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ORIGINAL ARTICLE

Comparing direct acting antivirals for hepatitis C using observational data – Why and how?

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Abstract

The World Health Organisation's goal of hepatitis C virus (HCV) elimination by 2030 will require lower drug prices. Estimates of comparative efficacy promote competition between pharmaceutical companies but direct acting antivirals have been approved for the treatment of HCV without comparative trials. We emulated a randomized trial to answer the question of whether easy to treat patients with genotype 1 HCV could be treated with sofosbuvir/ledipasvir (SOF/LDV) rather than sofosbuvir/velpatasvir (SOF/VEL). Patients without comorbidities or end stage liver disease were selected from the British Colombia Hepatitis Testers Cohort. To create a conceptual trial, we matched each patient starting SOF/VEL (a 'case') to the patient starting SOF/LDV with the closest propensity score (a 'control'). We estimated the probability of treatment failure under a Bayesian logistic model with a random effect for each case-control set and used that model to give an estimate of a risk difference for the conceptual trial. Treatment failure was recorded for 27 of 825 (3%) cases and for 29 of 602 (5%) matched controls. Estimates from our model were treatment success rates of 97% (95% credible interval, CrI, 95%-98%) for treatment with SOF/VEL, 95% (95% CrI 93%-97%) for treatment with SOF/LDV and a risk difference between treatments of 2% (95% CrI 0%-4%). This risk difference is evidence that SOF/LDV is not inferior to SOF/VEL for easy to treat patients with genotype 1 HCV. The approach is a template for comparing drugs when there are no data from comparative trials.

KEYWORDS

Bayesian, comparative effectiveness, direct acting antivirals, elimination, hepatitis C virus, propensity score

Abbreviations: BC, British Colombia; BC-HTC, British Colombia Hepatitis Testers Cohort; CrI, credible interval; DAA, direct acting antiviral; FDA, US Food and Drug Administration; HCV, hepatitis C virus; SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir.

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1 | INTRODUCTION

Direct acting antivirals (DAAs) have been developed and approved for the treatment of hepatitis C virus (HCV) without head-to-head trials comparing different treatments. The US Food and Drug Administration (FDA) prefers at least one pivotal phase III trial comparing a new treatment to a standard treatment,[1] but allows other designs and these have been used instead.[2,3] Many drugs are approved without comparative trials: the FDA has a statutory responsibility to focus on a new drug's safety and efficacy, but there is no requirement for a new drug to be as good as or better than existing alternatives.[4]

As a result, price negotiations between pharmaceutical companies and public and private insurers are taking place without evidence of comparative efficacy. The release of Gilead's generics for sofosbuvir/ledipasvir (SOF/LDV) and sofosbuvir/velpatasvir (SOF/VEL) is evidence that competition is lowering drug prices.[5] However, achieving the World Health Organisation's goal of HCV elimination by 2030 will require still lower drug prices.[6] In general, comparative efficacy data reduce the cost of health care because companies then compete on factors relevant to patient health.[7,8] However, the high cost of DAAs is a barrier to running comparative trials so that realistically only industry and governments are in a position to carry out appropriately powered trials [7] and to date, neither has done so.

Without comparative trials, subsequent pairwise or network meta-analyses of trial data have no common comparator. These analyses must then be based on comparisons between single arms rather than between randomized trials,[9] exposing the analysis to additional sources of bias.[10] Absolute efficacy is typically more variable than relative efficacy; hence pooling trial results using absolute rather than relative treatment effects also erodes precision.[11] In this environment, estimates of comparative efficacy might best be made from observational data under a target trial approach,[12,13] although it takes time for sufficient data to accrue. High treatment success rates make it difficult to estimate relative efficacy: the precision of the estimate is a function of the number of treatment failures, not the number of patients treated.[14]

In this study, we estimate the relative efficacy of treatment with either SOF/LDV or SOF/VEL using data from a single source, the British Colombia Hepatitis Testers Cohort (BC-HTC). We use propensity scores to control confounding rather than a regression model; with few failures it is difficult to both control confounding and estimate relative efficacy within a single model.[15,16] We emulate the randomized trial clinicians would prefer to see to answer the question of whether easy to treat patients with genotype 1 HCV could be treated with the less expensive SOF/LDV rather than with SOF/VEL.

