Markov model to evaluate health outcomes of sofosbuvir/velpatasvir/voxilaprevir for re-treatment of patients with Chronic Hepatitis C in the US

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Background

- Among chronic hepatitis C (CHC) patients currently being treated with oral direct acting antivirals (DAAs), 1 to 18% will not achieve sustained virologic response (SVR) and will require re-treatment (Afdhal 2016). The majority of these patients will have failed a regimen containing an NS5A inhibitor; a recent model projected ~85% patients failing treatment will have failed a regimen containing an NS5A inhibitor in 2017 (Chhatwal et al. 2016).
- Until recently, treatment options were limited for CHC patients who previously failed DAAs containing NS5A inhibitors with or without a protease inhibitor (TE-NS5A±PI population) or sofosbuvir (SOF) without NS5A inhibitors (TE-SOFminusNS5A).
- Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) received FDA approval on July 18, 2017, for the treatment of GT1-6 TE-NS5A patients and GT1a/3 TE-SOFminusNS5A patients. It is a novel all-oral, once-daily, single-tablet, SOF-based regimen that has demonstrated excellent efficacy and safety in TE-NS5A and TE-SOFminusNS5A patients.
- Glecaprevir/pibrentasvir (GLE/PIB) received FDA approval on August 3, 2017, as a daily 3 pill treatment regimen for GT1-6 CHC patients, and also for CHC GT1 patients previously treated with either an NS5A inhibitor or an NS3/4A protease inhibitor. GLE/PIB is not indicated for GT1 patients who have failed a regimen containing both an NS5A inhibitor and protease inhibitor (TE-NS5A+PI), nor GT2-6 TE-NS5A patients.

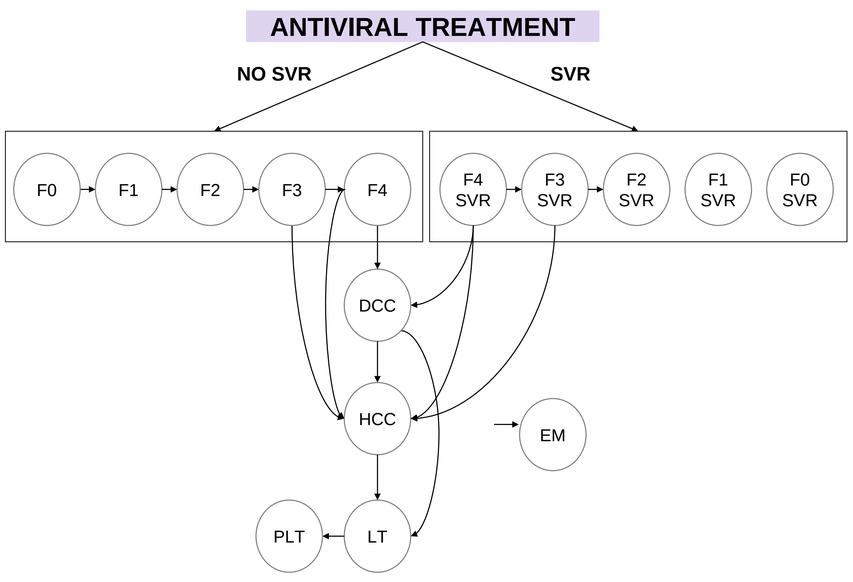
Aim

- This study evaluated the health and economic outcomes of SOF/VEL/VOX relative to other treatment options recommended by AASLD guidelines or per FDA label for CHC patients failing initial therapy and requiring re-treatment.

