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Hepatitis B Virus Reactivation Associated With Direct-Acting Antiviral Therapy for Chronic Hepatitis C Virus

A Review of Cases Reported to the U.S. Food and Drug Administration Adverse Event Reporting System

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Background: Direct-acting antiviral agents (DAAs) are used increasingly to treat hepatitis C virus (HCV) infection. Reports were published recently on hepatitis B virus (HBV) reactivation (HBV-R) in patients with HBV–HCV co-infection. Hepatitis B virus reactivation, defined as an abrupt increase in HBV replication in patients with inactive or resolved HBV infection, may result in clinically significant hepatitis.

Objective: To assess whether HBV-R is a safety concern in patients receiving HCV DAAs.

Design: Descriptive case series.

Setting: U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS).

Patients: 29 patients with HBV-R receiving HCV DAAs.

Measurements: Clinical and laboratory data.

Results: The FDA identified 29 unique reports of HBV-R in patients receiving DAAs from 22 November 2013 to 15 October 2016. Two cases resulted in death and 1 case in liver transplantation. Patients in whom HBV-R developed were heterogeneous regarding HCV genotype, DAAs received, and baseline HBV chacteristics. At baseline, 9 patients had a detectable HBV viral load, 7 had positive results on hepatitis B surface antigen (HBsAg) testing and had an undetectable HBV viral load, and 3 had negative results on HBsAg testing and had an undetectable HBV viral load. For the remaining 10 patients, data points were not reported or the data were uninterpretable. Despite provider knowledge of baseline HBV, HBV-R diagnosis and treatment were delayed in 7 cases and possibly 7 others.

Limitations: The quality of information varied among reports. Because reporting is voluntary, HBV-R associated with DAAs likely is underreported.

Conclusion: Hepatitis B virus reactivation is a newly identified safety concern in patients with HBV–HCV co-infection treated with DAAs. Patients with a history of HBV require clinical monitoring while receiving DAA therapy. Studies would help determine the risk factors for HBV-R, define monitoring frequency, and identify patients who may benefit from HBV prophylaxis and treatment. DAAs remain a safe and highly effective treatment for the management of HCV infection.

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An estimated 170 million persons worldwide have hepatitis C virus (HCV) infection (1), including 2.7 million to 3.9 million in the United States (2). The infection becomes chronic in about 75% to 85% of HCV-infected persons. Chronic HCV infection results in severe complications in 10% to 20% of patients and is the leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation in the United States. Approximately 15 000 persons die each year of HCV-related liver disease in the United States (3).

Until recently, HCV treatment regimens were cumbersome because of adverse drug effects, and only about half of all treated patients had a sustained virologic response (SVR) (4–6), defined as the absence of detectable HCV RNA in the serum 12 weeks after completion of therapy. With the availability of newer direct-acting antiviral agents (DAAs) for HCV, patients now have a very high likelihood of achieving SVR (7, 8), with fewer side effects. Sustained virologic response is associated with a decrease in all-cause and liver-related mortality, hepatocellular carcinoma, and hepatic decompensation (9, 10).

In the United States, acute hepatitis B virus (HBV) infection occurs primarily among injection drug users and men who have sex with men. Approximately 2% to 6% of U.S. adults with HBV infection become chronically infected (11). An estimated 850 000 to 2.2 million persons in the United States have chronic HBV infection, and an additional 5000 to 8000 become chronically infected each year (11). Worldwide, HBV is a major cause of liver disease, ranging from acute to chronic hepatitis, cirrhosis, and hepatocellular carcinoma.

Although estimates vary regarding the prevalence of HBV–HCV co-infection, it is common in geographic areas where both infections are endemic and in populations at high risk for both viruses because of their common routes of transmission (12, 13). The prevalence of HBV co-infection in 2 U.S. Veterans Affairs patient cohorts with chronic HCV infection was as high as 42% to 67% (14–17).

Hepatitis B virus reactivation (HBV-R) is defined as an abrupt increase in HBV replication in a patient with inactive or resolved HBV infection (18). Although HBV-R may occur spontaneously, it is more frequent in patients with immunodeficiency due to HIV (19), autoim-

See also:

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mune disease (20), or organ transplantation (21, 22), or it may be triggered by initiation of immunosuppressive therapy. Clinical manifestations of HBV-R range from asymptomatic to symptomatic, including acute liver failure and death (18).

