Evaluation of Hepatitis B Reactivation among 62,920 Veterans treated with Oral Hepatitis C Antivirals

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Summary: Nine patients in this large cohort of patients treated with direct acting antivirals had evidence of HBV reactivation occurring while on DAA treatment, though the occurrence of accompanying severe hepatitis was rare. Eight of the cases occurred in patients known to be HBsAg positive and 1 case occurred in a patient known only to be isolated anti-HBc positive.

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List of Abbreviations

anti-HBc – hepatitis B core antibody

anti-HBs – hepatitis B surface antibody

ALT – alanine aminotransferase

AST – aspartate aminotransferase

DAA – direct-acting antiviral

EOT – end of treatment

FDA – Food and Drug Administration

HBsAg – hepatitis B surface antigen

HBV – hepatitis B virus

HCV – hepatitis C virus

SVR – sustained virologic response

VA – Department of Veterans Affairs

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Abstract

Reactivation of hepatitis B virus (HBV) has been reported in hepatitis C virus (HCV) infected individuals receiving direct-acting antiviral (DAA) therapy. The overall risk among patients with current or prior HBV infection in the context of DAA treatment is unknown. The aim of this evaluation was to identify and characterize HBV reactivation among veterans treated with oral DAA therapy. This retrospective evaluation included 62,290 HCV-infected veterans completing oral DAA treatment. Baseline HBV infection status for each veteran was identified from HBV laboratory data performed prior to DAA initiation. To assess for HBV reactivation and hepatitis we identified all HBsAg, HBV DNA and ALT results obtained while on DAA treatment or seven days after. HBV reactivation was defined as a >3 log increase in HBV DNA or HBsAg detection in a person who was previously negative. Prior to DAA treatment 85.5% (53,784/62,920) had HBsAg testing and 0.70% (377/53,784) were positive; 84.6% (53,237/62,920) had an anti-HBs test of which 42.2% (22,479/53,237) were positive. In all, 9 of 62,290 patients treated with DAAs had evidence of HBV reactivation occurring while on DAA treatment. Eight occurred in patients known to be HBsAg positive and 1 occurred in a patient known to be isolated anti-HBc positive. Seventeen other patients had small increases (<3 log) in HBV DNA levels that did not qualify as HBV reactivation. Only 3 of the 9 patients identified with HBV reactivation in this cohort exhibited peak ALT elevations >2 times the upper limit of normal. **Conclusions**: HBV reactivation of varying severity, even in the setting of isolated anti-HBc, with or without accompanying hepatitis can occur --though the occurrence of accompanying severe hepatitis was rare.

Recently, several cases of hepatitis B virus (HBV) reactivation have been reported in patients receiving oral hepatitis C virus (HCV) antiviral therapy who were not already on HBV therapy, raising potential safety concerns.[1-7] HBV reactivation is thought to be the consequence of the rapid treatment-induced reduction in HCV, which is known to suppress HBV.[8,9] In clinical trials of oral HCV antivirals, patients with HBV infection were excluded, thus limiting understanding about the extent of reactivation in the setting of oral direct-acting antiviral agents (DAA). It is unknown what the overall population risk may be since many of these HBV reactivation reports have been single case reports or in limited data sets. Nevertheless, in light of these occurrences the US Food and Drug Administration (FDA) issued a Drug Safety Communication warning of the possibility of HBV reactivation in the setting of DAA therapy.[10]

HBV reactivation in other clinical context is most commonly reported in the setting of immune suppression in patients receiving cancer chemotherapy, especially rituximab-containing therapy for hematological malignancies and for those receiving stem cell transplantation.[11,12] No standard strategy has yet been established to prevent HBV reactivation, however, two options are often undertaken. One is pre-emptive therapy guided by serial HBV DNA monitoring as often as every one to three months, whereby HBV antiviral therapy is given once HBV DNA is detected, yet there is little evidence regarding the optimal interval and period for the serial monitoring. Alternatively, prophylactic HBV antiviral therapy may be initiated for patients who will be receiving high-risk therapies.

