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A guide to the economics of HCV cure in 2017

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Synopsis

This commentary reviews the core principals of cost-effectiveness and applies them to the rapidly evolving context of HCV treatment in the U.S. The article provides a substantial foundation of evidence that HCV treatment provides good economic value (is cost-effective), even though it is expensive, and even when treating people who inject drugs who are at high risk for HCV re-infection. The price of medications has fallen, but the high price continues to limit access to care. This wedge between cost-effectiveness and affordability stands front and center as one of the leading obstacles to elimination.

Keywords

Hepatitis C Virus; Cost-Effectiveness; Healthcare Economics

The availability of effective, oral treatments for Hepatitis C Virus (HCV) has transformed HCV infection from a chronic disease with few treatment options to a curable condition with as little as 8 weeks of oral therapy. The tremendous potential for HCV cure has generated enthusiasm for employing new treatments to eliminate HCV transmission in the U.S. The National Academies of Sciences, Engineering, and Medicine calls for this goal, as does the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Health and Human Services.¹ With effective treatment in hand, and the explicit goal of eliminating transmission, the challenge shifts from one of biology – how to cure a virus – to public health – how to identify and treat the >4 million people in the U.S. who are HCV infected.

The HCV elimination challenge is difficult when one considers that eliminating HCV transmission requires that we identify and treat the infection among those who are actively transmitting. Therefore, eliminating HCV transmission requires strategies to identify and treat HCV among people who inject drugs (PWID) a^{1–3} Working with current PWID is not

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always easy. There is concern that active PWID who achieve cure of their HCV infection might be re-infected if they continue to use injection drugs or relapse to use in the future.^{4,5} There is also concern that patients identified with HCV infection will not link to HCV care, or will not complete the treatment course.⁶

Adding to this challenge is the reality that HCV treatments are expensive. When first released, a typical course of sofosbuvir, one of the most effective and commonly employed agents for HCV treatment, cost approximately \$84,000.⁷ Since that time, multiple regimens have been FDA approved. There is competition in the market for HCV treatments, and prices have come down significantly. Even at the best price available on the market, however, a course of HCV treatment costs tens of thousands of dollars. Many of the PWID who transmit HCV rely on public payers, such as Medicaid, or Departments of Corrections, for their health care.⁸ The high cost of HCV treatment places substantial stress on health care budgets.

This combination of factors – a prevalent disease that has an expensive, but curative treatment, the potential for re-infection among those who achieve cure, and the burden of curing patients falling primarily on public payers, has generated significant economic barriers to HCV care.^{8–11} Payers are worried about the cost of treating HCV, especially if they are forced to pay for cure more than one time for those who are re-infected. Even when PWID with HCV are identified and linked to care, many payers restrict access to curative HCV treatments to those who have evidence of more advanced liver fibrosis and/or those who have been abstinent from drug use from 6–12 months.^{12–14}

There are many social determinants of health, such as poverty, lack of education, and drug use that create barriers to HCV care among PWID,^{8–10} but at this time there can be no debate that the economic barriers are substantial.¹⁴ HCV treatment is expensive.

Yet, many treatments and healthcare technologies that we routinely employ in the U.S. are expensive, and many of them are not as effective as HCV treatment. Cost is not the only axis by which to prioritize healthcare interventions. There is need for some outcome measure that considers both the cost of a treatment, and the benefit it provides to assess its value. How much benefit will we get for every dollar spent on HCV treatment? How does that ratio of cost to benefit compare to other treatments that we employ in the U.S.? In other words, is HCV therapy “worth it?” what is its *value*?

Cost-effectiveness is the field of research that focuses on defining the value of healthcare technologies.¹⁵ Cost-effectiveness seeks to estimate the cost of employing a new therapy, as well as the additional health benefits that therapy will provide, and ultimately to define a ratio of cost/benefit that one can compare to other possible interventions and make priorities.^{16–18} This article reviews the core concepts of cost-effectiveness research, clarifies the difference between cost-effectiveness and “affordability,” and then reviews the tension between cost-effectiveness and affordability when seeking to improve HCV care.

What is cost-effectiveness?

