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Cost-effectiveness of integrating buprenorphine-naloxone treatment for opioid use disorder into clinical care for persons with HIV/hepatitis C co-infection who inject opioids

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ABSTRACT

Background: Untreated opioid use disorder (OUD) affects the care of HIV/HCV co-infected people who inject opioids. Despite active injection opioid use, there is evidence of increasing engagement in HIV care and adherence to HIV medications among HIV/HCV co-infected persons. However, less than one-half of this population is offered HCV treatment onsite. Treatment for OUD is also rare and largely occurs offsite. Integrating buprenorphine-naloxone (BUP-NX) into onsite care for HIV/HCV co-infected persons may improve outcomes, but the clinical impact and costs are unknown. We evaluated the clinical impact, costs, and cost-effectiveness of integrating (BUP-NX) into onsite HIV/HCV treatment compared with the status quo of offsite referral for medications for OUD.

Methods: We used a Monte Carlo microsimulation of HCV to compare two strategies for people who inject opioids: 1) standard HIV care with onsite HCV treatment and referral to offsite OUD care (status quo) and 2) standard HIV care with onsite HCV and BUP-NX treatment (integrated care). Both strategies assume that all individuals are already in HIV care. Data from national databases, clinical trials, and cohorts informed model inputs. Outcomes included mortality, HCV reinfection, quality-adjusted life years (QALYs), costs (2017 US dollars), and incremental cost-effectiveness ratios.

Results: Integrated care reduced HCV reinfections by 7%, cases of cirrhosis by 1%, and liver-related deaths by 3%. Compared to the status quo, this strategy also resulted in an estimated 11/1,000 fewer non-liver attributable deaths at one year and 28/1,000 fewer of these deaths at five years, at a cost-effectiveness ratio of $57,100/QALY. Integrated care remained cost-effective in sensitivity analyses that varied the proportion of the population actively injecting opioids, availability of BUP-NX, and quality of life weights.

Conclusions: Integrating BUP-NX for OUD into treatment for HIV/HCV co-infected adults who inject opioids increases life expectancy and is cost-effective at a $100,000/QALY threshold.

Introduction

Untreated opioid use disorder (OUD) is leading to high rates of morbidity and mortality in the U.S. Drug overdoses have become the leading cause of deaths in persons under 50, the majority of which are opioid-related (Center for Medicare & Medicaid, 2018; Hedegaard, Warner, & Minino, 2017), and hospitalizations from opioid-related overdose increased more than 60% from 2007 to 2014 (Ronan & Herzig, 2016). While effects of the opioid crisis are permeating all aspects of society, persons with HIV (PWH) and hepatitis C (HCV) are disproportionately affected. Compared to HIV-uninfected persons who inject drugs, PWH who use drugs have a 74% greater risk of overdose

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Table 1
Key Model Inputs for Analysis of Cost-Effectiveness of Integrating Treatment for Opioid Use Disorder into Clinical HIV/HCV Treatment.