According to FDA and AASLD/IDSA guidance, to decrease the risk of HBV reactivation in patients co-infected with HBV and HCV, all patients should be screened for current or prior HBV infection before initiating treatment with DAAs by measuring HBV surface antigen (HBsAg), HBV core antibody (anti-HBc) and HBV surface antibody (anti-HBs).[10,13] In those with evidence of HBV infection, indicated by a

positive HBsAg, HBV DNA should be measured prior to DAA treatment; those meeting AASLD criteria for treatment of active HBV infection should receive HBV therapy during DAA treatment.[14] Patients with evidence of current or prior HBV infection who are not receiving HBV therapy during DAA treatment should be monitored clinically- including HBsAg, HBV DNA and serum aminotransferases- for evidence of HBV reactivation or hepatitis flare in order to initiate HBV treatment accordingly.[10,13-14] Insufficient data currently exist to provide recommendations for monitoring of patients who are isolated anti-HBc positive (with HBsAg and anti-HBs negative), but the possibility of HBV reactivation in this group remains a consideration, particularly in the event of unexplained increases in liver enzymes during DAA treatment.[10]

The prevalence of HBV/HCV coinfection among veterans is estimated to be approximately 1.4%, and is similar to that reported in the general US population.[15] Given the large number of veterans treated with oral DAAs and the availability of electronic data to assess HBV status in these veterans, evaluation of the HCV-infected veteran population can provide valuable insight regarding the frequency of HBV reactivation observed with DAA treatment. Our aim was to identify evidence of and characterize HBV reactivation among veterans treated with oral DAA therapy.

Methods

We retrospectively evaluated all veterans receiving Department of Veteran's Affairs (VA)-prescribed DAAs on or after 1 January 2014 who completed treatment by 30 September 2016, using the VA's Corporate Data Warehouse - a national repository of data obtained from VA electronic medical records from October 1, 1999 onward for veterans who have received VA care. Oral DAAs included sofosbuvir, simeprevir, ledipasvir/sofosbuvir, ombitasvir/paritaprevir/ritonavir plus dasabuvir, elbasvir/grazoprevir, and sofosbuvir/velpatasvir.

To assess baseline HBV infection status, for each veteran in the cohort, we identified HBV laboratory data including HBsAg, anti-HBc, anti-HBs and HBV DNA performed at any time prior to or on the DAA initiation date. For numeric calculations, HBV DNA test results of "<20" were treated as 0 IU/mL, "<20 detected" were treated as 19 IU/mL and results of ">170,000,000" were treated as 170,000,001 IU/mL . For patients with multiple tests, we used the test result closest to the DAA initiation date as the baseline result. Other baseline demographic and clinical variables were determined at the time of DAA treatment initiation and included age, sex, race/ethnicity, cirrhosis (defined by ICD-9/ICD-10 codes), history of decompensated liver disease (defined by ICD-9/ICD-10 codes for esophageal variceal hemorrhage, hepatic coma, hepatorenal syndrome or spontaneous bacterial peritonitis), HIV coinfection, alanine aminotransferase (ALT), aspartate aminotransferase (AST), FIB-4 score, HCV RNA, and HCV genotype. AST and ALT results had to be within one year of DAA initiation. The outcome from DAA treatment was assessed with data through 15 December 2016. Sustained virologic response (SVR) was defined as HCV RNA results below the limit of detection after the end of treatment (EOT) including at least one test 12 weeks or more after the EOT. The EOT was calculated as the last day covered by prescriptions using all the dates the medication was dispensed and the days' supply. Patients were categorized as not achieving SVR if they had a HCV RNA above the limit of detection after the EOT. Patients with HCV RNA below the limit of detection on their last HCV viral load test, either on treatment or after the EOT, but no test 12 weeks or more after the EOT have unknown DAA outcome status.

Using baseline HBV testing results, we identified two groups considered at high risk for HBV reactivation: those who were HBsAg positive prior to DAA initiation and those who were isolated anti-HBc positive prior to DAA initiation.[10,13] We did not include patients who were anti-HBs positive as this group was felt to be at low risk for reactivation. To assess for HBV reactivation in patients who were

identified as HBsAg positive prior to DAA initiation, we identified all HBV DNA results obtained while on DAA treatment or within seven days after the end of DAA treatment. To assess for HBV reactivation among veterans who were isolated anti-HBc positive prior to DAA initiation, we identified all HBsAg and HBV DNA results obtained while on DAA treatment or within seven days after the end of DAA treatment.

