Real-world effectiveness of sofosbuvir/velpatasvir for treatment of chronic hepatitis C in British Columbia, Canada: A population-based cohort study

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ABSTRACT

Background: Clinical trials show high efficacy of sofosbuvir/velpatasvir (SOF/VEL) but there is limited data from ‘real-world’ settings. We aimed to evaluate SOF/VEL effectiveness for all HCV genotypes (GTs) in British Columbia (BC), Canada.

Methods: We used the BC Hepatitis Testers Cohort, which includes all HCV cases in the province (1990-2015) linked to administrative databases, including prescriptions to end of 2018. We measured sustained virologic response (SVR; negative RNA ≥10 weeks after treatment end) and identified characteristics associated with non-SVR. Conservatively, we excluded individuals with no assessment for SVR if their last RNA test after treatment initiation was negative (but included if positive).

Results: Of 2,821 eligible participants, most were infected with GT1 (1076, 38.1%) or GT3 (1072, 38.0%) and a minority (278, 9.9%) treated with RBV. SVR was 94.6% (2670/2821) overall and 94.5% (1017/1076) for GT1, 96.4% (512/531) for GT2 and 93.7% (1004/1072) for GT3. When disaggregated by GT, treatment regimen and cirrhosis/treatment-experience, SVR was lowest (30/40, 75.0%) among treatment-experienced GT3 individuals treated with RBV. Characteristics associated with non-SVR in multivariable analysis included younger age, RBV addition, and being a person living with HIV (PLWH) or who injects/injected drugs (PWID). When treatment regimen (±RBV) was removed from multivariable model, treatment-experience was associated with non-SVR for GT3. Of 151 non-SVR individuals, 56.3% were non-virological failures (treatment incomplete/no assessment for SVR) and 43.7% were virological failures (non-response/relapse). A disproportionately high percentage of non-SVR among PWID was due to non-virological failure.

Conclusions: SOF/VEL was highly effective in this ‘real-world’ population-based cohort.
Additional supports are required for PWID/PLWH to reach SVR.

KEY WORDS: Hepatitis C; Treatment effectiveness; Observational Study; Administrative data; Sofosbuvir; Velpatasvir; Ribavirin
INTRODUCTION

Hepatitis C virus (HCV) and its associated morbidity and mortality is a significant public health issue in Canada and globally.\(^1,2\) In the absence of effective treatment, about 75% of individuals infected with HCV advance to chronic infection and 10-15% of chronically infected individuals develop liver cirrhosis within 20 years.\(^3\) People with cirrhosis are at higher risk of end stage liver disease and death.

Second generation oral direct acting antivirals (DAAs) are short course (8-24 weeks), have fewer adverse effects, and can cure more than 95% of people with HCV. This high cure rate and ease of use led the World Health Organization to issue the first Global Health Sector Strategy on Viral Hepatitis with the aim of eliminating HCV as a major public health issue by 2030.\(^4\) Sofosbuvir/velpatasvir (SOF/VEL) is the first of these DAAs to be pan-genotypic and require a single pill taken once daily. Registration SOF/VEL clinical trials published in 2015 demonstrated sustained virologic response (SVR) rates exceeding 97% for all genotypes (GTs) except for GT3 (94.7%).\(^5-10\) In 2016, SOF/VEL was approved by regulatory agencies in the United States (Food and Drug Administration), Canada (Health Canada) and the European Union (European Commission).\(^11,12\)

Although clinical trials show high efficacy of SOF/VEL, actual SVR in real-world clinical settings could be lower due to differences in patient populations, resources, and adherence to best practices.\(^13,14\) However, few large published studies have evaluated SOF/VEL in real-world settings using conservative intention to treat (ITT) approaches\(^15\) and, to the best of our knowledge, none have used a population-based data source (i.e. included all treated individuals within a jurisdiction). Conservative analytic approaches do not exclude individuals
lost to follow-up and are critical for understanding real-world factors contributing to lack of SVR.\textsuperscript{9,15} Conservative, real-world studies are particularly important to evaluate effectiveness in populations who often experience worse treatment outcomes for biological and/or social reasons, including people with cirrhosis, decompensated disease, HCV treatment-experience, GT3 infection and/or people who inject drugs. Further, there is limited data available from real-world settings on the effectiveness of SOF/VEL against various genotypes and it is unclear from real-world experience whether the addition of ribavirin (RBV) to SOF/VEL improves SVR.\textsuperscript{15–17} Finally, lack of population-based analyses limits generalizability of study results to all real-world practice within a jurisdiction. Therefore, additional studies are needed to evaluate SOF/VEL effectiveness outside of controlled clinical trial settings to inform decisions at the clinician, programming and policy levels.

In this study, we use a large population-based cohort and a conservative analytic approach to evaluate the effectiveness SOF/VEL±RBV in real-world clinical practice in British Columbia (BC).

\textbf{PATIENTS AND METHODS}

\textbf{Setting}

BC is Canada’s third largest province with a population of almost 5 million in 2018. The province’s rate of 48.5 new HCV diagnoses per 100,000 people is 55\% higher than the national rate and the 2\textsuperscript{nd} highest in the country.\textsuperscript{18} SOF/VEL became available in BC on July 14, 2016. Public coverage of SOF/VEL for certain populations started on April 2017 and was expanded to all HCV-positive individuals on April 2018.\textsuperscript{19–21} SOF/VEL±RBV is prescribed for treatment of all genotypes for 12 weeks. Treatment decisions are made at the clinician’s discretion, with...
decisions guided by Canadian (CASL), American (AASLD) or European (EASL) guidelines. In general, the addition of RBV to SOF/VEL is considered standard of care for decompensated patients, and is also accessible for those with GT3 cirrhosis.

