Efficient care delivery of effective hepatitis C virus treatments in Medicaid beneficiaries without cirrhosis

Received (in revised form): 23rd June, 2017

S. Mantravadi
is a health economist, with research interests in health economic analyses of health insurance.

University of West Florida, 11000 University Parkway, Pensacola, FL 32514, USA
E-mail: smantra2013@gmail.com

Abstract The hepatitis C virus (HCV) targets the liver and increases the chance of negative liver-related health outcomes. The recent wave of direct-acting antiviral (DAA) treatments is highly effective, with reduced side effects compared to prevailing options, and is recommended by the American Association for the Study of Liver Disease–Infectious Diseases Association (AASLD–IDSA), as of June 2017. In the administration of DAA treatment in Medicaid, however, patients with cirrhosis have been given priority. The extent of efficiency and cost savings associated with delivery of treatments in patients without cirrhosis is in question. The aim of this study was to analyse the efficiency of HCV treatment options and practice recommendations in Medicaid beneficiaries as a national cohort. To quantitatively evaluate treatment efficiency, treatments recommended by AASLD–IDSA were modelled using inputs from the published literature and the Medicaid National Average Drug Acquisition Cost. For modelled patients, ombitasvir/paritaprevir/ritonavir/dasabuvir/ribavirin would be the preferred, most efficient and effective treatment for Medicaid. Despite real world variation in treatment discontinuation, DAA treatment results in savings for Medicaid. The results suggest that DAA regimens as a first line of treatment is both an effective and an efficient practice in patients without cirrhosis, reducing all-cause health-care costs, preventing disease stage progression and averting morbidity.

KEYWORDS: efficient and effective delivery of services, hepatitis C virus treatments, direct-acting antivirals, Medicaid, business of healthcare delivery of treatments

INTRODUCTION

An estimated 170 million people are affected with chronic hepatitis C virus (HCV) infection worldwide,[1] and over 2.7–3.9 million people with HCV infection live in the United States.[2–9] A majority of these cases are prevalent rather than incident.[10] There are six variants of the HCV, from genotypes 1–6; genotype 1 is the most prevalent, with 75 per cent of Americans infected with this strain/variant of HCV.[11] The HCV genotype 1 consistently remains a difficult-to-treat variant.[12] The sequela of HCV infection ranges from acute to chronic forms of liver disease, cirrhosis and liver cancer. From 1,000 individuals with HCV infection, 750–850 individuals will progress to the chronic phase of HCV

infection. The HCV increases the risk of liver-related negative health outcomes. Currently, the Centers for Disease Control and Prevention recommends blood testing for those within the Baby Boomer age group and those with a higher risk for HCV infection, such as people who have had percutaneous blood exposure and/or received blood transfusions before 1992 (prior to HCV screening of blood supplies).[13] Further, HCV prevalence is highest in the population under the age of 55 years and disproportionately affects the poor;[14,15] three-quarters of the population infected with HCV are Baby Boomers.[16]

Since the disease progresses slowly, chronic HCV-infected patients often play a waiting game of no treatment. Prior to the emergence of the newly approved oral agents, most newly detected cases of HCV did not prompt antiviral medication use owing to side effects and limited efficacy of peginterferon/ribavirin regimens. In 2011, the cost of treating HCV totalled US$6.5bn, with a range of $4.3–8.4bn, and is expected to increase with the shift towards advanced liver disease.[17] The average lifetime costs of a patient infected with HCV were estimated at US$205,760 (for all ages and genders) in 2011 (incorporating medical inflation), and were accordingly higher for individuals with a longer life expectancy/younger individuals.[18] For example, patients with serious compensated cirrhosis may rack up costs totalling US$270,000 over a decade, owing to treatment costs;[19–21] these estimates are from private insurance claims data. Among HCV Medicaid patients, a study concerning Florida beneficiaries found that incremental costs associated with advanced liver disease are high (US$1,356 per patient per eligible month, with inpatient costs at US$1,272 per patient per eligible month), driven mainly by inpatient stays.[22]

Since currently there is no vaccine for HCV, the only option is to treat the disease itself. After treatment, the ultimate goal for a patient is to reach sustained virologic response (SVR); however, the virus may be undetectable at the conclusion of a full run of therapy, but may return later. Treatment to SVR is desirable as this reduces the risk of the noted sequelae of HCV infection. Traditional peginterferon/ribavirin therapies pose many adverse side effects that are difficult to tolerate, and many patients do not complete the therapy.[23] It has been estimated that 0–10 per cent of patients accept and complete a full dose of therapy.[24] When peginterferon/ribavirin treatment regimens are administered to patients with HCV genotype 1, the SVR rate is approximately 50–60 per cent, and SVR rate can be lower in subgroups.[25] Re-treatment results in less than 22 per cent of patients reaching SVR.[26]

The advent of direct-acting antiviral (DAA) treatments is spearheading a slow but sure shift away from interferon-based therapies towards new treatments, with fewer side effects and higher cure rates.[27] In contrast to prevailing regimens, DAAs administered as oral tablets are more efficacious and have significantly fewer and milder side effects and much lower discontinuation rates (2, 25, 40). The SVR rates of interferon-free DAA regimens have climbed beyond 90 per cent and much closer to 100 per cent.

The use of DAA treatments results in the avoidance of loss of productivity, liver transplant and treatments, liver cancer, negative liver-related health outcomes, especially for extremely ill patients.[28] The cost of HCV treatment goes beyond the direct medical costs of treatment pricing.[29] These initial investments and cost implications may become worthwhile if there is less resource expenditure and unnecessary health-care utilisation in the future. From Medicaid's perspective, the new DAA treatments are a unique situation.[30–36] The exact number of Medicaid beneficiaries infected with HCV is not well established.[37]

States currently vary greatly in the coverage of FDA-approved DAA regimens,

prioritising treatment coverage for patients with severe liver disease and cirrhosis; often programmes lack the necessary information needed to evaluate the impact and economic burden of new treatment regimens and changes in clinical practice. Treatment is now recommended for all patients, irrespective of the severity of liver disease/cirrhosis, by the nationally recognised American Association for The Study of Liver Diseases and Infectious Diseases Society of America (AASLD–IDSA).[38] Peginterferon–ribavirin, despite its low-to-modest efficacy, is implemented as standard of care in practice for Medicaid patients and many populations; although newer, effective DAA therapies have emerged, issues with lack of coverage and high costs have limited access to these new AASLD–IDSA recommended medications. The costs savings, however, from reaching SVR and the reduced risk of cirrhosis, liver cancer and liver transplantation that are associated with usage of DAA treatments are a key benefit, and such effective care needs to be evaluated in the context of efficient care. To evaluate efficiency, the use of cost–benefit analysis is more relevant/applicable owing to the budget constraints and decision-making situations that policymakers and providers are encountering.

