PI-Based HCV DAAs Are Associated with Increased Risk of Aminotransferase Elevations but Not Hepatic Dysfunction or Decompensation

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Word Count: Manuscript - 3,049; Abstract - 273

Tables and Figures: 3 tables, 3 figures

Conflict of Interest: D.B. has received research support to the NIH AIDS Clinical Trials Group (ACTG) from Abbvie and Regeneron for an ACTG-sponsored trial. All other authors declare no conflicts of interest. All other authors declare no conflicts of interest.

Financial Support: This study was funded, in part, by the National Cancer Institute (R01CA206465) and the National Institutes on Alcohol Abuse and Alcoholism (U01AA013566).

Authors' Contributions: All authors had access to relevant data, and participated in the writing, review, and approval of the final manuscript. Jessie Torgersen: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Craig W. Newcomb: study concept and design, acquisition of data, statistical analysis, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Dena M. Carbonari: study concept and design, analysis and interpretation of data, drafting of manuscript,

critical revision of the manuscript for important intellectual content. Christopher T. Rentsch: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Lesley S. Park: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Alyssa Mezochow: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Rajni L. Mehta: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Lynn Buchwalder: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Janet P. Tate: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Norbert Bräu: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Debika Bhattacharya: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Joseph K. Lim: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Tamar H. Taddei: study concept and design, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Amy C. Justice: study concept and design, acquisition of data, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content. Vincent Lo Re III: study concept and design, statistical analysis, analysis and interpretation of data, drafting of manuscript, critical revision of the manuscript for important intellectual content.

Keywords: acute liver injury; protease inhibitor, direct-acting antivirals, hepatitis C

ABSTRACT

Background & Aims: Cases of acute liver injury (ALI) have been reported among chronic hepatitis C virus-infected initiators of protease inhibitor (PI)-based direct-acting antiviral (DAA) regimens, predominately with decompensated cirrhosis in whom these therapies are contraindicated. No analyses have evaluated if initiators of PI versus non-PI-based DAAs have higher risk of ALI events, stratified by advanced hepatic fibrosis/cirrhosis. We compared the risk of three ALI outcomes among PI-based and non-PI-based DAA initiators, by baseline FIB-4.

Methods: We conducted a cohort study of 18,498 initiators of PI-based DAA therapy (paritaprevir/ritonavir/ombitasvir +/- dasabuvir, elbasvir/grazoprevir, glecaprevir/pibrentasvir) matched 1:1 on propensity score to non-PI-based DAA initiators (sofosbuvir/ledipasvir, sofosbuvir/velpatasvir) in the 1945-1965 Veterans Birth Cohort (2014-2019). During exposure to DAA therapy, we determined development of: 1) alanine aminotransferase (ALT) >200 U/L, 2) severe hepatic dysfunction (coagulopathy with hyperbilirubinemia), and 3) hepatic decompensation. Cox regression was used to determine hazard ratios (HRs) with 95% confidence intervals of each outcome, stratified by baseline advanced hepatic fibrosis/cirrhosis by FIB-4.

Results: Among persons with baseline FIB-4 ≤3.25, PI initiators had higher risk of ALT >200 U/L (HR, 3.98 [2.37-6.68]), but not severe hepatic dysfunction (HR, 0.67 [0.19-2.39]) or hepatic decompensation (HR, 1.01 [0.29-3.48]), compared to non-PI-initiators. For those with baseline FIB-4 >3.25, PI initiators had higher risk of ALT >200 U/L (HR, 2.15 [1.08-4.29]), but not severe hepatic dysfunction (HR, 1.23 [0.63-2.40]) or hepatic decompensation (HR, 0.87 [0.42-1.82]), compared to non-PI initiators.

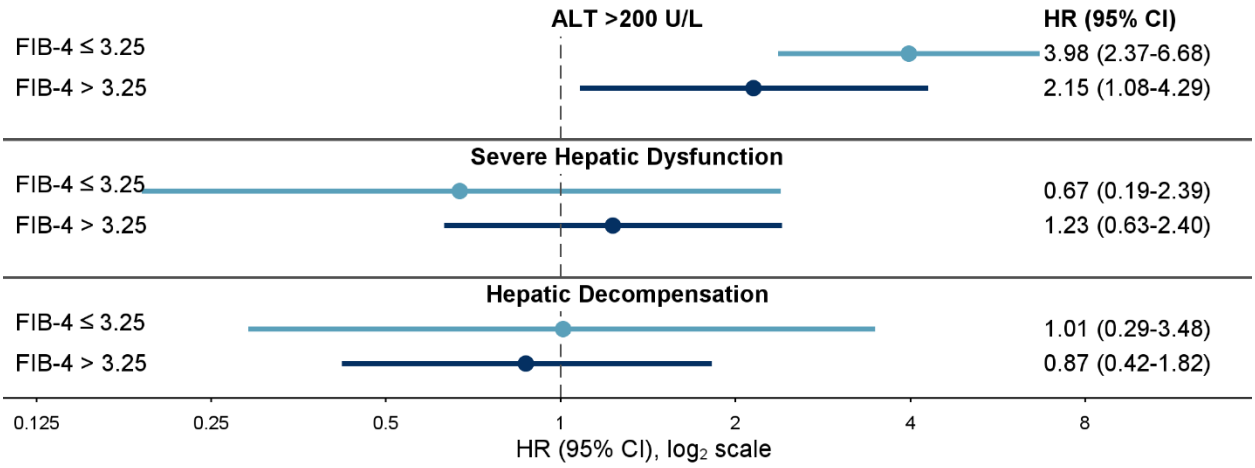
Conclusion: While risk of incident ALT elevations was increased among PI-based DAA initiators in both FIB-4 strata, risk of severe hepatic dysfunction and hepatic decompensation did not differ between PI and non-PI-based DAA initiators in either FIB-4 stratum.

Highlights

- Comparative analysis of 18,498 initiators of PI-based DAAs matched on propensity score to 18,498 initiators of non-PI-based DAAs to assess risk of 3 acute liver injury endpoints, according to advanced hepatic fibrosis/cirrhosis status by FIB-4.
- Propensity score-matched hazard ratios of ALT >200 U/L were higher for PI than non-PI-initiators in those with and without baseline advanced hepatic fibrosis/cirrhosis (i.e., FIB-4 >3.25 and FIB-4 ≤3.25, respectively).
- No differences in propensity score-matched hazard ratios of severe hepatic dysfunction or hepatic decompensation were observed between PI and non-PI-based DAA initiators, regardless of baseline advanced hepatic fibrosis/cirrhosis status by FIB-4.

Lay Summary: Cases of liver injury have been reported among patients treated with protease inhibitor-based direct-acting antivirals for hepatitis C infection, but it is not clear if risk of liver injury among people starting these drugs is increased compared to those starting non-protease inhibitor-based therapy. In this study, persons who initiated protease inhibitor-based treatment had higher risk of liver inflammation than non-protease inhibitor-based initiators, regardless of the presence of pre-treatment advanced liver fibrosis/cirrhosis. However, the risk of severe liver dysfunction and decompensation were not higher for protease inhibitor-based initiators.

Graphical Abstract. Hazard ratios (HRs) with 95% confidence intervals (CIs) of specified acute liver injury outcomes for propensity score matched cohorts of protease inhibitor and non-protease inhibitor-based direct-acting antiviral therapy initiators, by baseline advanced hepatic fibrosis/cirrhosis status by FIB-4.



INTRODUCTION

The increased efficacy of direct-acting antivirals (DAAs) compared to interferon-based regimens has revolutionized the treatment of chronic hepatitis C virus (HCV) infection.[1] While DAAs also have a superior safety profile over interferon-based therapy, post-marketing surveillance has identified acute liver injury (ALI) as a potentially important DAA-related toxicity. On October 22, 2015, the United States (US) Food and Drug Administration (FDA) released a Drug Safety Communication reporting cases of hepatic decompensation that developed among chronic HCV-infected patients with compensated cirrhosis during treatment with paritaprevir/ritonavir/ombitasvir (PRO), either alone or with dasabuvir (PROD).[2] A follow-up FDA communication on August 28, 2019 reported cases of hepatic dysfunction among chronic HCV-infected patients treated with glecaprevir/pibrentasvir, elbasvir/grazoprevir, and sofosbuvir/velpatasvir/voxilaprevir.[3] Notably, all of the DAA regimens implicated in these FDA reports included an HCV protease inhibitor (PI). In many of the reports, ALI occurred among patients who had moderate-to-severe liver impairment (i.e., Child-Pugh Class B and C), in whom these drugs are contraindicated.[4,5]

As a result of these reports, there have been major concerns that PI-based DAA therapy might be associated with an increased risk of ALI, particularly among persons with advanced hepatic fibrosis/cirrhosis, compared to non-PI-based treatment.[6] Chronic HCV-induced advanced liver fibrosis might impair cytochrome P450 activity.[4] This impaired activity could result in elevated serum PI concentrations during PI-based DAA treatment, which might precipitate an ALI event, particularly significant liver aminotransferase elevations, severe hepatic dysfunction (i.e., coagulopathy plus hyperbilirubinemia), or hepatic decompensation. However, no studies have examined whether PI-based DAA treatment is associated with higher risk of ALI compared to non-PI-based therapy. Moreover, it is unclear if the risk of ALI associated with PI-based DAA therapy is heightened among those with advanced hepatic fibrosis/cirrhosis. These data are needed to determine the real-world comparative hepatic safety

of DAAs among chronic HCV-infected patients, especially those with advanced hepatic fibrosis/cirrhosis.

