Original Article

Sofosbuvir-based Regimens with Task Shifting Is Cost-effective in Expanding Hepatitis C Treatment Access in the United States

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Abstract

Background and Aims: The current paradigm of specialist physician-managed treatment of chronic hepatitis C virus infection (HCV) is inefficient in absorbing the approximately 3 million patients awaiting treatment in the United States. Task shifting—whereby specialist physicians screen patients for treatment eligibility but on-treatment monitoring is devolved to more abundant non-physician clinicians—achieves non-inferior treatment outcomes with second generation direct-acting antivirals (2nd Gen DAAs), may increase treatment capacity, and may facilitate greater treatment access. We determined the cost effectiveness of 2nd Gen DAAs with respect to interferon-based first-generation DAAs (1st Gen DAAs) within a task-shifted treatment model. **Methods:** Using a previously described decision-analytic Markov structure, we modeled a hypothetical cohort of 1,000 patients with HCV genotype 1 infection over a lifetime horizon, based upon our outreach clinic's HCV treatment protocol. Treatment-naïve and treatment-experienced HCV cohorts were modeled separately, based upon our outr8each clinic's demographics. Treatment response to 2nd Gen DAAs was modeled based on our outreach clinic's data. Adverse events, utility, costing, and transition probabilities were sourced from the literature. **Results:** Driven by improved effectiveness and safety, as well as an expected increase in treatment capacity, 2nd Gen DAAs treatment monitored by non-physician clinicians was projected to improve health outcomes and be dominant from a cost-effective perspective versus that of 1st Gen DAAs. Trends were consistent across all assessed patient subpopulations. **Conclusions:** Based on an assumption of increased treatment capacity accompanying a task-shifted treatment model, 2nd Gen DAAs-based treatment was cost effective and cost saving as compared to 1st Gen DAAs-based treatment for all HCV patient subgroups assessed.

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Introduction

Chronic infection with hepatitis C virus (HCV) is estimated to affect over 3 million individuals,[1,2] and an estimated 80% of these individuals remain untreated.[3] Low treatment rates have been attributed to under-diagnosis of HCV—with approximately 50% of chronically-infected individuals unaware of their disease—and to the adverse effect-prone interferon-based treatment options which have represented the standard of care until recently.[4] Along with the recent guidelines from the Centers for Disease Control and Prevention that aim to expand HCV screening, highly effective and safe second generation direct-acting antivirals (2nd Gen DAAs) have the potential to close this treatment gap.[5]

While drug acquisition costs of 2nd Gen DAAs-based treatment may be a barrier to treatment access, the high effectiveness, short treatment durations, and safety of these agents bestow considerable overall cost effectiveness for treating HCV genotype 1, at levels remarkably less than a cost-effectiveness threshold of $50,000 per quality adjusted life year (QALY) gained, even in difficult-to-treat subpopulations.[6–9] Moreover, as more competing DAA regimens enter the market, drug cost as a proportion of treatment-related costs is likely to decline.

A less-addressed challenge to treatment access is the limited workforce available to deliver care to approximately 3 million HCV-infected patients in the United States. HCV treatment remains dominated by gastroenterologists, hepatologists, and infectious diseases specialists, who represent a workforce of approximately 19,000 and are typically located in urban referral medical centers.[10] Even when patients and specialists are geographically nearby, the proportion of patients linked to care is low. Indeed, recent data from

Keywords: Hepatitis C; Treatment access; Task shifting; Cost effectiveness.
Abbreviations: HCV, hepatitis C virus; DAA, direct-acting antiviral; QALY, quality adjusted life year; PR, pegylated interferon with ribavirin; LVN, licensed vocational nurse; SVR12, sustained virologic response 12 weeks after end of treatment; SOF, sofosbuvir; SMV, simeprevir; LDV, ledipasvir; HIV, human immunodeficiency virus; AASLD, American Association for the Study of Liver Diseases.
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Philadelphia County—a large urban center with a high concentration of medical specialists—demonstrate that only 6% of the estimated HCV-infected population was under regular care and that only 3% received treatment.[11] Patients in medically underserved areas, where 20% of the United States' population resides, therefore, appear even more likely to remain outside the continuum of HCV care.[12]