Data sources

We used data from the BC Hepatitis Testers Cohort (BC-HTC). Details of cohort creation and epidemiological characteristics have been reported previously. The BC-HTC inclusion criteria and data sources are also summarized in Supplementary Table 1. In brief, the cohort includes all individuals tested for HCV or human immunodeficiency virus (HIV), or reported as a case of hepatitis B virus (HBV), HCV, HIV or active tuberculosis, in BC between 1990 and 2015. These data are integrated with medical visits, hospitalizations, cancers, prescription drugs, deaths and BC Centre for Disease Control Public Health Laboratory (BCCDC-PHL) testing data. The dataset used for this analysis included prescription and death data updated until the end of 2018 and BCCDC-PHL HCV laboratory tests updated to April 9, 2019.

All residents in BC are registered in the publicly funded insurance plan that acts as a single payer system and covers services provided by fee for service practitioners. HCV screening and RNA testing for the entire province is performed at BCCDC-PHL except for <5% of screening tests performed at a regional laboratory which sends positive tests to BCCDC-PHL for confirmation and HCV RNA testing. All dispensed prescriptions in the province, including HCV treatments, are recorded in a central system called PharmaNet.

Study population and treatment

In this analysis, we included HCV-positive individuals who were in the cohort as of the end of 2015. HCV-positive individuals were defined as those who had tested positive for HCV
antibodies, had undergone HCV RNA or genotype testing, or were reported as a case of HCV to public health. Our datasets included data on SOF/VEL treatment to Dec 31, 2018 and HCV RNA testing data to April 9, 2019. To allow for adequate follow-up time (at least 12 weeks to assess treatment completion and 12 weeks to assess SVR), we excluded individuals initiating SOF/VEL after October 9, 2018.

**Modified intention-to-treat analysis and SVR definition**

Achievement of SVR was defined as record of a negative (below lower limit of detection) HCV RNA ≥10 weeks after treatment end. As in other studies, a 10 week time period instead of 12 weeks was chosen to account for variability in testing in clinical practice. Of individuals with an RNA test at week 10 or later in our data, only 1.9% (52/2750) were tested at weeks 10-11 and not ≥12 weeks.

Our modified ITT approach and non-SVR definition were conservative, similar to others. We excluded those with 1) no RNA test after treatment initiation or 2) a negative RNA test on their last test (either while on treatment or after treatment end) but no assessment for SVR (ie. no RNA test ≥10 weeks after treatment end). Participants included in the analysis were categorized as not achieving SVR (non-SVR) if they had: 1) any detectable HCV RNA after the end of treatment, 2) a positive RNA test during treatment and no viral load test after the end of treatment, or 3) a detectable HCV RNA on their last HCV viral load test (either while on treatment or within 10 weeks of the treatment end). Therefore, individuals with no assessment for SVR were excluded if their last RNA test was negative, but included if the RNA test was positive.
Plasma HCV RNA levels were determined using the Abbott RealTime HCV assay (Abbott Molecular Inc., Mississauga ON) with a lower limit of detection for HCV RNA of 12 IU/mL.

**Non-SVR categories**

We assessed the most likely reason for non-SVR using five hierarchical, mutually-exclusive categories. A completed treatment course was defined as ≥12 weeks of treatment and SVR assessment as a positive/negative RNA test ≥10 weeks after treatment end. The categories were defined as follows:

A) Non-virological failures (criteria: treatment incomplete and/or no assessment for SVR, and received a positive RNA test after treatment initiation)

1. Incomplete treatment (for reasons other than death): Individuals who did not complete treatment and did not die within 12 weeks of treatment initiation.

2. Death prevented treatment completion / SVR assessment: Individuals who did not receive SVR assessment and died either during treatment or within 14 weeks after treatment end.

3. Lost to follow-up (LTFU; for reasons other than death): Individuals who completed treatment, did not receive SVR assessment and did not die either during treatment or within 14 weeks after treatment end.

B) Virological failures (criteria: completed treatment and received a positive RNA test ≥10 weeks after treatment end)
4. Relapse: Individuals who received a negative RNA test either during or after treatment (but before 10 weeks after treatment end).

5. Non-response: Individuals who did not receive a negative RNA test either during or after treatment.

Assessment of covariates

Demographic characteristics included sex, age, birth cohort and social and material deprivation quintiles. Assessment of diabetes, history of injecting drugs, major mental illness, cirrhosis, decompensated cirrhosis, and problematic alcohol use was based on algorithms derived from medical visits, hospitalization or prescription dispensation data using fee-for-service, procedure, and/or diagnostic codes (Supplementary Table 2).

Analysis

We computed SVR overall and by GT, and compared the proportion achieving SVR across a range of participant characteristics. We performed multivariable logistic regression analyses to identify predictors of non-SVR.

All analyses were conducted in [SAS/STAT] Software version 9.4 and all tests were two-sided at a significance level of 0.05. This study was approved by the University of British Columbia Research Ethics Board (H14-01649).

