individual treated with sofosbuvir and ledipasvir.[18]

In October 2016, the US Food and Drug Administration issued a black box warning related to the risk of reactivation of current/previous HBV infection in persons treated with DAAs.[52] Of these initial cases, 2 resulted in death, while 1 required liver transplantation.[53] Among patients those that experienced reactivation, HCV genotype, DAA(s) received, and baseline HBV characteristics were heterogenous. Thus, clinical and virologic characteristics may be less helpful in predicting who develops HBV reactivation. In subsequent cohort studies of individuals receiving DAAs, HBV reactivation was common in those with detectable serum HBsAg and lower in individuals with isolated anti-HBc antibodies. In contrast, Sulkowski et al[45] evaluated 173 clinical trial participants from Taiwan and Korea receiving ledipasvir and sofosbuvir and found no cases of HBV reactivation. Wang et al[47] evaluated 327 Chinese patients receiving DAAs. Ten individuals were HBsAg positive, while 124 patients had occult HBV infection. Three cases of HBV reactivation were identified. In a meta-analysis comparing reactivation rates in patients with chronic versus occult infection, the incidence of HBV reaction was similar among individuals treated with IFN-based therapies or DAAs, although reactivation occurred earlier in the DAA treatment group.[54] Likewise, hepatitis due to reactivation was more common when treated with DAAs compared with IFN-based treatment (12.2% versus 0%). Hepatitis B virus reactivation and hepatitis were less common among individuals with occult HBV infection. These findings imply that more potent DAAs that suppress HCV replication effectively may lead to increased HBV replication more quickly than previous HCV regimens. Among 84 patients with resolved HBV infection receiving DAA regimens, 5 patients (5.9%) experienced reactivation or showed detectable HBV DNA.[44] In Taiwan, HBV reactivation was not observed among 57 patients with past HBV infection but was found in 4 of 7 patients with current infection.[43] Among 848 individuals treated with DAAs, no HBV reactivation was observed in HBsAg negative but anticore positive patients, although the cohort did include 8 patients with detectable HBV DNA but with titers less than 20 IU/mL at the end of treatment. In contrast, 5 of 9 HBsAg-positive patients experienced HBV reactivation, and 3 required HBV treatment.[49] In the largest study conducted to date, over 62 000 US veterans who were treated with DAAs were evaluated for HBV infection and reactivation.[50] Three hundred seventy seven were HBsAg positive, and 9 individuals—8 known to be HBsAg-positive and 1 who was isolated anti-

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HBc positive—experienced reactivation during treatment. Notably, cohort studies have only been conducted in 7 countries, including Taiwan,[43,45] Japan,[44,46] South Korea,[45] China,[42] Germany,[49] Spain,[48] and the United States.[50] Reactivation secondary to immunosuppressive therapy is thought to be because of generalized suppression of T-cell function, resulting in impairment or loss of cytotoxic T cells that are necessary for viral suppression. In contrast, treatment/cure of HCV may increase the replication space for HBV, which is otherwise limited in the presence of HCV due to the effects of interferon-stimulated genes.[55]

### 1.4 | Preventing HBV reactivation

To date, the prevention of HBV reactivation has focused primarily on prophylactic antiviral therapy. Nonetheless, preoperative antiviral therapy can reduce the likelihood of reactivation after rehepatectomy in patients with HBV-related HCC.[56] Similarly, in patients with HCC who lack detectable serum HBV DNA and underwent hepatic resection, HBV reactivation was associated with absence of antiviral therapy.[57] Unfortunately, there is no consensus as to the optimal therapy(s) or duration of treatment to prevent HBV reactivation. A recent meta-analysis reported that lamivudine significantly reduced chemotherapy-associated HBV flares in breast cancer patients.[58] Not surprisingly, lamivudine plus adefovir dipivoxil was better than lamivudine monotherapy in preventing reactivation in Chinese patients.[59] Among patients with lymphoma, 3 factors—hepatitis, reactivation, and chemotherapy disruption—were significantly higher in patients receiving lamivudine compared with entecavir.[60] A network meta-analysis suggested that tenofovir and entecavir may be the most potent agents to prevent HBV reactivation in patients undergoing chemotherapy.[61] Thus, in HBV/HCV coinfected patients in whom DAA therapy is being contemplated, determining chronic or occult HBV status is critical. It should also be noted that anti-HBc is a poor surrogate marker of occult HBV infection, as anti-HBc seronegative occult infections are relatively common, particularly among HIV-positive persons.[62–64] Clearly, the optimal antiviral therapy for HBV reactivation is one that limits the emergence of drug resistance while effectively suppressing viral replication. While tenofovir seems the ideal choice, it is not available everywhere, particularly in resource-limited settings.