Because of the foregoing situations and high incidence in low-income populations, it is worthwhile to have an empirical analysis of efficiency, using cost–benefit analysis, considering the short-and long-term impact of evidence-based regimens for clinical practice in patients without cirrhosis, from the perspective of Medicaid. For payers, an important component of addressing the risk and costs of HCV is to quantify the exposure to HCV and incorporate evidence regarding treatment,[39] and the use of cost–benefit analysis, a form of health economic evaluation, becomes relevant with concern about efficiency of care delivery. Economic evaluation appraises the relationship between costs of care and effectiveness of care, as per the Agency for Healthcare Research and Quality definitions of efficiency, finding the maximum value of care for the lowest costs (highest savings). This research modelled the cost and implicated savings/benefit of treatment regimens for HCV, over a ten-year period in order to quantitatively evaluate efficiency and long-term effects. A payers' perspective that considers all direct patient costs pertaining to Medicaid was used.

MATERIALS AND METHODS

In this study, the efficiency of a consistent use of HCV treatment care delivery was quantitatively modelled in a nationwide Medicaid cohort. Published data and reports were used to define the size of a modelled population of patients enrolled in Medicaid insurance only (regardless of state) and HCV genotype 1a infection.[40,41] The ten-year time frame is an ideal to evaluate the impact of these treatments for Medicaid decision makers. Since the qualifying age for Medicare is 65 years, the modelled cohort was limited to Medicaid beneficiaries 55 years and younger.[42] With this modelling 'exclusion criterion', the modelled population would have a full ten years of disease and health-care utilisation experience in the Medicaid system, before ageing into the Medicare system.[43] There were 377,000 HCV (all genotypes)-positive Medicaid beneficiaries in 2013.[44] It was assumed that 71.5 per cent of the population was not cirrhotic, as per estimates from the Chronic Hepatitis Cohort Study (CHeCS).[45] The model in this study assumes that the genotype and age distribution is the same as that of the HCV-infected Medicaid population.

Recommended AASLD–IDSA treatment regimens for maximum efficacy as of June 2017 in treatment-naïve patients infected with HCV genotype 1a[46] that were modelled in the study were elbasvir–grazoprevir for 12 weeks, sofosbuvir and ledipasvir for 12 weeks, ombitasvir/paritaprevir/ritonavir

and dasabuvir for 12 weeks, simeprevir and sofosbuvir for 12 weeks, sofosbuvir and velpatasvir for 12 weeks, daclatasvir–sofosbuvir for 12 weeks, ribavirin and peginterferon for 48 weeks, or a watch/wait strategy.

For the earlier treatment regimens, the SVR rates from published articles on the ION-1, ION-3, NEUTRINO, SAPPHIRE-1, SAPPHIRE-2, PEARL-4, TURQUOISE-2, OPTIMIST-1, OPTIMIST-2, C-EDGE TN, ALLY-1, ALLY-2 and ASTRAL-1 clinical trials. Treatment discontinuation for DAAs and peginterferon/ribavirin was obtained from the published literature.[47] This study considered treatment discontinuation as 8.1 per cent for DAA treatment regimens, as obtained from a CVS Health study of real world sofosbuvir treatment.[48] The treatment discontinuation for peginterferon/ribavirin is 12.3 per cent.[49,50]

Cost analysis

For all treatment regimens, total cost was calculated by determining an FDA-approved, guideline-recommended treatment regimen and aggregating the daily or weekly costs of the required medication to equal this complete treatment regimen. The National Average Drug Acquisition Cost (NADAC) values, as published by Medicaid, were used for medication costs of ribavirin, peginterferon, sofosbuvir and simeprevir–sofosbuvir, elbasvir–grazoprevir, and ombitasvir/paritaprevir/ritonavir and dasabuvir and daclatasvir. Costs included in the study were from December 2015 to March 2016. The cost of sofosbuvir–velpatasvir for treating HCV was obtained from Merck as wholesale acquisition costs.[51-53] Since this analysis is from the payers' perspective, there are no medication costs for no treatment.

Benefits/savings are the associated medical costs averted by treatment, calculated as the difference between medical costs encountered across the ten years for 'no treatment/watch and wait' and the medical costs for each treatment option, with corresponding costs across the following ten years. All-cause direct health-care (medical) costs for liver-related health outcomes and monitoring costs for each liver disease stage were extracted from the published literature.[54]

Natural history model

To incorporate natural history within the model, articles that had been published within one preceding year concerning the probability of F4, decompensated cirrhosis, liver cancer and liver transplantation were used for this study.[55] The transition probabilities listed are dimensionless and do not have units.

Table 1 summarises the earlier elements of costs, probabilities and disease progression in the natural history model.

Table 1: Base case values for probabilities, disease progression and costs

Input value/variable	References	Base case value (range)
Rate variable: Treatment response rate (SVR reached)		**Probabilities**
No treatment	56, 57	1% (0.7–1.7%)
Peginterferon–ribavirin	Pegasys, Pegintron, Copegus, Rebetol	41% (38–44%)
Elbasvir–grazoprevir, 12 weeks	C-EDGE TN	92% (94%)
Harvoni (sofosbuvir–ledipasvir), 12 weeks	ION 1,3; NEUTRINO trial; ION 1, double blind; NEUTRINO, open label	96% (89–100); Gilead '16; Range — genotype 1 Rx naïve NC; ION 1, 96–100; ION 3, 95–98; NEUTRINO, 89–95