RESULTS

Overall, 3,911 unique HCV-positive individuals initiated SOF/VEL±RBV treatment on or prior to Dec 31, 2018 (Fig 1). Of 3,442 with adequate follow-up time (initiated treatment on or prior to October 9, 2018), a total of 621 (18.0%) were excluded. Differences between included and
excluded individuals are shown in Supplementary Table 3. Of note, excluded individuals (particularly those with a negative RNA test) were more likely to be PWID.

A total of 2,821 eligible participants were included in the study and their characteristics are shown in Table 1. Most were infected with either GT1 (38.1%) or GT3 (38.0%), followed by GT2 (18.8%) and GT4-6 (5.1%). The majority of participants were male (62.6%), White (90.6%), aged 50+ years (76.3%) and born between 1945 and 1964 (65.3%)

HCV treatment

Overall, 98.0% of participants completed a treatment course 12 weeks or greater and 278 (9.9%) were treated with RBV. Treatment completion was lower for non-SVR vs. SVR (86.1% vs. 98.6%, p<0.0001) and SOF/VEL+RBV vs. SOF/VEL alone (94.6% vs. 98.3%, p<0.0001). Of non-SVR individuals who lacked SVR assessment due to death/LTFU, 82.5% had completed treatment. Differences between individuals treated with vs. without RBV are shown in Supplementary Table 4.

SVR rates

SVR was 94.6% (2670/2821) overall and 94.5% (1017/1076) for GT1, 96.4% (512/531) for GT2 and 93.7% for GT3 (1004/1072) (Table 2). For GT1, SVR was lowest for individuals with HIV co-infection (84.3%, 75/89), recent opioid substitution therapy (87.2%, 197/226), cirrhosis (88.5%, 23/26), decompensated cirrhosis (88.9%, 16/18) and history of injecting drugs (89.2%, 338/379). For GT3, SVR was lowest for those who were born pre-1945 (79.2%, 19/24), treated with RBV (87.0%, 120/138) and HCV treatment-experienced (89.8%, 123/137).
Figure 2A shows the percent achieving SVR by treatment regimen, GT and cirrhotic state. SVR rates were 90% or higher for all populations except GT1 cirrhotic patients treated with RBV (84.6%, 11/13) and GT3 non-cirrhotic patients treated with RBV (86.0%, 98/114). In contrast to the latter, GT3 non-cirrhotic patients treated without RBV had an SVR rate of 94.6% (856/905).

Figure 2B shows the percent achieving SVR by treatment regimen, GT and HCV treatment history. SVR rates were 90% or higher for all populations except for treatment-experienced GT3 patients treated with RBV (75.0%, 30/40). In further analysis of the latter, SVR was 88.9% (16/18) for those previously treated with DAAs and 63.6% (14/22) for those treated with interferon-based regimens. In contrast, treatment-experienced GT3 patients treated without RBV had an SVR rate of 95.9% (93/97).

In sensitivity analyses, inclusion of the 293 excluded individuals with a negative RNA test but no SVR assessment increased the SVR rate (if assumed to have achieved SVR) from 94.6% to 95.2% overall and from 91.6% to 93.5% among PWID – who are disproportionately represented among this excluded population. Of note, 98.6% of the 293 excluded individuals had completed ≥12 weeks of treatment and the median (interquartile range, IQR) time from treatment initiation to negative RNA test was 15 (IQR=13-18) weeks.

Predictors of non-SVR

Characteristics associated with non-SVR in multivariable models are shown in Table 3. In the overall model, age younger than 50 years (vs. >60, aOR=1.58, 95%CI 1.00-2.48), history of injecting drugs (aOR=2.35, 95%CI 1.51-3.66), HIV co-infection (aOR=1.67, 95%CI 1.02-2.75) and treatment with RBV (vs. SOF/VEL alone, aOR=1.93, 95%CI 1.19-3.13) were associated
with non-SVR. In GT1- and GT3-specific models, factors associated with non-SVR included history of injecting drugs (GT1, GT3), HIV co-infection (GT1) and treatment with RBV (GT3). GT, cirrhosis and HCV treatment-experience were not associated with non-SVR in any model.

In sensitivity analyses, model results were largely unchanged when the treatment regimen variable (SOF/VEL+RBV vs. SOF/VEL alone) was removed from the models (data not shown), with one exception. After removal of treatment regimen from the GT3 model, treatment-experience was associated with non-SVR (vs. treatment-naïve, aOR=2.03, 95%CI=1.06-3.89). Further, an interaction term between treatment regimen and HCV treatment-experience was significant in the full and GT3-specific models (data not shown). The interaction showed that SOF/VEL+RBV (vs. SOF/VEL alone) was associated with non-SVR in treatment-experienced individuals (aOR=11.5, 95%CI 3.2-41.6, full model) but not treatment-naïve individuals (aOR=1.9, 95%CI 0.8-4.2, full model). In an additional sensitivity analysis, models results were also largely unchanged when the 293 excluded individuals (negative RNA test post-treatment initiation but no SVR assessment) were included and assumed to have achieved SVR (data not shown).