Cost-effectiveness analysis (CEA) seeks to maximize public health benefits given the resources that are available for healthcare.¹⁹ The central question that CEA asks is “should we invest our limited healthcare dollars in a new treatment? Or should we instead use that money to invest in another healthcare intervention that would provide better outcomes for the same money invested?” CEA is not interested in reducing cost or saving money. Rather, CEA seeks to spend all of the available money, but to spend it well. CEA assumes that all available resources will be spent and provides a framework for prioritizing available treatment options.

The cost-effectiveness of a treatment is typically expressed as an incremental cost-effectiveness ratio (ICER)^{15,20}:

$$\frac{\text{cost new treatment} - \text{cost current treatment}}{\text{benefit new treatment} - \text{benefit current treatment}}$$

Estimating and interpreting the ICER requires that we answer three questions:

1. What are the costs with new and with old treatment and how much more will we spend? The additional cost of HCV treatments includes that of new medications, as well as the costs of staging and evaluation, and the costs that are avoided by preventing future complications of disease. Considering the prevention of long-term complications is especially important when analyzing the cost-effectiveness of HCV treatments, because the costs of the therapy are immediate, while costs avoided by preventing end-stage liver disease often accrue years in the future.²¹
2. What are the benefits of the interventions? One valuable measure of benefit is life expectancy, but considering only mortality benefits fails to recognize the value of treatments that improve quality of life. The quality-adjusted life year (QALY) provides a measure that integrates both longevity and quality of life and is the preferred outcome for CEA.²²

How can we interpret the ICER? The ideal CEA would list every possible healthcare intervention, its life-time medical cost, and QALYs lived. With such a list, we could theoretically prioritize spending perfectly to maximize QALY across the population. In reality, it is impossible to estimate lifetime costs and QALY for everything we do in healthcare. Instead, CEA compares the ICER for a specific treatment to a threshold value and rejects treatments that have an ICER great than the threshold as “not cost-effective.” The threshold value to which we compare an ICER is referred to as the “willingness-to-pay” (WTP) threshold.¹⁵ Importantly, the WTP threshold is not meant to be a valuation of how much we are “willing” to pay to save a life. WTP is not an ethical judgment or a valuation of how much life is worth. Rather, WTP is an attempt to quantify the opportunity cost of a new treatment. In other words, WTP is meant to reflect the return in QALY that we could expect if we did not use available budget to provide a new treatment and instead invested that money into the current healthcare system. For example, if I expect that a \$100,000 investment into an existing healthcare intervention will provide 1 additional QALY (\$100,000/QALY gained), but instead, I could invest the same \$100,000 into a new

treatment that results in an additional 1.25 QALY (\$80,000/QALY), then investing in the new treatment makes sense. We would conclude that the new treatment is cost-effective. If, on the other hand, my \$100,000 investment into a new treatment provides only 0.75 additional QALY (\$133,333/QALY), then I probably should not make that investment. We would then conclude that the new treatment is not cost-effective. In the United States, the willingness-to-pay threshold is typically considered to be either \$50,000 or \$100,000/QALY gained, but there is good reason to use a WTP \$100,000 – \$200,000/QALY.²³ The WTP threshold is country-specific and reflects the budgetary pressures and resources available in a given state.¹⁵ In an effort to provide some rubric for making cost-effectiveness conclusions, the World Health Organization defines an ICER less than per-capita GDP for a country as being “very cost-effective,” and less than 3× per-capita GDP as “cost-effective.”²⁴ However, while the concept of the WTP is grounded in sound economic theory, the actual value of the appropriate WTP in a given country is somewhat arbitrary. Certainly, WTP cannot be interpreted strictly, and some leaders in the field of cost-effectiveness feel that it is inappropriate to use WTP to label interventions as “cost-effective,” or not.²⁵

What do we know about the cost-effectiveness and affordability of treating HCV?