In the past, HBV-R was reported in patients with HBV–HCV co-infection treated with interferon (IFN)-based HCV therapy. A meta-analysis of 5 studies concluded that the proportion of HBV-R cases ranged from 11% to 33% in patients with HBV–HCV co-infection treated with pegylated (peg)-IFN and ribavirin. In those studies, HBV-R was most likely to occur in patients who had achieved an HCV SVR (odds ratio, 3.36 [95% CI, 1.35 to 8.38]) (23).

METHODS

Like many countries, the United States relies on a program to monitor spontaneous adverse events to oversee the safety of regulated products after they are approved and on the market. Health care professionals, consumers, drug manufacturers, and others may report adverse events associated with products regulated by the U.S. Food and Drug Administration (FDA) through its MedWatch program. Adverse events may be captured either through interaction with a drug manufacturer representative or directly via MedWatch. Reporting is voluntary for everyone except manufacturers; therefore the actual number of adverse events that are attributable to a particular drug and occur in the postmarketing setting is unknown (24, 25). Reports of adverse drug events (also known as MedWatch reports) submitted to the FDA are stored and queried through the FDA Adverse Event Reporting System (FAERS) database.

To determine the reported number of HBV-R cases in patients treated with DAAs, we queried FAERS with the following search terms from the Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 18.1): *hepatitis B*, *hepatitis B DNA increased*, *hepatitis B virus test positive*, *hepatitis B DNA assay positive*, *hepatitis B e antigen positive*, *hepatitis B core antibody positive*, and *hepatitis B antigen positive*. We included all reports of HBV-R among patients receiving any currently approved second-generation DAA between 22 November 2013 (the date of simeprevir approval in the United States) and 15 October 2016. A FAERS report was included if it contained a statement by the reporter that it was considered to be a case of HBV-R, documentation of baseline HBV data (hepatitis B surface antigen [HBsAg] or HBV DNA) before the initiation of DAAs, or documentation of an increase in HBV DNA level or a change in HBsAg status from negative to positive.

We also searched the literature for cases that were not reported to FAERS. We examined the PubMed, Google Scholar, EMBASE, and EBSCOhost databases for case series, case reports, and epidemiologic studies reporting HBV-R with DAA therapy. To be included in the series, cases found in the literature that were not reported to FAERS had to meet the same inclusion criteria as the FAERS cases.

Cases were compiled in Microsoft Excel, version 14, to produce descriptive (aggregate) attributes of the case series.

Statistical Analysis

No tests of statistical significance were planned or performed.

Role of the Funding Source

This study was not funded.

RESULTS

We reviewed 51 FAERS reports of HBV-R associated with DAA therapy, 28 of which met the criteria for inclusion in our series. Reasons for exclusion included duplicate reports (n = 8), HBV contracted while receiving DAA therapy (n = 2), and inability to meet criteria for HBV-R according to case definition (n = 13). One additional case included in this series was reported in the literature but not to FAERS. Table 1 shows the characteristics of the 29 patients included in the case series.

Nineteen of 29 reports (66%) were from Japan; 5 patients were from the United States. Mean patient age was 60.7 years; 16 patients (55%) were women. Of the 17 patients with HBV-R in whom the HCV genotype was known, 15 had genotype 1 virus. Baseline HCV and HBV viral characteristics of the 29 patients are outlined in Table 2.

Reactivation of HBV usually occurred 4 to 8 weeks after DAA initiation (mean time from DAA start to HBV-R, 53 days [range, 14 to 196 days]). Decompensated liver failure developed in 3 patients, 2 of whom died and 1 of whom required liver transplantation (26). One additional patient reported in an observational cohort study by Wang and colleagues (27) on HBV-R and DAA therapy (but not included in our case series because of insufficient information) also had fulminant hepatic failure.