Reasons for non-SVR

A total of 151 individuals did not achieve SVR. Overall, 56.3% were non-virological failures and 43.7% were virological failures. The underlying reasons for non-SVR were as follows: 18 (11.9%) did not complete treatment (for reasons other than death), death prevented treatment completion and/or SVR assessment for 7 (4.6%) individuals, 60 (39.7%) completed treatment but lacked SVR assessment (LTFU), 26 (17.2%) relapsed and 40 (26.5%) were non-responders. A total of 86.1% of non-virological failures completed a treatment course ≥12 weeks. Median
(IQR) duration of treatment was 4 (4-8) weeks for those who did not complete treatment. Among all non-virological failures, median (IQR) time from treatment initiation to positive RNA test was 11 (5-16) weeks.

Comparison of SVR and non-SVR populations by select characteristics is shown in Supplementary Tables 5 and 6. Of note, people who inject/injected drugs (PWID) composed 35.0% of the SVR population but 57.0% of non-SVR cases (63.5% of non-virological failures and 48.5% of virological failures; 62.8% of non-SVR among PWID was due to non-virological failure).
DISCUSSION

In this real-world population-based analysis of approximately 2,800 individuals treated with SOF/VEL±RBV who were mostly infected with GT1 or GT3, SVR rates were high although lower than observed in clinical trials. SVR rates in our study ranged from 93.7% for GT3 to 96.4% for GT2. In comparison, SVR12 rates in a pooled meta-analysis of six clinical trials ranged from 94.7% for GT3 to 99.4% for GT2. While the overall SVR rate in our study was lower for GT3-infected individuals, there was no statistically significant association between GT3 and non-SVR in multivariable analysis.

Our results are similar to the small number of large studies evaluating SOF/VEL effectiveness in real-world settings. In the largest real-world analysis published to date, Belperio et al. evaluated SOF/VEL±RBV among approximately 4,500 individuals with GT2 or GT3 infection in the US Department of Veterans Affairs registry. Similar to our study, effectiveness ranged from 90.7% for GT3 to 93.9% for GT2. In another large but unpublished study of 12 clinical practice cohorts across 8 countries in North America and Europe (n=4,491), overall SVR was 92.7%. In contrast, SVR was higher (98.5%) in a study of 1,319 patients from treatment centres in Italy. Seven other published real-world studies have evaluated SOF/VEL, but most were small and had a combined sample size of less than 1000.

Comparisons to other real-world studies should be made with caution. “Real-world” is a broad term for describing studies conducted outside of a clinical trial setting, yet there are important differences between studies. Some are not population-based but instead limited to specific treatment centers, registries or patient populations. Further, some studies use less conservative analytic approaches in which most/all individuals lacking SVR assessment are
excluded. For example, the Belperio et al. study was limited to patients receiving medical care through the Veterans Health Administration and excluded GT1-infected patients;\textsuperscript{15} the combined North America/Europe analysis excluded individuals with decompensated cirrhosis, previous DAA failure, and RBV added to their regimen;\textsuperscript{27} and the Italian study enrolled patients from treatment centers where closer monitoring was provided and excluded those with previous NS5A inhibitor therapy.\textsuperscript{17} In comparison to all three of these large studies, our analysis was population-based and thus potentially more generalizable to the real-world clinical setting. Given our more real-world setting and conservative approach, it is reassuring that our SVR rates were similarly high as observed in these other studies.

Our conservative analytic approach allowed for greater insight into underlying reasons for actual or potential non-SVR. Just over half of non-SVR cases were non-virological failures and about 80\% of these lacked SVR assessment and were assumed non-SVR. These individuals would be excluded from per-protocol (PP) analyses. Most non-SVR individuals were categorized as LTFU (treatment completed, last RNA test after treatment initiation was positive, no assessment for SVR). It is reasonable to assume that many of these individuals did not reach SVR, given the positive RNA test and that some of the same factors contributing to their loss to follow-up may have also impeded adherence to daily medication (e.g. housing instability, substance use, mental health issues). Even for those who did attain SVR, these individuals are still important to characterize as they may be at higher risk of re-infection due to challenges in remaining connected to the healthcare system and potentially receiving supports to prevent re-infection. Our non-virological failure rate was lower than the combined analysis of 12 cohorts in North America/Europe, where 80\% of non-SVR cases were non-virological.\textsuperscript{27} This may be partly due to their use of SVR12/24 rather than SVR10.
PWID and people living with HIV (PLWH) had lower SVR after adjustment for other factors. Notably, however, SVR rates for PWID and PLWH were higher than 92% for GT2 and GT3 but lower (89% and 84%, respectively) for GT1. Clinical trials have also demonstrated high SVR rates (≥94%) for SOF/VEL among PWID and PLWH. However, similar to our analysis and other analyses conducted by our team, the large Italian SOF/VEL real-world study found PWID to be associated with non-SVR. Increased odds of non-SVR among PWID and PLWH are likely due to social rather than biological factors. Indeed, a particularly high percentage of non-SVR among PWID was due to non-virological vs. virological failure, similar to our previous analyses of other HCV treatments. Of note, our analysis likely underestimates the true SVR rate among PWID as some of these non-virological failures may have achieved SVR, and PWID were also overly represented among excluded individuals who had a negative RNA test post-treatment initiation but no SVR assessment. Our findings should not be interpreted as a reason to withhold treatment from these populations, but rather a reminder that optimal scale-up to reach HCV elimination among PWID and PLWH will need to be done with additional support measures to prevent LTFU and achieve SVR.