Channeling patients from rural communities to specialist clinics in urban referral centers is impractical and inconvenient. An alternative strategy is to empower a more abundant and accessible local cadre of non-physician (mid-level) healthcare providers to deliver HCV care—a concept known as task shifting.[13] The viability of such programs at-scale is buttressed by the safety, effectiveness, and simplicity of interferon-free 2nd Gen DAAs (i.e. elbasvir+grazoprevir, ledipasvir+sofosbuvir (LDV/SOF), ombitasvir+paritaprevir +ritonavir, and dasabuvir, sofosbuvir+simeprevir (SOF+SMV)). We previously demonstrated that devolution of 2nd Gen DAAs-based HCV treatment to appropriately supervised, non-physician healthcare providers at outreach clinics in medically underserved areas in California achieved rates of treatment adherence, safety, and effectiveness that were comparable to those seen in pivotal clinical trials and to 'real world' experiences reported from tertiary medical centers.[14]

Task shifting models in medically underserved areas could, therefore, be instrumental to improving HCV treatment access in the United States. However, the scaling up of such models necessitates a better understanding of the budgetary impact and cost effectiveness of 2nd gen DAAs regimens vis-à-vis first generation DAAs-based treatment (1st Gen DAAs; e.g. pegylated interferon+ribavirin (PR) with boceprevir, simeprevir, or telaprevir). In this analysis, we determined the budgetary impact and cost-effectiveness of 2nd Gen DAAs-based treatment, across different treatment capacity scenarios as facilitated by task shifting, and compared to 1st Gen DAAs-based treatment.

Methods

Medically underserved areas

'Medically underserved area' is an official designation of the Health Resources and Services Administration of the United States Department of Health and Human Services. They are defined as geographic tracts that fall below a threshold of the Index of Medical Underservice—an index incorporating the ratio of primary medical care physicians per 1,000 population, infant mortality rate, and percentage of the population aged 65 years or over.

Task shifting in outreach clinic treatment

We operate three hepatology outreach clinics in medically underserved areas located 181 to 236 miles from our academic medical center. Our task-shifted treatment model, in contrast to the conventional treatment model involving frequent direct contact between the specialist physician and the patient, was instituted after our favorable experience that yielded very low rates of drug intolerance or adverse events with 2nd Gen DAAs.

In our treatment model, patients with HCV were evaluated in outreach clinics at least 3 days a month during a full-day hepatology clinic conducted by a hepatologist from our academic medical center. In patients prescribed 2nd Gen DAAs, routine follow-up was performed via telephone calls conducted by an experienced, part-time licensed vocational nurse (LVN) and the LVN's support staff of medical assistants, through which medication adherence, tolerance, adverse events, and timely routine laboratory testing were assessed. Laboratory results and adverse effects reported by the patients were remotely reviewed by the hepatologist, within 24 hours and through an electronic health record. On-call hepatology fellows and/or hepatologists were paged immediately with critical laboratory results and symptoms deemed urgent by the patients. In addition, chart checks were performed up to 5 times per month to review treatment tolerance and safety. Patients with persistent issues were scheduled for urgent clinical follow-up by the hepatologist on a case-by-case basis. The hepatologist and LVN remained available to patients by telephone and secure messaging though the electronic health record system, and could be scheduled for non-routine visits at the next clinic date or referred to local urgent care facilities for more pressing concerns. Patients requiring a higher level of care were afforded the option of being transferred to our academic medical center.

The hepatologist assessed all patients at the outreach clinic at approximately 12 weeks after completion of therapy, in order to determine achievement of viral clearance, which was defined as undetectable HCV RNA 12 weeks after end of treatment (sustained virologic response-12; SVR12).

Budgetary impact and cost-effectiveness modeling

Using a previously described decision-analytic Markov structure, we modeled a hypothetical cohort of 1,000 patients infected with HCV genotype 1 over a lifetime horizon based upon our outreach clinic's HCV treatment protocol.[8] We also modeled independent cohorts of treatment-naïve and treatment-experienced HCV genotype 1 patients from a US third-party payer perspective over a lifetime horizon.