To address these critical knowledge gaps, we evaluated the incidence and risk of ALI, defined by incident development of liver aminotransferase elevations, severe hepatic dysfunction, or hepatic decompensation, among chronic HCV-infected patients who newly initiated a PI-based compared to non-PI-based DAA regimen. Given the potential for advanced hepatic fibrosis to impair the metabolism of PI-based DAAs, we stratified our results according to baseline stage of hepatic fibrosis using the Fibrosis-4 Index for Hepatic Fibrosis (FIB-4), a non-invasive measure of advanced hepatic fibrosis/cirrhosis that has been validated compared to liver biopsy among chronic HCV-infected patients.[7]

PATIENTS AND METHODS

Study Design and Data Source

We conducted a retrospective cohort study among chronic HCV-infected patients who initiated DAA treatment between January 1, 2014 and June 30, 2019 within the US Department of Veterans Affairs (VA) using data from the 1945-1965 Veterans Birth Cohort (VBC).[8,9] The VBC consists of electronic health record data from all Veterans born between 1945 and 1965 who received any VA care since October 1, 1999, encompassing >6.6 million persons aged 54-75 years. We chose to use data from the VBC since persons born between 1945 and 1965 have a 6-fold higher prevalence of HCV infection compared to all other age groups.[10] Available data in the VBC include demographics, inpatient and outpatient diagnoses, laboratory results, and dispensed medications. Date of death is available from the VA Vital Status file.[11] The study was approved by the Institutional Review Boards of the University of Pennsylvania, VA Connecticut Healthcare System, and Yale University, and was conducted under a waiver of informed consent per 45 CFR §46.117(c).

Study Patients

Chronic HCV-infected patients were eligible if they: 1) newly initiated a DAA of interest (i.e., sofosbuvir/ledipasvir, elbasvir/grazoprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, or PRO/PROD) within the VA between January 1, 2014 and June 30, 2019, and 2) were in care in the VA for ≥2 years prior to DAA initiation (to permit capture of relevant baseline comorbidities, laboratory results, and medications). DAA prescriptions in the VA have been validated to accurately reflect patients receiving treatment for chronic HCV.[12] While PRO/PROD are no longer recommended DAA regimens, we included initiators of these drugs since they were commonly dispensed PI-based regimens during the period of interest and would provide additional evidence on the hepatotoxicity of PI-based DAAs.

We defined the index date as the date that the DAA of interest was initially dispensed in the VA on or after January 1, 2014. The 2 years prior to the index date represented the baseline period, during which baseline comorbidities and laboratory results were collected. Patients were excluded if during the baseline period they were: 1) diagnosed with HIV infection (since such patients may be on antiretroviral drugs that could increase the risk of ALI[13]); 2) dispensed warfarin or a direct-acting oral anticoagulant (i.e., apixaban, dabigatran, edoxaban, rivaroxaban), which would prevent identification of coagulopathy due to ALI; 3) identified with any prevalent ALI outcome (defined below), since we sought to ascertain incident events; 4) diagnosed with hepatocellular carcinoma (which could lead to misclassification of ALI); or 5) were missing all baseline laboratory results necessary to calculate FIB-4. We also excluded patients who were ever hepatitis B surface antigen-positive (to reduce the likelihood of detecting ALI due to hepatitis B virus reactivation[14]) or were dispensed a DAA within the VA at any time prior to the index date (since we wished to restrict the sample to new DAA initiators). We chose not to evaluate rates of ALI events among DAA initiators who had decompensated cirrhosis, since PI-based DAA regimens are contraindicated in this group.

Follow-up continued until: 1) study endpoint, 2) death, 3) switch to a different DAA, 4)

discontinuation of DAA (defined as no further fills within 30 days after the last prescription's supply), 5) dispensation of warfarin or a direct-acting oral anticoagulant, or 6) September 30, 2019, whichever occurred first. For patients who completed or discontinued DAA therapy, we included 30 additional days of exposure time after the last days' supply to ensure capture of hepatotoxic events potentially related to DAA use.

Study Outcomes

To determine the full spectrum of ALI events associated with PI-based DAAs, we examined 3 incident ALI outcomes. First, we evaluated incident liver aminotransferase elevations, defined as an inpatient or outpatient alanine aminotransferase (ALT) >200 U/L (approximately 5 times the upper limit of normal of the assays used), a threshold that represents clinically important hepatic injury,[15] and approximately 10 times what has been considered normal liver aminotransferase levels for females (19 U/L) and males (30 U/L).[16] As a secondary endpoint, we evaluated development of inpatient or outpatient ALT >400 U/L, consistent with the definition of grade 4 ALT elevations employed in clinical trials.[17]

Second, we evaluated severe hepatic dysfunction, defined by an inpatient or outpatient international normalized ratio (INR) ≥1.5 and total bilirubin >2 times the upper limit of normal within up to 30 days of each other. This definition of severe hepatic dysfunction has been used by the US FDA's Sentinel System to assess serious and clinically significant drug-induced ALI in the post-marketing period.[18] While Hy's Law has also been used by Sentinel to identify ALI, we selected the definition that identifies liver injury at an advanced stage, such that serum liver aminotransferases might not be sufficiently elevated to meet Hy's Law.[18] If the laboratory abnormalities presented on different dates, the event was considered to have occurred on the date that the latter abnormality occurred.

Third, we determined incident hepatic decompensation, defined by 1 hospital discharge diagnosis (principal or contributory) or 2 or more outpatient diagnoses (recorded within 1 year)

of ascites, spontaneous bacterial peritonitis, esophageal variceal hemorrhage, or hepatic encephalopathy (**Supplementary Table 1**).[19] The decompensation date was defined as the hospital discharge date (if event was identified by hospital diagnosis) or initial outpatient diagnosis date (if identified by outpatient diagnoses).

Data Collection

Baseline clinical data included age, sex, race/ethnicity, body mass index, diabetes mellitus (defined by random glucose ≥200 mg/dL, hemoglobin A1c ≥6.5%, and/or anti-diabetic medication use),[20] previously validated diagnoses of alcohol dependence/abuse,[21] and use of ribavirin as part of the DAA regimen. Baseline laboratory data included HCV RNA, HCV genotype, ALT, aspartate aminotransferase (AST), INR, total bilirubin, hemoglobin, platelets, and serum creatinine. Baseline FIB-4 was calculated by: (age [years] x AST [U/L])/(platelet count [10^9/L]) x (ALT [U/L])$^{1/2}$).[7] FIB-4 >3.25 identifies advanced hepatic fibrosis/cirrhosis (METAVIR stages F3 or F4) with a high degree of accuracy versus liver biopsy in chronic HCV infection.[7] When multiple laboratory results were assessed during the baseline period, we collected the result closest, but prior, to the index date. The estimated glomerular filtration rate (mL/min/1.73 m²) was calculated using the Modification of Diet in Renal Disease equation: 175 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (0.742, if female) x (1.212, if Black).[22] The Model for End-Stage Liver Disease (MELD) score was calculated by: 3.78∗ln[total bilirubin (mg/dL)] + 11.2∗ln[INR] + 9.57∗ln[creatinine (mg/dL)] + 6.43.[23]

Data collected during follow-up included: outpatient and inpatient ALT, INR, and total bilirubin results; diagnoses of hepatic decompensation; and sustained virologic response (SVR12; defined by undetectable HCV RNA on the first test ≥12 weeks after DAA treatment end date).