2 | PATIENTS AND METHODS

2.1 | Patient selection

We selected patients treated with either SOF/LDV or SOF/VEL from the BC-HTC. This cohort includes all individuals tested for HCV or HIV at a public health laboratory or reported to the public health authority as a case of HCV, HIV, hepatitis B, or active tuberculosis. Those in the cohort are linked to public health laboratory and surveillance data, medical visit and hospitalization data, prescription drug data, and cancer and mortality registries.[17] Data linkage was allowed under the British Colombia (BC) Centre for Disease Control's public health mandate; the BC-HTC was reviewed and approved by the University of British Columbia Behavioral Research Ethics Board (H14-01649). In BC, public funding for SOF/LDV began in March 2015 but was restricted to those with liver fibrosis level F2 or higher. Criteria were expanded in March 2017 allowing treatment with SOF/VEL and of those with lower levels of fibrosis but with one or more comorbidities (co-infection with HIV or hepatitis B, post-organ transplant, other co-existent liver disease, chronic kidney disease, diabetes).[18] Treatment was public funded for all without restriction in April 2018.

We selected a patient population thought to be easy to treat with either SOF/LDV or SOF/VEL. We included all adults chronically infected with genotype 1 HCV starting either SOF/LDV after 16 October 2014 or SOF/VEL after 11 July 2016, the respective dates these treatments were approved for use in Canada, and before 23 October 2018, with this end date set so that the outcome of treatment ought to be known from linked laboratory data (last update 9 April 2019). HCV treatment start dates were based on pharmacy dispense dates; treatment stop dates were inferred from the dispensed quantity or number of days supplied. We excluded patients who had, prior to treatment, either decompensated cirrhosis, a liver transplant, a hepatocellular carcinoma, chronic hepatitis B or severe renal impairment; and patients previously treated with any direct acting antiviral or starting treatment with ribavirin in addition to SOF/LDV or SOF/VEL. Comorbidities were identified from diagnostic codes or from the use of condition specific medications.

2.2 | Statistical methods

We used propensity scores to emulate the clinical trial that clinicians would prefer to see but which may never happen.[19,20] To create a conceptual trial, we matched by propensity score: for each patient starting SOF/VEL (a 'case'), we selected the patient starting SOF/LDV with the closest propensity score (a 'control'), provided the control's score was within a caliper. The caliper width was set to 0.2 standard deviations of the logit propensity score; a width recommended because of its theoretical properties and good performance in simulations.[21] This conceptual trial provides an answer to the question[22] 'what would have happened if instead of treating this patient with SOF/VEL, SOF/LDV had been used instead?' We matched cases to controls with replacement. Re-using controls allows closer matching between case and control patients and avoids case patients being discarded if an otherwise suitable control has already been assigned to another case. The data for analysis were then a sample of case control sets, each set with one or more cases for each control. We assessed balance between

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cases and controls using a weighted standardized difference,[23] and compared this difference to a reference distribution created by resampling[24] case-control sets with, in each sample, the control allocated at random within each set.

In a clinical trial, randomization assigns a known probability of treatment to each trial patient. With observational data, the probability of treatment is unknown and must be estimated. We estimated this probability – the propensity score – without reference to outcome data [19] using a logistic regression model with covariates which were thought to represent clinical decision-making. That is, there will be reasons why patients were given one of these two treatments and not the other, and the treatment assignment model must reflect those reasons. We considered that the following factors could potentially influence both the treatment received and whether treatment was successful[25,26]: age, gender, the Census material deprivation associated with their address,[27] living in an urban or rural setting, recent problematic alcohol use, recent injection drug use, co-infection with HIV, compensated cirrhosis when starting treatment, last HCV viral load before starting treatment, infection with genotype 1b HCV, and whether previously treated with interferon.

We defined treatment success as an undetectable HCV RNA based on the first measurement available at least ten weeks after treatment ended. We estimated the probability of a detectable HCV RNA with a Bayesian logistic model that included a random effect for each case control set, to allow for the correlation between outcomes induced by matching.[28] We used that model to give a marginal estimate of a risk difference for the conceptual trial, if all patients were treated with SOF/VEL or alternatively if all patients were treated with SOF/LDV.[29]

We used SAS 9.4 maintenance release 5 for this analysis, propensity score matching with PROC PSMATCH and fitting the Bayesian logistic model with PROC MCMC (Supporting Information; Appendix A). We provide a SAS macro for assessing balance when controls are selected with replacement (Supporting Information; Appendix B).