Mirroring our outreach clinic's demographics, the population modeled consisted of 11.7% treatment-naïve non-cirrhotic patients, 14.8% treatment-naïve cirrhotic patients, 32.4% treatment-experienced non-cirrhotic patients, and 41.1% treatment-experienced cirrhotic patients (Fig. 1). The average age was 62 years. The outcomes and costs were discounted at an annual rate of 3.0%, in accordance with Academy of Managed Care Pharmacy guidelines.[15]

Patients were modeled to receive treatment with either PR +1st Gen DAAs or an interferon-free 2nd Gen DAAs regimen. SVR12 rates for 1st Gen DAAs were taken from published real-world treatment outcome data for boceprevir+PR.[16] SVR12 rates for 2nd Gen DAAs were obtained from our experience in outreach clinics, published previously.[14] 1st Gen DAAs were modeled as a class, with effectiveness and drug acquisition costs assumed to be equivalent for both boceprevir- and telaprevir-containing regimens. 2nd Gen DAAs were also modeled as a class, with effectiveness inputs assumed equal to SOF+SMV, which was the only 2nd Gen DAA with sufficient data collected in our clinic at time of analysis. Drug wholesale acquisition costs for 2nd Gen DAAs were assumed equivalent to LDV+SOF for 12 weeks, given that patients in our setting were no longer typically prescribed the more expensive SOF+SMV regimen.

Given shorter treatment courses and fewer laboratory monitoring requirements, treatment with 2nd Gen DAAs was conservatively assumed to double treatment capacity—a phenomenon we have already experienced at our outreach clinics

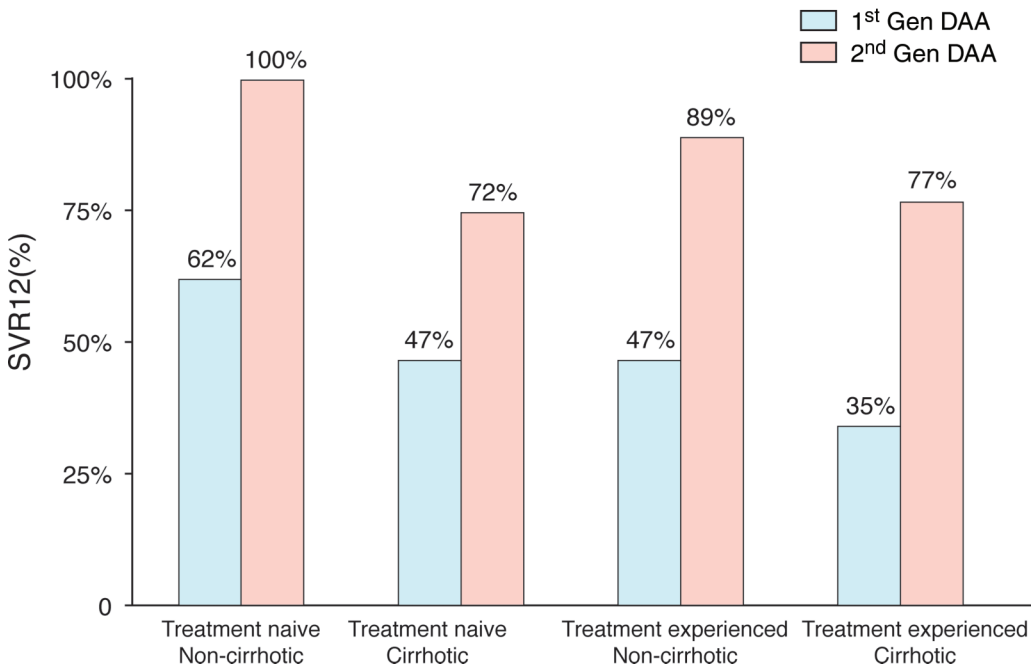

Fig. 1. Patient clinical characteristics inputs and sustained virologic response rates. SVR12, sustained virologic response 12 weeks after end of treatment; 1st Gen DAA, first generation direct-acting antiviral agents; 2nd Gen DAA, second generation direct-acting antiviral agents. Analysis only includes patients with hepatitis C genotype 1.

and demonstrated in other resource-limited settings with human immunodeficiency virus (HIV) infection patients.[14,17] Hence, the model consisted of 1,000 patients receiving 2nd Gen DAAs in the intervention arm, and in the comparator arm, 500 patients receiving PR+1st Gen DAAs and 500 patients remaining untreated.

We based healthcare utilization of 2nd Gen DAAs on American Association for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD) guidelines, current practice in our clinics, and hepatologist consensus (Table 1).[18] For 1st Gen DAAs, we used the monitoring paradigm recommended at the time by AASLD (accessed July, 2014).[8] For the model's base case, it was assumed that the LVN reimbursement rate for routine follow-up evaluation was incident to physician services (i.e. under the physician's Provider Identification Number) and, therefore, billed identically to the physician reimbursement rate. Transition probabilities, utilities, and cost estimates (in 2014 USD) were based on literature and hepatologist consensus, as described previously.[8]

A first sensitivity analysis assumed that reimbursement for LVN services was not incident to physician services, but to 85% of the physician reimbursement rate as per Section 1848(p) of the Social Security Act. A second sensitivity analysis varied the expected impact of task shifting on potential treatment capacity, from no increase to a 3-fold increase.