Parameter	Estimate (for the base case)	Range	Source
Clinical			
Median age (years) (SD)	45 (8)	25–55	(Chaudhry et al., 2011; Fishbein et al., 2004; Mehta et al., 2008)
Proportion HCV/HIV co-infected (%)	100		
Proportion male (%)	66		(United States Census Bureau, 2016; Hall et al., 2004)
Mean age of infection (years)	23 (5)	18–28	(Hagan et al., 2004; Suryaprasad et al., 2014)
Monthly death	Varies		(National Vital Statistics System, 2015)
SMR, active PWID			(Klein et al., 2014; Mathers et al., 2013)
Male	14.5	9.8–20.7	
Female	35.9	18.6–62.8	
SMR, former PWID	6.5	1.0–17	(Degenhardt et al., 2014; McAnulty et al., 1995; Miller et al., 2007)
Initial drug use state			
Current injection opioid use (%)	100		
Monthly probability of transition from current to former injection opioid use, PWID not on BUP-NX (%)	1.4	0.7–2.0	(Galai et al., 2003)
Monthly probability of transition from former to current injection opioid use, PWID not on BUP-NX (%)	3.0	1–5	(Galai et al., 2003)
Monthly probability of transition from current to former injection opioid use, PWID on BUP-NX (%)	1.8	0.92–2.6	(Fiellin et al., 2011)
Monthly probability of transition from former to current injection opioid use, PWID on BUP-NX (%)	1.0	0.7–03.0	(Fiellin et al., 2011)
Probability of HCV re-infection among people currently injecting opioids (cases/100 p-y)	12	6–33	(Sacks-Davis et al., 2015)
Duration BUP-NX, month (mean, SD)	12(6)	3–60	(Fiellin et al., 2011; Saloner et al., 2017)
BUP-NX Treatment initiation (%)	50	10–100	Expert opinion*
HCV treatment initiation (%)	94	50–100	(Grebely et al., 2018)
Healthcare Costs			
Non-HCV-related healthcare costs, including HIV care ($/month)	1,950–3,904		(AHRQ; Schackman et al., 2015)
Additional healthcare costs with active injection opioid use ($/month)	206	0–572	(Coffin & Sullivan, 2013; Murphy et al., 2017)
BUP-NX treatment ($/month)	705	266–961	(Schackman et al., 2011)
BUP-NX treatment initiation cost ($/person)	207	30–70	(Schackman et al., 2011)
Additional healthcare cost with chronic HCV infection, by METAVIR fibrosis stage ($/month)			(Davis et al., 2011)
f0	256	128–384	
f1	256	128–384	
f2	256	128–384	
f3	256	128–384	
f4	455	228–683	
decompensated	867	434–1301	
Additional healthcare cost after SVR, by METAVIR fibrosis stage ($/month)			Expert opinion
f0	128	64–192	
f1	128	64–192	
f2	128	64–192	
f3	128	64–192	
f4	228	114–342	
decompensated	434	217–651	
Quality of Life (QOL) Weights (Utilities)			
Age-specific QOL for PWH without HCV or injection drug use	0.65-0.78		(AHRQ; Schackman et al., 2002)
QOL for current injection opioid use	0.57	0.54–0.68	(Wittenberg et al., 2016)
QOL for former injection opioid use	0.77	0.74–0.82	(Wittenberg et al., 2016)
QOL for active HCV infection, by METAVIR fibrosis stage			(Sullivan & Ghushchyan, 2006)
f0	0.94	0.9–1.0	
f1	0.94	0.9–1.0	
f2	0.94	0.9–1.0	
f3	0.94	0.9–1.0	
f4	0.75	0.6–0.9	(McLernon et al., 2008)
decompensated	0.60	0.48–0.75	
QOL after SVR, by METAVIR fibrosis stage			Expert opinion
f0	0.97	0.94–1.0	
f1	0.97	0.94–1.0	
f2	0.97	0.94–1.0	
f3	0.97	0.94–1.0	

(*continued on next page*)

Table 1 (*continued*)

Parameter	Estimate (for the base case)	Range	Source
f4	0.94	0.75–0.97	
decompensated	0.75	0.60–0.94	

SD = standard deviation; SMR = standardized mortality ratio; PWID = people who inject drugs; BUP-NX = buprenorphine/naloxone; HCV = hepatitis C virus; SVR = sustained virologic response.

* Expert opinion: We surveyed 11 buprenorphine prescribers affiliated with an ID/HIV clinic in the Boston area (10 providers responded). We asked the following question: "What percentage of your HIV- or HCV-monoinfected or HIV/HCV coinfected patients accept buprenorphine when you offer it to them?" We calculated the mean from these responses.

(Green, McGowan, Yokell, Pouget, & Rich, 2012). More recently, outbreaks of HIV and HCV associated with injection opioid use have been documented in multiple states (Peters et al., 2016). Thus, the population of PWH and HCV who are also living with OUD is at increasing risk for overdose and other drug related complications.

In this context, the management of HIV/HCV co-infection among patients with OUD is a growing challenge. Although substance use is associated with loss to follow-up in HIV care, recent studies have found that persons with OUD, particularly those who receive medications for opioid use disorder (MOUDs) have high rates of retention in HIV care and virologic suppression (62–93%) (Nolan et al., 2017; Simeone, Shapiro, & Lum, 2017; Yehia et al., 2015). Persons who received integrated methadone and HIV primary care at an opioid treatment program had better HIV outcomes than when HIV primary care was delivered off-site (Simeone et al., 2017). Considering HCV treatment for such patients is recommended, but even with excellent medication adherence, ongoing injection drug use puts this population at risk for overdose and HCV reinfection.

Two Food and Drug Administration (FDA)-approved medications for opioid use disorder (MOUDs) are effective at reducing opioid use, improving mortality, decreasing criminal activity, and improving retention in care: methadone and buprenorphine (Kampman & Jarvis, 2015; Mattick, Breen, Kimber, & Davoli, 2014). Buprenorphine/naloxone (BUP-NX) is a partial opioid agonist that alleviates symptoms of craving and withdrawal and blocks exogenous opioids.

BUP-NX and methadone have also been shown to reduce new HIV and HCV infections (MacArthur et al., 2012; Platt et al., 2018), however, the integration of MOUDs into primary or specialty medical clinics is not uniform (Rapoport et al., 2018; Rosenblatt, Andrilla, Catlin, & Larson, 2015). A benefit of BUP-NX over methadone for OUD in the US is that it can be successfully prescribed in primary care settings and dispensed at retail pharmacies (Schackman, Leff, Polsky, Moore, & Fiellin, 2012; Walley et al., 2015). Studies have also shown the clinical benefits and cost-effectiveness of integrating BUP-NX into HIV care (Fiellin et al., 2011; Schackman et al., 2011). HCV co-infection care has additional clinical and cost considerations, but integrating BUP-NX onsite at the time of consideration for HCV treatment for this unique, high-risk population may improve HCV- and non-HCV-related outcomes. Thus, we evaluated the clinical impact, costs, and cost-effectiveness of integrating BUP-NX into onsite HIV/HCV treatment for this population compared with the status quo, namely, referral for MOUD treatment at a site physically separate from the treatment site for HIV and HCV.