2.3 | Sensitivity analyses

We considered two alternative treatment assignment models. In the original treatment assignment model, HCV viral load before treatment was represented as continuous per log 10 IU/ml. In the first alternative model, this variable was represented as a linear spline,[30] continuous per log 10 IU/ml but with a knot at 6 log 10 IU/ml. We thought this might better reflect prescribing behavior because guidelines allowed short duration treatment with SOF/LDV (eight weeks rather than 12) in patients with a viral load below 6 log 10 IU/ml [31] and so for some patients, SOF/LDV might have been used rather than SOF/VEL for cost reasons but with potential consequences for treatment success.

In a second alternative treatment assignment model, we used expanded definitions of past problematic alcohol and injection drug use. In the original model, these were based on information from the three years prior to treatment. In the second alternative model, we based used these two variables on any historical information and in addition, assumed past injection drug use if the patient had ever received opioid substitution therapy.

We considered two alternative definitions of treatment success, to assess the influence of missing outcomes on our estimates. In the main analysis, we based success on the patient's first HCV RNA measurement available at least ten weeks after treatment ended. We used ten weeks rather than 12 to minimize the number of patients with a missing outcome but in 20% of patients, this first measurement was more than 20 weeks after treatment ended. This then potentially created a higher percentage of missing outcomes among patients receiving SOF/VEL, the more recently approved treatment. For a first alternative definition of treatment success, we based treatment success on the patient's first HCV RNA measurement available between 12 and 20 weeks after treatment ended. For a second definition, we imputed success, where missing under our original definition, from HCV RNA measurements made prior to 10 weeks post-treatment: where available, we used the patient's first measurement at least 22 weeks after treatment started (if the patient had been treated for more than the usual 12 weeks); otherwise we used any last measurement available for that patient after treatment ended.

Finally we included prior information in our analysis. We asserted weakly informative priors[32] as a summary of existing studies both of treatment success under SOF/LDV and of the effectiveness of SOF/VEL relative to SOF/LDV and added these priors to our Bayesian logistic model (Supporting Information; Appendix C).

3 | RESULTS

3.1 | Patient selection

Among patients in the BC-HTC with genotype 1 HCV, 3843 were treated with SOF/LDV and 1456 were treated with SOF/VEL. Of these, 3011 and 1172 patients treated with SOF/LDV and SOF/VEL, respectively, were eligible for our conceptual trial. Common reasons for exclusion were either decompensated cirrhosis, chronic hepatitis B or severe renal impairment prior to starting treatment (Figure 1). Among eligible patients, 2723 (90%) and 825 (70%) of those treated with SOF/LDV and SOF/VEL respectively had both all covariate data and an HCV RNA measurement at least ten weeks after treatment ended. In the main analysis, all 825 cases treated with SOF/VEL were matched to 602 SOF/LDV controls.

The greatest differences in patient characteristics between those treated with SOF/LDV and SOF/VEL (Table 1) were a previous treatment with interferon (19% and 7%), compensated cirrhosis (8% and 1%), and the last HCV RNA before treatment (mean 5.8 and 5.3 log 10 copies/mL). Matching reduced these differences: after matching the greatest differences between SOF/LDV and SOF/VEL treatment groups were the last HCV RNA before treatment (mean 5.5 and 5.4 log 10 copies/mL) and genotype 1B (14% and 11%). In the unmatched data, 888 (29%) of those treated with SOF/LDV were treated for