In the last 5 years, several groups, working entirely independently, have been investigating the cost-effectiveness and cost of HCV treatment. With few exceptions, treatment with DAAs has an ICER <\$100,000/QALY gained, and therefore would typically be considered “good value” in the U.S.^{26–44} Some of the earliest studies, which employed the list price of the first treatment regimens available, determined that therapy was not cost-effective for some patient types or genotypes, but those conclusions pre-dated the availability of pan-genotypic regimens, nor did they reflect the substantial price reductions that have characterized the HCV treatment market in the past 1–2 years.^{28,30,45} Studies have compared “treat all patients” to various forms of treatment restrictions, and routinely determine that “treat all” is a cost-effective approach (Table).^{26,27,45}

Why is it cost-effective to treat early stage HCV if early HCV is a “silent disease?”

Studies that consider “treat all” vs. “treat advanced fibrosis only” strategies typically find that “treat all” provides good value when compared to a cost control strategy that limits HCV therapy to those with more advanced liver fibrosis.^{26,27,45} This finding may be counter-intuitive, given that early stage HCV is deemed a “silent disease.”⁴⁶ If HCV has no impact on mortality, quality of life, or health care utilization until it has advanced to a more advanced stage of liver fibrosis, then why bother treating HCV in its early stages, especially if resources are limited?

Although many patients with HCV infection do not know that they have the disease, data consistently demonstrate that the quality of life of patients with early stage HCV is lower than similar patients who do not have HCV infection, even when controlling for known confounders.^{47,48} Similarly, studies of healthcare utilization among patients with early stage HCV demonstrate significantly higher utilization and cost among those with HCV – even those without advanced liver fibrosis.^{45,49} If curing early HCV prevents accumulation of morbidity and cost while patients wait for cure, then it provides good value. In other words, if ultimately a patient will be treated for HCV at some point, then it is better to spend the

money now and prevent disability and healthcare costs that would have accumulated while waiting. In modeling studies, cost-effectiveness conclusions about treating early stage HCV are sensitive to assumptions about quality of life with early disease and the cost of early HCV infection.²⁶ If HCV were really a “silent” disease in its early stages – with no effect on quality of life or cost – then treating early disease would provide little value and it would be rational to defer treatment until HCV becomes a more active issue for the patient. However, empirical data suggest that HCV is not entirely silent.

Is it cost-effective to treat HCV among PWID given the risk of reinfection after HCV cure?

Given that HCV treatments cost the same when employed among PWID as the general population, those treatments might be expected to have similar cost-effectiveness ratios. Two factors, however, could reduce the cost-effectiveness of HCV therapies in PWID: 1) if treatment default and poor retention result in poor cure rates, or 2) if reinfection mitigates the benefit of cure. Several randomized controlled trials of DAAs among PWID, as well as real-world observational cohorts, demonstrate that PWID can be treated with DAAs and have treatment completion and cure rates similar to those among people who do not use drugs.^{8,50–53} In addition, providers are beginning to develop and evaluate effective models for delivering HCV treatment to PWID that both improve treatment completion, and are cost-effective.⁵⁴ While not all PWID are prepared for HCV treatment, it is increasingly clear that drug use itself should not be a categorical exclusion from HCV treatment.⁵⁵

Reinfection rates among PWID are relatively high, ranging between approximately 2 and 4 infections per 100 person-years observed after cure.^{56,57} Further, an honest discussion should acknowledge that as we become more aggressive treating HCV among PWID, reinfection rates will likely rise as we begin treating individuals with more recent histories of current drug use. Re-infection, however, has relatively little impact on cost-effectiveness conclusions.^{43,58} While perhaps counter-intuitive, the reality is that every course of HCV treatment provides good economic value and is, by itself, cost-effective.⁵⁸ Thus, while reinfection increases the ICER of HCV treatment and there is some hypothetical number of reinfections that would ultimately drive the ICER of treatment above \$100,000/QALY gained, HCV treatment remains cost-effective even when it is assumed that >90% of the cohort will be re-infected at least once in their lifetime.⁴³

Does reducing HCV transmission improve the cost-effectiveness of treatment?

Certainly, if every HCV cure actually provides more than one cure (because curing HCV in an index case prevents a future infection), then HCV treatment will appear even more cost-effective than it does when considering only the benefits in the index case. It is important to realize, however, that although “cure as prevention” it is an appealing concept, there are no data to prove that HCV “cure as prevention” works in the real-world. Several simulation modeling studies consider HCV “cure as prevention” and conclude that the approach is cost-effective, but the effectiveness of such an approach is not certain.^{28,58} Treating PWID who are currently or recently using drugs could have two effects: 1) it could prevent future transmissions by eliminating the infection, or 2) it could generate future opportunities for reinfection by increasing the pool of susceptible PWID. The real-world balance of these potential dynamics is not known.

