Cost-effectiveness of Hepatitis C Virus Treatment Models for People Who Inject Drugs in Opioid Agonist Treatment Programs

Sarah Gutkind,¹ Bruce R. Schackman,¹ Jake R. Morgan,² Jared A. Leff,¹ Linda Agyemang,³ Sean M. Murphy,¹ Matthew J. Akiyama,³ Brianna L. Norton,³ Alain H. Litwin,^{4,5,a} and Benjamin P. Linas^{2,6,a}

¹Department of Healthcare Policy & Research, Weill Cornell Medical College, New York; ²Department of Medicine, Section of Infectious Diseases, Boston Medical Center, Massachusetts;

³Department of Medicine, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, New York; ⁴Department of Medicine, University of South Carolina School of Medicine and Greenville Health System; ⁵Clemson University School of Health Research, South Carolina; and ⁶Department of Epidemiology, Boston University School of Public Health, Massachusetts

(See the Major Article by Assoumou et al on pages 1388–96.)

Background. Many people who inject drugs in the United States have chronic hepatitis C virus (HCV). On-site treatment in opiate agonist treatment (OAT) programs addresses HCV treatment barriers, but few evidence-based models exist.

Methods. We evaluated the cost-effectiveness of HCV treatment models for OAT patients using data from a randomized trial conducted in Bronx, New York. We used a decision analytic model to compare self-administered individual treatment (SIT), group treatment (GT), directly observed therapy (DOT), and no intervention for a simulated cohort with the same demographic characteristics of trial participants. We projected long-term outcomes using an established model of HCV disease progression and treatment (hepatitis C cost-effectiveness model: HEP-CE). Incremental cost-effectiveness ratios (ICERs) are reported in 2016 US\$/quality-adjusted life years (QALY), discounted 3% annually, from the healthcare sector and societal perspectives.

Results. For those assigned to SIT, we projected 89% would ever achieve a sustained viral response (SVR), with 7.21 QALYs and a \$245 500 lifetime cost, compared to 22% achieving SVR, with 5.49 QALYs and a \$161 300 lifetime cost, with no intervention. GT was more efficient than SIT, resulting in 0.33 additional QALYs and a \$14 100 lower lifetime cost per person, with an ICER of \$34 300/QALY, compared to no intervention. DOT was slightly more effective and costly than GT, with an ICER > \$100 000/QALY, compared to GT. In probabilistic sensitivity analyses, GT and DOT were preferred in 91% of simulations at a threshold of <\$100 000/QALY; conclusions were similar from the societal perspective.

Conclusions. All models were associated with high rates of achieving SVR, compared to standard care. GT and DOT treatment models should be considered as cost-effective alternatives to SIT.

Keywords. economic evaluation; simulation model; viral hepatitis; opioid use disorder; directly observed therapy.

It is estimated that up to 70% of people who inject drugs (PWID) in the United States are hepatitis C virus (HCV) antibody positive [1]. While curative, direct-acting antiviral HCV treatments are becoming widely available, barriers to obtaining access to these treatments remain for PWID, including fragmented healthcare delivery systems [2]. On-site HCV screening and care linkage in opiate agonist treatment (OAT) programs can be a cost-effective approach to addressing these barriers [3], but few evidence-based models exist for treating PWID on-site [4].

On-site HCV treatment in OAT settings may be more costly than treatment in a high-volume primary or specialty care practice, depending on the treatment model. There are also concerns about investing in these services due to treatment nonadherence, HCV reinfection, and competing mortality risks among PWID [5]. In a randomized trial of HCV treatment models in OAT programs in Bronx, New York (Prevent Resistance, Eliminate Virus and Improve Life [PREVAIL]: NCT01857245) investigators found high levels of HCV treatment adherence among PWID who were offered medication and monthly clinical evaluations on-site in OAT settings [6].

We assessed the cost-effectiveness of the on-site OAT HCV treatment models evaluated in the PREVAIL study. We used data from the trial and an established computer simulation model of HCV disease to project lifetime clinical outcomes, quality-adjusted life years (QALYs), and costs.

Received 7 December 2018; editorial decision 15 April 2019; accepted 8 May 2019; published online May 16, 2019.

^aA. H. L. and B. P. L. contributed equally to this manuscript.

Correspondence: B. R. Schackman, Weill Cornell Medical College, 425 E 61st St, Suite 301, New York, NY 10065 (brs2006@med.cornell.edu).