### 1.5 | Virologic characterization of reactivating HBV

Analysis of complete HBV genomes demonstrates that at least 8 genotypes exist that differ by >8% at the nucleotide level.[65,66] Hepatitis B virus genotype may influence chronicity, disease severity, and antiviral response rates.[66] As well within an individual, HBV exists as a population of highly related yet distinct viral variants termed the viral quasi species that enable rapid, adaptive changes in response to immune selection pressure and antiviral therapy. Quasi species diversity has consequences for viral persistence and HBV-associated disease.[67] Currently, very little is known about the specific viral characteristics that facilitate HBV reactivation as functional characterization of the reactivated HBV has been conducted in a limited number of studies (Table 2). Are reactivating viruses identical to nonreactivating viruses, thus suggesting that reactivating is due to nonviral features? If viral features do enable reactivation, what specific genomic regions are responsible? Some concern exists that HBV reactivation may represent reinfection that has been misclassified. Nonetheless, robust sequence analysis and comparison of prereactivation and post reactivation genetic distances, as well as evaluation of signature sequences, can address issue effectively.

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Unfortunately, most reports of reactivation during chemotherapy or antiretroviral therapy initiation or termination provide sequence data on the reactivating virus but fail to include sequences of other nonreactivating viruses circulating in the same geographic location or at-risk population.[76,79] Among HBsAg-negative patients who developed HBV reactivation during or after chemotherapy, no significant differences in the prevalence of basal core promoter/preCore (BCP/PC) variants were observed between the HBV reactivation and acute self-limited hepatitis groups, although immune escape mutants were found in 9 of 11 reactivation cases but none of the acute hepatitis cases.[75] Hass et al[71] reported 2 cases of occult HBV that reactivated and observed multiple mutations associated with altered protein expression and lower replication in vitro. Immune escape mutations, drug resistance mutations, and new N-glycosylation sites have been reported in stem cell transplant recipients treated with lamivudine.[68] In a large cohort of HBsAg-positive individuals in China, spontaneous HBsAg clearance occurred in 41 subjects.[69] Thirteen were tested for HBsAg several years later, and 4 became HBsAg positive. Surface gene sequences collected before seroclearance and after reappearance were > 99% similar suggesting that HBV reactivation (rather than infection with a new HBV strain) may occur years after HBsAg clearance. Similarly, longitudinal evaluation of sequence diversity can aid in distinguishing HBV reactivation from reinfection.[72] In a small pilot study, HBV reactivation was attributed to the A1896 pre Core stop codon mutation, although nonreactivating controls were not evaluated.[73] Among 14 HBsAg-negative but anti-HBc positive individuals that experienced HBV reactivation triggered by chemotherapy or immunosuppressive therapy, reactivation occurred during immunosuppressive therapy for 7 and after termination of therapy in 7.[78] Deep sequencing demonstrated that genetic heterogeneity of the reactivated HBV was significantly lower in patients with occult HBV compared with those with chronic HBV, while others have reported that viral evolution impacts reactivation.[27,70] A case control study of HBV reactivation in HBsAg-negative, anti-HBc positive individuals receiving chemotherapy found that reactivation was more common in men, individuals with an HBs antibody titre <100 IU/L and individuals who underwent >1 line of chemotherapy.[74] Another case control study compared 16 HBsAg-negative individuals who experienced HBV reactivation following chemotherapy and compared them with 51 individuals with chronic HBV infection.[76] Hepatitis B surface antigen and reverse transcriptase mutations were more common during HBV reactivation. Mutations known to impair HBsAg antigenicity were detected in all cases of reactivation.

Several features of the existing viral genomic data on HBV reactivation require careful consideration. First, most studies retrospectively identified cases of reactivation that were nonrandomly selected from a single institution. The limited longitudinal evaluation of virus diversity does not permit a robust understanding of how viral features evolve and contribute to HBV reactivation. Only a single study—including one individual with genotype A and a second with genotype E—evaluated functional aspects of the reactivating virus in vitro.[71] Second, no standard genomic region(s) are studied with respect to HBV reactivation; thus, comparison of distinct genomic regions and the considerable variability amongst the HBV genotypes could limit cross-study generalizability. Finally, it has been suggested that immune escape mutations may facilitate HBV reactivation.[69,74,75,80–82] However, the inherent variability of HBV within individuals and at the population level requires the

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inclusion of nonreactivating controls to establish specific viral mutations that are associated with HBV reactivation. Importantly, none of these sequencing studies included cases of HBV reactivation after initiation of DAAs.