Input value/variable	References	Base case value (range)
Simeprevir–sofosbuvir without ribavirin, 12 weeks	ION 1,3; NEUTRINO trial; ION 1, double blind; NEUTRINO, open label	97% (97%); Base case — treatment naïve, non-cirrhosis genotype 1, Range — genotype 1a
Viekira Pak–ribavirin 12 weeks	Pearl IV; Saphire I	95.3% (93–97.6%)
Daclatasvir–sofosbuvir	ALLY-1	96.4%
Treatment discontinuation		
All DAAs	58	8.1% (0–8.7)
Peginterferon–ribavirin	59	12.3% (0–12.3)
Transition Probabilities		
F3 to F4	60, 61	0.116
F4 with SVR to decompensated cirrhosis	62, 63	0.008
F4 without SVR to decompensated cirrhosis	64, 65	0.039
F4 with SVR to liver cancer	66, 67	0.005
F4 without SVR to liver cancer	68, 69	0.014
Decompensated cirrhosis to liver cancer	70, 71	0.068
Decompensated cirrhosis to liver transplant	72, 73	0.023
Treatment cost/day		$
Pegylated interferon–ribavirin	Medicaid National Average Drug Acquisition Cost	Pegylated interferon (pegasys proclick): 1,685.5 (1,264.15–2,106.8); ribavirin: 0.87 (0.66–1.1)
Elbasvir–grazoprevir	Medicaid National Average Drug Acquisition Cost[74]	Elbasvir–grazoprevir: 650 (487.5–812.5)
Sofosbuvir–velpatasvir	75	Sofsobuvir–velpatasvir: 890 (667.5–1,112.5)
Sofosbuvir–ledipasvir	Medicaid National Average Drug Acquisition Cost	Sofosbuvir–ledipasvir: 1,091.2 (818.4–1,364.0)
Simeprevir–sofosbuvir	Medicaid National Average Drug Acquisition Cost	Sofosbuvir: 981.5 (736.13–1,226.9) Simeprevir: 781.2 (585.96–76.5)
Ombitasvir–daclatasvir–paritaprevir–ribavirin	Medicaid National Average Drug Acquisition Cost	Viekira pak 243.5 (182.65–304.4) Ribavirin: 0.9 (0.7–1.1)
Daclatasvir–sofosbuvir	Medicaid National Average Drug Acquisition Cost	Sofosbuvir: 981.50 (736.1–1,226.9); Daclatasvir: 723.625 (542.74–904.53)
Cost: total/all-cause health-care cost/year		$/year
HCV infection monitoring	76	14,915.00 (14,464–16,686)
Decompensated cirrhosis	77	41,943.00 (38,670–44,936)
Compensated cirrhosis	78	16, 911.00 (15,313–26,354)
Liver cancer	79	58,208.00 (50,878–66,116)
Liver transplant + Medical cost, first and subsequent years	80	190,995.00 (182,973–199,017) SD = 8,022; subsequent years: 54,885.00 (50,476–59,294); SD = 4,409.00

Abbreviations: F0–F3, where F0 is mild hepatitis; HCV, hepatitis C virus; SD, standard deviation; SVR, sustained virological response.

The successive stages of the natural history of the disease included in this model were F0–F3, F4 compensated cirrhosis/fibrosis, decompensated cirrhosis, liver cancer and liver transplantation. Stages F0–F3 (no cirrhosis) were considered together for the context of the model.[81] The initial Medicaid HCV genotype 1a infected cohort was modelled year-by-year for a period of ten years. At each successive year, it was assumed that, unless the patient has experienced SVR as a result of treatment, a reliable, expected portion of the entire modelled cohort will advance along the range of disease progression, from baseline status up to liver transplantation. At baseline all patients are assumed to be without cirrhosis. The individual is modelled as treated, by one of the noted regimens, and either (1) reaches SVR or (2) fails to reach SVR. This model incorporated re-treatment of patients who did not reach SVR; 50 per cent of the patient population who failed to reach SVR were modelled to be re-treated in year 2 (ie 50 per cent chance of re-treatment for patient). Fifty per cent re-treatment was modelled to represent that not all patients who did not reach SVR could be re-treated, owing to access to care or cost of medications.

With SVR, the patient reaches a normal health status. If the patient does not reach SVR, the patient continues into liver disease progression stages. Each disease stage had a bivariate at each year: the individual may stay in the same health stage or progress through the disease stages, at each of the nine-year transitions (year 1 to year 2, etc., through year 9 to year 10). Patients could move from F0–F3 to F4/compensated cirrhosis, F4 to decompensated cirrhosis/or liver cancer, and from decompensated cirrhosis state to liver cancer/or liver transplantation.[82] Patients with liver cancer can either continue with liver cancer or move to liver transplantation. Thus, liver transplantation, liver cancer and decompensated cirrhosis are end points in the model.

Model outcomes and sensitivity analysis

Thus, the associated costs and benefits of each treatment option were computed by summing the yearly values, and final outcome measures (benefit cost ratio and net present value) were calculated using accumulated values. The benefit–cost ratio represents the ratio between the economic benefits of the intervention and the costs, while the net present value is the difference between the two values. If the benefit cost ratio is > 1 and the net present value is > 0, then care delivery of the treatment regimen is efficient, and the indicated benefits exceeded the costs (savings) and vice versa. When net present value $= 0$ and the benefit cost ratio $= 1$, benefits equal costs.

Assumptions of the results were modelled with sensitivity analyses. Sensitivity analyses were also conducted on discounting, probabilities, costs and treatment discontinuation rate, in order to determine the point at which the outcomes substantially change. The treatment discontinuation rate and probability of re-treatment were varied; evaluating the impact on efficiency if none versus the entire patient population without cirrhosis (who did not reach SVR) were re-treated. Sensitivity analysis was also conducted for SVR rates for DAAs. Sensitivity analysis for medication costs was conducted within ± 25 per cent of the known mean cost.

RESULTS

The total number of Medicaid HCV genotype 1a infected beneficiaries modelled in the study was 100,928 HCV genotype 1a infected Medicaid beneficiaries below 55 years of age, as of 2013, and 72,163 HCV genotype 1a infected Medicaid beneficiaries without cirrhosis.