Clinical Infectious Diseases® 2020;70(7):1397–405

© The Author(s) 2019. Published by Oxford University Press for the Infectious Diseases Society of America. All rights reserved. For permissions, e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/ciz384

METHODS

Overview

We used a decision analytic model to compare the cost-effectiveness of HCV treatment strategies in an OAT setting for individuals meeting the trial's HCV-related entry criteria [7]. We evaluated 4 treatment models: (1) no intervention in the OAT program; (2) self-administered individual treatment (SIT); (3) group treatment (GT); and (4) directly observed therapy (DOT). No intervention represents a referral to off-site testing and treatment that would occur in a setting where on-site treatment is not available [3]. The other 3 models were evaluated in the PREVAIL trial [7]. In the SIT arm, participants received all medications at the clinic from the clinic nurse on a weekly, biweekly, or monthly basis and self-administered all medications at home. Participants in the GT arm received medications and medical evaluations from a physician or physician assistant during weekly group therapy sessions focused on HCV concerns. In the DOT arm,

participants received medications from nurses during OAT visits at a medication window. Nurses at the OAT program directly observed participants to ensure medication adherence, although the number of observed doses varied according to the number of days the participant attended the program (1–6 times per week). Participants in both the SIT and DOT arms met monthly with a physician or physician assistant, individually and on-site, for HCV evaluations. The PREVAIL protocol was approved by the Albert Einstein College of Medicine Institutional Review Board and the economic evaluation was approved by the Weill Cornell Medical College Institutional Review Board.

Model Structure

A decision tree model programmed in TreeAge Pro version 2016 (Williamstown, MA) included all costs and clinical outcomes of HCV treatment in the OAT program (Figure 1). When simulated individuals reached the end of the decision tree, they were

Figure 1. Analytic overview. Abbreviations: HCV, hepatitis C virus; HEP-CE, hepatitis C cost-effectiveness model; OAT, opioid agonist treatment; SVR, sustained virologic response.

categorized as achieving sustained virologic response (SVR) or not. We then used an established computer simulation model of HCV disease and treatment (hepatitis C cost-effectiveness model: HEP-CE) [8] to project long-term outcomes, including HCV reinfection, treatment initiation after reinfection, treatment completion and SVR after reinfection, QALYs, and costs. HEP-CE is a Monte Carlo simulation model that uses state transition probabilities to move simulated individuals through 3 stages of chronic HCV liver disease: mild to moderate fibrosis, cirrhosis, and decompensated cirrhosis [9]. Each disease stage is associated with a quality-of-life decrement [10–12] and an increase in healthcare costs. If simulated individuals with chronic HCV become cirrhotic, they have an increased risk of mortality attributable to their liver disease. Simulated individuals who achieve SVR have a risk of HCV reinfection.

Simulated individuals who were coinfecting with HCV and human immunodeficiency virus (HIV) were assigned HIV-attributable mortality, HIV-related healthcare costs, and quality-of-life weights for each health state (HIV infection, HCV, and OAT). Quality-of-life weights were measured on a scale from 0 (equivalent to death) to 1 (equivalent to perfect health) and were multiplied for individuals experiencing multiple chronic health states, including HIV, chronic HCV, HCV treatment, and OAT, with values derived from cohort studies, a population survey, and a clinical trial [10–15]. All simulated PWID have an elevated mortality risk compared to the general population [16].

Projected clinical outcomes include the lifetime probability of achieving at least 1 SVR, taking into account that not all individuals initiate treatment, complete treatment, or achieve SVR when offered treatment on-site. Projected economic outcomes are lifetime costs (2016 US\$) and QALYs, both discounted at 3% annually. The relevant resources included in the healthcare sector and societal perspectives are presented in an impact inventory (Supplementary Table 1), as recommended in cost-effectiveness guidelines [17]. Lifetime costs estimated from the healthcare sector perspective included costs to OAT programs (which may not be reimbursed), downstream costs for HCV and HIV health care, and healthcare costs unrelated to the interventions (Supplementary Tables 2–6). The societal perspective included the opportunity cost of the individual's time spent obtaining treatment, costs associated with criminal activities, and reduced workplace productivity, in addition to the resources valued from the healthcare sector perspective.

Prevent Resistance, Eliminate Virus and Improve Life (PREVAIL) Trial Data

We used data from the PREVAIL study to inform the characteristics of simulated individuals, including age, proportion male, proportion HIV infected, proportion cirrhotic, and proportion currently using opioids (Table 1). We used trial data to inform the proportion of simulated individuals initiating treatment, completing treatment, and achieving SVR 12 weeks after treatment completion for HCV monoinfected and HCV/HIV

coinfecting individuals (Table 1). Eligibility criteria included being 18 years of age or greater, having HCV genotype 1, and receiving methadone or buprenorphine at a medication window [7]. Of 158 participants randomized, 150 initiated HCV treatment between October 2013 and May 2016 (Supplementary Figure), and follow-up occurred through April 2017. Treatment arm assignment was stratified by interleukin-28B (IL28B) genotype, HIV status, and stage of liver disease [6]. Participants completed study assessments at baseline, every 4 weeks until the end of treatment, and at 12 weeks after ending treatment. Participants completed an Audio Computer-Assisted Self-Interview (ACASI) that included questions to assess healthcare utilization outside of the intervention (Supplementary Table 7). Participants also reported criminal justice activity, which was included in the societal perspective costs (Supplementary Table 1).