Our study found RBV to be associated with non-SVR among GT3-infected individuals. These findings are similar to other real-world observational SOF/VEL studies suggesting little to no benefit with the addition of RBV, but contradict results from clinical trials. The lower SVR among RBV-treated individuals in our study was particularly noticeable for GT3-infected individuals with treatment-experience (75% achieved SVR). The contrasting findings between real-world studies and clinical trials may be due to a number of factors, including different patient populations, study designs and analytic approaches (PP vs. ITT). In particular, evaluation of RBV is limited by the observational nature of real-world studies such as ours (e.g. RBV is
more likely to be prescribed to individuals who are already less likely to achieve SVR), particularly when important confounding variables may be under-identified due to reliance on administrative data. For example, in our analysis, 80% of RBV-treated individuals had no evidence of cirrhosis (Supplementary Table 4), a key indication for RBV in BC. This finding is more likely to be due to under-identification of cirrhosis (due to reliance on diagnostic codes and lack of fibrosis assessment data) rather than inappropriate prescribing of RBV. As a result, residual confounding by indication may explain the lower SVR with RBV, although another real-world study found no benefit of RBV after controlling for FIB-4 score. In Further research is needed to better understand the underlying reasons for non-SVR among RBV-treated individuals and the utility of adding this medication in the real-world.

GT3 infection, treatment-experience and cirrhosis were not associated with non-SVR in our full multivariable model. In contrast, the large real-world Belperio et al. study found decompensated cirrhosis, FIB-4>3.25, and treatment-experience to be associated with reduced odds of SVR among GT3 patients treated with SOF/VEL or Daclatasvir/SOF. Another real-world SOF/VEL study found lower SVR among GT3-infected individuals previously treated with SOF-based regimens. Our ability to detect a difference may have been limited by the small sample size of some of these populations which, as already discussed, may be an artifact of our data source. Notably, treatment-experience was associated with non-SVR in our full and GT3-specific multivariable models when the treatment regimen variable (SOF/VEL+RBV vs. SOF/VEL alone) was removed.

Our study had some limitations. While our analysis was population-based for individuals in BC diagnosed with HCV to end of 2015 and dispensed SOF/VEL from 2016 to 2018, it did not include individuals who were newly tested and diagnosed from 2016 to 2018. We estimate...
that about 2000 individuals were newly diagnosed with HCV in this three year timeframe, but that most would not have received treatment with SOF/VEL by end of 2018. Our data did not contain any information on clinical fibrosis stage; previous HCV treatments received outside of BC; resistance associated substitutions; underlying reasons for treatment discontinuation (e.g. side-effects), LTFU or RNA testing; or adherence to daily pill-taking among those dispensed a full treatment course. As a result of the latter, we could not estimate the proportion of non-response due to suboptimal adherence. Furthermore, we are also not able to tease apart relapse from re-infection, which requires genome sequencing. Since most of our variables were based on administrative data, misclassification / under-ascertainment may have led to residual confounding in regression analyses. Treatment decisions in BC are made at the clinician’s discretion and may differ from other settings, where norms are different, limiting generalizability of our findings to other jurisdictions (e.g. differences in RBV use and GTs). Finally, while ITT and PP are terms commonly used in real-world observational studies, they were originally intended for describing randomized controlled trials. As such, it is important to emphasize that our analysis was observational and thus confounding could not be completely addressed.

In conclusion, our conservative population-based analysis of SOF/VEL showed high effectiveness in real-world clinical practice in the Canadian province of BC. Our results suggest room for further improvement in supporting individuals to obtain SVR and prevent LTFU, particularly among PWID and PLWH. The high proportion of non-SVR due to non-virological failure demonstrates the importance of a conservative analytic approach when conducting real-world studies. The lower SVR observed with RBV in our study may be due to residual confounding and requires further investigation.
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DISCLAIMER

All inferences, opinions, and conclusions drawn in this manuscript are those of the authors, and do not reflect the opinions or policies of the British Columbia Ministry of Health and the Data Steward(s).

CONFLICT OF INTEREST STATEMENT

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AUTHORSHIP STATEMENT

NJ conceived the analysis presented in this paper. NJ, AY, MA, MK participated in the study design. NJ guided the statistical analysis performed by SW and JW. JW wrote the first draft and incorporated revisions. All authors contributed in the interpretation of results, manuscript preparation and revisions. All authors read and approved the final manuscript.
DATA AVAILABILITY

Data not publicly available.
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Table 1. Characteristics of cohort participants treated with SOF/VEL±RBV by genotype, BC Hepatitis Testers Cohort, 2016 to 2018