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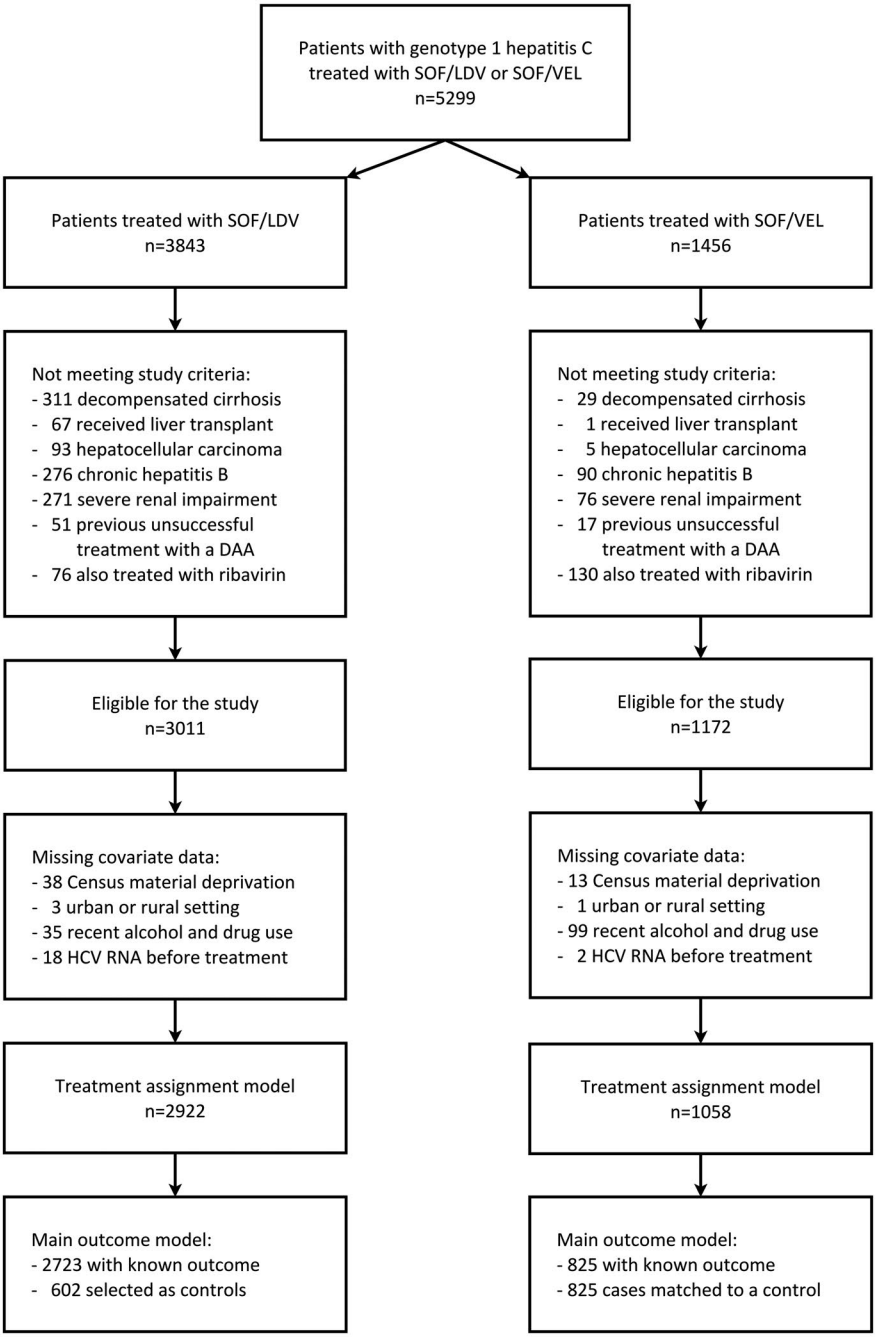

FIGURE 1 Patients selected from the British Colombia Hepatitis Testers Cohort for this study. Patient flow: (1) the number of cohort patients receiving each treatment, excluding those ineligible for the study for various reasons; (2) eligible patients used for treatment assignment modeling, excluding those with missing covariate information; and (3) available as cases or matched as controls, excluding those for whom the outcome of treatment was not known. Abbreviations: DAA, direct acting antiviral; HCV, hepatitis C virus; SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir

eight weeks; in the matched data 224 (37%) of those treated with SOF/LDV were treated for eight weeks.

3.2 | Treatment assignment modeling

We excluded compensated cirrhosis from our treatment assignment model. Few patients had compensated cirrhosis when starting SOF/VEL (Table 1), making it difficult to reliably estimate the association between cirrhosis and the treatment the patient received. However, because treatment success rates were known to be lower in cirrhotic patients (Supporting Information; Appendix C), we exact matched on cirrhosis status, and propensity score matched on all other covariates (Supporting Information; Appendix D). Propensity scores overlapped between the two treatment groups (Figure 2) so that in the main analysis, a control treated with SOF/LDV could be found for each case treated with SOF/VEL. As expected, SOF/LDV controls with a high probability of receiving SOF/VEL were re-used: for the most frequently used control, matched to six SOF/VEL cases, the probability of receiving SOF/VEL was 0.61.