Data for No Intervention Model

The hypothetical no intervention model represents referrals to off-site testing and treatment, which was the treatment model used in previous linkage-to-care studies [3, 24]. We assigned a probability of linking to HCV care following a reactive test, derived from an HCV linkage randomized trial conducted in OAT programs in New York and San Francisco, and we assigned a probability of achieving SVR among those who initiate treatment, derived from a multinational trial evaluating the effectiveness of off-site, direct-acting antiviral treatment in persons receiving OAT (Table 1) [3, 23].

Other Sources of Data for the Model

We assigned a risk of HCV reinfection to simulated individuals achieving SVR, based on the proportion of trial participants who reported substance use; the risk was derived from a recent, multinational trial of persons receiving HCV treatment in OAT [23]. Treatment medications and durations varied among trial participants. Most participants initiated treatment with once-daily ledipasvir/sofosbuvir (69% SIT; 79% GT; 61% DOT). For those who did not initiate or successfully complete on-site treatment, the probability of re-engaging in HCV care in the future was assumed to be the same as in the no intervention model.

Using Medicare reimbursement schedules, we estimated the costs of HCV viral load, HIV rapid testing, and the cost of an HCV evaluation visit for both the SIT and DOT treatment strategies (Supplementary Table 2) [32]. Using group treatment logs from the trial, we calculated time and utilization for the average group treatment session (Supplementary Table 3). We determined the labor cost of each session by assigning the relevant wage and fringe benefit rates to the time estimates for each provider at the weekly sessions (Supplementary Table 2) [33]. We calculated the cost of participant time from the societal perspective for each group session and each physician visit using the national minimum wage rate (81% of the trial participants were unemployed) [6]. We interviewed nurses at the OAT

Table 1. Model Inputs

Input	Base Case	Sensitivity Analysis	Source
Cohort characteristics			
Mean age (SD), years	51 (11)	41 (10)–61 (10)	PREVAIL
Mean age of infection (SD), years	26 (16)	16 (16)–36 (16)	[18]
Proportion male	0.647	0–1	PREVAIL
Proportion HIV infected ^a	0.162	0–1	PREVAIL
Proportion of HCV antibody positive with chronic HCV infection			
HIV uninfected	0.740	0.710–0.780	[19, 20]
HIV infected	0.870	0.800–0.870	[21, 22]
Proportion with IDU risk behavior ever ^b	0.946	0–1	PREVAIL
Proportion cirrhotic	0.237	...	PREVAIL
Proportion achieving SVR by treatment model			
No intervention (referral to off-site treatment)			
HIV uninfected	0.007	...	[3, 23]
HIV coinfectd	0.001	...	[3, 23]
Self-administered individual treatment			
HIV uninfected	0.884	0.884–0.867	PREVAIL
HIV coinfectd	0.800	0.800–1	PREVAIL
Group treatment			
HIV uninfected	0.869	0.869–0.941	PREVAIL
HIV coinfectd	0.833	0.833–1	PREVAIL
Directly observed therapy			
HIV uninfected	0.915	0.915–1	PREVAIL
HIV coinfectd	1	1	PREVAIL
Background testing and linkage to care by HCV status			
HCV testing, monthly probability ^c	0.042	...	[3, 24]
HCV linkage, monthly probability ^d			
HIV uninfected	0.0014	0.0011–0.0020	[3, 24]
HIV infected	0.0042	0.0026–0.0058	[3, 24]
Total on-site intervention costs, \$			
No intervention (referral to off-site treatment)			
Program	0	...	PREVAIL
Patient	0	...	PREVAIL
Self-administered individual treatment			
Program	2137	...	PREVAIL
Patient	91	...	PREVAIL
Group treatment			
Program	1852	...	PREVAIL
Patient	200	...	PREVAIL
Directly observed therapy			
Program	2199	...	PREVAIL
Patient	393	...	PREVAIL
HCV disease progression and reinfection			
Median time to cirrhosis from time of HCV infection, years	25	10–40	[9, 25]
Median time to first liver-related event after developing cirrhosis, years	11	6–19	[26]
Liver-related mortality with compensated cirrhosis, deaths per 100 PYs	1.39	0.96–1.82	[26]
Liver-related mortality with decompensated cirrhosis, deaths per 100 PYs	12	8.28–15.72	[26]
Multiplier for liver cirrhosis progression for HIV-infected	2.1	1.0–3.0	[27]
Reduction in liver-mortality after SVR, %	94	81–98	[28]
HCV reinfection rate among current IDUs, reinfections per 100 PYs	4.6	1.7–10.0	[23]
HCV treatment efficacy and cost			
Treatment efficacy			
Without cirrhosis	0.91	0.86–0.95	[23]
With cirrhosis	0.93	0.80–0.98	[23]
Total treatment cost, \$ ^e			
Telaprevir/pegylated interferon/ribavirin	75 230	75 230–92 060	[29, 30]
Sofosbuvir/ribavirin	50 260	50, 260–50 360	[29, 30]
Sofosbuvir/pegylated interferon/ribavirin	72 590	72 590–72 690	[29, 30]
Sofosbuvir/simeprevir	115 220	115 220–115 220	[29, 30]