Results

Driven by improved effectiveness and safety, 2nd Gen DAAs treatment monitored by non-physician clinicians was projected to improve health outcomes, with a reduction of 71% for cases of decompensated cirrhosis, 63% for hepatocellular carcinoma, 71% for liver transplantation, and 68% for liver-related death, relative to 1st Gen DAAs (Fig. 2). This trend was consistent across all subpopulations of patients (treatment-naïve, treatment-experienced, non-cirrhotic and cirrhotic) (Table 2), with the greatest relative improvements in health benefits seen in treatment-naïve non-cirrhotic patients and treatment-experienced non-cirrhotic patients where the treatments with 2nd Gen DAAs showed the highest treatment effectiveness in our cohort (Fig. 1).

When a doubling of treatment capacity with task shifting with 2nd Gen DAAs was assumed, on-treatment monitoring costs were reduced by 55% and total lifetime costs by 20% as compared with 1st Gen DAAs (Table 3). The 2nd Gen DAAs treatment monitored by non-physician clinicians was a dominant strategy (i.e. resulted in higher effectiveness in terms of life-years and quality-adjusted life years gained and lower total costs), relative to 1st Gen DAAs. These trends were consistent across treatment-naïve, treatment-experienced, non-cirrhotic and cirrhotic patient subpopulations. Across all patient subpopulations, 2nd Gen DAAs within a task-shifted treatment model remained the dominant treatment strategy from a cost-effectiveness perspective.

Results from the first sensitivity analysis were similar to the base case (Table 4), with reductions of 56% in monitoring costs and 20% in total costs, relative to 1st Gen DAAs, indicating that the analysis was not sensitive to small variations in provider reimbursement rates.

Our second sensitivity analysis varied expected increases in treatment capacity, from no increase to a 3-fold increase (Table 5). With a 3-fold increase in treatment capacity enabled by task shifting, relative to the base case where a 2-fold increase was assumed, advanced liver disease complications were projected to be even further reduced. Across all scenarios, task shifting remained a dominant strategy from a cost-effectiveness perspective.

Table 1. Monitoring health resource utilization inputs by regimen

ITEM	UNIT COST	2nd GEN DAA: NEW EVAL	2nd GEN DAA: W0	2nd GEN DAA: W4	2nd GEN DAA: W12 (or final)	PR+1st GEN DAA: NEW EVAL	PR+1st GEN DAA: ADD'L INVEST.	PR+1st GEN DAA: W0	PR+1st GEN DAA: W1	PR+1st GEN DAA: W4	PR+1st GEN DAA: W6	PR+1st GEN DAA: W10	PR+1st GEN DAA: W12	PR+1st GEN DAA: W14	PR+1st GEN DAA: W16	PR+1st GEN DAA: W18	PR+1st GEN DAA: W20	PR+1st GEN DAA: W22	PR+1st GEN DAA: W24	PR+1st GEN DAA: W28	PR+1st GEN DAA: W32	PR+1st GEN DAA: W34	PR+1st GEN DAA: W36	PR+1st GEN DAA: W38	PR+1st GEN DAA: W40	PR+1st GEN DAA: W42	PR+1st GEN DAA: W44	PR+1st GEN DAA: W45	PR+1st GEN DAA: W46
Outpatient visit																													
Additional time with mid-level provider	$ 20.06											x		x		x		x				x		x		x		x	
Time with physician or LVN	$ 107.83											x		x		x		x				x		x		x		x	
Clinic Administration	$ 173.74											x		x		x		x				x		x		x		x	
Inpatient Care (day case)																													
Clerking in patient***	$ 102.09																												
Test and investigations																													
Virology																													
HCV RNA PCR	$ 60.39																												
HCV genotype	$ 362.93																												
HBV surface antigen and antibody	$ 14.57																												
Chemical pathology																													
Liver function tests	$ 11.51											x		x		x		x				x		x		x		x	
Total iron, ferritin, transferrin saturation	$ 9.12																												
Urea and electrolytes	$ 42.09											x		x		x		x				x		x		x		x	
Pregnancy Test	$ 8.92											x		x		x		x				x		x		x		x	
Thyroid stimulating hormone and thyroxine	$ 71.07																												
Hematology																													
Complete blood count	$ 10.96											x		x		x		x				x		x		x		x	
Prothrombin time and international normalized ratio	$ 5.55																												
Blood Group	$ 4.21																												
Radiology and Procedures																													
Ultrasound scan of liver	$ 109.98																												
Chest X-ray	$ 24.00																												
ECG	$ 16.84																												
Abdominal CT or MRI Scan*	$ 340.32																												
Liver Biopsy*	$ 366.83																												
Fibrotest**	$ 83.41																												
Endoscopy*	$ 317.75																												