Most reports (19 of 29; 66%) did not include information on whether symptoms were associated with HBV-R. Eight (28%) of the patients were reported to have a clinical illness that accompanied the increase in HBV DNA levels; of these, 6 (75%) were hospitalized. Reported symptoms included malaise, fatigue, abdominal pain, jaundice, and encephalopathy. Among the 19 patients with minimal information, 5 discontinued DAA treatment because of HBV-R, 2 were hospitalized, and at least 7 were started on medication to treat HBV infection. Two patients did not become clinically ill as the result of their HBV-R event (28, 29). One of these patients was started on HBV treatment at the first indication of an increase in HBV viral load (Table 3) (29).

Among the 8 patients known to be clinically ill as a result of HBV-R, 5 had a decrease in HBV DNA and transaminase levels, as well as in hepatitis symptoms, with treatment. More than half the patients (15 of 29; 52%) eventually received HBV antiviral therapy (namely tenofovir or entecavir); 8 were specifically noted to have received no treatment for HBV infection. No reports of treatment were found for the remaining 6 patients (Table 3).

Among the 15 patients who received HBV therapy, treatment was delayed by 7 days or more after diagnosis in at least 7 (47%), 1 of whom died. In addition, a possible delay occurred in at least 7 other patients, 1 of whom required a liver transplant. All patients in the current series were receiving treatment for HCV infection and therefore were presumed to be undergoing monitoring for liver events. Despite provider knowledge of relevant baseline HBV status in these cases, diagnosis and treatment of HBV-R were delayed after an increase in transaminase or HBV DNA levels was noted, with delays ranging from 7 to 60 days to treatment.

The cases in our series were heterogeneous in terms of HCV genotype and baseline HBV viral characteristics (Table 2). No consistency was found with regard to the DAA regimen received, suggesting a potential association between HBV-R and all DAAs (Table 2). Six patients who were tested for hepatitis B core antibody (HBcAb) before receiving DAA therapy had positive results. Fifteen patients also were tested for baseline reactivity against hepatitis B e antigen (HBeAg), all of whom had negative results. Thirteen patients had positive results on HBsAg testing, and only 3 patients reported results for hepatitis B surface antibody (HBsAb), all of which were negative.

Discussion

We identified 29 cases in the FAERS database and the literature of HBV-R in patients receiving DAA therapy. In 10 cases, increasing transaminase levels led to suspicion of an adverse drug reaction due to DAA hepatotoxicity, and DAA therapy was discontinued. This approach was reasonable, particularly among patients receiving daclatasvir–asunaprevir, because asunaprevir has been associated with hepatotoxicity in some patients (30, 31). However, in patients whose disease deteriorated or failed to improve, HBV-R also was considered in the differential diagnosis. Thus, a common sequence of events among patients in our case series was as follows: initiation of DAA therapy; a rapid decrease in HCV RNA to undetectable levels within 1 to 2 weeks, with normalization of transaminase levels (if they were elevated); an increase in HBV DNA levels with or without increases in transaminase levels between weeks 4 and 8 (mean, 53 days); discontinuation of DAA therapy on observation of increasing transaminase levels (usually near week 8); then initiation of HBV-R treatment.

In our case series, the population was heterogeneous in terms of baseline HBV disease (Table 2) and fit into 3 general patient categories: those with a detectable HBV viral load (n = 9), those with positive results on HBsAg testing and an undetectable HBV viral load (n = 7), and those with negative results on HBsAg testing and an undetectable HBV viral load (n = 3). Regarding the other 10 patients, either their HBsAg status was not known or their baseline HBV viral load could not be interpreted because the accompanying units were missing and the reporter did not state whether the viral load was considered undetectable. To meet the case definition of HBV-R, patients had to have a documented increase in HBV DNA levels from baseline or HBsAg seroconversion after starting DAA therapy. One may reasonably assume that the barrier to viral reactivation and subsequent hepatitis flare might be lower for patients who already have low but detectable levels of HBV or surface antigenemia. In our population, however, the numbers of patients in each category were small, making it difficult to assess the risk for reactivation in subpopulations, such as those who tested positive for HBsAg or isolated HBcAb.