Table 1. Continued

Input	Base Case	Sensitivity Analysis	Source
Ledipasvir/sofosbuvir	85 500	85 500–113 400	[29, 30]
Elbasvir/grazoprevir	52 130	52 130–65 520	[29, 30]
Quality-of-life weights (0 = death, 1 = best possible health)			
Methadone maintenance treatment	0.72	0.69–0.76	[13]
HCV infected			
No to moderate fibrosis	0.89	0.75–1	[10–12]
Cirrhosis	0.62	0.55–0.75	[10–12]
Decompensated cirrhosis	0.48	0.40–0.60	[10–12]
HIV infected	0.83–0.87	0.74–1	[14]
On HCV treatment			
Receiving interferon-sparing therapy ^f	0.99	0.95–1	[15]
Major toxicity decrement ^g	0.16	0.09–0.25	[31]
Non-HCV, non-HIV mortality risk			
SMR	1.8	1.0–5.0	[16]

All costs are in 2016 US dollars.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; PREVAIL, Prevent Resistance, Eliminate Virus and Improve Life Clinical Trial; PY, person years; SD, standard deviation; SMR, standardized mortality ratio; SVR, sustained virologic response.

^a14% are also HIV infected in the base case (varied in sensitivity analysis between 0% and 100%).

^bProportion IDU calculated using patient report of ever having used injection drugs and opioids.

^cAssumes approximately 66% were tested by 2.08 years.

^dMonthly probability is calculated in order to reach half of the linkage rate observed in the control group in a randomized control trial examining HCV treatment, testing, and linkage in methadone maintenance programs within 10 years; sensitivity analysis probability range reflects sensitivity analysis ranges for control group linkage rates in 1-way sensitivity analyses.

^eThe medication costs from the Federal Supply Schedule fall within the range of the sensitivity analyses. The high end of the sensitivity analyses was calculated using the average whole-sale price.

^fMultiplied by patient's quality of life weight during the months the patient receives HCV therapy.

^gSubtracted from patient's health state utility during the month of a major toxicity event.

programs to estimate the costs of the incremental time required to administer HCV medication at the OAT medication window, and included labor costs for visit documentations and supervision (Supplementary Table 4). We estimated the cost of HCV medication preparation for the pharmacy technicians through interviews with pharmacy staff. Study staff provided information on training, equipment, and inventory requirements included in the site start-up costs (Supplementary Table 5).

We calculated the HCV medication cost for each trial participant (Table 1) using Federal Supply Schedule costs, following recent guidelines [17]. Unit costs associated with participant-reported outpatient and inpatient services outside of the study, criminal justice activities, and incarceration were estimated using recently published monetary conversion factors for substance use disorder treatment interventions (Supplementary Table 2) [34]. Multivariable generalized linear models and the method of recycled predictions generated predicted mean costs for each study arm [35]. We used the modified Park test to choose the family functions for the generalized linear models; the Pearson Correlation, Pregibon Link, and modified Hosmer and Lemeshow tests were used to help choose the link functions [35].

Societal Perspective

The societal perspective includes all resources from the health-care sector perspective, as well as participant costs, criminal justice costs, and workplace productivity (Supplementary Table 7). We assigned costs to the participants' time spent during the

intervention (physician visits, additional time at medication window, and weekly group treatment); participant transportation costs were not included, because no additional visits were required (Table 1) [34]. We projected future workplace productivity and consumption effects in the HEP-CE model. To value productivity across individuals, we multiplied the labor force participation rate reported by trial participants (18.7%) by the average national wage and fringe rate, stratified by age [36–38]. We also calculated age-specific, average, annual net consumption as total expenditures less healthcare expenditures.