Statistical Analysis

To reduce the potential for selection bias in examining rates of ALI events between PI-based DAA therapy (glecaprevir/pibrentasvir, elbasvir/grazoprevir, or PRO/PROD) and non-PI-based regimens (sofosbuvir/ledipasvir or sofosbuvir/velpatasvir), we developed propensity scores, which determine each patient's probability of being assigned to a particular treatment given their observed set of baselined covariates.[24] Propensity score methods allow for the reduction of bias when estimating treatment effects by accounting for the differential probability of receiving PI-based or non-PI-based DAA therapy. The propensity score model was developed using logistic regression, with potential determinants of PI-based DAA therapy as independent variables and PI-based DAA treatment exposure as the dependent variable.[25] Variables selected for the propensity score were those that might affect clinicians' decision to prescribe a PI or non-PI DAA regimen and influence risk of acute liver injury and included: age, sex, race/ethnicity, body mass index, diabetes, diagnosis of alcohol dependence/abuse, HCV genotype, hemoglobin, platelet count, ALT, AST, INR, total bilirubin, eGFR, MELD score, ribavirin use, and date of DAA initiation. Within FIB-4 strata, each PI initiator was matched on propensity score (nearest-neighbor matching within 0.02 of the propensity score) to one non-PI initiator. This matching allows us to create a comparison group of non-PI-treated patients whose baseline characteristics resemble those of PI-treated patients.[25] We compared the baseline characteristics between PI and non-PI initiators prior to and after propensity score matching using standardized differences, of which a value exceeding 0.1 is generally considered meaningful.[26]

For propensity score-matched PI and non-PI initiator cohorts, we determined incidence rates (events per 1,000 person-years) of each ALI outcome (as independent events) with 95% confidence intervals (CIs), stratified by baseline advanced hepatic fibrosis/cirrhosis status by FIB-4 (≤3.25 versus >3.25). Additionally, among PI-based and non-PI-based DAA initiators who had an ALI event defined by ALT >200 U/L, we evaluated the median ALT level within each 4-week period of treatment over 32 weeks of follow-up, by FIB-4. For individuals with multiple ALT

results within a given 4-week period, we analyzed the highest assessed ALT. We then determined the proportion whose ALT decreased to ≤100 U/L. To assess if development of ALT >200 U/L compromised likelihood of achieving HCV cure, we compared the proportions that achieved SVR12 for persons who did and did not develop ALT >200 U/L, by FIB-4 status, among those tested for SVR12.

Cox regression was then used to determine the hazard ratio (HR) of each ALI outcome associated with PI-based DAA therapy compared to use of non-PI-based regimens.[27] We confirmed the adequacy of the propensity score as a continuous variable by: 1) observing overlap in the distribution between PI-based and non-PI-based DAA users (**Supplementary Figs. 1** and **2**), and 2) confirming linearity of propensity score categories within outcome models. Results were stratified by baseline FIB-4 (≤3.25; >3.25). Proportionality of hazards was assessed by log-log plots and Schoenfeld residuals.[27] Data were analyzed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

We identified 96,720 chronic-HCV-infected persons who were dispensed one of the DAAs of interest between January 1, 2014 and June 30, 2019. After exclusions, 20,169 new initiators of a PI-based DAA regimen (5,994 PRO/PROD; 8,301 elbasvir/grazoprevir; 5,874 glecaprevir/pibrentasvir) and 51,222 non-PI-based initiators (43,813 sofosbuvir/ledipasvir; 7,409 sofosbuvir/velpatasvir) remained (**Fig. 1**).

Prior to propensity score matching, initiators of PI-based DAA regimens more commonly were Black, infected with HCV genotype 1, and had diabetes mellitus, severe anemia (hemoglobin <10 g/dL), and renal insufficiency (estimated glomerular filtration rate <30 mL/min/1.73 m^2) (**Tables 1** and **2**). Initiators of non-PI-based DAAs more commonly had alcohol dependence/abuse history and MELD score <10. Among those with baseline FIB-4 ≤3.25,

14,985 initiators of PI-based DAAs were propensity score-matched to 14,985 initiators of non-PI-based DAAs. Among those with baseline FIB-4 >3.25, 3,513 initiators of PI-based DAAs were propensity score-matched to 3,513 initiators of non-PI-based DAAs. Propensity score-matching generally balanced the frequencies of characteristics between the cohorts.

Incidence Rates of ALI Events, by Baseline FIB-4

Table 3 reports the absolute risk and unadjusted incidence rates of ALT >200 U/L, severe hepatic dysfunction, and hepatic decompensation for the propensity score-matched PI-based and non-PI-based initiator cohorts by baseline FIB-4. **Supplementary Table 2** reports the frequencies of specific decompensation diagnoses. **Supplementary Table 3** reports the absolute risk and unadjusted rates of ALI outcomes in the overall study sample prior to propensity score matching, by baseline FIB-4. Regardless of baseline FIB-4 score, the absolute risk of each ALI outcome was rare (<2%).

Among persons with baseline FIB-4 ≤3.25, incidence rates of ALT >200 U/L (**Table 3**) and ALT >400 U/L (**Supplementary Table 4**) were higher in magnitude for PI than non-PI initiators. Among PI and non-PI initiators who developed ALT >200 U/L, median ALT levels peaked at week 4 of treatment for PI-based initiators and at week 8 for non-PI-based initiators and then declined over follow-up (**Fig. 2A**). Similar proportions of PI-based and non-PI-based DAA initiators who developed ALT >200 U/L experienced subsequent decrease in ALT to ≤100 U/L (90.1% versus 88.9%, respectively; p=0.88). The proportion of DAA initiators achieving SVR12 did not differ between those who did and did not develop ALT >200 U/L (**Supplementary Table 5**). Incidence rates of severe hepatic dysfunction and hepatic decompensation were similar between PI- and non-PI-based DAA initiators for those with baseline FIB-4 ≤3.25.

For patients with baseline FIB-4 >3.25 (advanced hepatic fibrosis/cirrhosis), rates of both ALT >200 U/L (**Table 3**) and ALT >400 U/L (**Supplementary Table 4**) were higher in magnitude for PI-based initiators. Among patients who had ALT >200 U/L, median ALT levels peaked at

week 4 for PI-based and non-PI initiators, and then declined over follow-up (**Fig. 2B**). Similar proportions of PI-based and non-PI-based DAA initiators who developed ALT >200 U/L experienced subsequent decrease in ALT to ≤100 U/L (92.0% vs 100%%, respectively; p=0.31). There were no significant differences in achievement of SVR12 between those who did versus did not develop ALT >200 U/L (**Supplementary Table 5**). In contrast to findings among those with FIB-4 ≤3.25, incidence rates of severe hepatic dysfunction and hepatic decompensation were higher in magnitude for initiators of non-PI regimens.

Risk of ALI Events with PI-Based Versus Non-PI-Based DAAs, by Baseline FIB-4

Among persons with baseline FIB-4 ≤3.25, initiators of PI-based DAA regimens had higher relative hazards of ALT >200 U/L (HR, 3.98 [95% CI, 2.37-6.68]; **Fig. 3**) and ALT >400 U/L (HR, 3.02 [95% CI, 1.10-8.30]) than those who received a non-PI-based regimen. However, among persons in this FIB-4 stratum, PI initiators did not have significantly higher relative hazards of either severe hepatic dysfunction (HR, 0.67 [95% CI, 0.19-2.39]) or hepatic decompensation (HR, 1.01 [95% CI, 0.29-3.48]) than non-PI initiators.

For those with baseline FIB-4 >3.25, initiators of PI-based DAAs had significantly higher relative hazards of ALT >200 U/L (HR, 2.15 [95% CI, 1.08-4.29]), but not of ALT >400 U/L (HR, 1.52 [95% CI, 0.25-9.11), severe hepatic dysfunction (HR, 1.23 [95% CI, 0.63-2.40]), or hepatic decompensation (HR, 0.87 [95% CI, 0.42-1.82]) compared to non-PI initiators (**Fig. 3**).

DISCUSSION

In this national sample of treatment-naïve chronic HCV-infected patients within the VA system, we identified PI-based DAA initiators (glecaprevir/pibrentasvir, elbasvir/grazoprevir, or PRO/PROD) and matched them 1:1 on propensity scores to non-PI-based initiators (sofosbuvir/ledipasvir or sofosbuvir/velpatasvir) to ensure that the cohorts were similar with regards to the frequencies of important baseline demographic and clinical characteristics. We

observed that the absolute risk of the three ALI outcomes of interest was low (<2%) among initiators of both PI-based and non-PI-based DAAs. Regardless of baseline advanced hepatic fibrosis/cirrhosis status by FIB-4, incidence rates and relative hazards of ALT >200 U/L were higher for PI- than non-PI-based initiators. However, relative hazards of severe hepatic dysfunction and hepatic decompensation were not significantly increased among users of PI-based DAA regimens, regardless of baseline FIB-4.