Methods

- A model simulated the outcomes for CHC GT1-6 non-cirrhotic (NC) and compensated cirrhotic (CC) TE-NS5A and TE-SOFminusNS5A patients with an mean age of 52 using an adaptation of a previously published hybrid decision tree and Markov state-transition model (Younossi et al. 2015) capturing the natural history of CHC **(Figure 1).**
- 83.4% of each cohort was GT1; 4.3%, GT2; 11.2%, GT3; 1.0%, GT4; and, 0.1% GT5/6 (Chhatwal et al., 2016). 30.0% of GT1-2/4-6 patients were CC (42.0% for GT3). 85% of patients were assumed to have failed NS5A-containing regimens; 15% were assumed to have failed SOF-based regimens without NS5A inhibitors (Chhatwal et al. 2016).
- SOF/VEL/VOX or SOF/VEL (assumed to be used for TE-SOFminusNS5A patients with GT1b, 2, 4-6, where SOF/VEL/VOX is not indicated per label) for 12 weeks were compared with glecaprevir/pibrentasvir (GLE/PIB), AASLD-recommended treatment regimens for GT1 CC TE-NS5A and GT1-3 TE-SOFminusNS5A patients (detailed in Table 1) or no treatment (NT).
- The analysis was modelled from a third-party US payer perspective over a lifetime horizon.
- Future outcomes and costs were discounted at an annual rate of 3% (Gold et al. 1996).
- SVR rates **(Table 1)** were sourced from the appropriate clinical trials and consensus by a panel of hepatologists. For regimens where certain sub-populations are not indicated, an SVR rate of 0% was assumed for the regimen in that sub-population.
- Transition probabilities and utilities were based on a literature review and consensus by a panel of hepatologists.
- The model accounted for drug acquisition costs, monitoring costs and health state costs, which were sourced from the literature and adjusted to 2017 US dollars.
- Model outcomes included the number of cases of advanced liver disease (decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC), liver transplant (LT), and liver-related death) and projected long-term costs. Cost per SVR was calculated by dividing 1st year cost by SVR rate in treated patients.
- To test the robustness of the base-case results, a comprehensive deterministic sensitivity analysis was conducted for the lifetime incremental cost per QALY gained. Key parameters varied included SVR rates (±10% to a maximum of 100% for all-oral regimens), transition probabilities (95% CI), costs (±20%), and utility estimates (±20%).

Figure 1. Model Structure



DCC, decompensated cirrhosis; SVR, sustained virologic response; HCC, hepatocellular carcinoma; EM, extra mortality; LT, liver transplant; PLT, post-liver transplant