Sensitivity Analysis

We evaluated the impact of several alternative scenarios on our results. PREVAIL participants were not randomized to specific treatment regimens and were enrolled over a period when treatment guidelines were changing, so the average cost per participant varied within each arm and across arms. In a sensitivity analysis, we used only trial data from participants who received once-daily ledipasvir/sofosbuvir ($n = 104$); in this scenario, we used the weighted average medication cost across all arms for those participants who achieved SVR and we assumed that the cost of medications was the same in all treatment arms for those who completed treatment (although the cost of treatment delivery still varied by treatment model). In a separate scenario, we evaluated the impact of assuming a higher rate of HCV reinfection on our results, increasing from the base case of 4.6 reinfections per 100 years to 10 reinfections per 100

person years (Table 1) [23]. Finally, we considered whether the quality-of-life improvement associated with HCV treatment might differ for PWID in OAT, whose overall quality-of-life is lower than that of individuals in the general population. In this scenario, we followed a recent recommendation to use the minimum quality-of-life weight when evaluating conditions co-occurring with opioid use disorder [39]. We also varied the following parameters in 1-way sensitivity analyses across relevant ranges: elevated mortality risk compared to the general population, chronic HCV disease progression rate, liver-related mortality rate, probability of no intervention testing, probability of no intervention linkage, treatment initiation after linking to care, SVR rate, HCV treatment efficacies, and costs. We varied age, age of infection, sex, HCV prevalence, and HIV prevalence using confidence intervals from trial data.

We ran 100 000 simulations to produce cost-effectiveness acceptability curves that describe uncertainty in cost-effectiveness findings. The cost-effectiveness acceptability curves were evaluated within the recommended threshold range for the United States, of \$100 000/QALY to \$200 000/QALY, which more appropriately reflects contemporary medical costs than the \$50 000/QALY threshold used in earlier studies [40, 41].

RESULTS

The no intervention model resulted in 22% of the simulated cohort achieving at least 1 SVR over a lifetime, the GT model resulted in 86% of the simulated cohort achieving at least 1 SVR over a lifetime, the SIT model resulted in 89% achieving at least 1 SVR over a lifetime, and the DOT model resulted in 89% achieving at least

Table 2. Base Case and Scenario Analyses Results

Strategy	Total cost per person, \$	Total QALY per person	Incremental cost per person, \$	Incremental QALY per person	Incremental cost-effectiveness ratio, \$/QALY
Base case results					
No intervention	161 300	5.493	...	...	...
GT	231 400	7.536	70 100	2.043	34 300
Self-administered individual treatment	245 500	7.207	14 100	−0.329	Dominated
DOT	246 700	7.611	1200	0.404	204 000
High reinfection scenario^a					
No intervention	161 700	5.492	...	...	...
GT	232 400	7.604	70 800	1.946	36 400
Self-administered individual treatment	246 500	7.276	14 100	−0.327	Dominated
DOT	247 700	7.683	1200	0.398	216 100
Quality-of-life minimum estimator scenario					
No intervention	161 300	5.562	...	...	...
GT	231 400	7.603	70 100	1.9843	35 300
Self-administered individual treatment	245 500	7.279	14 100	−0.324	Dominated
DOT	246 700	7.678	1200	0.399	204 200
Ledipasvir/sofosbuvir treatment data scenario					
No intervention	161 300	5.493	...	...	...
GT	229 500	7.580	68 200	2.087	dominated ^b
DOT	229 900	7.871	500	0.292	28 900
Self-administered individual treatment	236 200	7.427	6300	−0.153	Dominated
Societal perspective					
No intervention	200 900	5.494	...	...	...
GT	274 600	7.523	73 800	2.029	36 400
Self-administered individual treatment	289 100	7.196	14 400	−0.326	Dominated
DOT	290 200	7.598	1100	0.401	208 400
Societal perspective ledipasvir/sofosbuvir treatment data scenario					
No intervention	161 300	5.493	...	...	...
GT	229 500	7.580	68 200	2.087	dominated ^c
DOT	230 000	7.871	500	0.292	29 000
Self-administered individual treatment	236 200	7.427	6200	−0.153	Dominated

All costs are in 2016 US dollars. The lower case d in dominated because it indicates extended dominance.

Abbreviations: DOT, directly observed therapy; GT, group treatment; QALY, quality-adjusted life year.

^aHigh reinfection is 10.0 reinfections per 100 person-years.

^bCost-effectiveness ratio of GT compared to no intervention is \$32 700 per QALY and cost-effectiveness ratio of DOT compared to no intervention is \$28 900 per QALY; GT is dominated (extended dominance).

^cCost-effectiveness ratio of GT compared to no intervention is \$32 800 per QALY and cost-effectiveness ratio of DOT compared to no intervention is \$29 000 per QALY; GT is dominated (extended dominance).