Importantly, however, the cost-effectiveness of HCV treatments does not depend on transmission benefits. Preventing future infections is important to elimination goals, but it is not actually very important to economic conclusions about HCV therapy. Treating a person for HCV, even if that person has very early disease and is a current PWID, provides benefit to the individual being treated today and is cost-effective. Advocacy for HCV treatment need not depend on claims to prevention.

If HCV treatment is cost-effective, why aren't more people being treated?

The short answer to this question is that payers in the U.S. do not make their coverage decisions based on economic “value,” they make decisions based on budgetary impact, or cost. An intervention that is “cost-effective” is not necessarily affordable.^{28,58} Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a HCV treatment for all who might need or want it within that year. Several characteristics of CEA limit its ability to speak to the budget impact of interventions being implemented in the real world:

1. **Perspective on cost:** CEA seeks to inform decisions about how society should prioritize healthcare spending and therefore typically assumes a societal perspective on cost. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses. Costs and savings that are routinely incorporated into CEA are appropriately omitted from assessments of budgetary impact. One example of how the cost perspective fundamentally changes economic conclusions about HCV therapy is in Departments of Corrections. In many states, the Department of Corrections budget is responsible for paying for HCV treatments for those living behind bars, but it does not cover the cost of hospitalizations in the community, and certainly does not cover those costs after a person completes his/her sentence and is released to the community.⁵⁹ As a result, the Department of Corrections sees all of the cost of HCV medicines, but little of the savings that accrue from curing HCV. As a result, a Department of Corrections might rationally conclude that although HCV therapy is cost-effective, it is not affordable.
2. **Time horizon:** CEA uses a lifetime time horizon, meaning that it considers lifetime costs and benefits, including those that occur in the distant future. Businesses however, typically assume a 1-year to 5-year perspective on budgets. Savings that accrue 30 years from now have no impact on spending decisions today, because they have little bearing on the solvency of the budget today. An example of how time horizon directly impacts decision making about HCV treatment is in Medicaid programs. When Medicaid provides HCV treatment, the costs of the therapy accrue immediately. The benefits, however, may not be apparent for decades. As a result, those future savings have very little meaning for budgeting today.^{60,61}
3. **Weak association between willingness to pay and the real-world bottom line:** Societal WTP thresholds in CEAs are not based on actual budget calculations and have little relationship to a payer's bottom line. Willingness to pay is meant

to be an estimate of the opportunity cost of investing in a new therapy. When payers make decision about coverage, the calculation is more straightforward and relates to the cost of meds and the amount of money in the budget. Given the rapid development of new technologies, funding all of them, even if they all fell below the societal willingness-to-pay threshold, would likely lead to uncontrolled growth in demand and would likely exceed the limited healthcare budget.⁶²

This is not to say that payers ignore data comparing the economic value of alternative treatments. All things being equal, any rational payer would rather cover the treatment that provides the best “bang for the buck.” But demonstrating that HCV therapy has an ICER < \$100,000/QALY does not address the reality that treatment is expensive and that any given payer is likely responsible for treatment for tens or even hundreds of thousands of HCV-infected people covered by their plans. The simple arithmetic of (Number infected) × (cost of treatment) adds up to numbers in the hundreds of billions of dollars across the U.S.⁵⁹

What is the budgetary impact of treating HCV?

There is no single budgetary impact of treating HCV. As discussed above, budgetary impact is entirely specific to the budget being analyzed. All of this being said, the budgetary impact of HCV treatment is not as high as it once was. The cost of HCV treatment has come down substantially in the U.S. Whereas the 2014 list price of a 12-week treatment course of ledipasvir/sofosbuvir was approximately \$ 94,500, the cost of a complete 8-week course of glecaprevir/pibrentasvir is \$26,400 – without any price negotiation or discounting.²⁸ Still, many payers, the media, and even progressive advocacy groups seem to remain captivated by the “\$1,000 per day” narrative around HCV treatment.⁶³ HCV treatment is expensive, and the price point for such a prevalent disease creates barriers to care, but in 2017 some of those barriers are created by advocacy that is intended to pressure pharmaceutical companies to lower prices, but instead has had an unintended consequence of reinforcing payer concerns about cost.