Since HBV testing during DAA treatment may not have been routinely performed in patients prior to the FDA communication released in October 2016, we also looked independently at ALT results of patients receiving DAA treatment.[10] We identified all patients whose most recent ALT result, while on DAA treatment, was not normal. Abnormal ALT values were defined per AASLD HBV guidelines as an ALT ≥19 U/L for females and ≥30 U/L for males.[14] Among those whose latest ALT while on DAA therapy was not normal, we searched for HBsAg and HBV DNA testing that occurred while on DAA treatment or within seven days after the end of DAA treatment.

For this analysis, we defined HBV reactivation as a >3 log increase in HBV DNA or the detection of HBsAg in a person who was previously HBsAg negative. HBV treatment at baseline was determined by a prescription fill for adefovir, entecavir, lamivudine, telbivudine or tenofovir within 89 days prior to DAA initiation.

This analysis was performed as part of VHA health care operations and was considered exempt from institutional review board review, as determined by the VHA Office of Research Oversight.

Results

In all, 62,920 veterans initiated VA-prescribed oral DAA treatment and stopped treatment by 30 September 2016. Prior to initiation of DAA treatment 85.5% (53,784/62,920) had a HBsAg test of which 0.70% (377/53,784) were positive; 84.6% (53,237/62,920) had an anti-HBs test of which 42.2% (22,479/53,237) were positive; 64.2% (40,383/62,920) had an anti-HBc test of which 45.7% (18,462/40,383) were positive. Of those with positive anti-HBc testing, 39.5% (7,295/18,462) were identified as isolated anti-HBc positive. Baseline characteristics of the patients who were HBsAg positive or isolated anti-HBc positive are shown in Table 1.

Among the 377 patients who were known to be HBsAg positive prior to DAA initiation, 25.5% (96/377) were on HBV treatment at the start of DAA therapy. HBV DNA testing was performed while on DAA treatment in 22.3% (84/377) of HBsAg positive patients, of which 35.7% (30/84) were detectable (median 215 IU/mL [IQR 9210.5](range <20 detected-22,200,000). Details about the 30 HBsAg positive individuals with detectable HBV DNA while on DAA treatment appear in Table 2. Eight patients qualified as HBV reactivation based on a >3 log increase in HBV DNA from baseline level, with 1 of the 8 patients on HBV treatment with tenofovir at DAA initiation. Six of the 8 patients had a peak ALT while on DAA treatment that was abnormal although the peak ALT was markedly increased (1540 U/L) only in the one patient with the largest log increase in HBV DNA (7.35 log). All eight achieved SVR.

Among the 7,295 patients who were known to be isolated anti-HBc positive prior to DAA initiation, 4.1% (299/7,295) were on HBV treatment at the time of DAA initiation. HBsAg testing was performed in 5.3% (390/7,295) of these patients while on DAAs and none were positive (0/390); 17 of the 390 were receiving HBV treatment prior to DAA initiation. HBV DNA testing was performed while on DAA treatment in 2.4% (173/7,295) of patients known to be isolated anti-HBc positive and 4/173 were

detectable. Details about the 4 isolated anti-HBc individuals with detectable HBV DNA while on DAA treatment appear in Table 3. Of the 4 patients with detectable HBV DNA while on DAA treatment, none of whom were receiving HBV treatment, two had baseline HBV DNA testing: one was undetectable and the other "<20 detected". After initiation of DAAs, 3 of the 4 had low level HBV DNA. The fourth patient had a 5.40 log increase in HBV DNA from undetectable to 253,219 IU/mL and thus had evidence of HBV reactivation. SVR testing has not yet been completed for this patient.