1 SVR over a lifetime (Supplementary Tables 8A and B). The GT model resulted in a mean discounted lifetime cost of \$231 390 per person and a quality-adjusted life expectancy of 7.54 QALYs, corresponding to an incremental increased lifetime cost of \$70 100 and 2.04 QALYs, compared to no intervention (Table 2). The incremental cost of GT, compared to no intervention, included the cost of weekly group therapy led by a physician, nurse, or peer, and medication preparation by a pharmacist or pharmacy technician (Supplementary Table 3). The GT model had an ICER of \$34 300 per QALY, compared to the no intervention model, from the healthcare sector perspective (Table 2).

The SIT model resulted in an incremental lifetime cost of \$14 100 and 0.33 fewer QALYs, compared to the GT model (Table 2). Because the SIT model was less effective and more expensive than the GT model, it was a less efficient use of resources and was considered a dominated model. The DOT model resulted in an incremental lifetime cost of \$15 200 and an additional 0.08 QALYs, compared to the GT model. The DOT model had an ICER of \$204 000 per QALY gained, compared to the GT model.

The SIT model remained dominated in all 1-way sensitivity analyses. In these analyses, the ICER for the GT model, compared to the no intervention model, varied between an additional \$27 500/QALY when we reduced the average age of the population by 10 years and an additional \$55 000/QALY when we increased the standardized mortality ratio for PWID in OAT settings above the base case (Supplementary Table 9). When we evaluated the impact of assuming a higher rate of HCV reinfections or varying quality-of-life assumptions, the ICER for the GT model remained <\$50 000/QALY (Table 2). The ICER for the DOT model varied between \$161 200/QALY when we reduced the average age of the population by 10 years to \$399 800/QALY when we increased the cost of HCV medication. Results for DOT, varying reinfection risk and quality-of-life assumptions, were consistent.

When we limited the analysis to data from trial participants who received once-daily ledipasvir/sofosbuvir, the DOT model

had a greater QALY benefit than the GT model, and the additional cost of DOT compared to GT decreased. As a result, the DOT model became the preferred model, with an ICER of \$28 900 (Table 2). At a willingness-to-pay threshold of \$100 000/QALY, GT was the preferred model in 54% of probabilistic sensitivity analyses and DOT was preferred in 38% of probabilistic sensitivity analyses (Figure 2). Either the GT or the DOT model was preferred in over 90% of the probabilistic sensitivity analyses, at willingness-to-pay thresholds of \$100 000/QALY and \$200 000/QALY. Total costs for all models from the societal perspective were higher than from the healthcare sector perspective, because they also included criminal justice costs and participant costs associated with intervention visits. Incremental costs were similar, however, resulting in similar ICERs from both perspectives (Table 2).

DISCUSSION

We evaluated the cost-effectiveness of novel HCV treatment models for PWID in an OAT setting using data from a randomized trial conducted in Bronx, New York. We found that dispensing HCV medications and providing HCV evaluations in a group treatment setting has a cost-effectiveness ratio of \$34 300/QALY, compared to no intervention, from the healthcare sector perspective. This is very attractive compared to the commonly accepted \$100 000/QALY willingness-to-pay threshold and is a more efficient use of resources compared to individual HCV evaluation visits with a medical provider in an OAT setting and SIT, because it is less expensive and results in more QALYs gained. Modified DOT at the medication window had similar outcomes and became the preferred model when we limited data to participants receiving once-daily ledipasvir/sofosbuvir, due to smaller differences in lifetime costs between the GT and DOT models. Probabilistic sensitivity analyses indicated that either model is more attractive than SIT. Results were consistent when we considered both the societal and healthcare

Figure 2. Cost-effectiveness acceptability curves. The willingness to pay thresholds are reported in 2016 US dollars per QALY. Abbreviation: QALY, quality-adjusted life year.

sector perspectives, when we considered alternative scenarios regarding rates of reinfection and quality-of-life assumptions, and in 1-way sensitivity analyses.

Our analysis is subject to limitations. The clinical trial began during the era of interferon-containing treatment regimens, which could have adversely affected participation and SVR rates in early participants across all treatment arms and could have resulted in an overestimate of effect sizes. Approximately two-thirds of those randomized received once-daily ledipasvir/sofosbuvir and 86–89% achieved SVR across all treatment arms over a lifetime. Trial participants were also attending OAT programs multiple times per week. This could have improved HCV treatment adherence and outcomes, compared to other OAT settings; however, our results were consistent when we varied SVR rates across all treatment arms. We did not consider any long-term benefits of HCV treatment on productivity or labor force participation. Although actual negotiated HCV medication costs are unknown, our conclusions remained consistent when we varied these costs in sensitivity analyses. Trial participants also did not experience access restrictions to obtaining insurance coverage for HCV treatment, and the OAT programs had on-site providers capable of delivering HCV care, which could affect the applicability of the results to other OAT settings. However, insurance coverage limitations affecting PWID have been successfully challenged, and evidence of effectiveness and cost-effectiveness can encourage the greater availability of integrated on-site care.