Methods

Analytic overview

We used the Hepatitis C Cost-Effectiveness (HEP-CE) model, a Monte Carlo microsimulation model of HCV infection, screening and treatment (Linas et al., 2014), to compare the cost-effectiveness of two approaches to managing OUD treatment among HIV/HCV co-infected patients who have OUD and are being considered for HCV treatment: 1) standard HIV care with onsite HCV treatment and referral to offsite OUD care (status quo) to 2) standard HIV care with onsite HCV and BUP-NX treatment (integrated care). Specifically, integrated care refers to ability of patients to receive their HIV, HCV, and BUP-NX in one clinical setting (e.g., primary care, HIV specialty clinic). The care may be provided by one or more providers (e.g., primary care providers or infectious disease specialists trained to prescribe treatment for HIV and HCV, as well as BUP-NX which requires a special registration from the U.S. Drug Enforcement Agency via the "Narcotic Addict Treatment Act" of 1974). Such clinical settings do not have to be infection specific (e.g., HIV/HCV co-infections only). The simulated population is a cohort of persons with OUD who are aware of their HIV/HCV co-infection, and engaged in HIV care at the time of considering HCV treatment.

We employed the simulation to estimate long-term outcomes for the cohort including liver- and non-liver attributable mortality, HCV re-infections, life expectancy, quality adjusted life years (QALYs), costs (2017 US dollars), and incremental cost-effectiveness ratios (ICERs). We projected lifetime medical costs assuming a healthcare system perspective and applied a 3% discount rate to both costs and QALYs (Neumann, Russell, Sanders, Siegel, & Ganiats, 2017).

We used standard methods to calculate the incremental cost-effectiveness ratio (ICER) of each testing strategy as the additional cost per person divided by the QALYs gained compared to the next less expensive strategy (Neumann et al., 2017). We interpreted ICERs using a willingness-to-pay (WTP) threshold of $100,000/QALY gained (Neumann et al., 2017).

We used data from national databases, clinical trials, and observational cohorts to inform parameter values (Table 1). We conducted one-way and two-way deterministic sensitivity analyses as a means of understanding the heterogeneity among populations in the data sources.

HEP-CE model structure and inputs

Model structure

The model is a closed cohort Monte Carlo microsimulation of HCV infection, disease progression, testing, and treatment. All individuals are tracked from model initiation until death. We used the model to simulate the lifetime course of a hypothetical cohort that has the demographics of co-infected persons with OUD in an HIV clinic. The model includes several modules described below and in the Supplementary Appendix:

HIV infection. The simulated cohort includes patients diagnosed with HIV and receiving HIV care. Adherence to antiretroviral treatment is estimated based on CD4 count. The distribution of CD4 count is drawn from the literature and is assigned based on age and sex. CD4 count is assigned at the beginning of the simulation and does not increase or decrease throughout the simulation.

HCV infection. HCV re-infection, mortality from non-HCV causes, health care costs, and quality of life (QoL) weights depend on current injection opioid use status. The incidence of HCV re-infections in the cohort is conditional on current active injection opioid use. In the model, this corresponds to higher HCV incidence among younger people due to higher prevalence of active injection opioid use in that

Table 2
Base case results of integrated care versus status quo for onsite treatment for opioid use disorder among HIV/HCV coinfected persons in the U.S. actively injecting opioids.

Strategy	Lifetime liver-related deaths*	Non-liver related deaths*		Lifetime Cost (US$)		Life Expectancy		ICER (US $/QALY)
		1-year	5-year	Undiscounted	Discounted	Undiscounted Life Expectancy**	Discounted QALYs	
Status quo	100.0	63.0	269.0	$457,500	$364,400	55.80	3.58	—
Integrated care	97.0	52.0	241.0	$474,000	$377,500	56.14	3.81	—
Difference	−3.0	−1.0	−28.0	+$16,500	+$13,100	+0.34	+0.23	$57,100

ICER = incremental cost-effectiveness ratio (discounted costs/discounted QALYs); QALY = quality-adjusted life-year.
* Number/1,000 persons.
** Median age of the simulated cohort is 45 years.