Overall, 84.3% (53,029/62,920) of patients who started DAAs had ALT testing performed while on DAA treatment and in 27.1% (14,386/53,029) of those, the latest ALT result was not normal (mean±SD, 48.0±46.0 [range:19-4948]). HBsAg testing was performed in 5.0% (714/14,386) of patients with an elevated ALT while on DAAs and 11 were positive, however, all 11 were also HBsAg positive prior to DAA treatment. Twenty of the 714 with HBsAg testing while on DAAs were receiving HBV treatment at DAA initiation including 4 of the 11 who were HBsAg positive while on DAAs. On-treatment HBV DNA results were available for 0.9% (132/14,386) of patients with an elevated ALT on DAA treatment. HBV DNA results were detectable in 21 of these (Table 4); 19 of 21 had HBV DNA testing prior to DAA initiation, 9 of which were positive (median 1681; range <20 detected - >170,000,000) and 10 which were negative; 2 of the 21 had no prior HBV DNA results. Of the 21 patients with detectable HBV DNA on DAA treatment, 17 were HBsAg positive prior to DAA initiation and were previously identified in Table 2. Three patients of the 21 had a >3 log increase in HBV DNA consistent with HBV reactivation, all three of whom had also previously been identified in Table 2 and all three of whom were not on HBV treatment. One additional patient not on HBV treatment had a HBV DNA of 3,123,580 IU/mL prior to DAA therapy and the HBV DNA remained elevated at 1,918,020 IU/mL while on DAA treatment. Five of the 21 were receiving HBV treatment at DAA initiation and had decreases or small increases (<3 log) in HBV DNA between baseline and testing performed while on DAAs. The other 12 patients all of whom were not receiving HBV treatment while on DAA therapy had low level detectable HBV DNA (<700

IU/mL) while on DAAs and did not qualify as HBV reactivation, including 8 patients previously identified in Group 1 and 2 patients previously identified in Group 2.

Discussion

In all, 9 unique patients out of 62,290 patients treated with DAAs had evidence of HBV reactivation when defined by a >3 log increase in HBV DNA occurring while on DAA treatment. Eight of the cases occurred in patients known to be HBsAg positive and 1 case occurred in a patient known only to be isolated anti-HBc positive. None had received immunomodulatory medications. One of the patients known to HBsAg positive had been prescribed tenofovir at baseline thus the >3 log increase in HBV DNA may represent a true HBV reactivation in the context of tenofovir non-adherence or may represent a tenofovir failure of HBV suppression. Seventeen other patients had small increases (<3 log) in HBV DNA levels that did not qualify as HBV reactivation. In patients with HBV reactivation, severe hepatitis appeared to be rare and some patients with HBV reactivation maintained normal ALTs. HBV reactivation occurred in HCV-infected patients with and without detectable HBV DNA prior to DAA initiation. HBV reactivation did not appear to be impacted by baseline HCV RNA level, presence of cirrhosis or HCV DAA regimen and, in this cohort, did not appear to affect SVR.

One of the difficulties in determining reactivation in prior reports has been the lack of documentation of HBsAg and HBV DNA levels before DAA treatment.[6,12,16] Baseline HBsAg testing in this population was high (85.5%) affording the opportunity to reliably identify 377 patients with the highest risk for reactivation, namely those with positive HBsAg status (0.6% of the entire cohort and 0.7% of those with HBsAg testing). The anti-HBc testing rate for the cohort was lower at 64.2% but given the size of the cohort we could still identify 7,295 patients with positive isolated anti-HBc also felt to be at high risk for reactivation. Similarly, in those with detectable HBV DNA levels while on DAA treatment, all but 2

patients had documented HBV DNA testing prior to initiation of DAA therapy which allowed for a comparison of the magnitude change associated with HBV reactivation.

HBV reactivation has generally been defined clinically as an abrupt reappearance or rise in HBV DNA in a patient with previously resolved or inactive HBV infection often followed by hepatitis manifested as an increase in transaminase levels and clinical symptoms.[12,14] Such a description , however, does not specify how much of an increase in HBV DNA or ALT qualifies as a significant reactivation. We used a >3 log increase in HBV DNA to provide an objective and consistent criteria to identify HBV reactivation. While spontaneous HBV reactivation in patients not undergoing DAA treatment is usually accompanied by elevations in ALT, only 3 of the 9 patients identified with HBV reactivation in this cohort, including the one person prescribed tenofovir at baseline, exhibited peak ALT elevations >2 times the upper limit of normal – a criterion used to define active HBV.[14] The patient with the largest increase in HBV DNA (7.35 log) did have the highest peak ALT (1540 U/L) but the patient with the next largest increase in HBV DNA (5.40 log) had a normal peak ALT (17 U/L) during DAA treatment. Most patients in this cohort appeared to have "silent" or "mild" HBV reactivation characterized by normal ALT or less than a 2-fold change in ALT.[12] The occurrence of HBV reactivation without hepatitis in the setting of DAA treatment has also been observed as the most common presentation by others.[6,9,17]