|                          | Overall n(%) | GT1 n(%) | GT2 n(%) | GT3 n(%) |
|--------------------------|--------------|----------|----------|----------|
| **Total (N)**            | 2821         | 1076     | 531      | 1072     |
| **Birth Cohort**         |              |          |          |          |
| <1945                    | 104(3.7)     | 26(2.4)  | 36(6.8)  | 24(2.3)  |
| 1945-1964                | 1843(65.3)   | 734(68.2)| 408(76.9)| 621(58)  |
| 1965-1974                | 525(18.6)    | 200(18.6)| 64(12)   | 237(22.1)|
| ≥1975                    | 349(12.4)    | 116(10.8)| 23(4.4)  | 190(17.7)|
| **Age – median (IQR)**   |              |          |          |          |
| <50                      | 667(23.7)    | 234(21.7)| 60(11.3) | 337(31.4)|
| 50-60                    | 1086(38.5)   | 419(39)  | 187(35.2)| 440(41)  |
| >60                      | 1068(37.8)   | 423(39.3)| 284(53.5)| 295(27.5)|
| **Sex**                  |              |          |          |          |
| Female                   | 1055(37.4)   | 369(34.3)| 225(42.4)| 406(37.9)|
| Male                     | 1766(62.6)   | 707(65.7)| 306(57.6)| 666(62.1)|
| **Ethnicity**            |              |          |          |          |
| White                    | 2555(90.6)   | 1030(95.7)| 493(92.8)| 961(89.7)|
| Others                   | 266(9.5)     | 46(4.3)  | 38(7.2)  | 111(10.4)|
| **Treatment regimen**    |              |          |          |          |
| SOF/VEL                  | 2543(90.2)   | 976(90.7)| 500(94.2)| 934(87.1)|
| SOF/VEL+RBV              | 278(9.9)     | 100(9.3) | 31(5.8)  | 138(12.9)|
| **HCV treatment-experience** | 310(11.0) | 108(10.1)| 51(9.6)  | 137(12.8)|
| **Cirrhosis**            | 105(3.7)     | 26(2.4)  | 21(4.0)  | 53(5.0)  |
| **Decompensated cirrhosis** | 66(2.3)   | 18(1.7)  | 12(2.3)  | 33(3.1)  |
| **OST**                  |              |          |          |          |
| Recent                   | 630(22.3)    | 226(21)  | 59(11.1) | 322(30.1)|
| Past                     | 168(5.9)     | 60(5.6)  | 25(4.7)  | 78(7.3)  |
| None                     | 2023(71.7)   | 790(73.4)| 447(84.1)| 672(62.7)|
| **HBV**                  | 187(6.7)     | 59(5.5)  | 36(6.8)  | 76(7.1)  |
| **HIV**                  | 248(8.8)     | 89(8.3)  | 21(4)    | 123(11.4)|
| **Diabetes**             | 354(12.6)    | 128(11.9)| 71(13.4) | 128(11.9)|
| **History of injecting drugs** | 1021(36.1) | 379(35.2)| 131(24.6)| 478(44.6)|
| **Problematic alcohol use** | 833(29.6) | 333(30.9)| 134(25.2)| 343(32)  |
| **Mental illness**       | 987(35)      | 376(34.9)| 159(29.9)| 423(39.5)|
| **Statin use**           | 357(12.6)    | 140(13)  | 89(16.8) | 102(9.5) |
| **Material deprivation** |              |          |          |          |
| Unknown                  | 34(1.2)      | 15(1.4)  | 5(1)     | 13(1.2)  |
| Q1 (least)               | 384(13.6)    | 146(13.6)| 78(14.6) | 140(13)  |
| Q2                       | 434(15.4)    | 176(16.4)| 99(18.7) | 138(12.9)|
| Q3                       | 539(19.1)    | 198(18.4)| 103(19.4)| 204(19)  |
|       | Q4          | Q5 (most)   |       | Q5 (most)   |
|-------|-------------|-------------|-------|-------------|
|       | 686(24.4)   | 744(26.4)   | 252   | 320(29.9)   |
| Social deprivation |   |             |       |             |
| Unknown | 34(1.2)     | 15(1.4)     | 5(1)  | 13(1.2)     |
| Q1 (least) | 279(9.9)   | 83(7.7)     | 45(8.5) | 126(11.7)  |
| Q2     | 335(11.9)   | 118(11)     | 78(14.7) | 112(10.5)  |
| Q3     | 458(16.3)   | 186(17.3)   | 110(20.8) | 140(13)    |
| Q4     | 628(22.3)   | 248(23)     | 120(22.6) | 231(21.6)  |
| Q5 (most) | 1087(38.6) | 426(39.6)   | 173(32.6) | 450(42)    |
| Elixhauser index |   |             |       |             |
| 0      | 1223(43.4)  | 464(43.1)   | 243(45.8) | 435(40.5)  |
| ≥1     | 1598(56.7)  | 612(56.9)   | 288(54.3) | 637(59.4)  |

Notes: Column percentages shown. OST, opioid substitution therapy; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; IQR, interquartile range; Q, quintile.
Table 2. SVR rates for SOF/VEL±RBV by genotype and participant characteristics, BC Hepatitis Testers Cohort, 2016 to 2018