We observed that PI-based DAA therapy was associated with higher risk of liver aminotransferase elevations, but not severe hepatic dysfunction or hepatic decompensation, compared to non-PI therapy. Transient elevations in liver aminotransferases have been reported following initiation of PI-based DAA regimens, particularly PRO/PROD and elbasvir/grazaprevir.[28-30] The biologic mechanism remains unclear but may be due to either immune-mediated hepatocyte injury in the setting of viral clearance or idiosyncratic drug-induced ALI.[31,32] These reports have suggested that ALT elevations during PI-based DAA therapy are largely asymptomatic and that levels normalize by week 8.[28,29] Consistent with those findings, we observed that among PI-based and non-PI-based DAA initiators who developed an ALT >200 U/L, median ALT levels generally decreased after 4 weeks following the initial event. These findings suggest that the majority of ALT elevations during DAA therapy are transient. Furthermore, our findings suggest that the ALT elevations did not decrease the likelihood of achieving SVR12.

In our primary analysis, we found no association between PI therapy and severe hepatic dysfunction or hepatic decompensation, regardless of baseline advanced hepatic fibrosis/cirrhosis status by FIB-4. This is a valuable observation particularly for patients with baseline advanced hepatic fibrosis/cirrhosis, since compensated cirrhosis may predispose to increased PI exposure and subsequently an increased risk of hepatotoxicity.[33-35] Our findings suggest that the risk of serious ALI events is not increased among chronic HCV-infected persons without decompensated cirrhosis who initiated PI-based versus non-PI-based DAA therapy.

Prior studies evaluating the real-world safety of DAAs estimated that the absolute risk of hepatic decompensation following DAA initiation was 0.2-1.1%, similar to our findings.[34,36-38] One multicenter observational study of 33,808 initiators of DAAs from 2012-2017 reported the incidence of hepatic decompensation to be 23.8 events/1,000 person-years.[37] However, rates were not stratified by cirrhosis status, as in this study. A previous study among US Veterans observed more than 10-fold higher incidence rates of hepatic decompensation among initiators of PRO/PROD and sofosbuvir/ledipasvir with cirrhosis compared to those without cirrhosis.[34] In this study, we found that rates of each ALI outcome were substantially higher among persons with FIB-4 >3.25, highlighting how cirrhosis might modify the risk of ALI associated with DAA therapy.

Our study had several limitations. First, we undertook these analyses from an epidemiological standpoint, comparing the relative incidences and risk of ALI events according to PI-based DAA status in order to identify hepatotoxicity signals. However, we were unable to ascertain the etiology of each ALI event given the challenges in confirming a drug-induced etiology of ALI in clinical practice. Second, there is potential for confounding by indication,[39] since patients were assigned to PI-based DAA treatment by clinician choice. Our implementation of propensity score matching attempted to account for this in our risk models by matching patients on the probability of receipt of PI-based versus non-PI-based DAA therapy to create comparable cohorts for analysis. Third, we were unable to capture alcohol use that might have begun during DAA therapy as well as concomitant use of hepatoxic medications during treatment, and these factors might have contributed to ALI events. Fourth, since ALT was assessed as part of routine clinical care and not per standardized protocol, our secondary analysis examining median ALT over 4-week periods of DAA treatment may not have accurately assessed the course of ALT increase over time. Finally, our study sample was predominantly comprised of male US Veterans and may not be generalizable to women. Our study is also not generalizable to patients with decompensated cirrhosis prior to DAA treatment.

Our study had a number of strengths. We included a large, national cohort of patients who initiated different DAA therapies. We evaluated a spectrum of clinically relevant ALI outcomes and stratified results by baseline FIB-4 to assess the risk of these events by advanced hepatic fibrosis/cirrhosis status. Finally, we used propensity scores to account for important variables that might influence prescription of PI versus non-PI-based DAA therapy and which might be associated with ALI.

In conclusion, our study found that PI-based DAA therapy was associated with higher risk of liver aminotransferase elevations, but not severe hepatic dysfunction or hepatic decompensation events, compared to non-PI therapy. Liver aminotransferase elevations during PI-based DAA therapy might be due to immune-mediated inflammation accompanying viral eradication or transient drug-induced ALI; however, clinically apparent acute severe hepatic dysfunction or hepatic decompensation were not more common among PI-based DAA initiators. These findings demonstrate the comparable hepatic safety of PI-based and non-PI-based DAA therapies among chronic HCV-infected persons without decompensated cirrhosis.

Abbreviations: ALI, acute liver injury; ALT, alanine aminotransferase; CI, confidence interval; DAA, direct-acting; antivirals; FDA, Food and Drug Administration; FIB-4, Fibrosis-4 Index for Hepatic Fibrosis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HR, hazard ratio; INR, international normalized ratio; PI, protease inhibitor; PRO, paritaprevir/ritonavir/ombitasvir; PROD, paritaprevir/ritonavir/ombitasvir/dasabuvir; RNA, ribonucleic acid; US, United States; VA, Veterans Administration; VBC, Veterans Birth Cohort

REFERENCES

1. Falade-Nwulia O, Suarez-Cuervo C, Nelson DR, Fried MW, Segal JB, Sulkowski MS. Oral direct-acting agent therapy for hepatitis C virus infection: A systematic review. *Ann Intern Med* 2017; **166**(9): 637-48.

2. United States Food and Drug Administration. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. Oct 22, 2015. Accessed at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-warns-serious-liver-injury-risk-hepatitis-c-treatments-viekira-pak. Accessed on March 28, 2021.

3. United States Food and Drug Administration. FDA Drug Safety Communication: FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease. Accessed at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and. Accessed on March 28, 2021.

4. Mak LY, Seto WK, Lai CL, Yuen MF. An update on the toxicological considerations for protease inhibitors used for hepatitis C infection. *Expert Opin Drug Metab Toxicol* 2018; **14**(5): 483-91.

5. American Association fir the Study of Liver Diseases/Infectious Diseases Society of America. HCV Guidance: Recommendations for testing m, and treating hepatitis C. Accessed at: https://www.hcvguidelines.org. Accessed on March 28, 2021.

6. Kiser JJ. Safety of Hepatitis C Viral Protease Inhibitors in Compensated Cirrhotics: Lingering Concerns Put to Rest? *Clin Infect Dis* 2019; **69**(10): 1665-6.

7. Chou R, Wasson N. Blood tests to diagnose fibrosis or cirrhosis in patients with chronic hepatitis C virus infection: a systematic review. *Ann Intern Med* 2013; **158**(11): 807-20.

8. Sarkar S, Esserman DA, Skanderson M, Levin FL, Justice AC, Lim JK. Disparities in hepatitis C testing in U.S. veterans born 1945-1965. *J Hepatol* 2016; **65**(2): 259-65.

9. Njei B, Esserman D, Krishnan S, et al. Regional and Rural-Urban Differences in the Use of Direct-acting Antiviral Agents for Hepatitis C Virus: The Veteran Birth Cohort. *Med Care* 2019; **57**(4): 279-85.

10. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med* 2014; **160**(5): 293-300.

11. Fisher SG, Weber L, Goldberg J, Davis F. Mortality ascertainment in the veteran population: alternatives to the National Death Index. *Am J Epidemiol* 1995; **141**(3): 242-50.

12. Rentsch CT, Cartwright EJ, Gandhi NR, et al. Provider verification of electronic health record receipt and nonreceipt of direct-acting antivirals for the treatment of hepatitis C virus infection. *Ann Epidemiol* 2018; **28**(11): 808-11.

13. Gowda C, Newcomb CW, Liu Q, et al. Risk of Acute Liver Injury With Antiretroviral Therapy by Viral Hepatitis Status. *Open Forum Infect Dis* 2017; **4**(2): ofx012.

14. Belperio PS, Shahoumian TA, Mole LA, Backus LI. Evaluation of hepatitis B reactivation among 62,920 veterans treated with oral hepatitis C antivirals. *Hepatology* 2017; **66**(1): 27-36.

15. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther* 2011; **89**(6): 806-15.

16. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. *Ann Intern Med* 2002; **137**(1): 1-10.

17. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002; **35**(1): 182-9.

18. Lo Re V, 3rd, Haynes K, Goldberg D, et al. Validity of diagnostic codes to identify cases of severe acute liver injury in the US Food and Drug Administration's Mini-Sentinel Distributed Database. *Pharmacoepidemiol Drug Saf* 2013; **22**(8): 861-72.