3.3 | Outcome modeling

In the main analysis, a detectable HCV RNA measurement was recorded at least 10 weeks after treatment ended for 27 of the 825

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TABLE 1 The characteristics of patients in the British Colombia Hepatitis Testers Cohort

Covariate (mean or percent)	Eligible patients		Matched patients in the main analysis			
	SOF/LDV n = 3011	SOF/VEL n = 1172	SOF/LDV n = 602	SOF/VEL n = 825	Standardized difference[a]	Reference distribution[b]
Demographic characteristics						
Age, years	57	55	55	56	0.09	±0.09
Female, %	31	35	31	34	0.06	±0.09
Rural setting, %	19	18	22	19	−0.05	±0.09
Census material deprivation[c]	54	57	56	56	0.00	±0.09
Disease characteristics						
Genotype 1B, %	17	11	14	12	−0.04	±0.08
HCV RNA before treatment, log 10 copies/mL	5.8	5.3	5.5	5.5	−0.01	±0.05
Previously treated with interferon, %	19	7	8	10	0.05	±0.06
Compensated cirrhosis, %	8	1	1	1	0.00	±0.00
Risk factors for treatment failure						
Co-infection with HIV, %	8	6	7	7	0.03	±0.10
Recent problematic alcohol use, %[d]	8	5	6	5	−0.04	±0.09
Recent injection drug use, %[d]	10	10	10	9	−0.04	±0.09

Note: Patient characteristics when starting treatment with either sofosbuvir/ledipasvir (SOF/LDV) or sofosbuvir/velpatasvir (SOF/VEL).

Abbreviations: HCV, hepatitis C virus.

[a]Weighted standardized difference between case and control means.[23]

[b]2.5 and 97.5 percentiles of a reference distribution created by resampling [24]; in each sample, randomly assigning the control within each case-control set.

[c]Census material deprivation was an ordered categorical variable representing the deprivation quintiles from the 2016 Census. This variable was represented in the treatment assignment model by a ridit score, over the range zero (most privileged) to 100 (most deprived), such that a value of 50 represents median deprivation.[52]

[d]Recent use was defined as two alcohol (or injection drug) related billing or hospitalization codes (or ambulatory care codes for injection drug use) with the second of these codes within three years prior to starting treatment.

SOF/VEL treated cases and for 29 of the 602 SOF/LDV treated controls (Table 2). Using these data and noninformative priors (Supporting Information; Appendix A), estimates from our Bayesian logistic model were success rates of 97% (95% credible interval, CrI, 95 to 98%) for treatment with SOF/VEL, 95% (95% CrI 93 to 97%) for treatment with SOF/LDV and a risk difference between the two treatments of 2% (95% CrI 0 to 4%).

3.4 | Sensitivity analyses

Estimated risk differences were similar in all sensitivity analyses (Table 2). The greatest difference came when we imputed missing outcomes. In the main analysis, of those patients included in the treatment assignment model, the outcome of treatment was unknown for 199 of 2922 (6.8%) and 233 of 1058 (22%) of those treated with SOF/LDV and SOF/VEL respectively (Figure 1). By imputing missing outcomes, we reduced missing outcomes to 92 (3.1%) and 126 (12%) of those treated with SOF/LDV and SOF/VEL respectively. Using these data, the estimated risk difference between treatments was 0% (95% CrI −2 to 2%).

Adding weakly informative prior information (Supporting Information; Appendix C) made no material difference, reducing the credible interval width from 4.0 to 3.7 percentage points.

4 | DISCUSSION

Our results show that SOF/LDV is not inferior to SOF/VEL for easy to treat patients with genotype 1 HCV. In all our analyses, the risk difference between the two treatments was less than 5%, the non-inferiority margin recommended by the FDA when treatment success rates are above 95%.[1] This supports the use of SOF/LDV for such patients in settings where a price difference exists. In India, generic SOF/VEL is currently more expensive than generic SOF/LDV, although at a lower price SOF/VEL could soon be cost-saving