|                          | GT1 % (n/N) | GT2 % (n/N) | GT3 % (n/N) |
|--------------------------|------------|------------|------------|
| Overall                  | 94.5 (1017/1076) | 96.4 (512/531) | 93.7 (1004/1072) |
| Birth Cohort             |            |            |            |
| <1945                    |            |            |            |
| 1945-1964                |            |            | 79.2 (19/24) |
| 1965-1974                |            |            |            |
| ≥1975                    |            |            |            |
| Age                      |            | 89.7 (210/234) | 88.3 (53/60) |
| <50                      |            |            |            |
| 50-60                    | 96.2 (403/419) | 99.5 (186/187) | 94.8 (417/440) |
| >60                      | 95.5 (404/423) | 96.1 (273/284) | 93.9 (277/295) |
| Sex                      |            |            |            |
| Female                   | 95.9 (354/369) | 96 (216/225) | 95.1 (386/406) |
| Male                     | 93.8 (663/707) | 96.7 (296/306) | 92.8 (618/666) |
| Ethnicity                |            |            |            |
| White                    | 94.4 (972/1030) | 96.6 (476/493) | 93.4 (898/961) |
| Others                   | 97.8 (45/46) | 94.7 (36/38) | 95.5 (106/111) |
| Treatment regimen        |            |            | 87.0 (120/138) |
| SOF/VEL                  | 94.6 (923/976) | 96.2 (481/500) | 94.7 (884/934) |
| SOF/VEL+RBV              | 94.0 (94/100) | 100 (31/31) |            |
| HCV treatment-experience |            |            |            |
| No                       | 94.6 (916/968) | 96.3 (462/480) | 94.2 (881/935) |
| Yes                      | 93.5 (101/108) | 98 (50/51) | 89.8 (123/137) |
| Cirrhosis                |            |            |            |
| No                       | 94.7 (994/1050) | 96.3 (491/510) | 93.6 (954/1019) |
| Yes                      | 88.5 (23/26) | 100 (21/21) | 94.3 (50/53) |
| Decompensated cirrhosis  |            |            |            |
| No                       | 94.6 (1001/1058) | 96.3 (500/519) | 93.5 (971/1039) |
| Yes                      | 88.9 (16/18) | 100.0 (12/12) | 100.0 (33/33) |
| OST                      |            |            |            |
| Recent                   | 87.2 (197/226) | 91.5 (54/59) | 93.8 (302/322) |
| Past                     | 95 (57/60) | 96 (24/25) | 97.4 (76/78) |
| None                     | 96.6 (763/790) | 97.1 (434/447) | 93.2 (626/672) |
| HBV                      |            |            |            |
| No                       | 94.7 (963/1017) | 96.2 (476/495) | 93.7 (933/996) |
| Yes                      | 91.5 (54/59) | 100 (36/36) | 93.4 (71/76) |
| HIV                      |            |            |            |
| No                       | 95.4 (942/987) | 96.5 (492/510) | 93.8 (890/949) |
| Yes                      | 84.3 (75/89) | 95.2 (20/21) | 92.7 (114/123) |
|                        | No         | Yes       | Mean    | SD      |
|------------------------|------------|-----------|---------|---------|
| **Diabetes**           |            |           |         |         |
| No                     | 94.3 (894/948) | 96.1 (442/460) | 94.0 (887/944) |
| Yes                    | 96.1 (123/128)  | 98.6 (70/71)   | 91.4 (117/128)  |
| **History of injecting drugs** |            |           |         |         |
| No                     | 97.4 (679/697)  | 96.8 (387/400) | 94.6 (562/594)  |
| Yes                    | **89.2 (338/379)** | 95.4 (125/131) | 92.5 (442/478)  |
| **Problematic alcohol use** |            |           |         |         |
| No                     | 95.2 (707/743)  | 96.5 (383/397) | 93.3 (680/729)  |
| Yes                    | 93.1 (310/333)  | 96.3 (129/134) | 94.5 (324/343)  |
| **Mental illness**     |            |           |         |         |
| No                     | 94.9 (664/700)  | 96.5 (359/372) | 94.0 (610/649)  |
| Yes                    | 93.9 (353/376)  | 96.2 (153/159) | 93.1 (394/423)  |
| **Statin**             |            |           |         |         |
| No                     | 94.6 (885/936)  | 96.2 (425/442) | 94.0 (912/970)  |
| Yes                    | 94.3 (132/140)  | 97.8 (87/89)   | 90.2 (92/102)   |
| **Material deprivation** |          |           |         |         |
| Unknown                | 100 (15/15)   | **60 (3/5)** | 92.3 (12/13)   |
| Q1 (least)             | 96.6 (141/146) | 93.6 (73/78)  | 94.3 (132/140) |
| Q2                     | 96.6 (170/176) | 97 (96/99)    | 91.3 (126/138) |
| Q3                     | 93.9 (186/198) | 97.1 (100/103)| 95.6 (195/204) |
| Q4                     | 91.9 (250/272) | 99.2 (125/126)| 93.8 (241/257) |
| Q5 (most)              | 94.8 (255/269) | 95.8 (115/120)| 93.1 (298/320)|
| **Social deprivation** |            |           |         |         |
| Unknown                | 100 (15/15)   | **60 (3/5)** | 92.3 (12/13)   |
| Q1 (least)             | 95.2 (79/83)  | 93.3 (42/45)  | 93.7 (118/126) |
| Q2                     | 96.6 (114/118) | 96.2 (75/78)  | 97.3 (109/112) |
| Q3                     | 96.2 (179/186) | 96.4 (106/110)| 90.7 (127/140) |
| Q4                     | 96 (238/248)   | 100 (120/120) | 93.1 (215/231) |
| Q5 (most)              | 92 (392/426)   | 96 (166/173)  | 94.0 (423/450) |
| **Elixhauser index**   |            |           |         |         |
| 0                      | 96.8 (449/464) | 96.3 (234/243) | 94.3 (410/435) |
| ≥1                     | 92.8 (568/612) | 96.5 (278/288) | 93.2 (594/637) |