Fortunately, many payers do see the changing cost landscape and have begun to loosen their treatment restrictions. In the fall of 2017, for example, both North Carolina and Vermont Medicaid lifted HCV treatment restrictions based on disease stage.^{64,65} Importantly, however, neither state changed restrictions on HCV treatment which require abstinence from drugs.. Indeed, even as states are loosening treatment restrictions based on liver fibrosis stage, they typically maintain restrictions based on recent or active drug use.⁶⁶ Although eliminating HCV requires treatment for PWID and treating current PWID is cost-effective, the specter of paying for HCV treatment more than one time leads payers to restrict access.

How can I use these data to improve care for my patients?

The bottom line to all of the above discussion and data is that although HCV treatment is clearly cost-effective and provides good economic value compared to other healthcare interventions that we routinely employ in the U.S., the combination of high cost, high prevalence, and need to treat a difficult to reach, stigmatized group clearly continues to limit access to HCV cure. At this point, the barriers are about cost, not effectiveness and not value. Based on sophisticated work from multiple independent investigative teams, HCV

treatment is cost-effective – even with early stage disease, even with a high risk of HCV re-infection, and even if we ignore any potential benefit of cure on HCV transmission. But while it is true that HCV treatments continue to be expensive, it is important to ensure that when we are discussing those costs, we use the most up-to-date data. HCV treatment no longer costs “\$1,000/day,” and any policy that is using the \$1,000 price tag to inform decision-making is misguided and misleading.

The every day role that HCV treatment providers and advocates can play to mitigate that barrier is being aware of price when choosing regimens. There are now multiple once a day treatment options for HCV.¹⁴ Typically, for any combination of HCV genotype, treatment experience, and disease stage it is possible to find several once daily options. Some are one tablet and some are multiple tablets. Some require extra testing for resistance, or extending therapy among some patient sub-groups, but all have >95% cure rate in clinical trials. In such a context of choice, it is appropriate to think about the societal context of decision-making and to choose a regimen that may not be the prescriber’s favorite option, but that has the lowest price. This may require discussions with payers, who confidentially negotiate discounts and rebates that lead to certain regimens being substantially less expensive than others. Doing so would limit the budgetary impact of treatment and make cure available to more people. Insisting that all patients have access to all regimens at all times may paradoxically limit the availability of therapy.⁶⁷

Above all, providers should practice comfortably knowing that when they are aggressive about treating HCV – in patients with early disease and in those who have histories of current or recent drug use – they are employing a high value intervention that provides cure and improves both quality of life and life expectancy. When thinking about the costs and the benefits of HCV treatment – from the perspective of the patient or that of society – HCV treatment provides excellent economic value and is “worth” the cost of treatment.