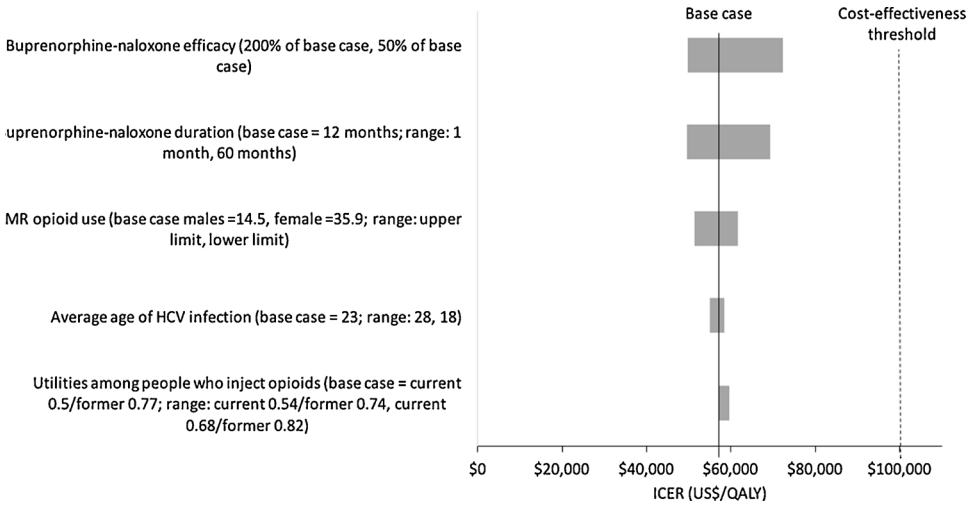

Fig. 1. Tornado diagram of one-way sensitivity analyses.
A range of parameters varied in one-way sensitivity analyses are displayed on the vertical axis. The ICER (US dollars/QALY) of integrated care compared to the status quo is represented on the x-axis. The solid vertical line indicates the ICER of the base case (US$51,700/QALY). The dashed vertical line represents the willingness-to-pay threshold of US$100,000/QALY. For each parameter, the horizontal bar represents the range of ICERs that result from varying that parameter along the range of values indicated in the parentheses; the first value listed in the parentheses is the one that results in the lowest ICER. SMR = standardized mortality ratio; HCV = hepatitis C virus.

group and the greater probability that individuals reduce or leave injection opioid use or die of overdose as they age.

As individuals advance through stages of fibrosis, their QoL decreases, and their health care costs increase. Liver-attributable mortality occurs only among individuals who have reached METAVIR stage F4 (cirrhosis). Individuals with decompensated cirrhosis face a higher mortality probability than those with compensated cirrhosis, which reflects observed data (Bruno et al., 2009).

HCV cure resulting from effective treatment halts fibrosis progression (Gonzalez & Duarte-Rojo, 2016; Zator & Chung, 2013), decreases stage-specific HCV-attributable costs (Davis, Mitra, Medjedovic, Beam, & Rustgi, 2011), and improves HCV-related QoL weights as follows: if cured prior to having cirrhosis, then the HCV-attributable QoL weight improves to that of an uninfected person; if cured with F4 disease, then the QoL weight improves to that of a person with early stage HCV; and if cured with decompensated cirrhosis, then the QoL weight improves to that of a person with compensated F4 disease. Finally, following cure, liver-related mortality among cirrhotic individuals is reduced (van der Meer et al., 2012).

Injection opioid use. There are two relevant states of injection opioid use in the model: current active injection opioid use and former injection opioid use. The current active use state (referred to as "current use") describes the behavior of individuals who inject opioids on a regular basis, defined as the majority of days in the past month. The former use state describes the behavior of individuals who have stopped using injection opioids. The model allows for bidirectional movement between current use and former use. Individuals identified with current use have a probability of being offered and accepting MOUD treatment; in this case, the modeled onsite MOUD is BUP-NX. In general, we model the effects of MOUDs as an increased probability of moving from current use to former use and a decreased probability of moving from former use to current use. However, some individuals remain in current use even while maintained on MOUDs. Because retention on MOUDs is poor (Morgan, Schackman, Leff, Linas, & Walley, 2017), we also model attrition from MOUD treatment by assigning each individual on MOUDs a duration of OUD treatment. When individuals stop the MOUD, they can remain in HCV and HIV care.

For the base case, we simulate an offer of BUP-NX treatment at the point of initiating HCV treatment. This assumption is explored further in sensitivity analysis detailed below. If patients refuse this initial offer, or they accept it but subsequently stop taking the medication, they subsequently experience transitions in and out of injection opioid use and mortality risks that reflect the average experience of people with OUD in the US, which includes a probability of receiving offsite MOUDs (i.e., BUP-NX, methadone, or naltrexone).