At the Medicaid HCV-infected population level, ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin have the highest

efficiency (net present value), in comparison with no treatment. Peginterferon–ribavirin would save only US$618m for Medicaid. Although daclatasvir–sofosbuvir and simeprevir–sofosbuvir have negative net present values, medical costs are significantly lower and equivalent to those of other DAAs; for these treatments medical costs are only US$1bn, in comparison with medical costs for no treatment (US$10bn) and peginterferon (US$2.4bn). The savings, due to averted health complications, of daclatasvir–sofsobuvir and simeprevir–sofsobuvir are overshadowed by the high costs of the medication — and thus these medications appear inefficient. Sofosbuvir–ledipasvir and peginterferon–ribavirin each save approximately US$1 per person, for every US$1 invested. Daclatasvir–sofosbuvir and simeprevir–sofosbuvir each provide only approximately 80 cents for every US$1 invested. These results are presented in Table 2.

At the individual level, treatment with ombitasvir/paritaprevir/ritonavir and dasabuvir and ribavirin results in Medicaid saving US$107,812 per person with HCV genotype 1a infection over the next ten years. Elbasvir–grazoprevir saves Medicaid approximately US$67,919 per person over the next ten years. Sofosbuvir–ledipasvir results in a US$26,099 savings per person to Medicaid. Peginterferon–ribavirin results in only US$8,563 per person in savings to Medicaid as payer. Finally, daclatasvir–sofosbuvir and simeprevir–sofosbuvir cost Medicaid the most per person, with only US$31,384 and US$38,277 in costs per person over a ten-year period, respectively.

Tables 3 and 4 report the result of the cost–benefit analysis, while varying a variety of parameter groups, using the range of low and high input values presented in Table 1. All sensitivity analyses indicated that the ombitasvir–paritaprevir–ritonavir–ribavirin, elbasvir–grazoprevir and sofosbuvir–ledipasvir regimens were cost-saving and efficient despite variations in any individual model input. Although the numeric value/quantity of the cost–benefit analysis results changed, however, the overall results and preferred treatments did not. Thus, the overall study outcomes and care delivery efficiency of each treatment were not affected by treatment discontinuation, re-treatment or minor variations in SVR rate.[83]

Sensitivity analysis compared no re-treatment versus re-treatment of the entire population. Compared with no re-treatment, the net present value (and thus care efficiency) increased from US$122m to US$4.6bn for elbasvir–grazoprevir, when the entire population who did not reach a 'cure' was re-treated. Other DAAs, including daclatasvir–sofosbuvir, displayed a similar trend.

Table 2: Cost–benefit analysis results: Net present value and benefit cost ratios

Strategy	NPV ($)	BCR
No treatment	–	–
Ombitasvir/paritaprevir/ritonavir and dasabuvir–ribavirin	$7,780,056,214	5.61
Elbasvir–grazoprevir	$4,901,243,870	2.09
Sofosbuvir–velpatasvir	$3,378,186,160	1.55
Sofosbuvir–ledipasvir	$1,883,357,011	1.25
Peginterferon–ribavirin	$617,952,988	1.08
Daclatasvir–sofosbuvir	−$2,264,809,463	0.81
Simeprevir–sofosbuvir	−$2,762,175,135	0.77

Abbreviation: BCR, benefit–cost ratio; NPV, net present value.

Table 3: One-way sensitivity analysis: varying re-treatment from 0% to 100% (none versus all patients who do not reach SVR)

Re-treatment	Strategy	NPV ($)	BCR
0%	No treatment	–	–
	Ombitasvir/paritaprevir/ritonavir and dasabuvir +ribavirin	$4,188,475,964	2.68
	Elbasvir–grazoprevir	−$122,525,026	0.98
	Sofosbuvir–velpatasvir	−$2,249,376,673	0.75
	Sofosbuvir–ledipasvir	−$4,512,216,834	0.60
	Peginterferon–ribavirin	−$7,009,332,815	0.38
	Daclatasvir–sofosbuvir	−$10,630,432,455	0.39
	Simeprevir–sofosbuvir	−$11,351,301,401	0.37
100%	No treatment	–	
	Ombitasvir/paritaprevir/ritonavir and dasabuvir–ribavirin	$8,934,156,106	4.59
	Elbasvir–grazoprevir	$4,597,850,379	1.69
	Sofosbuvir–velpatasvir	$2,458,224,271	1.27
	Sofosbuvir–ledipasvir	$239,974,695	1.02
	Ribavirin/peginterferon	−$1,933,094,730	0.82
	Daclatasvir–sofosbuvir	−$5,875,378,645	0.66
	Simeprevir–sofosbuvir	−$6,592,058,411	0.64

Abbreviation: BCR, benefit–cost ratio; NPV, net present value

Variations in treatment effectiveness (SVR rate) were evaluated to determine the impact on care delivery efficiency. At first glance, it appears that the increased effectiveness of care is associated with decreased efficiency, as the net present value changed weakly as the probability of SVR increased (the probability of no SVR reduced). Considering variation in SVR, the modelled savings from ombitasvir/paritaprevir/ritonavir and dasabuvir–ribavirin, and elbasvir–grazoprevir decreased as SVR increased. Increased effectiveness results in improved outcomes and increased number of patients in the earlier stages of HCV — indicating care delivery that is both effective and efficient. As mentioned, sensitivity analysis of effectiveness of treatment did not change the outcomes of this study; the DAAs remain cost-saving and care-efficient. As expected, the probability of negative liver-related outcomes and disease progression decreases as the likelihood of SVR increases; this is illustrated in Table 4. At the same time, with higher effectiveness, the proportion of patients who are in the earlier stages of the disease increases, driving up the medical costs associated with disease monitoring in these stages. On the other hand, the difference in medication costs, which overshadows the reduction in savings, explains the opposite effect for sofosbuvir–ledipasvir and peginterferon–ribavirin.