Although more than half the patients (15 of 29) in the series eventually received antiviral therapy active against HBV (either tenofovir or entecavir), at least 7 specifically were reported to have received no treatment. According to current guidelines from the Ameri-

Table 1. Descriptive Characteristics of Cases of Confirmed HBV-R From 22 November 2013 to 15 October 2016 (n = 29)*

Characteristic	Value
Age, *y* (*n* = 29)	
Mean	60.7
Median	58
Range	36–85
Sex, *n*	
Male	13
Female	16
Time to event, *d* (*n* = 28)	
Mean	53
Median	46
Range	14–196
Treatment delay, *n*	
Yes	7
Possible	7
No delay	2
No treatment given	7
Treatment not stated	6
Baseline HCV viral characteristics, *n*	
Genotype 1	16
Other genotype	2
Not reported	11
Baseline HBV viral characteristics, *n*	
HBsAg	
Positive	13
Negative	4
Not reported	12
HBcAb	
Positive	6
Not reported	23
HBsAb	
Negative	3
Not reported	26
HBV DNA	
Undetectable	16
Detectable	9
Baseline not reported or detectability status unclear	4

FAERS = U.S. Food and Drug Administration Adverse Event Reporting System; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HBV-R = HBV reactivation; HCV = hepatitis C virus.
* For more complete data on viral characteristics, see Table 2.

Table 2. Baseline HBV/HCV Viral Characteristics and DAA Received

Case Number (Reference)	HCV Genotype	HBV Genotype	HBsAg	HBsAb	HBcAb	HBeAg	HBeAb	HBV DNA Level, *copies/mL**	DAA	Country of Report
1	1a	NR	NR	NR	NR	Negative	Positive	2700 (elevated)	Viekira Pak (AbbVie)/RBV	United States
2 (42)	1b	NR	Positive	NR	Positive	Negative	Positive	2.5 $\log_{10}$ (elevated)	DCV/ASV	Japan
3	NR	NR	NR	NR	NR	Negative	Positive	Undetectable	DCV/ASV	Japan
4	1b	NR	Positive	NR	NR	Negative	Positive	3.9 $\log_{10}$ (elevated)	DCV/ASV	Japan
5 (29)	1a	NR	NR	NR	NR	Negative	Positive	2300 (elevated)	SIM/SOF	United States
6 (29)	1a	NR	Negative	Negative	Positive	NR	NR	Undetectable	SIM/SOF	United States
7 (26)	1	NR	Negative	Negative	Positive	NR	NR	Undetectable	SIM/SOF/RBV	United States
8	3a	NR	Positive	NR	NR	NR	NR	244 (elevated)	SOF/RBV	Portugal
9 (38)	4	D	Negative	Negative	Positive	Negative	Positive	Undetectable	LDV/SOF	France
10 (28)	NR	NR	Positive	NR	NR	NR	NR	Undetectable	LDV/SOF	United States
11	NR	NR	NR	NR	Positive	NR	NR	Undetectable	LDV/SOF	Japan
12 (43)	1	B	Positive	NR	NR	Negative	Positive	Undetectable	SIM/PEG/RBV	Japan
13	1	A	Positive	NR	NR	Negative	Positive	Undetectable	SOF/RBV	Japan
14	NR	B	Positive	NR	NR	NR	NR	1.3 $\log_{10}$ (elevated)	LDV/SOF	Japan
15	1b	B	Positive	NR	NR	Negative	Positive	2.7 $\log_{10}$ (elevated)	DCV/ASV	Japan
16	NR	C	Positive	NR	NR	NR	NR	Undetectable	LDV/SOF	Japan
17	1a	NR	Positive	NR	Positive	Negative	Negative	Undetectable	DCV/SOF/RBV	Australia
18	NR	NR	NR	NR	NR	Negative	Positive	3.6 $\log_{10}$ (elevated)	LDV/SOF/RBV	Japan
19	1b	NR	Positive	NR	NR	Negative	Positive	<2.1 $\log_{10}$†	DCV/ASV	Japan
20	1b	NR	Positive	NR	NR	Negative	Positive	Undetectable	DCV/ASV	Japan
21	1	NR	NR	NR	NR	Negative	Negative	Undetectable	DCV/ASV	Japan
22	1	NR	NR	NR	NR	NR	NR	<2.1 $\log_{10}$†	DCV/ASV	Japan
23	NR	NR	NR	NR	NR	NR	NR	Undetectable	DCV/ASV	Japan
24	NR	C	NR	NR	NR	Negative	NR	3.3 $\log_{10}$ (elevated)	DCV/ASV	Japan
25	NR	NR	NR	NR	NR	NR	NR	Undetectable	DCV/ASV	Japan
26	NR	B	NR	NR	NR	NR	NR	<2.1 $\log_{10}$†	LDV/SOF	Japan
27	NR	NR	NR	NR	NR	NR	NR	Undetectable	LDV/SOF	Japan
28	NR	NR	Negative	NR	NR	NR	NR	NR	LDV/SOF/RBV	France
29 (44)	1b	NR	Positive	NR	NR	NR	Positive	Undetectable	LDV/SOF	China