Non-HIV and HCV risks of death. In addition, HIV and HCV-attributable mortality, individuals in the model face a risk of death from competing risks that reflect age and sex adjusted comorbid conditions and OUD. Because mortality among patients with active opioid use is high, we employ standardized mortality ratios (SMRs) to upward adjust age and sex specific mortality from causes other than HIV or HCV. The SMRs are higher for those with current use than they are for those with former use. Because opioid use behaviors are dynamic in the model, competing risk of mortality is time updated to reflect changes in both opioid use and age.

Costs. We estimate costs from the health sector perspective in 2017 US dollars (see supplementary appendix for a complete discussion of costs in the model). During each month, persons accrue costs related to HIV care, HCV care, and OUD care. HIV-specific costs vary by age, sex, and CD4 count, with higher costs with advancing age and lower CD4

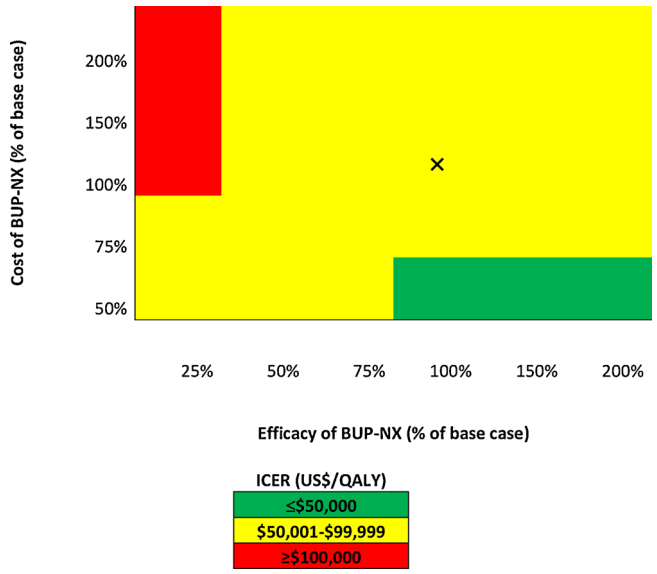

Fig. 2. Two-way sensitivity analysis of cost and efficacy of buprenorphine-naloxone (BUP-NX) in the integrated care strategy compared to the status quo. Projected ICERs with the integrated care strategy compared to the status quo in two-way sensitivity analysis varying the efficacy and cost of buprenorphine-naloxone. The base case is indicated by the X in the figure. The figure demonstrates that the integrated care strategy is cost-effective compared to the status quo with an ICER ≤$50,000/QALY when the cost is halved and the efficacy greater than or equal to the base case. Compared to the status quo, the integrated care strategy is no longer cost effective at a willingness-to-pay threshold of $100,000/QALY when the efficacy is 25% of the base case and the cost is greater than or equal to the base case. Efficacy is defined as the likelihood that an individual transitions from active to former injection use and does not transition back to active use.

(Schackman et al., 2015); HCV-specific costs vary by disease stage, with the highest costs among those with decompensated cirrhosis (Davis et al., 2011); OUD care costs vary by injection opioid state with additional costs for those with current use (Coffin & Sullivan, 2013). Additionally, there are initial and monthly costs of treatment for OUD. Finally, we include age- and sex-stratified costs of healthcare services that are not attributable to HCV, HIV, or OUD.

Quality of life weights. Individuals are assigned QoL weights (utilities) that are estimated based on their HIV and HCV infections, injection opioid use behaviors, age, and sex. In general, QoL weights decrease with lower CD4 count, more advanced liver disease, active injection opioid use, and older age. To take into account all of these effects, we employ the multiplicative approach, which uses the product of the single health states estimates (e.g., HIV, HCV, OUD, and age/sex QoL weight estimates) in a time updated manner (rather than the minimum estimator approach, which uses the lowest value of the four). There is debate as to the best approach, therefore, we performed a sensitivity analysis in which the "minimum estimator approach" was used (Wittenberg et al., 2017).

Model inputs

Simulated cohort demographics. Table 1 outlines key input parameters for the base case. We used cohort studies and a randomized trial of BUP-NX in HIV clinics to inform the demographics of the cohort (Chaudhry et al., 2011). The cohort was 66% male with a mean age 45 years (SD 8 years) (US Census Bureau, 2016; Chaudhry et al., 2011; Fishbein, Lo, Reinus, Gourevitch, & Klein, 2004; Hall, Charlebois, Hahn, Moss, & Bangsberg, 2004).

HIV infection. We estimated age- and sex-stratified CD4 count among HIV-infected persons who inject opioids from the published literature (Hoots, Finlayson, Broz, Paz-Bailey, & Group, 2017). We assumed that all individuals were linked to and engaged in care with a provider, however, not all persons linked to HIV care were adherent to antiretroviral treatment (ART). We modeled ART adherence based on CD4 count; ≤200 cells/mm^3 is assumed to be non-adherent and > 200 cells/mm^3 is assumed to be adherent.