Medication costs were varied by 25 per cent in order to test the extent to which the care delivery efficiency in Medicaid would change based on treatment affordability and pricing. As expected, increased medication costs resulted in significantly large decreases in net present value for all recommended treatments, indicating reduced efficiency

Table 4: One-way sensitivity analysis: low versus high SVR

Strategy	SVR	NPV ($)	BCR
No treatment	0.0070 (low SVR comparison)	–	–
	0.0169 (high SVR comparison)	–	–
Elbasvir–grazoprevir	0.6015	$7,295,264,402	2.39
	0.6094	$7,255,663,385	2.39
Sofosbuvir–velpatasvir	0.613259	$5,368,588,080	1.75
	0.624689	$5,520,567,802	1.78
Sofosbuvir–ledipasvir	0.5893	$3,535,963,455	1.40
	0.6321	$3,829,498,591	1.43
Peginterferon–ribavirin	0.3161	$1,866,146,965	1.22
	0.3560	$2,207,313,875	1.26
Daclatasvir–sofosbuvir	0.6186	−$1,036,993,493	0.92
Simeprevir–sofosbuvir	0.6209	$295,375,531	1.02

Abbreviation: BCR, benefit–cost ratio; NPV, net present value; SVR, sustained virologic response.

with increasing treatment costs. The savings associated with ombitasvir/paritaprevir/ritonavir/dasabuvir and ribavirin decreased from US$11.1bn to US$10bn, yet savings remained positive. The same downward trend in savings occurs for most DAAs. Variation in peginterferon costs was shown to have the greatest impact on the net present value, as peginterferon is the most expensive component of the peginterferon–ribavirin regimen for Medicaid.

CONCLUSION

This economic evaluation provides an analysis of long-term savings versus cost associated with HCV treatment, indicating whether it is cost-saving and efficient for Medicaid care delivery of DAAs in patients without cirrhosis and whether to continue peginterferon/ribavirin treatment or delay treatment. The ten-year costs and benefits for Medicaid adopting the policy of paying for DAA treatment, and re-treatment, of enrollees with chronic HCV, up to the age of 55, were modelled. In view of the high savings and improved patient outcomes, it is pertinent for Medicaid to consider treating HCV infection with the emerging DAAs, as a first-line regimen, to improve both the effectiveness and the efficiency of care delivery of HCV treatments among patients without cirrhosis. Current use of peginterferon–ribavirin and watch/wait strategies due to delayed access to effective treatments is inefficient for current care delivery. This cost–benefit analysis provides timely and significant data for Medicaid policymakers, meeting the pressing need for data on benefits and short- and long-term resource impacts of these new HCV treatments.

Overall, the model suggests that DAAs result in reduced all-cause health-care costs, prevent disease stage progression and avert morbidity. As modelled, treatment discontinuation does not significantly affect savings for DAA treatments. In comparison with no treatment and peginterferon–ribavirin, most of the modelled cohort remained in the earlier stages of the HCV infection progression; on the other hand, a larger amount of the cohort progressed to end stage liver disease outcomes. Thus, for

DAAs, most of the costs are due to the earlier stages of the disease (F0–F3, F4), while for peginterferon–ribavirin and watch and wait/no treatment, a notable portion of the costs are incurred as the cohort progresses to the end stages of liver disease (liver cancer, liver transplantation) in the ten-year time frame.

All treatment options result in cost savings for Medicaid, relative to a watch and wait strategy. For patients without cirrhosis, ombitasvir/paritaprevir/ritonavir and dasabuvir–ribavirin are currently the leading choice for treatment, in view of the cost savings to be reaped for the next ten years. The next highest cost-saving options applied to the entire HCV genotype 1a infected Medicaid population without cirrhosis are elbasvir–grazoprevir and sofosbuvir–velpatasvir, which result in cost savings of US$6.9bn and US$3.4bn to Medicaid, respectively. For future implementation of coverage, the ombitasvir/paritaprevir/ritonavir and dasabuvir–ribavirin and elbasvir–grazoprevir treatment options can be feasibly implemented as well. Both ombitasvir/paritaprevir/ritonavir and dasabuvir-ribavirin and elbasvir-grazoprevir are on the lower end of the gradient of HCV treatment cost savings, but these treatment options have a lower likelihood of complications and higher SVR rates than peginterferon–ribavirin. Although daclatasvir–sofosbuvir and simeprevir–sofosbuvir result in negative net present value for patients without cirrhosis, however, the low health-care costs (both liver and non-liver-related) from these medications indicate potential benefit in the future. This study provided similar results in comparison with other economic evaluations of DAAs, as well as the only other cost–benefit analysis of DAAs (sofosbuvir alone) in the literature.[84]

Even when varying treatment discontinuation, there is no substantial change in net present value for all treatments in patients without cirrhosis. This indicates that despite real world variation in treatment discontinuation, implementation of coverage for DAAs results in savings for Medicaid. One of the prevalent critiques of coverage for DAAs is that patients must be adherent to treatment regimens, although there is no strong evidence that discontinuation affects outcomes.[85] Sensitivity analysis shows that even when there is maximum treatment discontinuation, there is still overall benefit and savings, as the benefit of treatment is averaged out. The net present value is still above zero.

In addition, re-treatment resulted in savings; there is a significant increase in cost savings if re-treatment with DAAs is routinely covered for patients without cirrhosis, especially for ombitasvir/paritaprevir/ritonavir and dasabuvir–ribavirin, elbasvir–grazoprevir and sofosbuvir–ledipasvir treatment options; savings incurred from these DAA options increase as the probability of re-treatment increases.

Among the many barriers to care that preclude the savings involved with DAA treatment is lack of patient awareness. The increased costs of DAA treatments are accompanied by complicated treatment algorithms, presenting challenges for patients and providers alike; for effective care delivery, barriers to treatments need to be addressed, especially lack of awareness.[86] Out of four populations with HCV (those undiagnosed/not treated, diagnosed/not treated, diagnosed/treated and diagnosed/re-treated, those undiagnosed/not treated would benefit from screening. Overall, the HCV infection awareness is low, representing the single largest barrier to treatment.[87] According to a national representative National Health and Nutrition Examination Survey (NHANES) sample, less than 50 per cent of individuals with HCV are aware of their status.[88] Cost effectiveness of screening increases the cost effectiveness of treatment. Further, the effectiveness of screening is improved when treatment is expanded to the early stages

of the disease.[89] In general, HCV testing is a cost-effective alternative to treating advanced liver disease,[90] with screening resulting in reduced costs and improved effectiveness compared with future liver disease treatment.[91] A systematic review of the cost effectiveness illustrated the evidence for care is high.[92] Screening and treating individuals in the earlier stages brings US$824 in monetary benefit.[93]