Table 1. SVR Inputs

GT	Population	Regimen	Duration	F0	F1	F2	F3	F4	Source
GT1	NS5A±PI	SOF/VEL/VOX	12	98.9%	98.9%	98.9%	98.9%	95.2%	Bouliere 2016
		GLE/PIB	16[a]	94%	94%	94%	94%	94%	Poordad 2017
		SOF/VEL^	24+R	N/A	N/A	N/A	N/A	97%	Gane 2016
		LDV/SOF^	24+R	N/A	N/A	N/A	N/A	100%	Lawitz 2015
		SOF+SMV^	24+R	N/A	N/A	N/A	N/A	100%	Lawitz 2015
		SOF+EBR/GRZ^	12+R	N/A	N/A	N/A	N/A	90%	Lawitz 2015
		SOF+OBV/PTV/r+DSV^	12/24+R[b]	N/A	N/A	N/A	N/A	100%	Poordad 2015
	SOFminusNS5A±PI	SOF/VEL/VOX (GT1a)	12	98.9%	98.9%	98.9%	98.9%	97.3%	Zeuzem 2016
		SOF/VEL (GT1b)	12	99.5%	99.5%	99.5%	99.5%	90.6%	Zeuzem 2016
		GLE/PIB	8[c]	99.1%	99.1%	99.1%	99.1%	N/A	Zeuzem 2016
			12[c]	N/A	N/A	N/A	N/A	98.5%	Forns 2017
			12[d]	100%	100%	100%	100%	100%	Poordad 2017
		LDV/SOF	12+R	100%	100%	100%	100%	N/A	Wyles 2015
		LDV/SOF	24+R	N/A	N/A	N/A	N/A	98%	Reddy 2015
		LDV/SOF^,[d]	24+R	N/A	N/A	N/A	N/A	100%	Lawitz 2015
		SOF+SMV^,[d]	24+R	N/A	N/A	N/A	N/A	100%	Lawitz 2015
		SOF+EBR/GRZ^,[d]	12+R	N/A	N/A	N/A	N/A	90%	Lawitz 2015
		SOF+OBV/PTV/r+DSV^,[d]	12/24+R[b]	N/A	N/A	N/A	N/A	100%	Poordad 2015
GT2	NS5A	SOF/VEL/VOX	12	100%	100%	100%	100%	100%	Bouliere 2016
	SOFminusNS5A	SOF/VEL	12	100%	100%	100%	100%	92.1%	Zeuzem 2016
		GLE/PIB	8	97.9%	97.9%	97.9%	97.9%	N/A	Kowdley 2016
			12	N/A	N/A	N/A	N/A	100%	Forns 2017
		SOF+DCV^	24+R	100%	100%	100%	100%	100%	Sulkowski 2014; Wyles 2015
GT3	NS5A	SOF/VEL/VOX	12	97.2%	97.2%	97.2%	97.2%	92.1%	Bouliere 2016
	SOFminusNS5A	SOF/VEL/VOX	12	95.1%	95.1%	95.1%	95.1%	93.6%	Zeuzem 2016
		GLE/PIB	16	95.5%	95.5%	95.5%	95.5%	95.7%	Wyles 2016
		SOF+DCV^	24+R	N/A	N/A	N/A	N/A		Nelson 2015
		SOF+EBR/GRZ^	12+R	N/A	N/A	N/A	N/A	100%	Foster 2016
GT4	NS5A	SOF/VEL/VOX	12	93.2%	93.2%	93.2%	93.2%	88.3%	Bouliere 2016
	SOFminusNS5A	SOF/VEL	12	100%	100%	100%	100%	100%	Zeuzem 2016
		GLE/PIB	8	93.5%	93.5%	93.5%	93.5%	N/A	Asselah 2016
			12	N/A	N/A	N/A	N/A	100%	Forns 2017
GT5/6	NS5A	SOF/VEL/VOX	12	100%	100%	100%	100%	100%	Bouliere 2016
	SOFminusNS5A	SOF/VEL	12	100%	100%	100%	100%	100%	Zeuzem 2016
		GLE/PIB	8	91.7%	91.7%	91.7%	91.7%	N/A	Asselah 2016
			12	N/A	N/A	N/A	N/A	100%	Forns 2017

[a]Only in TE-NS5A (no PI) patients; [b]GT1b / GT1a; [c]TE-SOFminusNS5A (no PI) patients; [d]TE-SOFminusNS5A+PI patients; ^Recommended by AASLD guidelines; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; SOF, sofosbuvir; VEL, velpatasvir; GLE/PIB, glecaprevir/pibrentasvir; SVR, sustained virologic response; GT, genotype

Results

- In the overall CHC re-treatment population, SOF/VEL/VOX and SOF/VEL provide the best future health outcomes and fewest cases of DCC (94% reduction vs. NT), HCC (88% reduction vs. NT), LT (94% reduction vs. NT), and liver-related mortality (92% reduction vs. NT) (**Table 2**).
- The overall cost per SVR for SOF/VEL/VOX and SOF/VEL was $78,028. Cost per SVR cannot be reported for those regimens where there is no data for the selected retreatment population.
- GLE/PIB, AASLD guideline therapies, and NT are all dominated (i.e., are less effective and more costly) when compared to SOF/VEL/VOX and SOF/VEL. SOF/VEL/VOX results in a 32%, 54%, and 51% reduction in lifetime costs relative to GLE/PIB, AASLD guideline regimens, and NT, respectively, and a 20%, 22%, and 41% increase in QALYs, respectively.
- The sensitivity analysis found that, for all parameters varied, SOF/VEL/VOX and SOF/VEL in the CHC re-treatment population result in lower costs and higher QALYs than GLE/PIB, AASLD guideline therapies, and NT. Thus, SOF/VEL/VOX and SOF/VEL remain cost-effective even when clinical, cost, and natural history parameters are varied across wide yet plausible ranges.