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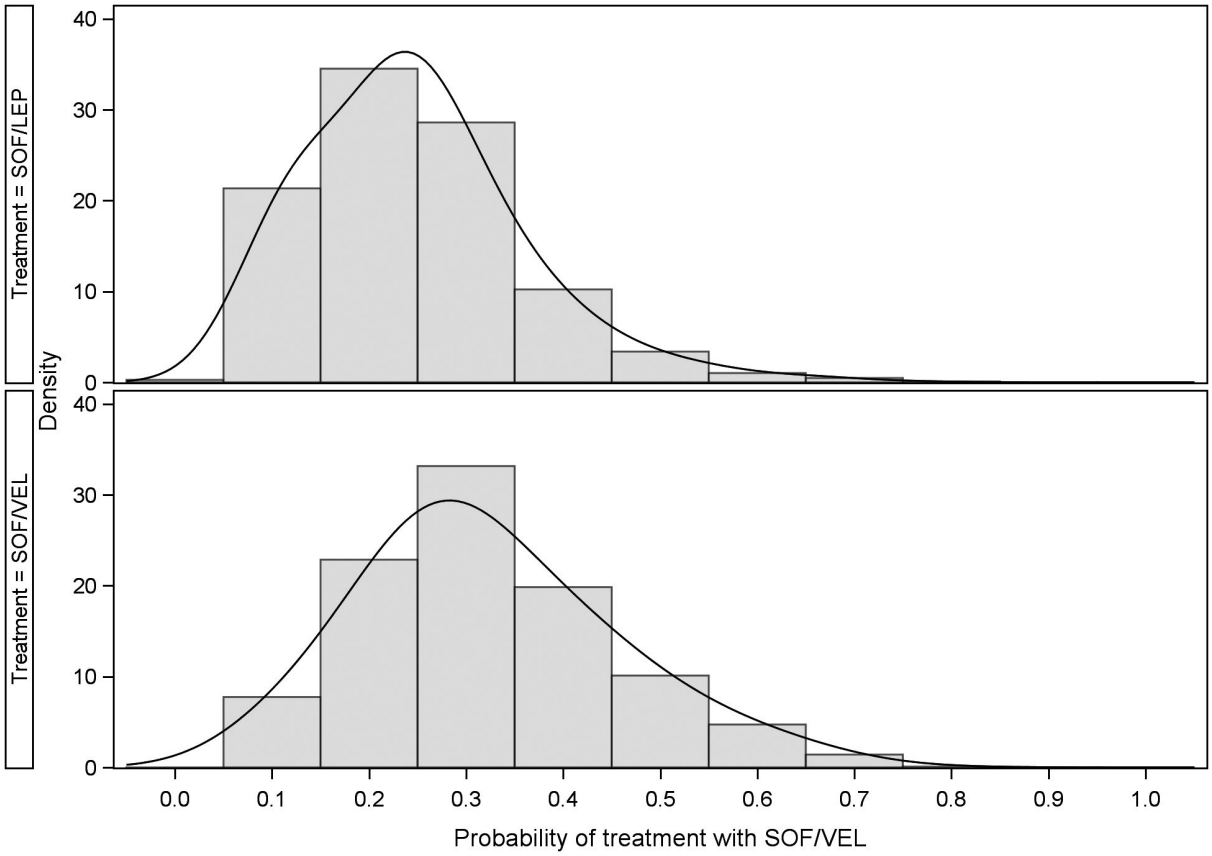

FIGURE 2 Propensity scores from the treatment assignment model for the main analysis. For patients included in treatment assignment modeling, the probability of being treated with SOF/VEL for those patients that were treated with SOF/LDV (top) and for those patients that were treated with SOF/VEL (bottom). Abbreviations: SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir

while still more expensive because it can be used without genotype testing.[33] Indian generics are sold in other low and middle income countries, so any price difference there has implications for other parts of Asia, the Pacific and Africa.[33]

Our study illustrates how observational data can be used to emulate a phase 3 randomized trial with a standard of care control arm. Our study suggests that when treatment success rates are over 95%, roughly speaking at least one thousand patients on each treatment will be needed to emulate a trial with adequate power. The exact number will depend on the patient population of interest and the research question – these factors drive patient selection and matching processes. Fewer patients will be needed if both treatments were used exclusively in the same homogenous patient population. Compared to drug registration trials in easy to treat patient populations, our estimated success rate of 95% (95% CrI 93 to 97) with SOF/LDV is lower than in ION-1 (99%, 95% CI, confidence interval, 96 to 100) but similar to ION-3 (95%, 95% CI 92 to 98)[2,34,35]; and our estimated success rate of 97% (95% CrI 95 to 98) with SOF/VEL is lower than in ASTRAL-1 (99%, 95% CI 98 to >99).[3,36] Note that the precision in our estimates is similar to that achieved in these trials.