Expanding screening provides the largest health-care value;[94] I would recommend a Medicaid wide screening policy for HCV — due to limitations with coverage, however, screening of the high-risk population is a priority. One-time screening of younger individuals, aged 15–30, in high-risk localities for HCV has been shown to be cost-effective.[95] Akin to the programme recommended by the Department of Health and Human Services,[96] I would recommend a screening programme — for Medicaid individuals — as there are the high-risk population for HCV. Individuals who have continued percutaneous blood exposure or a blood transfusion before 1992 should be tested. This has also been recommended by the Centers for Medicare and Medicaid Services.[97] In addition, I recommend screening, as per Centers for Disease Control and Prevention (CDC) guidelines, for individuals with persistently elevated liver enzymes/reduced liver function, as well as for those on hemodialysis (CDC), on a continuous, yearly basis.[98]

The feasibility of screening in Medicaid patients, however, may be reduced, for want of healthcare access to primary care physicians or timely care. Despite medical coverage, financial barriers are common in 50 per cent of patients with HCV.[99] Other barriers in the HCV population that restrict awareness, and thus effective care delivery, are the confusion and lack of heath literacy regarding interpretation of screening tests and modes of transmission.[100] Healthcare professionals often lack the experience to address the needs of the HCV population, and surveys show only 69 per cent of primary care physicians screen for known risk factors for HCV; further, patient level perceived physician ineptitude is another barrier to care and screening.[101]

Currently, risk-based screening is not fully implemented in the healthcare system, as over 75 per cent of those infected with HCV are not aware of their status.[102] Insurance coverage and a usual source of care affect whether or not a HCV positive person had seen a healthcare professional, which further affects the likelihood of screening. Barriers of care at the payer level such as inadequate funding, in addition to both patient and payer awareness, restrict the likelihood of HCV screening, as well as treatment/care.[103] Further collaboration is needed between all levels of HCV stakeholders, from patients to payers to providers, in order to bridge the gap in fragmented systems, HCV screening and surveillance, education to improve awareness, and care services.[104]

The lack of use of effective, efficient, evidence-based treatment options for HCV has negative consequences on care delivery, affecting the health of patients, public health of the population and the payer as well. Inefficient and ineffective care delivery of HCV treatments affect the incentive to participate in HCV screening, missed opportunities to reduce disease transmission within and across states, and identify/select patients who qualify for appropriate, evidence-based HCV treatments.[105] Inconsistencies in treatment across programmes result in health outcome and cost inefficiencies in the healthcare system, necessitating greater consistency in the care delivery of DAAs.[106]

AUTHOR'S NOTE

The author would like to thank Drs Rowan, Zhang, and Shegog for their earlier work on direct acting-antivirals, and the previous AASLD-IDSA recommendations made prior to 25th June, 2016.

References

1. Foster, G.R. (2010) 'Pegylated interferons for the treatment of chronic hepatitis C', *Drugs*, Vol. 70, No. 2, pp. 147–165.
2. U.S. Department of Veterans Affairs. (2016) 'Homepage', available at: http://www.va.gov/ (accessed February, 2017).
3. Afdhal, N., Zeuzem, S., Kwo, P., Chojkier, M., Gitlin, N., Puoti, M., Romero-Gomez, M., Zarski, J.P., Agarwal, K., Buggisch, P., Foster, G.R. (2014) 'Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection', *New England Journal of Medicine*, Vol. 370, No. 20, pp. 1889–1898.
4. Afdhal, N., Reddy, K.R., Nelson, D.R., Lawitz, E., Gordon, S.C., Schiff, E., Nahass, R., Ghalib, R., Gitlin, N., Herring, R., Lalezari, J. (2014) 'Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection', *New England Journal of Medicine*, Vol. 370, No. 16, pp. 1483–1493.
5. Kowdley, K.V., Gordon, S.C., Reddy, K.R., Rossaro, L., Bernstein, D.E., Lawitz, E., Shiffman, M.L., Schiff, E., Ghalib, R., Ryan, M., Rustgi, V. (2014) 'Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis', *New England Journal of Medicine*, Vol. 370, No. 20, pp. 1879–1888.
6. U.S. Food and Drug Administration. (2016). 'Homepage', available at: http://www.fda.gov/ (accessed February, 2017).
7. Armstrong, G.L., Wasley, A., Simard, E.P., McQuillan, G.M., Kuhnert, W.L., Alter, M.J. (2006) 'The prevalence of hepatitis C virus infection in the United States, 1999 through 2002', *Annals of Internal Medicine*, Vol. 144, No. 10, pp. 705–714.
8. Belousova, V., Abd-Rabou, A.A., Mousa, S.A. (2015) 'Recent advances and future directions in the management of hepatitis C infections', *Pharmacology and Therapeutics*, Vol. 145, pp. 92–102.
9. Centers for Disease Control and Prevention. (2015) 'Viral Hepatitis', available at: https://www.cdc.gov/hepatitis/hcv/guidelinesc.htm (accessed 16th February, 2018).
10. Ditah, I., Ditah, F., Devaki, P., Ewelukwa, O., Ditah, C., Njei, B., Luma, H.N., Charlton, M. (2014) 'The changing epidemiology of hepatitis C virus infection in the United States: National Health and Nutrition Examination Survey 2001 through 2010', *Journal of Hepatology*, Vol. 60, No. 4, pp. 691–698.
11. Spach, D.H., Kim, H.N. 'Treatment of HCV Genotype 1', available at: http://www.hepatitisc.uw.edu/go/treatment-infection/treatment-genotype-1/core-concept/all (accessed February, 2017).
12. Pharmaceutical Research and Manufacturers of America. 'Twenty-five years of progress against hepatitis C: setbacks and stepping stones', available at: http://www.phrma.org/sites/default/files/pdf/Hep-C-Report-2014-Stepping-Stones.pdf (accessed February, 2017).
13. U.S. Preventive Services Task Force. (2013) 'Final recommendation statement *hepatitis C: screening'*, available at: http://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/hepatitis-c-screening (accessed February, 2017).
14. Menzin, J., White, L.A., Nichols, C., Deniz, B. (2012) 'The economic burden of advanced liver disease among patients with hepatitis C virus: a large state Medicaid perspective', *BMC Health Services Research*, Vol. 12, No. 1, p. 459.
15. Rice, J.P. (2015) 'Hepatitis C treatment: back to the warehouse', *Clinical Liver Disease*, Vol. 6, No. 2, pp. 27–29.
16. Ibid., ref. 9 above.
17. Razavi, H., ElKhoury, A.C., Elbasha, E., Estes, C., Pasini, K., Poynard, T., Kumar, R. (2013) 'Chronic hepatitis C virus (HCV) disease burden and cost in the United States', *Hepatology*, Vol. 57, No. 6, pp. 2164–2170.
18. Ibid.
19. PricewaterhouseCoopers (PwC's), 'Health Research Institute. Medical cost trend: behind the numbers', available at: https://www.pwc.com/us/en/health-industries/top-health-industry-issues/assets/pwc-hri-medical-cost-trend-2015.pdf (accessed 16th February, 2018).
20. Reau, N.S., Jensen, D.M. (2014) 'Sticker shock and the price of new therapies for hepatitis C: is it worth it?' *Hepatology*, Vol. 59, No. 4, pp. 1246–1249.
21. Gordon, S.C., Pockros, P.J., Terrault, N.A., Hoop, R.S., Buikema, A., Nerenz, D., Hamzeh, F.M. (2012) 'Impact of disease severity on healthcare costs in patients with chronic hepatitis C (CHC) virus infection', *Hepatology*, Vol. 56, No. 5, pp. 1651–1660.
22. Ibid., ref 14 above.
23. Alter, H.J., Liang, T.J. (2012) 'Hepatitis C: the end of the beginning and possibly the beginning of the end', *Annals of Internal Medicine*, Vol. 156, No. 4, pp. 317–318.
24. Mitchell, A.E., Colvin, H.M., Palmer, B.R. (2010) 'Institute of Medicine recommendations for the prevention and control of hepatitis B and C'. *Hepatology*, Vol. 51, No. 3, pp. 729–733.
25. Poynard, T., Colombo, M., Bruix, J., Schiff, E., Terg, R., Flamm, S., Moreno-Otero, R., Carrilho, F., Schmidt, W., Berg, T., McGarrity, T. (2009) 'Peginterferon alfa-2b and ribavirin: effective in patients with hepatitis C who failed interferon alfa/ribavirin therapy', *Gastroenterology*, Vol, 136, No. 5, pp. 1618–1628.
26. Ibid.
27. Ibid., ref 23 above.
28. Ibid., ref 19 above.
29. Aronsohn, A., Jensen, D. (2014) 'Expanding access to hepatitis C virus care: a call to deconstruct individualized therapy', *Hepatology*, Vol, 59, No. 1, pp. 13–15.
30. Etzion, O., Ghany, M.G. (2015) 'A cure for the high cost of hepatitis C virus treatment', *Annals of Internal Medicine,* Vol, 162, No. 9, pp. 660–661.
31. Appleby, J. (2014) 'There's a life-saving hepatitis C drug. But you may not be able to afford it', available at: http://khn.org/news/insurers-debate-who-should-get-costly-hepatitis-c-drug/ (accessed February, 2017).
32. Appleby, J. (2014) 'Should healthier patients be asked to wait to use costly hepatitis C drugs?' available at: http://khn.org/news/should-healthier-patients-be-asked-to-wait-to-use-costly-hepatitis-c-drugs/ (accessed February, 2017).