19. Lo Re V, 3rd, Lim JK, Goetz MB, et al. Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic decompensation events in the Veterans Aging Cohort Study. *Pharmacoepidemiol Drug Saf* 2011; **20**(7): 689-99.

20. Butt AA, McGinnis K, Rodriguez-Barradas MC, et al. HIV infection and the risk of diabetes mellitus. *AIDS* 2009; **23**(10): 1227-34.

21. Justice AC, McGinnis KA, Atkinson JH, et al. Psychiatric and neurocognitive disorders among HIV-positive and negative veterans in care: Veterans Aging Cohort Five-Site Study. *AIDS* 2004; **18 Suppl 1**: S49-59.

22. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med* 2006; **145**(4): 247-54.

23. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**(2): 464-70.

24. Perkins SM, Tu W, Underhill MG, Zhou XH, Murray MD. The use of propensity scores in pharmacoepidemiologic research. *Pharmacoepidemiol Drug Saf* 2000; **9**(2): 93-101.

25. Braitman LE, Rosenbaum PR. Rare outcomes, common treatments: analytic strategies using propensity scores. *Ann Intern Med* 2002; **137**(8): 693-5.

26. Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ* 2005; **330**(7497): 960-2.

27. Hosmer DW LS. Applied Survival Analysis: Regression Modeling of Time-to-Event Data. . New York, NY: John Wiley & Sons, Inc.; 1999.

28. Bean M, Tang L, Kottilil S, Beavers KL, Meissner EG. On-Treatment Elevation in Hepatic Transaminases during HCV Treatment with Ombitasvir, Paritaprevir, Dasabuvir, Ritonavir, and Ribavirin: A Case Series. *Case Rep Infect Dis* 2016; **2016**: 6151570.

29. Jacobson IM, Lawitz E, Kwo PY, et al. Safety and efficacy of elbasvir/grazoprevir in patients with hepatitis C virus iinfection and compensated cirrhosis: An integrated analysis. *Gastroenterology* 2017; **152**(6): 1372-82 e2.

30. Smolders EJ, Jansen AME, Ter Horst PGJ, Rockstroh J, Back DJ, Burger DM. Viral hepatitis C therapy: Pharmacokinetic and pharmacodynamic considerations: A 2019 update. *Clin Pharmacokinet* 2019; **58**(10): 1237-63.

31. Martin B, Hennecke N, Lohmann V, et al. Restoration of HCV-specific CD8+ T cell function by interferon-free therapy. *J Hepatol* 2014; **61**(3): 538-43.

32. Alao H, Cam M, Keembiyehetty C, et al. Baseline intrahepatic and peripheral innate immunity are associated with hepatitis C virus clearance during direct-acting antiviral therapy. *Hepatology* 2018; **68**(6): 2078-88.

33. Lin CW, Menon R, Liu W, et al. Exposure-safety response relationship for ombitasvir, paritaprevir/ritonavir, dasabuvir, and ribavirin in patients with chronic hepatitis C virus genotype 1 infection: Analysis of data from five phase II and six phase III studies. *Clin Drug Investig* 2017; **37**(7): 647-57.

34. Butt AA, Ren Y, Marks K, Shaikh OS, Sherman KE, study E. Do directly acting antiviral agents for HCV increase the risk of hepatic decompensation and decline in renal function? Results from ERCHIVES. *Aliment Pharmacol Ther* 2017; **45**(1): 150-9.

35. Gane E, Poordad F, Zadeikis N, et al. Safety and pharmacokinetics of glecaprevir/pibrentasvir in adults with chronic genotype 1-6 hepatitis C virus infections and compensated liver disease. *Clin Infect Dis* 2019; **69**(10): 1657-64.

36. Calleja JL, Crespo J, Rincon D, et al. Effectiveness, safety and clinical outcomes of direct-acting antiviral therapy in HCV genotype 1 infection: Results from a Spanish real-world cohort. *J Hepatol* 2017; **66**(6): 1138-48.

37. McGlynn EA, Adams JL, Kramer J, et al. Assessing the safety of direct-acting antiviral agents for hepatitis C. *JAMA Netw Open* 2019; **2**(6): e194765.

533 38. Lampertico P, Carrion JA, Curry M, et al. Real-world effectiveness and safety of
534 glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: A meta-
535 analysis. *J Hepatol* 2020; **72**(6): 1112-21.
536 39. Walker AM. Confounding by indication. *Epidemiology* 1996; **7**(4): 335-6.

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Table 1. Baseline characteristics of patients with FIB-4 ≤3.25 prescribed protease inhibitor-based and non-protease inhibitor (PI)-based direct-acting antiviral regimens of interest for chronic hepatitis C virus infection prior to and after propensity score matching.

	Prior to Propensity Score Matching			After Propensity Score Matching		
Characteristics	**PI-Based DAA Regimen* (n=16,353)**	**Non-PI-Based DAA Regimen† (n=40,639)**	**SDP**	**PI-Based DAA Regimen* (n=14,985)**	**Non-PI-Based DAA Regimen† (n=14,985)**	**SDP**
Age			0.17			0.02
<55 years	611 (3.7%)	2,290 (5.6%)		584 (3.9%)	552 (3.7%)	
55-59 years	3,430 (21.0%)	9,994 (24.6%)		3,233 (21.6%)	3,255 (21.7%)	
60-64 years	6,259 (38.3%)	15,592 (38.4%)		5,751 (38.4%)	5,834 (38.9%)	
65-69 years	5,114 (31.3%)	11,428 (28.1%)		4,610 (30.8%)	4,585 (30.6%)	
≥70 years	939 (5.7%)	1,335 (3.3%)		807 (5.4%)	759 (5.1%)	
Male sex	15,848 (96.9%)	39,245 (96.6%)	0.02	14,509 (96.8%)	14,487 (96.7%)	<0.01
Race/ethnicity			0.17			0.05
Black	8,140 (49.8%)	17,153 (42.2%)		7,187 (48.0%)	7,096 (47.4%)	
White	6,665 (40.8%)	19,733 (48.6%)		6,359 (42.4%)	6,587 (44.0%)	
Hispanic	831 (5.1%)	1,822 (4.5%)		769 (5.1%)	617 (4.1%)	
Other/Unknown	717 (4.4%)	1,931 (4.8%)		670 (4.5%)	685 (4.6%)	
Body mass index			0.27			0.06
Underweight (<18.50 kg/m^2)	291 (1.8%)	680 (1.7%)		267 (1.8%)	267 (1.8%)	
Normal (18.50-24.99 kg/m^2)	4,682 (28.6%)	11,872 (29.2%)		4,263 (28.4%)	4,343 (29.0%)	
Overweight (25.00-29.99 kg/m^2)	5,679 (34.7%)	14,985 (36.9%)		5,221 (34.8%)	5,303 (35.4%)	
Obesity (30.00-34.99 kg/m^2)	2,917 (17.8%)	8,096 (19.9%)		2,716 (18.1%)	2,757 (18.4%)	
Morbid obesity (≥35.00 kg/m^2)	1,215 (7.4%)	3,684 (9.1%)		1,118 (7.5%)	1,146 (7.6%)	
Unknown	1,569 (9.6%)	1,322 (3.3%)		1,400 (9.3%)	1,169 (7.8%)	
Diabetes mellitus	5,259 (32.2%)	11,402 (28.1%)	0.09	4,439 (29.6%)	4,425 (29.5%)	<0.01
Alcohol dependence/abuse diagnosis	8,430 (51.6%)	21,501 (52.9%)	0.03	7,795 (52.0%)	7,822 (52.2%)	<0.01
HCV RNA >800,000 IU/mL	11,220 (68.6%)	28,285 (69.6%)	0.08	10,473 (69.9%)	10,014 (66.8%)	0.09
HCV genotype			0.49			0.06
Genotype 1a	7,553 (46.2%)	25,057 (61.7%)		7,006 (46.8%)	6,781 (45.3%)	
Genotype 1b	6,123 (37.4%)	7,053 (17.4%)		5,467 (36.5%)	5,759 (38.4%)	
Genotype 1, subtype unknown	261 (1.6%)	980 (2.4%)		253 (1.7%)	231 (1.5%)	
Genotype 2	702 (4.3%)	2,714 (6.7%)		664 (4.4%)	618 (4.1%)	
Genotype 3	330 (2.0%)	1,701 (4.2%)		318 (2.1%)	376 (2.5%)	
Other genotype	906 (5.5%)	2,424 (6.0%)		839 (5.6%)	862 (5.8%)	
Hemoglobin <10 g/dL	368 (2.3%)	261 (0.6%)	0.14	170 (1.1%)	138 (0.9%)	0.02
Alanine aminotransferase			0.15			0.03
<30 U/L	4,287 (26.2%)	8,503 (20.9%)		3,622 (24.2%)	3,457 (23.1%)	
30-60 U/L	7,689 (47.0%)	19,078 (46.9%)		7,159 (47.8%)	7,196 (48.0%)	
>60 U/L	3,734 (22.8%)	10,931 (26.9%)		3,603 (24.0%)	3,728 (24.9%)	
Aspartate aminotransferase			0.11			0.02
<30 U/L	4,785 (29.3%)	10,461 (25.7%)		4,127 (27.5%)	4,013 (26.8%)	
30-60 U/L	8,850 (54.1%)	21,926 (54.0%)		8,265 (55.2%)	8,305 (55.4%)	
>60 U/L	2,055 (12.6%)	5,953 (14.6%)		1,972 (13.2%)	2,049 (13.7%)	
Platelet count			0.04			<0.01
≥150,000/μL	14,923 (91.3%)	37,388 (92.0%)		13,757 (91.8%)	13,725 (91.6%)	
<150,000/μL	1,388 (8.5%)	3,104 (7.6%)		1,186 (7.9%)	1,218 (8.1%)	
Total bilirubin			<0.01			<0.01
≤2 mg/dL	16,323 (99.8%)	40,563 (99.8%)		14,956 (99.8%)	14,961 (99.8%)	
>2 mg/dL	30 (0.2%)	76 (0.2%)		29 (0.2%)	24 (0.2%)	
International normalized ratio			0.03			<0.01