ASV = asunaprevir; DAA = direct-acting antiviral agent; DCV = daclatasvir; HBcAb = hepatitis B core antibody; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; LDV = ledipasvir; NR = not reported; PEG = pegylated interferon; RBV = ribavirin; SIM = simeprevir; SOF = sofosbuvir.

* Values interpreted as undetectable only if specifically stated as such in the U.S. Food and Drug Administration Adverse Event Reporting System report. Values expressed by a numeral, provided without units, and/or not specifically stated as undetectable were interpreted as elevated/detectable.

† Values preceded by "<" were regarded as uninterpretable if not specifically stated as undetectable.

can Association for the Study of Liver Diseases (AASLD), patients with immune-active chronic HBV infection are candidates for treatment (32). Under these recommendations, immune-active HBV infection is defined as an alanine aminotransferase level greater than twice the upper limit of normal or evidence of significant histologic disease plus an HBV DNA level greater than 2000 IU/mL (in HBeAg-negative disease) or 20 000 IU/mL (in HBeAg-positive disease), or an HBV DNA level greater than 2000 IU/mL in patients with cirrhosis regardless of alanine aminotransferase level. On the basis of these guidelines, we determined that at least 26 of the 29 patients (90%) in this series should have received treatment at the first indication of increasing HBV DNA levels. We note, however, that most of the cases were from outside the United States, from countries where both HBV and HCV infections are endemic and medical practice may differ from AASLD guidelines.

Other drug classes known to be associated with HBV-R include rituximab (B-cell–depleting agent) (33), etanercept (tumor necrosis factor inhibitor) (34), doxorubicin (anthracycline derivative) (35), and imatinib (tyrosine kinase inhibitor) (36). Because these agents suppress the immune system and reactivate HBV in more than 10% of patients with HBsAg- and HBcAb-positive disease, antiviral prophylaxis is recommended when planning treatment with these drugs (37). In contrast, the DAAs are not known to cause immunosuppression; instead, they act by inhibiting the viral proteins required for HCV replication. The mechanism through which HBV-R occurs with the use of the DAAs is unknown. Hepatitis B virus–HCV viral interference, defined as the inverse relationship in the replication of HCV and HBV, has been reported in patients with HBV–HCV coinfection. One plausible explanation for HBV-R is that actively replicating HCV produces a host immune state favorable for controlling HBV replication, and DAA therapy disrupts this immune state (28). However, more recent studies refuted the theory of viral interference by demonstrating that HCV and HBV can replicate in the same hepatocyte (12, 13). At this time, the molecular mechanisms involved in HBV–HCV interference remain controversial and incompletely understood (12, 38). The previous HCV standard of care included peg-IFN and ribavirin, a regimen that was not very effective: Nearly half the patients treated did not achieve HCV SVR. Limited response to peg-IFN and ribavirin, as well as the fact that IFNs also treat HBV infection, may be

why HBV-R was not previously identified as a safety concern.

This work has both weaknesses and strengths. The limitations include those inherent in spontaneous reporting systems used in pharmacovigilance, such as underreporting of events, variable data quality in reports, and the inability to quantify risk from the case reports. In addition, without a control group, causality is difficult to determine from the cases alone. However, in our series, the onset of reactivation was relatively short and consistent (4 to 8 weeks after DAA initiation). The strengths of this work include our ability to detect a serious adverse event that was not observed during the clinical development program for DAAs. Clinical trials often have exclusions; this was the case in DAA development studies, which excluded patients with HBV co-infection. Finally, to our knowledge, this is the largest published series of DAA-associated HBV-R cases to date. The data from these cases will help provide insight into the need for early recognition of HBV–HCV co-infection and prompt treatment of clinically significant HBV-R.