The observed incidence of HBV reactivation among HBsAg positive patients of 8.3% (7/84) and the incidence of HBV reactivation with evidence of biochemical hepatitis of 2.4% (2/84) warrants use of HBV prophylaxis in this setting. Notably, there was an apparent lack of association with baseline HBV DNA levels as three of the eight with reactivation had undetectable pre-DAA HBV DNA levels. Although we could not assess for clinical symptoms in this evaluation, the potential risk observed here and described in previous reports of liver failure and death support prophylaxis in this setting.[7,10] The lower

incidence of concurrent hepatitis observed in this and similar cohorts suggests that reactivation of HBV in the setting of HCV DAA therapy may be less severe than that reported with immunosuppressive therapy where the reported incidence of hepatitis associated with HBV reactivation is as high as 30%.[6,17-19] Despite the apparent lack of associated hepatitis flare associated with HBV reactivation in this cohort other reports have described liver failure and death.[7,10] Nonetheless, given the tolerability and safety of HBV antivirals and because some serious risk exists, it seems prudent to initiate HBV prophylaxis in patients who will be initiating DAA treatment and are HBsAg positive, regardless of serum HBV DNA. This approach is generally consistent with guidance from FDA, AASLD/IDSA and EASL.[10,13,20]

While general consensus exists for the risk and plan for possible HBV reactivation in patients with positive HBsAg, the risk and action in those with isolated anti-HBc is not as clear. Far fewer reports of HBV reactivation exist in this scenario but at least one case of fulminant hepatic failure has been recognized.[2-4] Others that have examined this scenario in retrospective observational evaluations failed to identify any cases of reactivation in limited cohorts.[6,18] In this cohort, only 1 patient of 7,295 with isolated anti-HBc was identified as experiencing HBV reactivation - without hepatitis - substantiating that the risk in this population is extremely low, even when limiting only to those that had HBV DNA testing done while on DAA treatment (1/173, 0.58%). This rate is lower than the reported HBV reactivation rate of 1%-2% per year in persons with inactive disease.[14] Thus providers should recognize that patients with isolated anti-HBc are at some risk, albeit less, and that identifying these patients prior to DAA treatment and assessing HBV DNA status can heighten recognition of reactivation. While HBV prophylaxis may be generally overzealous in this scenario, providers should be cognizant of the risk of reactivation in this population and strive to identify these patients prior to DAA treatment and monitor patients clinically and as suggested in guidelines by checking HBV DNA around week 4 of treatment with periodic assessment of ALT, and initiating treatment where appropriate. [10,13,20]

Persons with a viral load between 1,000 and 2,000 IU/mL are reported to be at the highest risk for reactivation.[14] This cohort had only one patient with an HBV DNA in that range (1,001 IU/mL) who did have a HBV reactivation using a > 3 log definition (3.68 log) but with a near normal peak ALT of 45 U/L. According to AASLD HBV treatment guidelines, a HBV DNA >2000 IU/mL should prompt consideration of HBV treatment. Only 2 patients with a HBV DNA > 2000 IU/mL at baseline who had a subsequent detectable HBV DNA while on DAA treatment were not receiving HBV treatment at the time of DAA initiation, 1 of whom had a HBV reactivation with hepatitis.

Limitations

This was an observational analysis of routine medical care with no requirement for HBV testing, therefore not all patients had complete HBV testing prior to DAA initiation nor did all patients have complete testing and monitoring performed while on DAAs. Thus, we could only assess HBsAg, HBV DNA and ALT results to the extent that these laboratory tests were performed while on treatment. We could not infer why a particular lab was or was not done in a given patient or if a provider had a clinical suspicion of HBV based on other signs or symptoms which may have prompted testing in those that received such testing. Clinical symptoms of acute hepatitis flare or jaundice could not be determined from the available electronic data. We defined HBV reactivation as a >3 log increase in HBV DNA. Given the uncertainty around objective criteria for HBV reactivation, however, individual providers may favor higher or lower levels. HBV reactivation which may have occurred more than seven days after the discontinuation of DAA therapy was not assessed. Two hundred ninety-two of the 299 isolated anti-HBc positive patients receiving HBV treatment at the time of DAA initiation were also HIV co-infected and receiving treatment with tenofovir and/or lamivudine for their HIV-infection. Their receipt of these antiretrovirals would have suppressed any potential HBV reactivation that may have otherwise been observed. Nevertheless,

this cohort provides the largest population sample examining the potential occurrence of HBV reactivation in the context of DAA treatment.