33. Appleby, J. (2014) 'Who should get pricey hepatitis C drugs?', available from: http://khn.org/news/sovaldi-who-should-get-pricey-drug/ (accessed February, 2017).
34. Canary, L.A., Klevens, R.M., Holmberg, S.D. (2015) 'Limited access to new hepatitis C Virus Treatment Under State Medicaid Programs Limited Access to New HCV Treatment', *Annals of Internal Medicine*, Vol. 163, No. 3, pp. 226–228.
35. Humer, C. (2014) 'Express scripts drops Gilead hepatitis C drugs for cheaper AbbVie rival. Reuters', available at: http://www.reuters.com/article/us-express-scripts-abbvie-hepatitisc-idUSKBN0K007620141222 (accessed February, 2017).
36. Barua, S., Greenwald, R., Grebely, J., Dore, G.J., Swan, T., Taylor, L.E. (2015) 'Restrictions for Medicaid reimbursement of sofosbuvir for the treatment of hepatitis C virus infection in the United States', *Annals of Internal Medicine*, Vol. 163, No. 3, pp. 215–223.
37. Ibid., ref 35 above.
38. Ibid., ref 36 above.
39. Milliman, Inc. 'Health care reform and hepatitis C: a convergence of risk and opportunity', available at: http://us.milliman.com/uploadedFiles/insight/2013/convergence-of-risk-and-opportunity.pdf (accessed February, 2017).
40. Ibid., ref 9 above.
41. Ibid., ref 39 above.
42. Chidi, A.P., Bryce, C.L., Donohue, J.M., Fine, M.J., Landsittel, D.P., Myaskovsky, L., Rogal, S.S., Switzer, G.E., Tsung, A., Smith, K.J. (2016) 'Economic and public health impacts of policies restricting access to hepatitis C treatment for Medicaid patients', *Value in Health*, Vol. 19, No. 4, pp. 326–334.
43. Ibid.
44. Ibid., ref 9 above.
45. Gordon, S.C., Lamerato, L.E., Rupp, L.B., Holmberg, S.D., Moorman, A.C., Spradling, P.R., Teshale, E., Xu, F., Boscarino, J.A., Vijayadeva, V., Schmidt, M.A. (2015) 'Prevalence of cirrhosis in hepatitis C patients in the Chronic Hepatitis Cohort Study (CHeCS): a retrospective and prospective observational study'. *The American Journal of Gastroenterology*, Vol. 110, No. 8, pp. 1169–1177.
46. American Association for the Study of Liver Diseases and the Infectious Diseases Society of America. AASLD - IDSA. (2017) 'HCV guidance: recommendations for testing, managing, and treating hepatitis C', available at: http://www.hcvguidelines.org/full-report-view (accessed February, 2017).
47. CVS Health. (2014) 'CVS Health Research Institute provides first look at treatment with new hepatitis C therapies', available at: http://www.cvshealth.com/content/cvs-health-research-institute-provides-first-look-treatment-new-hepatitis-c-therapies (accessed February, 2017).
48. Ibid.
49. Hauser, G., Awad, T., Brok, J., Thorlund, K., Štimac, D., Mabrouk, M., Gluud, C., Gluud, L.L. (2014) 'Peginterferon plus ribavirin versus interferon plus ribavirin for chronic hepatitis C', *The Cochrane Library*, No. 2, pp. CD005441.
50. Poonsapaya, J.M., Einodshofer, M., Kirkham, H.S., Glover, P., DuChane, J. (2015) 'New all oral therapy for chronic hepatitis C virus (HCV): a novel long-term cost comparison', *Cost Effectiveness and Resource Allocation*, Vol. 13, No. 1, p. 17.
51. Ibid.
52. Merck. 'Merck receives FDA approval of ZEPATIER™ (elbasvir and grazoprevir) for the treatment of chronic hepatitis C virus genotype 1 or 4 infection in adults following priority review', available at: https://www.merckconnect.com/static/pdf/zepatier-news-release.pdf (accessed 16th February, 2018).
53. University of Washington. 'Hepatitis C online', available at: http://www.hepatitisc.uw.edu/(accessed 16th February, 2018).
54. McAdam-Marx, C., McGarry, L.J., Hane, C.A., Biskupiak, J., Deniz, B., Brixner, D.I. (2011) 'All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective', *Journal of Managed Care Pharmacy*, Vol. 17, No. 7, pp. 531–546.
55. Chhatwal, J., Kanwal, F., Roberts, M.S., Dunn, M.A. (2015) 'Cost-effectiveness and budget impact of hepatitis C virus treatment with Sofosbuvir and Ledipasvir in the United States cost-effectiveness of HCV treatment with Sofosbuvir and Ledipasvir', *Annals of Internal Medicine*, Vol. 162, No. 6, pp. 397–406.
56. Ibid., ref 33 above.
57. Ibid., ref 39 above.
58. Ibid., ref 30 above.
59. Ibid., ref 31 above.
60. Ibid., ref 33 above.
61. Ibid., ref 39 above.
62. Ibid., ref 33 above.
63. Ibid., ref 39 above.
64. Ibid., ref 33 above.
65. Ibid., ref 39 above.
66. Ibid., ref 33 above.
67. Ibid., ref 39 above.
68. Ibid., ref 33 above.
69. Ibid., ref 39 above.
70. Ibid., ref 33 above.
71. Ibid., ref 39 above.
72. Ibid., ref 33 above.
73. Ibid., ref 39 above.
74. Ibid., ref 34 above.
75. Ibid., ref 35 above.
76. Ibid., ref 36 above.
77. Ibid., ref 36 above.
78. Ibid., ref 36 above.
79. Ibid., ref 36 above.
80. Ibid., ref 36 above.
81. Brogan, A.J., Talbird, S.E., Thompson, J.R., Miller, J.D., Rubin, J., Deniz, B. (2014) 'Cost-effectiveness of Telaprevir combination therapy for chronic hepatitis C', *PLoS One*, Vol. 9, No. 3, p. e90295.
82. Ibid., ref 55 above.
83. Drummond, M.F., Sculpher, M.J., Torrance, G.W., O'Brien, B.J., Stoddart, G.L. (2005) '*Methods for the Economic Evaluation of Health Care Programmes'*, Oxford University Press, Oxford, UK, 2005.