**Note:** Bold indicates percentage <90%. OST, opioid substitution therapy; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir; Q, quintile. Row percentages shown.
Table 3. Logistic regression analyses assessing characteristics associated with non-SVR among individuals treated with SOF/VEL, BC Hepatitis Testers Cohort, 2016 to 2018

|                     | Overall | GT1             | GT3             |
|---------------------|---------|-----------------|-----------------|
|                     | aOR (95%CI) | aOR (95%CI) | aOR (95%CI) |
| **Age (vs. >60 years)** |         |                 |                 |
| <50                 | 1.58 (1.00-2.48) | 1.23 (0.60-2.56) | 1.82 (0.90-3.68) |
| 50-60               | 0.64 (0.41-1.01) | 0.53 (0.26-1.12) | 0.88 (0.45-1.72) |
| **Sex (male vs. female)** |         |                 |                 |
|                    | 1.41 (0.98-2.02) | 1.79 (0.95-3.35) | 0.67 (0.39-1.17) |
| **HCV treatment-experience (yes vs. no)** |         |                 |                 |
|                    | 1.36 (0.83-2.24) | 1.14 (0.46-2.8) | 1.73 (0.89-3.36) |
| **Cirrhosis (yes vs. no)** |         |                 |                 |
|                    | 1.21 (0.52-2.80) | 2.64 (0.66-10.59) | 0.66 (0.19-2.34) |
| **History of injecting drugs (yes vs. no)** |         |                 |                 |
|                    | 2.35 (1.51-3.66) | 3.82 (1.8-8.12) | 2.32 (1.24-4.36) |
| **OST (vs. none)** |         |                 |                 |
| Recent              | 1.08 (0.70-1.66) | 1.69 (0.85-3.35) | 0.52 (0.27-1.01) |
| Past                | 1.36 (0.83-2.24) | 0.77 (0.21-2.77) | 0.23 (0.05-1.02) |
| **Problematic alcohol use (yes vs. no)** |         |                 |                 |
|                    | 0.74 (0.5-1.09) | 0.72 (0.39-1.34) | 0.61 (0.33-1.12) |
| **HIV (yes vs. no)** |         |                 |                 |
|                    | 1.67 (1.02-2.75) | 2.39 (1.13-5.04) | 1.06 (0.48-2.35) |
| **HBV (yes vs. no)** |         |                 |                 |
|                    | 0.74 (0.37-1.49) | 0.76 (0.26-2.22) | 1.16 (0.43-3.14) |
| **Genotype (vs. GT1)** |         |                 |                 |
| GT2                 | 0.78 (0.46-1.35) | NA              | NA              |
| GT3                 | 1.00 (0.69-1.44) | NA              | NA              |
| GT4-6               | 0.64 (0.25-1.66) | NA              | NA              |
| **SOF/VEL+RBV (vs. SOF/VEL)** | 1.93 (1.19-3.13) | 0.97 (0.38-2.53) | **3.10 (1.67-5.76)** |

Notes: Bold indicates p<0.05, NA, not applicable; OST, opioid substitution therapy; GT, genotype; RBV, ribavirin; SOF, sofosbuvir; VEL, velpatasvir. GT2 not shown. When treatment variable (SOF/VEL vs. SOF/VEL+RBV) removed from model, ‘HCV treatment-experience’ significant for GT3 model (aOR=2.03, 95%CI=1.06-3.89).
FIGURE LEGENDS

Fig 1. Study flow chart, BC Hepatitis Testers Cohort, 2016 to 2018. RNA, ribonucleic acid; SOF, sofosbuvir; VEL, velpatasvir; RBV, ribavirin; SVR, sustained virologic response.

Fig 2. SVR rates by genotype, treatment regimen and A) cirrhotic state or B) HCV treatment-experience, BC Hepatitis Testers Cohort, 2016 to 2018. SOF, sofosbuvir; VEL, velpatasvir; RBV, ribavirin; SVR, sustained virologic response. Cirrhotic individuals includes those with compensated or decompensated cirrhosis. † Denominator less than 15.
Figure 1

Treated with SOF/VEL±RBV (2016-2018)  
N=3,911

Patients with adequate follow-up time  
(Initiated treatment prior to Oct 10, 2018)  
N=3,442

Excluded (N=621)  
- No RNA test after treatment initiation (N=328)  
- Negative RNA test from treatment initiation to 10 weeks after treatment end but no RNA test after (N=293)

Eligible for analysis  
N=2,821

SOF/VEL  
N=2,543
- SVR  
N=2,417  
1. Death (n=7)  
2. Incomplete treatment (n=18)  
3. Lost to follow-up (n=60)  
4. Relapse (n=26)  
5. Non-response (n=40)
- Non-SVR  
N=126

SOF/VEL+RBV  
N=278
- SVR  
N=253
- Non-SVR  
N=25
Figure 2

A)  

- GenoType 1: 92.3% 94.6%
- GenoType 2 SOF/VEL: 100.0% 96.1%
- GenoType 3: 96.6% 94.6%
- GenoType 1 SOF/VEL+RBV: 84.6% 95.4%
- GenoType 2 SOF/VEL+RBV: 100.0% 100.0%
- GenoType 3: 91.7% 96.0%

- Cirrhosis
- No cirrhosis

B)  

- GenoType 1: 94.1% 94.6%
- GenoType 2 SOF/VEL: 97.6% 96.1%
- GenoType 3: 95.9% 94.5%
- GenoType 1 SOF/VEL+RBV: 91.3% 94.8%
- GenoType 2 SOF/VEL+RBV: 100.0% 100.0%
- GenoType 3: 75.9% 91.8%

- Treatment-experienced
- Treatment-naive