HCV infection and treatment. The median time to cirrhosis from HCV infection (mean age of infection 23 years) was 25 years (Hagan, Thiede, & Des Jarlais, 2004; Smith, Combellick, Jordan, & Hagan, 2015; Suryaprasad et al., 2014; Thein, Yi, Dore, & Krahn, 2008), and the rate of liver-related deaths with cirrhosis was 3 per 100 person-years (Bruno et al., 2009). We modeled an oral, pan-genotypic HCV regimen for all fibrosis stages. In the base case, there were no treatment restrictions. Treatment duration and outcomes were derived from cohort studies and clinical trials (Asselah et al., 2018; Bourliere et al., 2017; Curry et al., 2015; Forns et al., 2017; Wyles et al., 2017).

Injection opioid use. We modeled movement between injection opioid states over the course of the simulation using AIDS Linked to the Intravenous Experience (ALIVE) cohort data. ALIVE is a longitudinal cohort of persons with active injection drug use in Baltimore, Maryland that characterized the longitudinal transitions between drug use states (Galai, Safaeian, Vlahov, Bolotin, & Celentano, 2003).

We modeled sublingual BUP-NX with an average daily dose of 16 mg for treatment of OUD (Schackman et al., 2011). We chose to model BUP-NX since it can be prescribed in primary care and in subspecialty practices. The probability of BUP-NX initiation was 50%, which was derived from expert opinion, and a mean duration of treatment of 12 months (S.D. 6 months) (Fiellin et al., 2011; Saloner, Daubresse, & Alexander, 2017). The monthly probability of relapse from former to current opioid use was three times lower among persons actively treated with BUP-NX compared to those not receiving the medication (Fiellin et al., 2011; Galai et al., 2003).

Table 3
Results of alternative scenarios in which smaller proportions of patients are actively injecting opioids at the time of HCV treatment offer.

Strategy		Lifetime liver-related deaths*	Non-liver related deaths*		Lifetime Cost (US$)		Life Expectancy		ICER (US $/QALY)
			1-year	5-year	Undiscounted	Discounted	Undiscounted Life Expectancy**	Discounted QALYs	
50% active; 50% former	Status quo	97.0	47.0	242.0	$470,300	$373,900	56.14	3.82	—
	Integrated care	95.0	42.0	228.0	$479,100	$380,800	56.34	3.94	—
	Difference	−2.0	−5.0	−14.0	+$8800	+$6900	+0.20	+0.12	$57,400
5% active; 95% former	Status quo	93.3	32.0	217.0	$482,200	$382,500	56.49	4.03	—
	Integrated care	93.4	31.0	215.0	$483,000	$383,300	56.52	4.05	—
	Difference	+0.1	−1.0	−2.0	+$800	+$800	+0.03	+0.02	$38,600

ICER = incremental cost-effectiveness ratio (discounted costs/discounted QALYs); QALY = quality-adjusted life-year.

* Number/1,000 persons.

** Median age of the simulated cohort is 45 years.

Competing risks of death. We modeled SMRs separately for men and women using the published literature, which demonstrates a higher SMR among women (Klein et al., 2014; Mathers et al., 2013). In the model, after individuals transitioned to former drug use their SMR was lower and it did not differ between men and women (Degenhardt, Larney, Randall, Burns, & Hall, 2014; McAnulty, Tesselaar, & Fleming, 1995; Miller, Kerr, Strathdee, Li, & Wood, 2007).

Costs. We derived HIV-related costs and OUD associated costs from the published literature and the 2016 laboratory and physician fee schedules from Centers for Medicare and Medicaid Services (CMS) and inflated all costs to 2017 US dollars (Agency for Healthcare Research and Quality; Center for Medicare & Medicaid, 2016a; Center for Medicare & Medicaid, 2016b; Coffin & Sullivan, 2013; Murphy et al., 2017; Schackman et al., 2015, 2011). HCV treatment costs were derived by using the wholesale acquisition cost (WAC). The cost of a complete course of HCV treatment, including the cost of managing toxicities, ranged from $26,400 to $74,760 (Supplementary Table 2) (Center for Medicare & Medicaid, 2018).

Health-related quality of life weights. We used published health literature estimates to derive health state-related QoL weights on a scale of 0–1.0, where 0 represents death and 1.0 represents perfect health (McLernon, Dillon, & Donnan, 2008; Schackman et al., 2002; Sullivan & Ghushchyan, 2006; Wittenberg et al., 2016, 2017). QoL weights for current and former injection opioid use are 0.57 and 0.77, respectively (Wittenberg et al., 2016). All QoL weights are outlined in Table 1.

Sensitivity analyses. To assess the robustness of our results, we examined the impact of varying key inputs over a wide range of values. We considered two-way analyses to examine outcomes influenced by simultaneous variation in those variables found to be most influential in the one-way sensitivity analyses.