CONCLUSIONS

On-site HCV treatment in OAT programs can address treatment barriers faced by PWID, resulting in substantial lifetime benefits even when taking into account their higher risk of reinfection, increased mortality, and poorer quality-of-life, compared to other HCV patients. GT and DOT models should be considered cost-effective alternatives to individual on-site treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Disclaimer. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the views of the funding agencies or the US government.

Financial support. This work was supported by the National Institute on Drug Abuse (grant numbers R01DA034086 and P30DA040500) and by Gilead Sciences (grant number IN-337–1779 to A. H. L.), which provided support for the Prevent Resistance, Eliminate Virus and Improve Life clinical trial and supplied the study medication of sofosbuvir in combination with ledipasvir.

Potential conflicts of interest. All coauthors have received grant funding from the National Institutes of Health. M. J. A. has served on an advisory board for Gilead Sciences, outside the submitted work. B. L. N. reports grants from Merck and Co., outside the submitted work. A. H. L. reports grants from Gilead Sciences during the conduct of the study and grants and personal fees

from Gilead Sciences and Merck Pharmaceuticals, as well as personal fees from AbbVie, outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Nelson PK, Mathers BM, Cowie B, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. *Lancet* **2011**; 378:571–83.
2. Bruggmann P, Grebely J. Prevention, treatment and care of hepatitis C virus infection among people who inject drugs. *Int J Drug Policy* **2015**; 26(Suppl 1):S22–6.
3. Schackman BR, Gutkind S, Morgan JR, et al. Cost-effectiveness of hepatitis C screening and treatment linkage intervention in US methadone maintenance treatment programs. *Drug Alcohol Depend* **2018**; 185:411–20.
4. Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. *Clin Infect Dis* **2013**; 57(Suppl 2):S56–61.
5. Grebely J, Tyndall MW. Management of HCV and HIV infections among people who inject drugs. *Curr Opin HIV AIDS* **2011**; 6:501–7.
6. Akiyama MJ, Norton BL, Arnsten JH, Agyemang L, Heo M, Litwin AH. Intensive models of hepatitis C care for people who inject drugs receiving opioid agonist therapy: a randomized controlled trial intensive models of hepatitis C care for people who inject drugs. *Ann Intern Med* **2019**; **170**: 594–603.
7. Akiyama MJ, Agyemang L, Arnsten JH, et al. Rationale, design, and methodology of a trial evaluating three models of care for HCV treatment among injection drug users on opioid agonist therapy. *BMC Infect Dis* **2018**; **18**:74.
8. Linas BP, Morgan JR, Pho MT, et al. Cost effectiveness and cost containment in the era of interferon-free therapies to treat hepatitis C virus genotype 1. *Open Forum Infect Dis* **2017**; **4**: ofw266.
9. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology* **2008**; **48**:418–31.
10. Chong CA, Gulamhussein A, Heathcote EJ, et al. Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* **2003**; **98**:630–8.
11. Grieve R, Roberts J, Wright M, et al. Cost effectiveness of interferon alpha or peginterferon alpha with ribavirin for histologically mild chronic hepatitis C. *Gut* **2006**; **55**:1332–8.
12. Stein K, Dalziel K, Walker A, et al. Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice. *Health Technol Assess* **2002**; **6**:1–122.
13. Wittenberg E, Bray JW, Aden B, Gebremariam A, Nosyk B, Schackman BR. Measuring benefits of opioid misuse treatment for economic evaluation: health-related quality of life of opioid-dependent individuals and their spouses as assessed by a sample of the US population. *Addiction* **2016**; **111**:675–84.
14. Schackman BR, Goldie SJ, Freedberg KA, Losina E, Brazier J, Weinstein MC. Comparison of health state utilities using community and patient preference weights derived from a survey of patients with HIV/AIDS. *Med Decis Making* **2002**; **22**:27–38.
15. Stepanova M, Nader F, Cure S, Bourhis F, Hunt S, Younossi ZM. Patients' preferences and health utility assessment with SF-6D and EQ-5D in patients with chronic hepatitis C treated with sofosbuvir regimens. *Aliment Pharmacol Ther* **2014**; **40**:676–85.
16. Evans E, Li L, Min J, et al. Mortality among individuals accessing pharmacological treatment for opioid dependence in California, 2006–10. *Addiction* **2015**; **110**:996–1005.
17. Neumann PJ, Ganiats TG, Russell LB, Sanders GD, Siegel JE. Cost-effectiveness in health and medicine. 2nd ed. New York, New York: Oxford University Press, **2017**.
18. Freeman AJ, Dore GJ, Law MG, et al. Estimating progression to cirrhosis in chronic hepatitis C virus infection. *Hepatology* **2001**; **34**:809–16.
19. Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Annals of Internal Medicine* **2014**; **160**:293–300.
20. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *J Viral Hepat* **2006**; **13**:34–41.
21. Schnuriger A, Dominguez S, Guiguet M, et al; French National Agency for Research on AIDS and Viral Hepatitis (ANRS HC EP21) study group. Acute hepatitis C in HIV-infected patients: rare spontaneous clearance correlates with weak memory CD4 T-cell responses to hepatitis C virus. *AIDS* **2009**; **23**:2079–89.
22. Soriano V, Mocroft A, Rockstroh J, et al; European multi-national observational cohort of HIV infected people across Europe (EuroSIDA) Study Group. Spontaneous viral clearance, viral load, and genotype distribution of hepatitis C virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. *J Infect Dis* **2008**; **198**:1337–44.
23. Dore GJ, Altice F, Litwin AH, et al; A phase III clinical trial to study the efficacy and safety of the combination regimen of MK-5172/ MK-8742 in treatment