Green: initial assessment; Red: follow-up assessment. * 20% of patients; **80% of patients; ***50% of patients; x, in cirrhotic patients only.

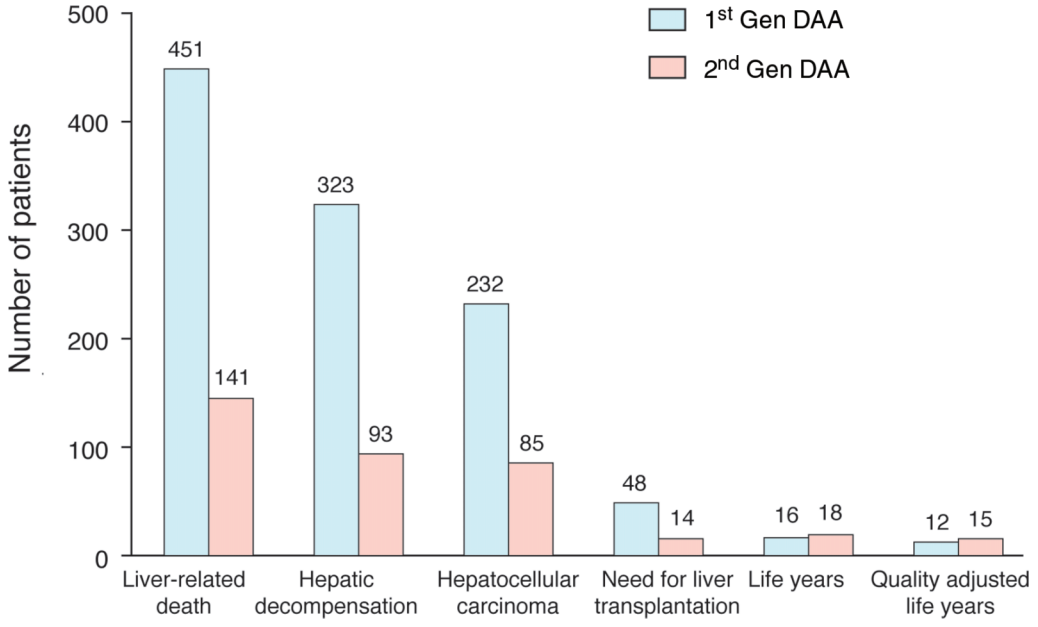

Fig. 2. Model results: health outcomes. 1st Gen DAA, first generation direct-acting antiviral agents; 2nd Gen DAA, second generation direct-acting antiviral agents. Analysis only includes patients with hepatitis C genotype 1.

Table 2. Health outcomes by patient subpopulation (per 10,000 patients)

Cases of:	Treatment naïve non-cirrhotic		Treatment naïve cirrhotic		Treatment experienced non-cirrhotic		Treatment experienced cirrhotic	
	2nd Gen DAA	1st Gen DAA + not treated	2nd Gen DAA	1st Gen DAA + not treated	2nd Gen DAA	1st Gen DAA + not treated	2nd Gen DAA	1st Gen DAA + not treated
Hepatic decompensation	-	1,990.8	1,533.9	3,883.7	326.9	2,211.4	1,444.0	4,143.4
Hepatocellular carcinoma	23.7	1,493.3	1,397.7	2,771.4	264.6	1,656.2	1,345.2	2,923.2
Liver transplantation	-	273.9	229.4	592.5	44.2	304.2	215.8	632.6
Liver-related death	20.5	2,718.6	2,417.4	5,506.9	456.4	3,017.4	2,302.3	5,847.9
Life years	19.5	17.9	17.3	14.6	19.2	17.7	17.4	14.3
Quality adjusted life years	16.2	14.1	13.8	11.0	16.0	13.9	13.9	10.6

1st Gen DAA, first generation direct-acting antiviral agents; 2nd Gen DAA, second generation direct-acting antiviral agents. Analysis only includes patients with hepatitis C genotype 1. Results are presented per 10,000 patients.