We simulated alternative scenarios in which 5%–50% of the initial cohort were actively injecting opioids (versus 100% in the base case) while the remaining persons in the cohort were those who formerly used opioids, since the base case assumption regarding continued HIV clinic attendance may be more consistent with a lower proportion of people who are actively injecting engaged in HIV care. The alternative scenarios explore the cost-effectiveness of integrating BUP-NX into those clinical situations in which between 95% and 50% of the population is not actively injecting at the time that HCV treatment is offered. We also examined a scenario in which BUP-NX was available onsite as part of the usual care rather than only with the offer of HCV treatment.

We also examined a number of alternative scenarios related to QoL weights, including; 1) using the minimum estimator approach rather than the multiplicative approach (Wittenberg et al., 2017); 2) assuming no QoL decrement associated with HIV infection itself; 3) assuming no QoL decrement associated with early stage HCV (≤F2 disease) and, thus, no QoL benefit associated with treating early stage HCV; and 4) higher QoL for persons with current or former injection opioid use.

Results

Base case

Clinical outcomes

Compared to the status quo, integrated care resulted in modest lifetime reductions in all HCV reinfections from 642/1,000 to 598/1,000, identified HCV reinfections from 251/1,000 to 232/1,000, cases of cirrhosis from 381/1,000 to 377/1,000, and liver-related deaths from 100/1,000 to 97/1,000 (Table 2). Additionally, integrated care resulted in approximately 11/1,000 fewer non-liver attributable deaths at one year and over 28/1,000 fewer at five years. Integrated care resulted in an increase in life expectancy from 55.8 to 56.1 years and an average 0.23 additional discounted QALYs compared to the status quo.

Costs

The total discounted lifetime costs in integrated care were $377,500 per person compared to $364,400 for the status quo (Table 2). Although integrated care reduced lifetime risk of non-liver attributable deaths, it also resulted in higher HCV-attributable costs due to the cost of initial HCV treatment and retreatment. Consequently, the expected lifetime costs of HCV treatment are higher in the integrated care arm than the status quo arm.

Cost-effectiveness

The ICER of integrated care compared to the status quo is $57,100/QALY (Table 2). In one-way sensitivity analyses, integrated care has an ICER less than $100,000/QALY compared to the status quo across broad parameter ranges (Fig. 1; Supplementary Table 3). Results were not sensitive to reinfection rates; when reinfection rates were three times are high as the base case, the clinical and cost-effectiveness outcomes did not qualitatively change (Supplementary Table 3). Even in an analysis in which the reinfection rate was even higher than three times the base case, integrated care remained cost-effective at a threshold of $100,000/QALY.

In two-way sensitivity analysis that varied the efficacy and cost of BUP-NX, integrated care remained a cost-effective strategy compared to the status quo in all instances unless the efficacy was 25% of the base case and the cost was greater than or equal to the base case cost (Fig. 2). Alternatively, integrated care was cost-effective at an ICER of $50,000/QALY when the cost was 50% of the base case and the efficacy was greater than or equal to the base case.

Alternative scenarios

In the alternative scenarios in which 5%–50% of the initial cohort was actively injecting opioids, while the remainder of the cohort formerly injected opioids, the effect of BUP-NX on life expectancy and OUD-related deaths was decreased compared to the base case (in which 100% of the initial cohort was actively injecting opioids), however, the intervention remained cost-effective (Table 3). In the scenario in which we assumed that BUP-NX was available onsite as part of usual care (Supplementary Table 3), total costs increased as did life expectancy, and the intervention remained cost-effective. Additionally, none of the alternative scenarios in which we adjusted the approach to combining QoL weights (minimum estimator instead of multiplicative approach) or QoL estimates or assumptions qualitatively changed our results from the base case (Supplementary Table 3).

Discussion

We evaluated the clinical benefits, costs, and cost-effectiveness of integrating BUP-NX into onsite HIV/HCV treatment compared with the status quo of separating OUD treatment from medical treatment. Our evaluation shows that an integrated care strategy (BUP-NX onsite alongside HIV/HCV treatment) improves HCV-related outcomes by reducing the lifetime prevalence of cirrhosis, the lifetime risk of liver-related death, and the lifetime risk of HCV reinfection after cure. Perhaps most notable, however, is that integrated care substantially reduces one- and five-year non-liver related deaths, thereby contributing to improved life expectancy as well as improving QoL. Thus, while the effects of integrating BUP-NX into HIV/HCV care on HCV-related outcomes are important, these findings suggest that offering MOUDs as a way to improve HCV treatment adherence and outcomes is only one path engaging patients in OUD care. To the extent that the desire for HCV treatment motivates MOUD initiation, the HCV treatment can also be seen as a way to improve OUD outcomes. The combined effects of BUP-NX on liver- and non-liver related outcomes are substantial, increasing the lifespan by nearly one-third of a year compared to the status quo. Compared to the status quo, we found that integrated care was cost-effective assuming a $100,000/QALY WTP threshold, with an ICER of $57,100/QALY.