In general a lack of information harms decision making. The situation is likely to be particularly acute with high priced drugs.[37] Pharmaceutical companies then compete on factors other than efficacy and safety.[8] Comparative efficacy data do not necessary mean the price of every drug falls – rather that drugs are then priced according to their relative ability to achieve patient health outcomes.[7] Across the entire health care system, savings are likely [7] because many new treatments are no more effective than standard care and therefore should not cost more.[37]

HCV elimination by 2030 will require lower drug prices.[6] The release of Gilead's generics for SOF/LDV and SOF/VEL is evidence of competition but high drug prices in high income countries is one reason why countries like Canada and the US are not on track to achieve elimination with treatment denied to the disadvantaged.[5,38,39] High drug prices have led to both treatment and re-treatment restrictions for people who inject drugs;[40] elimination will be more difficult under such restrictions.[41] In addition, many highburden uppermiddle income countries are unable to access voluntary licensing schemes and cannot afford current market prices.[39] While comparative efficacy data should help lower drug prices, the cost of RNA diagnostic testing needs to fall further too.[6,39]

In the absence of randomized trials comparing DAAs, observational data will be needed to compare newer pan-genotypic treatments. With these, the cost and delay of genotype testing can be avoided. Unfortunately observational data take time to accrue, allowing prescribing patterns to become entrenched.[8] Trial data suggest that sofosbuvir/daclatasvir may not be inferior to SOF/VEL for patients with genotype 3 HCV.[9] Other pan-genotypic options

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TABLE 2 The outcome of treatment with either sofosbuvir/ledipasvir (SOF/LDV) or sofosbuvir/velpatasvir (SOF/VEL)

Treatment assignment	Main model	Linear spline for HCV viral load[a]	Any substance use rather than recent[b]	Main model	Main model
Treatment success	**Main definition**	**Main definition**	**Main definition**	**Restricted[c]**	**Expanded[d]**
Matched data: failures/patients					
SOF/LDV	29/602	28/606	29/644	17/452	31/667
SOF/VEL	27/825	27/823	27/897	15/598	41/931
Estimated success rates (95% CrI)					
SOF/LDV	95 (93-97)	95 (94-97)	0.96 (0.94-0.97)	0.96 (94-98)	95 (94-97)
SOF/VEL	97 (95-98)	97 (95-98)	0.97 (0.96-0.98)	0.98 (96-99)	96 (94-97)
Relative effectiveness of SOF/VEL (95% CrI)					
Odds ratio	0.69 (0.42-1.1)	0.72 (0.44-1.2)	0.68 (0.41-1.1)	0.68 (0.35-1.3)	0.96 (0.62-1.5)
Risk difference	2 (0-4)	1 (−1-3)	1 (0-3)	1 (−1-3)	0 (−2-2)

Note: Treatment outcomes for matched patients from the British Colombia Hepatitis Testers Cohort.

Abbreviations: CrI, credible interval; HCV, hepatitis C virus.

[a]HCV viral load before treatment represented as a linear spline,[30] continuous per log 10 IU/ml but with a knot at 6 log 10 IU/ml.

[b]Problematic alcohol and injection drug use based on any historical information and in addition, past injection drug use assumed if the patient had ever received opioid substitution therapy.

[c]Treatment success assessed using the first HCV RNA measurement available between 12 and 20 weeks after treatment ended.

[d]Treatment success imputed where missing under the main definition: if available, we used a first measurement at least 22 weeks after treatment started; otherwise we used any last measurement available after treatment ended but before 10 weeks post-treatment.

include glecaprevir/pibrentasvir and sofosbuvir/ravidasvir [42] – the latter particularly important because of its potential to be both effective and affordable – but beyond this, drug development appears to have ceased.[43] Our results support another public health treatment strategy: cheaper generic SOF/LDV could be used without genotype testing in high-burden regions where genotype 1 predominates, such as in parts of China,[44] with glecaprevir/pibrentasvir re-treatment where necessary.[39] Genotype 1 HCV predominates in high and high-middle income countries.[45]