Table 3. Model results: cost outcomes

	Intervention	Comparator		
	2nd Gen DAA n = 1000	1st Gen DAA + not treated n = 500 + 500	1st Gen DAA n = 1000	Not treated n = 1000
Per patient total treatment cost*	$131,398	$165,101	$170,305	$159,897
Cost per SVR12	$117,331	N/A	$187,058	N/A
Per patient monitoring cost	$944.75	$2,116	$4,232	$0
Total budget impact (mn)	$131.4	$165.1	N/A	N/A
ICER	Dominant	Referent	N/A	N/A

* Product prices reflect wholesale acquisition cost and physician reimbursement costs are per the United States Centers for Medicare and Medicaid Services fee schedule.
Abbreviations: SVR12, sustained viral response 12 weeks after end of treatment; mn, million; ICER, incremental cost-effectiveness ratio.

Table 4. Sensitivity analysis results: LVN reimbursement rate

	Intervention	Comparator		
	2nd Gen DAA n = 1000	1st Gen DAA + not treated n = 500 + 500	1st Gen DAA n = 1000	Not treated n = 1000
Per patient total treatment cost	$131,321	$165,069	$170,241	$159,897
Cost per SVR12	$117,306	N/A	$186,867	N/A
Per patient monitoring cost	$935.33	$2,102	$4,204	$0
Total budget impact (mn)	$131.3	$165.1	N/A	N/A
ICER	Dominant	Referent	N/A	N/A

Abbreviations: SVR12, sustained viral response 12 weeks after end of treatment; mn, million; ICER, incremental cost-effectiveness ratio.

Discussion

Task shifting is widely used to manage chronic conditions including, most notably, HIV infection in areas where healthcare human resources are limited. The safety and effectiveness of task shifting in HIV treatment, and its ability to facilitate increases in treatment capacity, despite lifelong treatment durations and more complex and adverse effect-prone regimens than 2nd Gen DAAs therapy, was demonstrated in several large studies and two subsequent Cochrane Database

Table 5. Sensitivity analysis results: treatment capacity

	No increase in treatment capacity	Base case (2-fold increase)	3-fold increase in treatment capacity
Patients treated with 2nd Gen DAA	500	1000	1500
Decompensated cirrhosis	−75.20	−230.06	−384.92
Hepatocellular carcinoma	−47.94	−147.47	−247.00
Liver transplantation	−11.04	−34.13	−57.21
HCV-related death	−98.76	−305.98	−513.19
Life years	0.08	0.24	0.40
Quality adjusted life years	0.09	0.27	0.45
Cost per SVR	$ (34,863.64)	$ 23,801.66	$ 82,466.96
Total costs	$ (19,453.34)	$ (33,702.56)	$ (47,951.78)
Monitoring costs	$ (1,643.42)	$ (1,171.05)	$ (698.67)
Budget impact	$ (19,453,335.52)	$ (33,702,556.39)	$ (47,951,777.27)

Results are represented as the difference between the current scenario (500 patients treated with 1st Gen DAA) and the comparative scenarios (increased treatment capacity with 2nd Gen DAA).

meta-analyses.[17,19,20] Based on the success of HIV therapy in such settings, and the safety, effectiveness, and simplicity of interferon-free 2nd Gen DAAs regimens, task shifting has been proposed as a strategy to expand access to HCV treatment as well.[13,21] We previously demonstrated that, in medically underserved areas, 2nd Gen DAAs-based HCV treatment can be administered effectively, despite devolving routine on-treatment monitoring to a non-physician clinician with very limited direct involvement of specialist physicians. In our experience, the treatment-related adverse events were no different from those at an academic medical center, and the availability of an on-call hepatologist to supervise non-physician clinicians served as a means to minimize patient risk.[14] Scaling-up task shifting in HCV, however, mandates demonstrating favorable cost effectiveness and budgetary impact of 2nd Gen DAAs as compared with traditional interferon-based 1st Gen DAA regimens within these task-shifted treatment models. In this analysis using a previously validated decision analytic Markov model, we evaluated the real-world budgetary impact and cost effectiveness of 2nd Gen DAAs compared to 1st Gen DAAs within a task-shifted treatment model, and across scenarios of increased treatment capacity.