In this large cohort very few cases of HBV reactivation were identified. Those cases that did occur generally manifested as mild or silent HBV reactivation. Increases in HBV replication tended to be small and were not usually associated with an accompanying rise in ALT. These data provide context for the frequency with which this phenomenon might occur in those deemed most at risk. Effective HBV screening prior to DAA therapy to identify those at potential risk for HBV reactivation, documentation of HBV DNA and ALT prior to DAA initiation and monitoring of HBV DNA and ALT in those who are HBsAg positive can effectively identify patients at risk for HBV reactivation in the setting of DAA therapy. For those who are isolated anti-HBc positive the signal is less clear, however, a conservative approach would suggest monitoring of ALT and obtaining a HBV DNA between weeks 4 and 8 of DAA treatment. HBV reactivation of varying severity, even in the setting of isolated anti-HBc, with or without accompanying hepatitis can occur --though the occurrence of accompanying severe hepatitis was rare.

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Table 1. Baseline Demographics and Disease Characteristics

	HBsAg positive N=377	Isolated anti-HBc positive N=7,295
Age mean±SD (range)	60.6±6.0 (34.7-77.0)	63.4±4.7 (35.6-90.8)
< 55	51 (13.5%)	251 (3.4%)
55-64	238 (63.1%)	4379 (60.0%)
≥ 65	88 (23.3%)	2665 (36.5%)
Male sex	367 (97.3%)	7,190 (98.6%)
Race/ethnicity		
African-American	171 (45.4%)	3,529 (48.4%)
Asian	2 (0.5%)	19 (0.3%)
Caucasian	179 (47.5%)	2,949 (40.4%)
Hispanic	5 (1.3%)	424 (5.8%)
Other/multiple	20 (5.3 %)	374 (5.1 %)
HIV coinfected	52 (13.8%)	667 (9.1%)
ALT (U/L)	65.6±46.5(9-267)	67.1±51.6 (6-602)
AST (U/L)	61.2±41 (13-251)	62.9±48 (9-1760)
FIB-4 mean±SD (range)	3.5±3.6 (0.3-27.4)	3.4±3.5 (0.3-75.4)
<1.45	86/367 (23.4%)	1,265/7,009 (18.1%)
1.45-3.25	160/367 (43.6%)	3,422/7,009 (48.8%)
>3.25	121/367 (33.0%)	2,322/7,009 (33.1%)
Genotype		
1 unspecified/mixed	24 (6.4%)	374 (5.1%)
1a	196 (52.0%)	4,112 (56.4%)
1b	107 (28.4%)	1,886 (25.9%)
2	21 (5.6%)	534 (7.3%)
3	21 (5.6%)	288 (3.9%)
4	5 (1.3%)	73 (1.0%)
6	0 (0.0%)	3 (0.0%)
Other	3 (0.8%)	25 (0.3%)
Baseline HBV DNA testing	238 (63.1%)	1,659 (22.7%)
Detectable HBV DNA	58	19
HBV DNA (IU/mL) median[IQR] (range)	128 [1,203] (<20 detected->170,000,000	33.9 [196] (<20 detected-9,900)
HBV treatment, n	96	299
Adefovir	2	0
Adefovir+entecavir	1	0
Adefovir+lamivudine	1	0
Entecavir	31	7
Entecavir+tenofovir	1	0
Lamivudine	3	63
Lamivudine+tenofovir	2	8
Tenofovir	55	221

Continuous variables reported as mean±SD (range) except for HBV DNA which is reported as median[IQR](range). Categorical variables reported as n (%). Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; SD, standard deviation.