Table 2. Model Results

	Cases of DCC (% reduction vs. NT)	Cases of HCC (% reduction vs. NT)	LTs (% reduction vs. NT)	HCV deaths (% reduction vs. NT)	LYs (% increase vs. NT)	QALYs (% increase vs. NT)	Lifetime costs (% difference vs. NT)	ICER, comparator vs. SOF/VEL/VOX
ALL PATIENTS								
SOF/VEL/VOX or SOF/VEL	205 (-94%)	308 (-88%)	37 (-94%)	385 (-92%)	17.73 (+25%)	14.76 (+41%)	$86,610 (-51%)	REFERENT
GLE/PIB	1,952 (-46%)	1,543 (-42%)	325 (-45%)	2,788 (-44%)	15.89 (+12%)	12.53 (+20%)	$120,398 (-32%)	DOMINATED
AASLD GUIDELINES	2,285 (-37%)	1,873 (-30%)	374 (-37%)	3,253 (-35%)	15.79 (+11%)	12.14 (+16%)	$189,924 (+7%)	DOMINATED
NT	3,601	2,668	593	5,016	14.23	10.44	$177,308	DOMINATED
GT1 ONLY								
SOF/VEL/VOX or SOF/VEL	186 (-95%)	285 (-89%)	34 (-94%)	352 (-93%)	17.77 (+23%)	14.79 (+39%)	$85,795 (-51%)	REFERENT
GLE/PIB	1,629 (-53%)	1,267 (-50%)	268 (-53%)	2,293 (-52%)	16.34 (+13%)	12.99 (+22%)	$110,595 (-37%)	DOMINATED
AASLD GUIDELINES	1,974 (-43%)	1,620 (-36%)	318 (-44%)	2,772 (-42%)	16.27 (+12%)	12.60 (+18%)	$188,637 (+8%)	DOMINATED
NT	3,491	2,528	570	4,799	14.48	10.65	$175,013	DOMINATED
GT2-6 ONLY								
SOF/VEL/VOX or SOF/VEL	301 (-93%)	422 (-87%)	54 (-92%)	547 (-91%)	17.57 (+35%)	14.59 (+55%)	$90,705 (-52%)	REFERENT
GLE/PIB	3,573 (-14%)	2,925 (-13%)	610 (-14%)	5,268 (-14%)	13.67 (+5%)	10.19 (+8%)	$169,646 (-10%)	DOMINATED
AASLD GUIDELINES	3,850 (-7%)	3,147 (-7%)	656 (-7%)	5,667 (-7%)	13.38 (+3%)	9.85 (+5%)	$196,394 (+4%)	DOMINATED
NT	4,156	3,371	709	6,109	12.97	9.41	$188,840	DOMINATED

GT, genotype; SOF/VEL/VOX, sofosbuvir/velpatasvir/voxilaprevir; QALY, quality-adjusted life year; ICER, incremental cost effectiveness ratio; NT, no treatment; DCC, decompensated cirrhosis; HCC, hepatocellular*Ir carcinoma; LT, liver transplant; LY, life years; Referent = reference therapy; dominated = reference therapy is more effective and less costly

Conclusion

- SOF/VEL/VOX as re-treatment of DAA failure patients offers the most favorable health and economic outcomes in the overall CHC population when compared with currently available therapies (94% reduction in DCC, 88% reduction in HCC, 94% reduction in LT, 92% reduction in liver-related mortality, 51% reduction in lifetime costs, and 41% increase in QALYs relative to NT).
- This analysis uses SVR rates from clinical trials, which may differ from those in the real-world. Real-world SVR data for SOF-based regimens are consistent with those from clinical trials (Kowdley et al. 2017, Tsai et al. 2017, Curry et al. 2017, Khalili et al. 2017, Buggisch et al. 2017, Christensen et al. 2017). Real-world SVR rates are uncertain for newer regimens and consideration should be given to lack of clinical trial data, how well the clinical trial population reflects real-world patients (i.e. the percentage of patients with cirrhosis), potential drug-drug-interactions, and higher pill burden.

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References on request.