Given our experiences in scaling up of HCV therapy while simultaneously being able to scale back the direct involvement of the hepatologist during routine treatment monitoring, we assumed that 2nd Gen DAA regimens could double treatment capacity. Based on this assumption, we demonstrate that 2nd Gen DAAs-based treatment is cost effective and cost saving as compared to 1st Gen DAAs-based treatment, and these benefits extend to patient populations of treatment-naïve non-cirrhotics, treatment-experienced non-cirrhotics, treatment-naïve cirrhotics, and treatment-experienced cirrhotics (Table 2). The magnitude of projected relative cost savings was smallest for the treatment-naïve cirrhotics, as this subpopulation had the smallest relative difference in SVR rate with 2nd Gen DAA regimens versus 1st Gen DAA regimens (Fig. 1). Even with an assumption of tripling treatment capacity, the 2nd Gen DAA regimens remained cost effective and cost saving (Table 5). While cost effectiveness of 2nd Gen DAA regimens versus 1st Gen DAA regimens or no treatment has been previously demonstrated, and are reconfirmed here, our analysis represents the first, to our knowledge, that demonstrates the extension of these benefits when treatment capacity is expanded through workforce multiplication strategies such as task shifting.[6–8]

A key benefit of task shifting is the lower reimbursement rates of non-physician clinicians as compared to specialist physicians. Reduced reimbursement rates of non-physician clinicians, however, did not appear to contribute significant cost savings in our analysis; rather, the main driver was cost offsets from the avoidance of downstream advanced liver disease complications. This is unsurprising when the costs of 2nd Gen DAA regimens and advanced liver disease events are considered. However, with increased marketplace competition among DAA regimens and anticipated shorter treatment durations, it can be envisaged that direct drug cost will decline further and provider reimbursement rates will proportionately be a larger component of the total cost of treatment.

Our model is limited by not accounting for differential reimbursement rates for services administered to patients covered under different types of insurers (i.e. commercial vs. Medicare vs. Medicaid) since all costs were sourced from Medicare databases. Given that patients in underserved areas of the United States are most likely to be insured by Medicaid, with lower reimbursement rates, the overall budget impact could be expected to be even lower than projected in this analysis. Secondly, 2nd Gen DAAs and 1st Gen DAAs were modeled as a class; differences in efficacy and cost between distinct all-oral 2nd Gen DAA regimens (e.g. elbasvir+grazoprevir, LDV+SOF, ombitasvir+paritaprevir+ritonavir and dasabuvir, or SOF+SMV) and 1st Gen DAA regimens (e.g. boceprevir+PR, simeprevir+PR, or telaprevir+PR) were not taken into account. The potential impact of using 2nd Gen DAA regimens with even shorter treatment duration and costs (e.g. LDV+SOF for 8 weeks in selected patients) was not accounted for. Our clinic's demographics are also not typical of the general HCV-infected population in the United States, which has lower rates of prior treatment experience and cirrhosis.[22–24] These differences, however, are likely to underestimate the magnitude of our findings, given the anticipated lower SVR rates seen in patients with prior treatment experience and cirrhosis. Our analysis also relied on real-world

SVR rates for 2nd Gen DAA regimens obtained from a relatively small population, and results should be validated in larger, real-world cohort studies.

In conclusion, we demonstrate here the cost effectiveness and cost-saving potential of 2nd Gen DAAs-based HCV treatment within the context of task shifting and expansion of treatment capacity. These findings support the consideration of 2nd Gen DAAs within task-shifted treatment models a means of increasing access to HCV treatment where linkages to specialist-level care are weak.

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Conflict of interest

Dr. Beckerman and Smith are consultant to Gilead, Dr. Wong is advisory board membership of Gilead and received research grants from Gilead, Dr. Younossi is consultant of AbbVie, Bristol Myers Squibb, Gilead, Glaxo Smith Kline, and Intercept, Dr. Ahmed is advisory board membership of AbbVie, Gilead, Intercept, Janssen, and Shire, and received research grants from Gilead and Intercept. The others have no conflict of interest to declare.

Author contributions

Conceived the study (AA, CRJ), obtained the funding (RB, AA, CRJ), acquired the data (AA, CRJ), developed the models (RB, NS), interpreted the data and drafted the manuscript (CRJ, RB, AA), critically reviewed the data and contributed to writing of the manuscript (RBP, RJW, ZMY).

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