Our analyses—both the base case, which assumed limited availability of BUP-NX, and the alternative scenario, which assumed that BUP-NX was available onsite as part of usual care—demonstrate the importance of OUD treatment in reducing mortality even in the setting of competing risks due to HCV and HIV infection. In both scenarios, there was an increased life expectancy compared to the status quo. The increased life expectancy was likely due, in large part, to the reduction in non-liver related deaths. Both short- and long-term non-liver related deaths were lower with integrated care. While we did not explicitly model the specific causes of non-liver related deaths, we can infer from the published literature that the majority of these deaths were drug-related (i.e., overdoses) or due to complications of HIV/AIDS (Degenhardt et al., 2011; Nosyk et al., 2015; Veldhuizen & Callaghan, 2014). Additionally, the modest reduction in liver-related outcomes is likely explained by the competing risks of death in this population, with non-liver related death being much more likely than liver-related.

Additionally, results of the sensitivity analysis in which reinfection rates were three times higher than the base case provides further evidence regarding the cost-effectiveness of providing HCV treatment for persons who actively inject drugs. There has been debate among policymakers and healthcare providers regarding how many times, if at all, persons who inject drugs should be provided curative HCV treatment since their risk of reinfection and the cost of HCV treatment are both high (Sacks-Davis et al., 2013). Despite there being more reinfections in this alternative analysis compared to the base case, the ICERs were not qualitatively different. This demonstrates that the QoL and life expectancy benefits conferred by repeat treatment still balance the high HCV treatment costs.

In the sensitivity analysis in which background cessation rates were three times lower and relapse rates were three times higher than the base case (Supplementary Table 3) integrated care may not be cost-effective (ICER = $100,000/QALY). However, in this scenario when the efficacy of BUP-NX doubled from the base case, integrated care was cost-effective (ICER = $70,100/QALY). Therefore, in populations most at risk for relapse and least likely to receive OUD treatment offsite (e.g., community providers), an integrated care approach with emphasis on adequate dosing of and adherence to BUP-NX may be needed.

This study has several limitations. First, we did not evaluate the cost-effectiveness of integrated treatment with other MOUDs such as methadone and naltrexone, which may limit the generalizability in settings where there are a limited number of providers willing and able to prescribe BUP-NX. BUP-NX has been shown to have good, if not better, clinical outcomes compared to naltrexone (Morgan et al., 2017), and current US regulations do not allow for the provision of methadone for treatment of OUD outside of federally regulated opioid treatment programs. Second, we did not explicitly investigate the impact of HIV disease characteristics other than CD4 cell count at the time of the offer of HCV treatment, including subsequent changes in CD4 count. This assumption, however, biases the findings against the cost-effectiveness of integrated care because we did not incorporate improvements in ART adherence and virologic suppression outcomes associated with OUD treatment. Third, the HEP-CE model is not able to perform probabilistic sensitivity analysis to provide estimates of the impact of simultaneous parameter uncertainty. Our extensive deterministic sensitivity analyses, however, provide insight into how variation in our assumptions impact outcomes. The standardized mortality ratios (SMRs) for active opioid use are one example of an uncertain parameter for which we perform extensive sensitivity analyses (see Supplementary Table 3). Fourth, our analysis may be limited due to simplifying assumptions, one of which is that the probability of cessation from active use is constant over time. In reality, it is highest following treatment initiation. Finally, we are not able to model transmission of HIV or HCV infection, or decrements thereof. However, our cost-effectiveness conclusions are conservative (bias away from cost-effectiveness of integrated care) since we have retained all of the “drawbacks” of treating persons in active use (e.g., costs of reinfection after cure) without any of the benefit (e.g., transmission reduction).

Our results have important implications for the care of PWH and HCV in the United States. OUD is exceedingly common among HCV mono-infected and HCV/HIV co-infected persons, and opioid overdose is now a leading cause of death in these individuals. Integrating BUP-NX alongside HCV care may be particularly beneficial in regions like Appalachia that have resource constraints and have seen a recent surge in both injection opioid use and HCV (Zibbell et al., 2018). The results of this analysis can be used to inform discussions between patients and clinicians and between clinicians and policy makers, providing quantitative evidence about the health and economic benefits of BUP-NX treatment among those who receive HIV and HCV care.

Author contribution statement

Dr. Barocas led and supervised all aspects of this project from conceptualization. Drs. Freedberg, and Linas assisted with project conceptualization. Drs. Fiellin, Schackman, and Stein assisted with data curation. Dr. Morgan and Mrs. Eftekhari Yazdi assisted with formal analysis and software development. Drs. Freedberg, Schackman, and Linas assisted with methodology. All authors contributed to writing the manuscript and approved the final draft.

Conflicts of interest

The authors have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugpo.2019.05.010.

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