84. Ibid., ref 50 above.
85. Clements, K.M., Clark, R.E., Lavitas, P., Kunte, P., Graham, C.S., O'Connell, E., Lenz, K., Jeffrey, P. (2016) 'Access to new medications for hepatitis C for Medicaid members: A Retrospective Cohort Study', *Journal of Managed Care and Specialty Pharmacy*, Vol. 22, No. 6, pp. 714–722b.
86. McGowan, C.E., Fried, M.W. (2012) 'Barriers to hepatitis C treatment', *Liver International*, Vol. 32, No. s1, pp. 151–156.
87. Ibid.
88. Denniston, M.M., Klevens, R.M., McQuillan, G.M., Jiles, R.B. (2012) 'Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001–2008', *Hepatology*, Vol. 55, No. 6, pp. 1652–1661.
89. Linthicum, M.T., Gonzalez, Y.S., Mulligan, K., Moreno, G.A., Dreyfus, D., Juday, T., Marx, S.E., Lakdawalla, D.N., Edlin, B.R., Brookmeyer, R. (2016) 'Value of expanding HCV screening and treatment policies in the United States', 'The American Journal of Managed Care', Vol. 22, No. 6 Spec No., pp. SP227–SP235.
90. Ibid.
91. Carlson, B. (2005) 'HCV testing cost-effective alternative to treating advanced disease', *Biotechnol Healthcare Journal*, Vol. 2, No. 5, pp. 12,14.
92. Coward, S., Leggett, L., Kaplan, G.G., Clement. F. (2016) 'Cost-effectiveness of screening for hepatitis C virus: a systematic review of economic evaluations', *BMJ Open*, Vol. 6, No. 9, p. e011821.
93. Ibid., ref 89 above.
94. Ibid., ref 89 above.
95. Assoumou, S., Tasillo, A., Leff, J.A., Shackman, B.R., Drainoni, M.L., Horsburgh, C.R., Barry, A., Regis, C., Kim, A., Marshall, A., Saxena, S. (2016) 'The cost-effectiveness of hepatitis C screening strategies among adolescents and young adults in primary care settings', *Open Forum Infectious Diseases*, Vol. 3, No. suppl 1, p. 1786.
96. U.S. Department of Health & Human Services, 'Hepatitis C Basic Information', available at: https://www.hhs.gov/hepatitis/learn-about-viral-hepatitis/hepatitis-c-basics/index.html (accessed February, 2017).
97. Centers for Medicare & Medicaid Services, 'Decision memo for screening for hepatitis C virus (HCV) in adults', available at: https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=272 (accessed February, 2017).
98. Ibid., ref 9 above.
99. Ibid., ref 86 above.
100. Ibid., ref 86 above.
101. Ibid., ref 86 above.
102. Ibid., ref 88 above.
103. Ibid., ref 86 above.
104. Ibid., ref 86 above.
105. Ibid., ref 29 above.
106. Ibid., ref 20 above.