- naive subjects with chronic HCV GT1, GT4, GT6 infection who are on opioid substitution therapy (C-EDGE CO-STAR) Study Group. Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. *Ann Intern Med* **2016**; 165:625–34.
24. Masson CL, Delucchi KL, McKnight C, et al. A randomized trial of a hepatitis care coordination model in methadone maintenance treatment. *Am J Public Health* **2013**; 103:e81–8.
 25. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* **1997**; 349:825–32.
 26. Bruno S, Zuin M, Crosignani A, et al. Predicting mortality risk in patients with compensated HCV-induced cirrhosis: a long-term prospective study. *Am J Gastroenterol* **2009**; 104:1147–58.
 27. Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* **2008**; 22:1979–91.
 28. van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* **2012**; 308:2584–93.
 29. Truven Health Analytics. Hepatitis C: drug therapy. Available at: <http://www.micromedexsolutions.com/micromedex2/librarian/>. Accessed 10 January 2017.
 30. Veterans Affairs Office of Acquisition and Logistics. The federal supply schedule. Available at: <https://www.va.gov/oal/business/fss/pharmPrices.asp>. Accessed 1 April 2016.
 31. Schackman BR, Teixeira PA, Weitzman G, Mushlin AI, Jacobson IM. Quality-of-life tradeoffs for hepatitis C treatment: do patients and providers agree? *Med. Decis. Making* **2008**; 28:233–42.
 32. Tumei JW, Moore SG, Shapiro R, Flowers CR. Practical approach for using Medicare data to estimate costs for cost-effectiveness analysis. *Expert Rev Pharmacoecon Outcomes Res* **2005**; 5:153–62.
 33. US Bureau of Labor Statistics. Occupational employment statistics. Available at: <https://data.bls.gov/oes/#/geoOcc/Multiple%20occupations%20for%20one%20geographical%20area>. Accessed 1 April 2016.
 34. McCollister K, Yang X, Sayed B, French MT, Leff JA, Schackman BR. Monetary conversion factors for economic evaluations of substance use disorders. *J Subst Abuse Treat* **2017**; 81:25–34.
 35. Glick HA, Doshi JA, Sonnad SS. *Economic evaluation in clinical trials*. 2nd ed. Oxford, United Kingdom: Oxford University Press, **2014**.
 36. US Bureau of Labor Statistics. Civilian labor force participation rate by age, gender, race, and ethnicity. Available at: https://www.bls.gov/emp/ep_table_303.htm. Accessed 1 April 2017.
 37. US Bureau of Labor Statistics. Employer costs for employee compensation historical listing. Available at: <https://www.bls.gov/ncs/ect/sp/eccecqrtn.pdf>. Accessed 1 April 2017.
 38. US Census Bureau. Current population survey. Available at: http://thedataweb.rm.census.gov/ftp/cps_ftp.html#cpsbasic. Accessed 1 April 2017.
 39. Wittenberg E, Bray JW, Gebremariam A, Aden B, Nosyk B, Schackman BR. Joint utility estimators in substance use disorders. *Value Health* **2017**; 20:458–65.
 40. Neumann PJ, Cohen JT, Weinstein MC. Updating cost-effectiveness—the curious resilience of the \$50,000-per-QALY threshold. *N Engl J Med* **2014**; 371:796–7.
 41. Braithwaite RS, Meltzer DO, King JT Jr, Leslie D, Roberts MS. What does the value of modern medicine say about the \$50,000 per quality-adjusted life-year decision rule? *Med Care* **2008**; 46:349–56.