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Table

Recent cost-effectiveness studies of HCV directly acting antivirals

Cost-effectiveness of DAA regimens compared to IFN-based treatments		
Chhatwal et. al 2015 ²⁸	LDV/SOF to IFN-based treatment	ICER < \$100,000 for all genotypes and fibrosis stage
Najafzadeh et al. 2015 ²⁹	Genotype-specific SOF regimens to IFN-based regimens	ICER < \$100,000 for all genotypes but genotype 2. Predated current GT2 regimens
Linás et al. 2015 ³⁰	SOF-based regimens for GT 2 and 3 to IFN-based regimens	ICER < \$100,000 for all patients when accounting for 2017 prices
Younossi et al 2015a ³¹	LDV/SOF compared to IFN-based treatment for GT1	LDV/SOF cost saving
Chidi et al. 2016 ³²	LDV/SOF compared to PROD and IFN-based in the VA system	PROD without restrictions is cost saving at VA prices for PROD
Saab S et al. 2016b ³³	PROD, LDV/SOF, and SOF/SMV vs. PEG/RBV for GT1 and 4	ICER of DAA in all scenarios <\$100,000
Zhang et al. 2016 ³⁴	Genotype appropriate DAA therapy compared to IFN-based treatment	ICER <\$100,000 for DAA regimens
Saint-Laurent Thibault C et. al 2017 ³⁰	SOF/DCV vs. SOF/RBV for GT3 infection	SOF/DCV cost saving compared to SOF/RBV
Chhatwal J et al. 2017 ³⁶	Meta analysis of cost effectiveness studies of DAA therapy. Adjusted treatment prices to current market	At best estimate of current price, DAA treatment cost saving in 71% of studies and cost-effective in 93%
Costs and Cost-effectiveness of HCV treatment restrictions		
Leidner et al. 2015 ²⁶	DAA therapy prioritized by stage of liver fibrosis	ICER for treating all patients compared to limiting to more advanced fibrosis <\$100,000
Chahal et al. 2016 ⁴⁵	LDV/SOF treatment prioritized by disease stage	Treating patients with F1 disease ICER < \$100,000 compared to treating F2+
Linás et al. 2016 ⁴⁴	Cost control by treatment restrictions compared to cost control by price negotiation	Aggressive price negotiation in exchange for formulary preference better than fibrosis stage restrictions.
Cost-effectiveness of implementation models to increase HCV treatment capacity		
Channa R. Jayasekera et al 2017 ³⁷	Expanding capacity for DAA by task-shifting to specialized nurses compared to treating fewer patients with MD provider	Treating more patients with specialized nurses cost-saving and better outcomes
Cost-effectiveness of HCV treatment in key populations		
Martin et al 2016 ⁶⁸	Treatment for PWID with and without advanced fibrosis. Included impact of HCV cure on future transmission	Treating PWID with moderate or mild HCV cost-effective compared to delay until cirrhosis, except when reinfection risk is very high
Elbasha E et al. 2017 ³⁸	EBR/GZR vs. PEG/RBV among patients with <u>chronic kidney disease</u>	ICER < \$100,000 for treatment with EBR/GZR
Saab S et al. 2016 ³³	PROD and LDV/SOF vs. PEG/RBV/SOF in <u>HIV/HCV Co-infected</u>	ICER for both PROD and LDV/SOF <\$100,000/QALY
Assoumou et al. 2018 ⁴³	Screening of young PWID based on the type of screening method. Targeted vs. routine; rapid vs. standard testing; and physician vs. counselor	ICER < \$100,000 for routine rapid testing by a counselor. Routine rapid screening of young PWID was cost effective when prevalence >0.59%
Cost-effectiveness of HCV therapy in liver transplant		
Ahmed et al. 2017 ³⁹	DAA therapy on wait list vs. treating after liver transplant	ICER for treatment before transplant < \$50,000
Salazar J et al 2017 ⁴⁰	DAA therapy on wait list vs. treating after liver transplant Allows for availability of HCV+ livers in deferred treatment strategy	Deferring to treat post-transplant provides best outcomes and is cost saving

Njei B et al. 2016 ⁴¹	DAA therapy on wait list vs. treating after liver transplant considered by MELD category	MELD <25, treatment pretransplant best outcomes and is cost saving. MELD ≥25, treating post-transplant best outcomes and cost-saving.
Tapper EB et al. 2017 ⁴²	DAA therapy on wait list vs. treating after liver transplant considered by MELD category	Treatment prior to transplant provides best outcomes and is cost saving in all but MELD<10

LDV/SOF- ledipasvir/sofosbuvir; IFN- interferon; ICER- incremental cost-effectiveness ratio; SOF-sofosbuvir; GT-genotype; PROD paritaprevir/ritonavir/ombitasvir/dasabuvir; VA-Veterans Health Administration; SOF/SMV- sofosbuvir/simeprevir; PEG/RBV-peginterferon/ribavirin; DAA-direct acting antivirals; SOF/DCV- sofosbuvir/daclatasvir; SOF/RBV-sofosbuvir/ribavirin; PWID-people who inject drugs; EBR/GZR- elbasvir/grazoprevir; PEG/RBV/SOF- peginterferon/ribavirin/sofosbuvir; MELD- model for end-stage liver disease