Table 2. Characteristics of 30 HBsAg Positive Patients with detectable HBV DNA while on Direct Acting Antiviral Treatment

Patient ID	GT	Cirrhosis*	HIV	Baseline HBeAg	Baseline HCV RNA	DAA Regimen	Peak on-DAA ALT	Baseline HBV DNA	On-DAA HBV DNA	HBV DNA log change	Baseline HBV Medication	Outcome of DAA treatment
A	1a			Neg	167,000	LDV/SOF	71	<20	21	1.32		SVR
B	2	Y		Neg	932,891	SOF+RBV	30	<20	29	1.46		SVR
C	1	Y*	Y	Neg	212,900	LDV/SOF	31	<20	39	1.59	tenofovir	No SVR
D	1b			Neg	1,813,102	LDV/SOF	49	<20	60	1.78		Unknown
E	1a			Neg	99,000	LDV/SOF	46	<100	150	2.18		SVR
F	1a	Y		NA	1,800,000	SOF+SIM+RBV	90	<20	400	2.60	tenofovir	Unknown†
G	1a	Y		Neg	3,412,598	LDV/SOF	30	<20	411	2.61		Unknown
H	1a	Y		NA	4,545,944	LDV/SOF+RBV	37	<20	520	2.72		Unknown
I	1a			Neg	42,400	LDV/SOF	20	<20	890	2.95		SVR
J	**3a**			**Neg**	**327,080**	**SOF+RBV**	**72**	**<20**	**3,491**	**3.54**	**tenofovir**	**SVR**
K	**1a**			**Neg**	**57,600,000**	**PrOD+RBV**	**18**	**<20**	**9,303**	**3.97**		**SVR**
L	**1a**			**Neg**	**2,810,000**	**LDV/SOF**	**86**	**<20**	**173,075**	**5.24**		**SVR**
M	1a	Y*		NA	379,000	SOF+SIM+RBV	69	<20 detected	174	2.19		SVR
N	1a			Neg	6,675,682	LDV/SOF	22	22	20	decrease		SVR
O	1b			Pos	1,798,312	PrOD+RBV	27	28	<20 detected	decrease	entecavir	SVR
P	1a			Neg	3,730,000	LDV/SOF	20	34	71	1.57		SVR
Q	3a			Neg	1,109,529	SOF+RBV	42	45	634	2.77		No SVR
R	1b	Y*		Neg	3,969,338	LDV/SOF	86	46	<20 detected	decrease	entecavir	SVR10†
S	**1b**			**Neg**	**1,536,553**	**EBR/GZR**	**18**	**100**	**43,800**	**4.64**		**SVR**
T	**1/4**			**NA**	**168,000**	**PrOD+RBV**	**40**	**100**	**78,000**	**4.89**		**SVR**
U	2	Y		Neg	1,770,000	SOF+RBV	124	180	43	decrease		SVR
V	2b			Pos	7,251,238	SOF+RBV	23	250	30	decrease	tenofovir	SVR
W	**1b**			**Neg**	**26,112**	**LDV/SOF**	**31**	**330**	**6,430**	**3.79**		**SVR**
X	**3a**	**Y***		**Neg**	**99,653**	**SOF+RBV**	**45**	**1,001**	**5,733**	**3.68**		**SVR**
Y	**1a**	**Y**		**Neg**	**1,300,000**	**SOF+SIM**	**1540**	**2,361**	**22,200,000**	**7.35**		**SVR**
Z	2b	Y	Y	Pos	132,736	SOF+RBV	30	3,170	1,200	decrease	entecavir+tenofovir	SVR
AA	1a	Y*		Neg	1,100,000	LDV/SOF	190	1,100,000	9,200	decrease	entecavir	SVR
BB	1a			Neg	3,123,580	LDV/SOF	1197	3,123,580	1,918,020	decrease		SVR
CC	1a	Y		NA	33,017,000	SOF+RBV	28	33,017,000	4,380	decrease	tenofovir	SVR
DD	1b	Y*		Pos	6,234	LDV/SOF	162	>170,000,000	12,190	decrease	entecavir	No SVR

*Indicates history of prior decompensation. Abbreviations: ALT, alanine aminotransferase; DAA, direct acting antiviral; EBR/GZR, elbasvir/grazoprevir; GT, genotype; LDV/SOF, ledipasvir/sofosbuvir; NA, not available; Neg, negative; Pos, positive; PrOD, paritaprevir/ritonavir/ombitasivr +dasabuvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; Y, yes

Table 3. Characteristics of 4 isolated anti-HBc Positive Patients with detectable HBV DNA while on Direct Acting Antiviral Treatment