The strength and weaknesses of this study, and of this approach in general, can be assessed according to criteria proposed for regulatory use of real world data.[13,46] In general, the approach has the strengths of an active comparator (rather than placebo), with new user designs possible to ensure that covariates are measured prior to treatment. Clinical outcomes are preferred to surrogate outcomes: here the outcome is considered a validated surrogate by the FDA, known to predict clinical benefit.[1] The database content available is a strength of this particular study, with a wide range of electronic records available to capture clinical data and care, but this is a potential weakness. Depletion of susceptibles is a potential weakness in general: treatment restrictions during the early DAA era meant sicker patients were treated first. Overcoming this weakness requires adjustment for confounding by disease severity and so the database must contain appropriate variables. In some situations, as in this example, any residual confounding will be conservative when considering whether an earlier treatment is noninferior to a more recent treatment. Another general weakness arises because of irregular measurement. The BC-HTC receives data from its linked registries periodically rather than continuously and so missing outcomes were more common among those treated with the more recent treatment, SOF/VEL, and a lower percentage of these patients were known to have decompensated cirrhosis (and were excluded, Figure 1) or compensated cirrhosis (Table 1). Such weaknesses necessitate sensitivity analyses: when we imputed missing outcomes using reasonable assumptions, if anything we had stronger evidence for non-inferiority. This implies a form of 'walking well' missingness such that those with a early negative test did not see the need to return for another test. There is a residual missingness potentially due to patients lost to follow up because of negative health outcomes but that residual seems relatively low (3% of those treated with the earlier treatment, SOF/LDV). Any failure to either exclude patients with decompensated cirrhosis or identify patients with compensated cirrhosis when matching would have the effect of making SOF/VEL appear less effective than it is. However, our estimated success rate for patients treated with SOF/VEL in clinical practice is not much less than the rate achieved in a clinical trial, and this gives us confidence in the reliability of our results.

Our Bayesian method of analysis is more complicated but offers real advantages. With it, we can accommodate alternative matching methods beyond the standard one to one matched pairs. Here we re-use controls, matching with replacement, to minimize biases that arise through either incomplete or inexact one to one matching.[47] Alternative matching methods complicate subsequent analysis – analysis via conditional logistic regression does not provide marginal estimates that are equivalent to those from a randomized trial,[26,29] while estimates from generalized estimating equations are not likelihood-based and so cannot be combined with prior information; in addition, standard error formula are not always available when matching with replacement.[48] With our approach, these

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problems are circumvented via simulation, by drawing samples from a posterior distribution. Simulation can also be used to provide interval estimates for statistics derived from our model, so the model can be benchmarked against existing trial data.[13,46] Here, we report treatment success rates for each arm: our model suggests slightly lower success rates in clinical practice than those achieved in a trial setting, as one would expect. The price paid for these advantages is not as high as it once was, because specialist software is no longer necessary – we fit our model in SAS (Supporting Information; Appendix A). Finally background information can be combined with limited data: this controls small sample bias and can improve precision.[32] We illustrate the process of asserting contextually sensible prior distributions (Supporting Information; Appendix C).

This study provides good evidence that it is reasonable to use generic SOF/LDV rather than SOF/VEL in easy to treat patients with genotype 1 HCV when this strategy is cost saving. Competition with and between generic manufacturers, or just the threat of local generic production, were important in driving down the price of antiretrovirals, enabling wider use by the disadvantaged and in developing countries, and HCV elimination by 2030 will require a similar price trajectory.[49] However, unlike DAAs, comparative efficacy trials were required under the approval process for antiretroviral drugs.[1,50] With these results, and with this approach as a template, we hope to provide better evidence for selecting the best DAA given the economic context.[51]

DISCLAIMER

All inferences, opinions, and conclusions drawn in this publication are those of the authors, and do not necessarily reflect the opinions or policies of the BC Ministry of Health.

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CONFLICTS OF INTEREST

JY reports an advisory board honorarium from ViiV Healthcare, outside the submitted work. MK reports grants for investigator-initiated studies from ViiV Healthcare, Merck, and Gilead; research grants from Janssen; personal fees from ViiV Healthcare, Merck, AbbVie and Gilead; all outside the submitted work. NJ and SW report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available from the BC Centre for Disease Control for researchers who meet the criteria for access to confidential data. Requests for data should be sent to Naveed Janjua (naveed.janjua@bccdc.ca).

OPEN RESEARCH BADGE

This article has earned an Open Materials badge for making publicly available the digitally-shareable data necessary to reproduce the reported results. The data is available in article supplementary material which contains core SAS code and macro.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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