<1.5	13,132 (80.3%)	32,172 (79.2%)		11,904 (79.4%)	11,869 (79.2%)	
≥1.5	3,221 (19.7%)	8,467 (20.8%)		3,081 (20.6%)	3,116 (20.8%)	
Model of End-Stage Liver Disease (MELD) score‡			0.39			0.09
<10	10,721 (65.6%)	29,849 (73.4%)		10,500 (70.1%)	10,709 (71.5%)	
10-14	1,199 (7.3%)	2,218 (5.5%)		1,126 (7.5%)	1,060 (7.1%)	
≥15	1,233 (7.5%)	161 (0.4%)		290 (1.9%)	140 (0.9%)	
Estimated glomerular filtration rate <30 mL/min/1.73m^2	1,320 (8.1%)	116 (0.3%)	0.40	298 (2.0%)	115 (0.8%)	0.11
Use of ribavirin as part of DAA regimen	3,075 (18.8%)	3,441 (8.5%)	0.30	2,899 (19.3%)	3,003 (20.0%)	0.02
Year of DAA initiation			0.58			0.38
2014-2015	3,701 (22.6%)	9,167 (22.6%)		3,595 (24.0%)	1,990 (13.3%)	
2016-2017	7,557 (46.2%)	27,579 (67.9%)		6,813 (45.5%)	9,520 (63.5%)	
2018-2019	5,095 (31.2%)	3,893 (9.6%)		4,577 (30.5%)	3,475 (23.2%)	

DAA, direct-acting antiviral; FIB-4, Fibrosis-4 index for liver fibrosis; HCV, hepatitis C virus; IQR, interquartile range; PI, protease inhibitor; RNA, ribonucleic acid; SDP, standardized difference in proportion

* Includes glecaprevir/pibrentasvir, elbasvir/grazoprevir, or paritaprevir/ritonavir/ombitasvir with or without dasabuvir

† Includes sofosbuvir/ledipasvir or sofosbuvir/velpatasvir

‡ MELD score calculation: 3.78 x ln[total bilirubin (mg/dL)] + 11.2 x ln[INR] + 9.57 x ln[creatinine (mg/dL)] + 6.43

Table 2. Baseline characteristics of patients with FIB-4 >3.25 prescribed protease inhibitor-based and non-protease inhibitor (PI)-based direct-acting antiviral regimens of interest for chronic hepatitis C virus infection prior to and after propensity score matching.

Characteristics	Prior to Propensity Score Matching			After Propensity Score Matching		
	PI-Based DAA Regimen* (n=3,816)	Non-PI-Based DAA Regimen† (n=10,583)	SDP	PI-Based DAA Regimen* (n=3,513)	Non-PI-Based DAA Regimen† (n=3,513)	SDP
Age			0.12			0.04
<55 years	80 (2.1%)	324 (3.1%)		75 (2.1%)	62 (1.8%)	
55-59 years	619 (16.2%)	1,971 (18.6%)		585 (16.7%)	610 (17.4%)	
60-64 years	1,465 (38.4%)	4,124 (39.0%)		1,366 (38.9%)	1,347 (38.3%)	
65-69 years	1,400 (36.7%)	3,644 (34.4%)		1,260 (35.9%)	1,276 (36.3%)	
≥70 years	252 (6.6%)	520 (4.9%)		227 (6.5%)	218 (6.2%)	
Male sex	3,738 (98.0%)	10,310 (97.4%)	0.04	3,442 (98.0%)	3,426 (97.5%)	0.03
Race/ethnicity			0.16			0.05
Black	1,771 (46.4%)	4,138 (39.1%)		1,552 (44.2%)	1,491 (42.4%)	
White	1,611 (42.2%)	5,296 (50.0%)		1,546 (44.0%)	1,637 (46.6%)	
Hispanic	248 (6.5%)	641 (6.1%)		237 (6.7%)	220 (6.3%)	
Other/Unknown	186 (4.9%)	508 (4.8%)		178 (5.1%)	165 (4.7%)	
Body mass index			0.11			0.03
Underweight (<18.50 kg/m^2)	87 (2.3%)	229 (2.2%)		80 (2.3%)	77 (2.2%)	
Normal (18.50-24.99 kg/m^2)	1,201 (31.5%)	3,112 (29.4%)		1,088 (31.0%)	1,065 (30.3%)	
Overweight (25.00-29.99 kg/m^2)	1,303 (34.1%)	3,758 (35.5%)		1,196 (34.0%)	1,211 (34.5%)	
Obesity (30.00-34.99 kg/m^2)	671 (17.6%)	2,025 (19.1%)		624 (17.8%)	611 (17.4%)	
Morbid obesity (≥35.00 kg/m^2)	321 (8.4%)	1,010 (9.5%)		305 (8.7%)	323 (9.2%)	
Unknown	233 (6.1%)	449 (4.2%)		220 (6.3%)	226 (6.4%)	
Diabetes mellitus	1,230 (32.2%)	3,197 (30.2%)	0.04	1,056 (30.1%)	1,095 (31.2%)	0.02
Alcohol dependence/abuse diagnosis	2,136 (56.0%)	6,161 (58.2%)	0.05	1,997 (56.8%)	2,002 (57.0%)	<0.01
HCV RNA >800,000 IU/mL	2,522 (66.1%)	6,946 (65.6%)	0.04	2,338 (66.6%)	2,306 (65.6%)	0.05
HCV genotype			0.54			0.10
Genotype 1a	1,841 (48.2%)	6,635 (62.7%)		1,715 (48.8%)	1,835 (52.2%)	
Genotype 1b	1,458 (38.2%)	1,704 (16.1%)		1,302 (37.1%)	1,162 (33.1%)	
Genotype 1, subtype unknown	60 (1.6%)	280 (2.6%)		59 (1.7%)	51 (1.5%)	
Genotype 2	74 (1.9%)	495 (4.7%)		71 (2.0%)	55 (1.6%)	
Genotype 3	109 (2.9%)	664 (6.3%)		108 (3.1%)	108 (3.1%)	
Other genotype	206 (5.4%)	575 (5.4%)		192 (5.5%)	225 (6.4%)	
Hemoglobin <10 g/dL	113 (3.0%)	157 (1.5%)	0.10	64 (1.8%)	49 (1.4%)	0.03
Alanine aminotransferase			0.06			<0.01
<30 U/L	326 (8.5%)	748 (7.1%)		237 (6.7%)	235 (6.7%)	
30-60 U/L	1,109 (29.1%)	3,051 (28.8%)		1,007 (28.7%)	1,008 (28.7%)	
>60 U/L	2,145 (56.2%)	6,108 (57.7%)		2,054 (58.5%)	2,061 (58.7%)	
Aspartate aminotransferase			0.10			0.02
<30 U/L	94 (2.5%)	156 (1.5%)		62 (1.8%)	57 (1.6%)	
30-60 U/L	951 (24.9%)	2,365 (22.3%)		822 (23.4%)	847 (24.1%)	
>60 U/L	2,530 (66.3%)	7,325 (69.2%)		2,408 (68.5%)	2,398 (68.3%)	
Platelet count			0.09			0.03
≥150,000/μL	1,182 (31.0%)	2,859 (27.0%)		1,103 (31.4%)	1,055 (30.0%)	
<150,000/μL	2,619 (68.6%)	7,690 (72.7%)		2,397 (68.2%)	2,445 (69.6%)	
Total bilirubin			0.17			<0.01
≤2 mg/dL	3,765 (98.7%)	10,152 (95.9%)		3,462 (98.5%)	3,463 (98.6%)	
>2 mg/dL	51 (1.3%)	431 (4.1%)		51 (1.5%)	50 (1.4%)	