Patient ID	GT	Cirrhosis*	HIV	Baseline HBeAg	Baseline HCV RNA	DAA Regimen	Peak on-DAA ALT	Baseline HBV DNA	On-DAA HBV DNA	HBV DNA log change	Baseline HBV Medication	Outcome of DAA treatment
EE	1	Y*		Neg	14,751,000	LDV/SOF+RBV	31		180	2.26		SVR
FF	1b	Y*		NA	7,949,927	EBV/GZR	42		332	2.52		No SVR
GG	**1a**			**NA**	**1,677,454**	**LDV/SOF**	**17**	**<20**	**253,219**	**5.40**		**Unknown**
HH	1a			NA	409,000	LDV/SOF	13	<20 detected	25	0.78		SVR

*Indicates history of prior decompensation. Abbreviations: ALT, alanine aminotransferase; DAA, direct acting antiviral; EBV/GZR, elbasvir/grazoprevir; GT, genotype; LDV/SOF, ledipasvir/sofosbuvir; NA, not available; Neg, negative; RBV, ribavirin; SVR, sustained virologic response; Y, yes

Table 4. Characteristics of 21 Patients with elevated ALT and detectable HBV DNA while on Direct Acting Antiviral Treatment

Patient ID	GT	Cirrhosis*	HIV	Baseline HBeAg	Baseline HCV RNA	DAA Regimen	Peak on-DAA ALT	Baseline HBV DNA	On DAA HBV DNA	HBV DNA log change	Baseline HBV Medication	Outcome of DAA treatment
EE^	1	Y*		Neg	14,751,000	LDV/SOF+RBV	31	-	180	2.26		SVR
FF^	1b	Y*		Neg	7,949,927	EBR/GZR	42	-	332	2.52		No SVR
II	1a			Neg	374,000	LDV/SOF	72	<20	20	0.00		Unknown
B**	2	Y		Neg	932,891	SOF+RBV	30	<20	29	1.46		SVR
C**	1	Y*	Y	Neg	212,900	LDV/SOF	31	<20	39	1.59	tenofovir	No SVR
D**	1b			Neg	1,813,102	LDV/SOF	49	<20	60	1.78		Unknown
E**	1a			Neg	99,000	LDV/SOF	46	<100	150	2.18		SVR
F**	1a	Y		NA	1,800,000	SOF+SIM+RBV	90	<20	400	2.60	tenofovir	Unknown†
G**	1a	Y		Neg	3,412,598	LDV/SOF	30	<20	411	2.61		Unknown
H**	1a	Y		NA	4,545,944	LDV/SOF+RBV	37	<20	520	2.72		Unknown
L**	**1a**			**Neg**	**2,810,000**	**LDV/SOF**	**86**	**<20**	**173,075**	**5.24**		**SVR**
JJ	1a			NA	3,255,174	PrOD+RBV	135	<169	<20 detected	1.28		SVR
M**	1a	Y*		NA	379,000	SOF+RBV	69	<20 detected	174	2.19		SVR
Q**	3a			Neg	1,109,529	SOF+RBV	42	45	634	2.77		No SVR
R**	1b	Y*		Neg	3,969,338	LDF/SOF	86	46	<20 detected	decrease	entecavir	SVR10†
U**	2	Y		Neg	1,770,000	SOF+RBV	124	180	43	decrease		SVR
X**	**3a**	**Y***		**Neg**	**99,653**	**SOF+RBV**	**45**	**1,001**	**5,733**	**3.68**		**SVR**
Y**	**1a**	**Y**		**Neg**	**1,300,000**	**SOF+SIM**	**1540**	**2,361**	**22,200,000**	**7.35**		**SVR**
AA**	1a	Y*		Neg	1,100,000	LDV/SOF	190	1,100,000	9,200	decrease	entecavir	SVR
BB**	1a			Neg	3,123,580	LDV/SOF	1197	3,123,580	1,918,020	decrease		SVR
DD**	1b	Y*		Pos	6,234	LDV/SOF	162	>170,000,000	12,190	decrease	entecavir	No SVR

*Indicates history of prior decompensation. **Previously identified in Group 1. ^Previously identified in Group 2. Abbreviations: ALT, alanine aminotransferase; DAA, direct acting antiviral; EBR/GZR, elbasvir/grazoprevir; GT, genotype; LDV/SOF, ledipasvir/sofosbuvir; NA, not available; Neg, negative; Pos, positive; PrOD, paritaprevir/ritonavir/ombitasivr +dasabuvir; RBV, ribavirin; SIM, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response; Y, yes