Hepatitis B virus reactivation associated with DAAs is a newly identified safety concern in patients previously infected with HBV. Patients with a history of HBV infection require clinical monitoring while receiving DAA therapy. The FDA has asked the sponsors of all DAAs to update their labeling with this new safety concern. FDA considers this an important step to ensure dissemination of this information to health care providers so that they may screen and monitor patients with known HBV–HCV co-infection. In addition, the AASLD, in coordination with the Infectious Disease Society of America, recently updated its recommendations for managing patients with HBV–HCV co-infection (39). The guidelines recommend that all patients starting therapy with HCV DAAs be evaluated for HBV co-infection by being tested for HBsAg, HBsAb, and HBcAb status. Pa-

Table 3. Clinical Outcomes

Case Number (Reference)	Time to Event, *d*	Clinically Ill With HBV Reactivation	DAA Therapy Status	Hospitalized	HBV Treatment
1	33	Not stated	Discontinued	Yes	Tenofovir
2 (42)	43	Not stated	Discontinued	No	Entecavir
3	49	Yes: Jaundice and increasingly elevated aminotransferase levels; the patient died; the patient refused entecavir at another hospital	Discontinued	Yes (patient died)	Entecavir
4	67	Yes: The patient died	Discontinued	Yes (patient died)	Entecavir
5 (29)	56	Yes: Jaundice, tender hepatomegaly, malaise, nausea, and epigastric pain	Discontinued	–	Tenofovir–emtricitabine
6 (29)	14	No: The patient began therapy with tenofovir at the first indication of an increase in the HBV viral load (HIV-negative and no history of organ therapy, chemotherapy, or other immunosuppression)	Completed	–	Tenofovir
7 (26)	77	Yes: Encephalopathy and liver transplantation	Discontinued	Yes (transplantation)	Tenofovir
8	42	Not stated: Minimal increase in alanine aminotransferase levels	Completed	–	Entecavir
9 (38)	56	Yes: Jaundice and hospitalized; also HIV co-infection	Completed	Yes	Tenofovir
10 (28)	28	No	Completed	–	No treatment
11	42	Not stated: The patient had influenza at the same time	Discontinued	–	No treatment
12 (43)	56	Not stated	Discontinued	Yes	Entecavir
13	70	Not stated	Completed	–	No treatment
14	64	Not stated	Completed	–	Not stated
15	56	Not stated	Discontinued	–	Entecavir
16	57	Not stated	Completed	–	No treatment
17	42	Not stated	Completed	–	No treatment
18	56	Yes: Malaise and hospitalized with very elevated aminotransferase levels	Discontinued	Yes	No treatment
19	196	Not stated, but baseline α_1-fetoprotein level was 5.2 μg/L	Completed	–	No treatment
20		Not stated	Completed	–	Not stated
21	28	Not stated	Not stated	–	Not stated
22	84	Not stated	Completed	–	Not stated
23	42	Not stated	Not stated	–	Entecavir
24	28	Not stated	Not stated	–	Not stated
25	14	Not stated	Completed	–	Not stated
26	29	Not stated	Completed	–	No treatment
27	42	Not stated	Not stated	–	Entecavir
28	77	Yes: Jaundice	Not stated	Yes	Tenofovir
29 (44)	28	Yes: Weakness, poor appetite, and jaundice	Not stated	–	Entecavir

DAA = direct-acting antiviral agent; HBV = hepatitis B virus.

tients with positive for results on HBsAg testing and are not already receiving HBV suppressive therapy should have their HBV DNA levels monitored during DAA therapy and for several weeks after stopping treatment. Antiviral therapy for HBV infection should be given if criteria for HBV treatment are met (32). These steps are particularly important because the DAAs are a well-tolerated class of drugs and are more likely to be used by nonspecialty physicians and physician extenders in the future (40, 41). Additional studies would help determine the monitoring frequency and risk factors for HBV-R among patients receiving DAAs to fully define which patients would benefit from HBV prophylaxis and treatment. Therefore, with proper screening, monitoring, and treatment, HBV-R is a manageable adverse event. We conclude that DAAs remain a safe and highly effective treatment for HCV infection.

From U.S. Food and Drug Administration, Silver Spring, Maryland.

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