International normalized ratio			0.04			0.02
<1.5	3,310 (86.7%)	9,036 (85.4%)		3,033 (86.3%)	3,010 (85.7%)	
≥1.5	506 (13.3%)	1,547 (14.6%)		480 (13.7%)	503 (14.3%)	
Model of End-Stage Liver Disease (MELD) score‡			0.32			0.06
<10	2,635 (69.1%)	7,696 (72.7%)		2,569 (73.1%)	2,588 (73.7%)	
10-14	426 (11.2%)	1,310 (12.4%)		411 (11.7%)	395 (11.2%)	
≥15	282 (7.4%)	114 (1.1%)		80 (2.3%)	53 (1.5%)	
Estimated glomerular filtration rate <30 mL/min/1.73m^2	281 (7.4%)	42 (0.4%)	0.37	62 (1.8%)	41 (1.2%)	0.05
Use of ribavirin as part of DAA regimen	1,320 (34.6%)	2,434 (23.0%)	0.26	1,236 (35.2%)	1,344 (38.3%)	0.06
Year of DAA initiation			0.25			0.18
2014-2015	1,337 (35.0%)	3,515 (33.2%)		1,260 (35.9%)	1,001 (28.5%)	
2016-2017	1,722 (45.1%)	5,828 (55.1%)		1,545 (44.0%)	1,844 (52.5%)	
2018-2019	757 (19.8%)	1,240 (11.7%)		708 (20.2%)	668 (19.0%)	

DAA, direct-acting antiviral; FIB-4, Fibrosis-4 index for liver fibrosis; HCV, hepatitis C virus; IQR, interquartile range; PI, protease inhibitor; RNA, ribonucleic acid; SDP, standardized difference in proportion

* Includes glecaprevir/pibrentasvir, elbasvir/grazoprevir, or paritaprevir/ritonavir/ombitasvir with or without dasabuvir

† Includes sofosbuvir/ledipasvir or sofosbuvir/velpatasvir

‡ MELD score calculation: 3.78 x ln[total bilirubin (mg/dL)] + 11.2 x ln[INR] + 9.57 x ln[creatinine (mg/dL)] + 6.43

Table 3. **Absolute risk and unadjusted incidence rates of specified acute liver injury outcomes among propensity score-matched protease inhibitor (PI) and non-PI initiators, by baseline advanced hepatic fibrosis/cirrhosis status by FIB-4.** Incidence rates are reported as events per 1,000 person-years.

Regimen	No. Exposed	ALT >200 U/L			Severe Hepatic Dysfunction*			Hepatic Decompensation†		
		No. Events	Absolute Risk	Incidence Rates (95% CI)	No. Events	Absolute Risk	Incidence Rates (95% CI)	No. Events	Absolute Risk	Incidence Rates (95% CI)
FIB-4 ≤3.25										
PI-based	14,985	71	0.47%	16.96 (13.44-21.40)	4	0.03%	0.95 (0.36-2.54)	5	0.03%	1.19 (0.50-2.86)
Gle/Pib	4,739	5	0.11%	4.42 (1.84-10.61)	1	0.02%	0.88 (0.12-6.27)	0	0.00%	-
Elb/Gra	5,938	17	0.29%	9.57 (5.95-15.39)	2	0.03%	1.12 (0.28-4.50)	1	0.02%	0.56 (0.08-3.99)
PRO/PROD	4,308	49	1.1%	38.35 (28.98-50.74)	1	0.02%	0.78 (0.11-5.52)	4	0.09%	3.11 (1.17-8.29)
Non-PI-based	14,985	18	0.12%	4.23 (2.66-6.71)	6	0.04%	1.41 (0.63-3.13)	5	0.03%	1.17 (0.49-2.82)
Sof/Led	12,711	14	0.11%	3.91 (2.31-6.60)	4	0.03%	1.12 (0.42-2.97)	5	0.04%	1.39 (0.58-3.35)
Sof/Vel	2,274	4	0.18%	5.92 (2.22-15.77)	2	0.09%	2.96 (0.74-11.82)	0	0.00%	-
FIB-4 >3.25										
PI-based	3,513	25	0.71%	24.35 (16.45-36.04)	19	0.54%	18.48 (11.79-28.97)	13	0.37%	12.63 (7.33-21.75)
Gle/Pib	691	2	0.29%	10.92 (2.73-43.65)	1	0.14%	5.45 (0.77-38.70)	0	0.00%	-
Elb/Gra	1,356	5	0.37%	12.40 (5.16-29.79)	3	0.22%	7.43 (2.40-23.04)	3	0.22%	7.43 (2.40-23.03)
PRO/PROD	1,466	18	1.2%	40.88 (25.76-64.89)	15	1.0%	34.03 (20.51-56.44)	10	0.68%	22.63 (12.17-42.05)
Non-PI-based	3,513	12	0.34%	11.17 (6.35-19.67)	16	0.46%	14.92 (9.14-24.35)	16	0.46%	14.91 (9.13-24.34)
Sof/Led	2,943	10	0.34%	11.13 (5.99-20.69)	13	0.44%	14.49 (8.41-24.95)	15	0.51%	16.71 (10.07-27.72)
Sof/Vel	570	2	0.35%	11.40 (2.85-45.57)	3	0.53%	17.12 (5.52-53.09)	1	0.18%	5.70 (0.80-40.48)

ALT, alanine aminotransferase; CI, confidence interval; Elb, elbasvir; FIB-4, Fibrosis-4 Index for Hepatic Fibrosis; Gle, glecaprevir; Gra, grazoprevir; Led, ledipasvir; PI, protease inhibitor; Pib, pibrentasvir; PRO, paritaprevir/ritonavir/ombitasvir; PROD, paritaprevir/ritonavir/ombitasvir with dasabuvir; Sof, sofosbuvir; Vel, velpatasvir

* Severe hepatic dysfunction defined by 1 inpatient or outpatient international normalized ratio ≥1.5 and total bilirubin >2 times the upper limit of normal within 30 days of each other.

† Hepatic decompensation defined by 1 hospital discharge diagnosis or 2 or more outpatient diagnoses of ascites, spontaneous bacterial peritonitis, esophageal variceal hemorrhage, or hepatic encephalopathy. The decompensation date was defined as the hospital discharge date (if event was identified by hospital diagnosis) or initial outpatient diagnosis date (if identified by outpatient diagnoses).

PI-Based HCV DAAs Are Associated with Increased Risk of Aminotransferase Elevations but Not Hepatic Dysfunction or Decompensation