Though new HCV treatments have revolutionized care for HCV infected patients, thoughtful pretreatment evaluation and management of HBV coinfections will improve patient safety and yield optimal treatment results. Hepatitis B virus reactivation will likely increase in frequency, as DAAs are more commonly prescribed.

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**TABLE 1**

Studies of HBV reactivation in HCV-positive individuals treated with DAAs

| Reference | Sample Size (Number with Reactivation) | Country | DAA Regimen |
|---|---|---|---|
| Case reports | | | |
| 36 | 2(2) | United States | Sofosbuvir + simeprevir |
| 37 | 1(1) | France | Sofosbuvir + ledipasvir |
| 38 | 1(1) | United States | Sofosbuvir + simeprevir + ribavirin |
| 18 | 1 (1) | Italy | Sofosbuvir + ledipasvir |
| 39 | 1 (1) | Japan | Daclatasvir + asunaprevir |
| 40 | 1 (1) | Japan | Simeprevir + PEG-IFN + ribavirin |
| 41 | 1 (1) | Japan | Daclatasvir + asunaprevir |
| 42 | 1 (1) | Japan | Daclatasvir + asunaprevir |
| Cohort studies | | | |
| 43 | 64 (4) | Taiwan | Multiple IFN-free regimens |
| 44 | 84(5) | Japan | Multiple IFN-free regimens |
| 45 | 103 (0) | Taiwan and South Korea | Sofosbuvir + ledipasvir |
| 46 | 183 (4) | Japan | Sofosbuvir + ledipasvir or Sofosbuvir + ribavirin |
| 47 | 327 (3) | China | Multiple IFN-free regimens |
| 48 | 352 (6) | Spain | Multiple IFN-free regimens |
| 49 | 808 (13) | Germany | IFN-based regimens Multiple IFN-free regimens |
| 50 | 62 290 (9) | United States | Multiple IFN-free regimens |

Abbreviations: DAA, direct-acting agents.

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**TABLE 2**

Functional characterization of HBV reactivation

| | | | Sequencing Approach | HBV Genotypes (N) |
|---|---|---|---|---|
| **Reference** | **Study Population** | **Treatment** | **HBV Genomic Region(s)** | **Country** |
| 68 | Stem cell transplant recipients | Lamivudine or none | Population sequencing | Genotype D (3) |
| | | | | Genotype F (1) |
| | | | P/S | Italy |
| 69 | HBsAg spontaneous clearers | None | Clonal sequencing | Genotype C (2) |
| | | | | Genotypes C + I (1) |
| | | | S | China |
| 27 | Occult HBV + HIV | Lamivudine-containing ART | Population sequencing | Genotype D (1) |
| | | | P/S | Italy |
| 70 | Occult HBV | Chemotherapy | Clonal sequencing | Genotype not reported (3) |
| | | | PreS/S | Italy |
| 71 | Occult HBV | ART | Clonal sequencing | Genotype A (1) |
| | | | | Genotype E (1) |
| | | | Full genome | Germany & Zaire |
| 72 | Occult HBV + HIV | Interruption of ART | Population sequencing | Genotype A (1) |
| | | | P, S, PreC | Italy |
| 73 | Chronic + occult HBV | Chemotherapy | Clonal sequencing | Genotype not reported (1) |
| | | | PreC/Core | Greece |
| 74 | Occult HBV | Chemotherapy | Population & clonal sequencing | Genotype C (2) |
| | | | | Genotype D (5) |
| | | | P/S | France |
| 75 | Occult HBV | Chemotherapy | Population sequencing | Genotype A (1) |
| | | | | Genotype B (2) |
| | | | | Genotype C (8) |

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| Reference | Study Population | Treatment | Sequencing Approach | HBV Genotypes (N) |
|---|---|---|---|---|
| | | | HBV Genomic Region(s) | Country |
| | | | P/S | Japan |
| 76 | Occult HBV | Chemotherapy | Population sequencing | Genotype A (1)<br>Genotype C (2)<br>Genotype D (13) |
| | | | P/S | France |
| 77 | Occult HBV | Chemotherapy | Population sequencing | Genotype D (5) |
| | | | Full genome | Egypt |
| 78 | Occult HBV | Termination of immunosuppressive therapy | Deep sequencing | Genotype B (5)<br>Genotype C (9) |
| | | | Full genome | Japan |
| 79 | Occult HBV | Chemotherapy | Clonal sequencing | Genotype C (1) |
| | | | Full genome | Japan |

Abbreviations: ART, antiretroviral therapy; HBsAg, hepatitis B surface antigen; P, polymerase gene; PreC, PreCore region; PreSurface region; S, surface gene.