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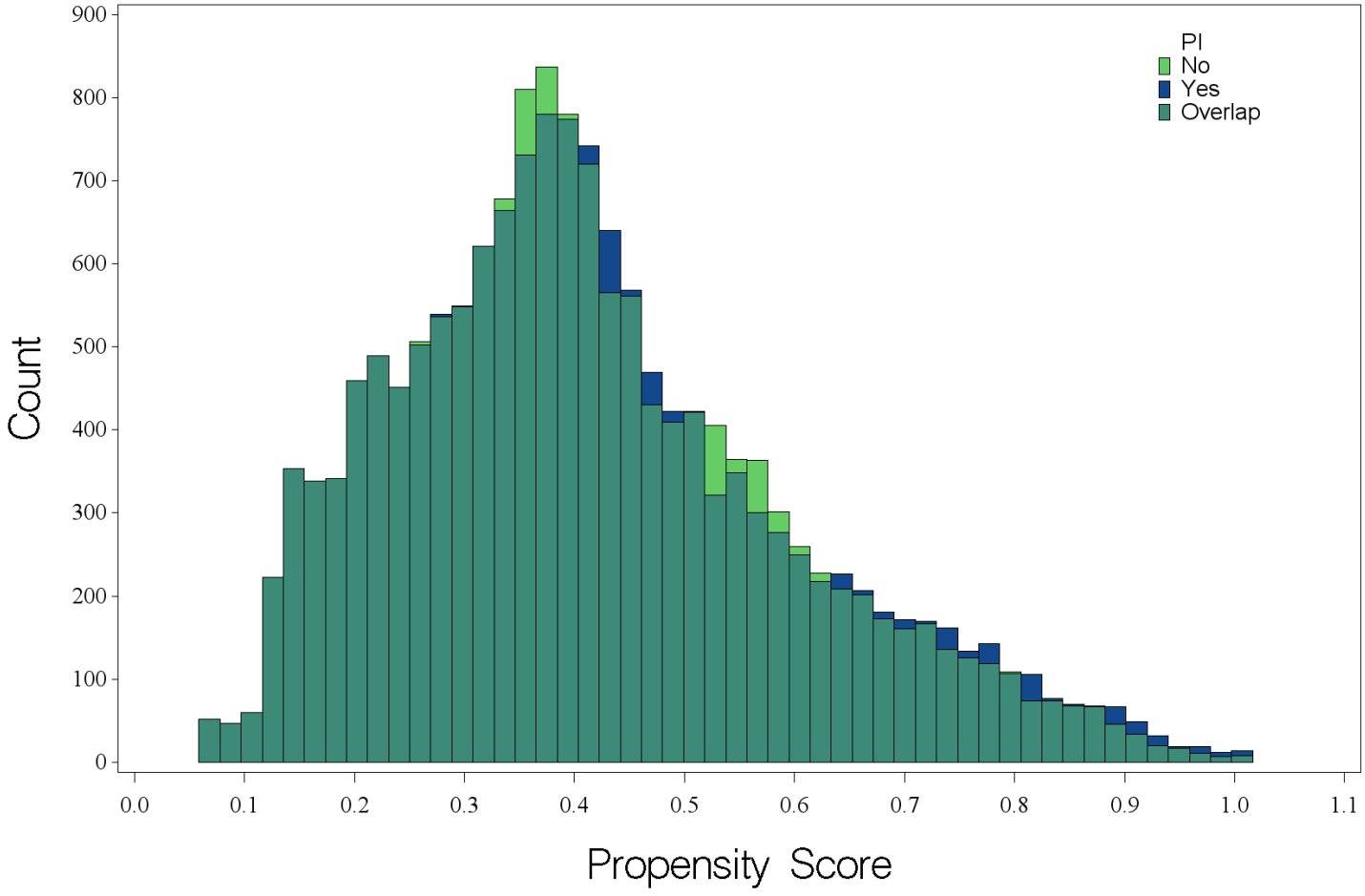
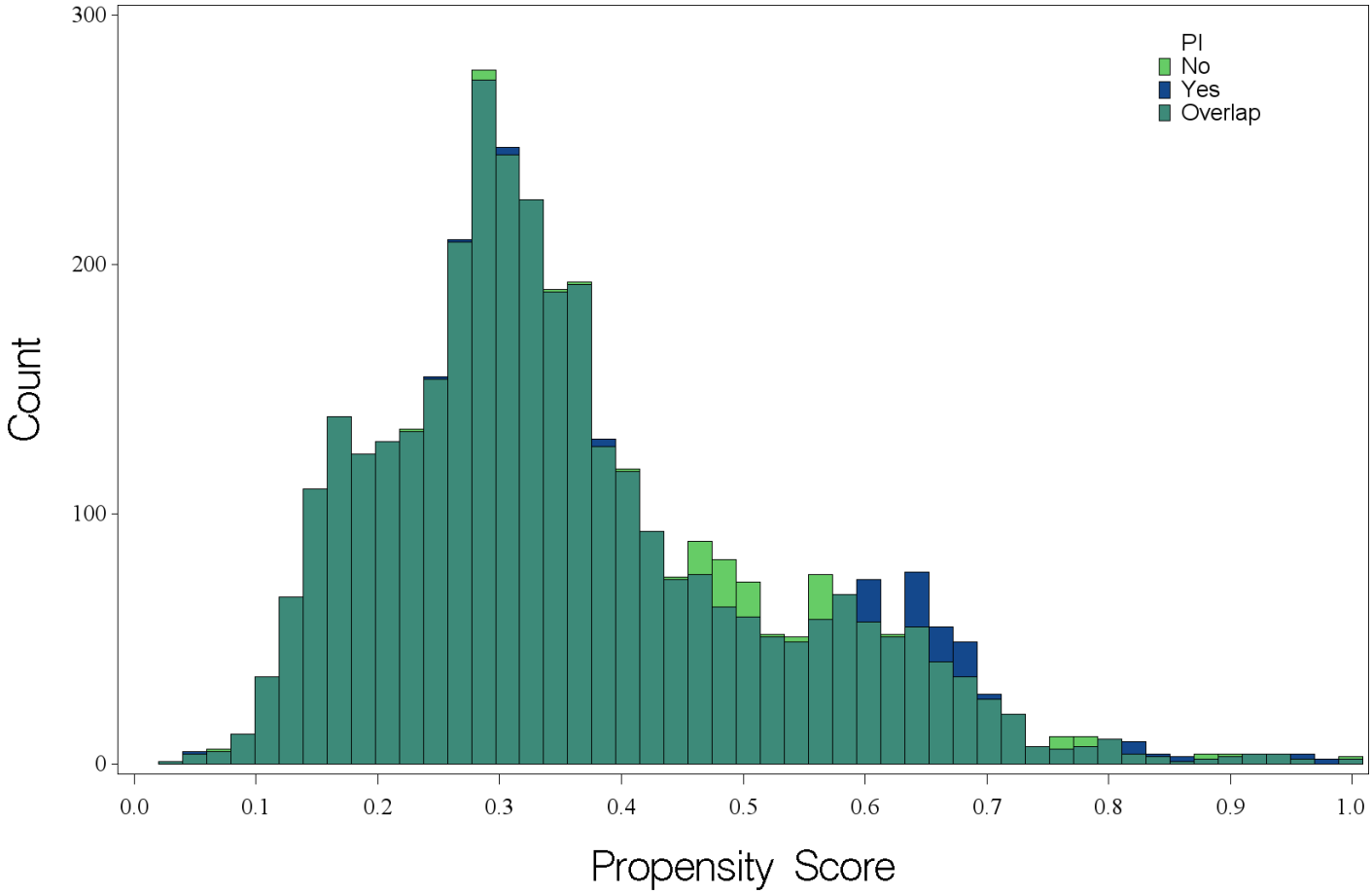
Supplementary Figure 1. Propensity score histogram by protease inhibitor (PI)-based and non-PI-based direct-acting antiviral (DAA) therapy for patients with FIB-4 ≤3.25. Distribution illustrated as percent of patients receiving PI-based (light green) and non-PI-based (blue) DAA therapy by propensity score and overlap (dark green) of these two groups.



Supplementary Figure 2. Propensity score histogram by protease inhibitor (PI)-based and non-PI-based direct-acting antiviral (DAA) therapy for patients with FIB-4 >3.25. Distribution illustrated as percent of patients receiving PI-based (light green) and non-PI-based (blue) DAA therapy by propensity score and overlap (dark green) of these two groups.



Supplementary Table 1. International Classification of Diseases, Ninth Revision (ICD-9) and International Classification of Diseases, Tenth Revision (ICD-10) diagnoses used to identify hepatic decompensation events among protease inhibitor and non-protease inhibitor-based direct-acting antiviral initiator cohorts.

ICD-9 Code(s)	ICD-10 Code(s)	Description
456.0; 456.2	I85.01; I85.11	Esophageal Varices With Bleeding
567.23	K65.2	Spontaneous Bacterial Peritonitis
572.2	K70.41; K72.11; K72.91	Hepatic Coma; Hepatic Failure With Coma
789.5; 789.59	K70.11; K70.31; K71.51; R18.8	Ascites
572.4	K76.7	Hepatorenal Syndrome
--	K76.81	Hepatopulmonary Syndrome

Supplementary Table 2. Frequencies of specific hepatic decompensation diagnoses among propensity score-matched protease inhibitor (PI) and non-PI initiators, by baseline advanced hepatic fibrosis/cirrhosis status by FIB-4.

Regimen	Bleeding Esophageal Varices	Spontaneous Bacterial Peritonitis	Hepatic Coma	Ascites	Hepatorenal Syndrome	Hepatopulmonary Syndrome
FIB-4 ≤3.25						
PI-based	0	1	0	3	1	0
Non-PI-based	1	0	0	4	0	0
FIB-4 >3.25						
PI-based	3	0	3	7	0	0
Non-PI-based	4	1	1	9	0	1

FIB-4, Fibrosis-4 index for liver fibrosis; PI, protease inhibitor