UNIVERSITY OF CALIFORNIA SAN DIEGO

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Modeling Impact and Cost-Effectiveness of Strategies for Hepatitis C Virus (HCV) Prevention and Treatment in High-Risk Populations in Low- and Middle-Income Settings

A dissertation submitted in partial satisfaction of the
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in

Public Health (Epidemiology)

by

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2020

The Dissertation of Lara K Marquez is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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DEDICATION

Above all, I dedicate this dissertation to my family. Your continuous and unwavering support over the many long and costly years of my academic career. This is yet a small recognition of what is deserved for the lifetime of championing and encouragement.

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EPIGRAPH

A vida é muito curta para ser pequena.

Benjamin Disraeli

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LIST OF ABBREVIATIONS

ART	Antiretroviral therapy
CAP	Compulsory abstinence program
CI	Confidence interval
DAA	Direct-acting antiviral therapy
DAC	Daclatasvir
DALY	Disability-adjusted life year
DC	Decompensated cirrhosis
EASL	European Association for the Study of the Liver
GDP	Gross domestic product
HCC	Hepatocellular carcinoma
HCNSP	High-coverage needle and syringe exchange program
HCV	Hepatitis C virus
HR	Harm reduction
ICER	Incremental cost-effectiveness ratio
LMIC	Low- and middle-income countries
MoH	Ministry of Health
MSF	Médecins sans Frontières
NSP	Needle and syringe exchange program
OAT	Opiate agonist therapy
PPP	Purchasing power parity
PWID	People who inject drugs
RBV	Ribavirin
SOF	Sofosbuvir
SVR	Sustained virologic response
WHO	World Health Organization
WTP	Willingness-to-pay

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ABSTRACT OF THE DISSERTATION

Modeling Impact and Cost-Effectiveness of Strategies for Hepatitis C Virus (HCV) Prevention and Treatment in High-Risk Populations in Low- and Middle-Income Settings

by

Lara K Marquez

Doctor of Philosophy in Public Health, Epidemiology

University of California San Diego, 2020

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Background: With the World Health Organization (WHO) hepatitis C virus (HCV) global elimination goals to reduce HCV incidence and mortality by 2030, there is an urgent need to consider disproportionately affected populations including people who inject drugs (PWID) and HIV-infected individuals. Although curative direct-acting antiviral (DAA) treatments for HCV are now available, barriers to access and affordability have slowed progress towards achieving the WHO goals, particularly in low-middle income country (LMIC) settings where the vast majority of HCV burden resides. This thesis uses modeling to inform HCV elimination programs among vulnerable populations in LMIC settings.

Objectives: Specific aims of this dissertation include: (1) to determine what combination intervention scale-up is needed to achieve the WHO HCV elimination goals among current and former PWID in Tijuana, Mexico; (2) to evaluate the cost-effectiveness of HCV incidence elimination strategies among PWID in Tijuana, Mexico; (3) to evaluate real-world cost and cost-effectiveness of DAAs for HCV/HIV-coinfected individuals in Dawei, Myanmar.

Methods: In Chapter 2, I used a dynamic, deterministic model of HCV transmission, progression, and harm reduction. In Chapter 3, I extended the model in Chapter 2 to perform a cost-effectiveness analysis of HCV elimination strategies from a healthcare provider perspective among PWID in Tijuana, Mexico. In Chapter 4, I performed a micro-costing analysis of an HCV treatment program among HIV-infected individuals in Dawei, Myanmar and used a Markov model to evaluate the cost-effectiveness of this program compared to no treatment.

Results: In Chapter 2, findings showed that achieving both HCV incidence and mortality elimination goals in Tijuana required additional DAA investment. Further, combination harm reduction scale-up plus DAAs required fewer treatments compared to DAAs alone, so may be more feasible given limited treatment allocation nationally. In Chapter 3, results showed that all elimination strategies were cost-effective in Tijuana. While a treatment only strategy was the least costly, combination harm reduction and treatment provided more health benefits compared to treatment alone and is cost-effective. Chapter 4 findings demonstrated that HCV DAA treatment for HCV/HIV-coinfected individuals was cost-effective in Myanmar, and even more so with simplified treatment algorithms.

Conclusions: Findings from these studies highlight the feasibility and cost-effectiveness of HCV elimination programs for PWID and HIV-positive individuals in two LMIC settings. Expansion of HCV screening and treatment programs for these populations are urgently

required, coupled with evidence-based harm reduction interventions to prevent reinfection and ensure that the WHO HCV elimination goals are achieved by 2030.

CHAPTER 1: INTRODUCTION

Hepatitis C Virus (HCV), a leading cause of morbidity and mortality worldwide, is a blood-borne disease and one of several in a family of viral infections which cause inflammation of the liver. In 2015, there were an estimated 71 million (62-79 million) people living with chronic HCV infection and an estimated 1.75 million new HCV infections diagnosed globally [1]. Without treatment, chronic HCV infection can progress to serious liver complications including cirrhosis, liver cancer, or end-stage liver disease [2]. Infected individuals have a risk of liver cirrhosis between 20-30% within 15-25 years of infection [3]. One of the main risk groups for HCV transmission are people who inject drugs (PWID), where approximately 52% globally have a history of HCV infection [4]. Due to shared transmission routes, another risk group for HCV transmission are individuals infected with HIV, an estimated 17.8% (95% CI: 10.8-24.8) of PWID are infected with HIV [4] and 6.2% (95% CI: 3.4-11.9) of HIV-infected individuals are coinfected with HCV, globally [5]. Due to the substantial and rising morbidity and mortality associated with HCV globally, in 2016 the World Health Organization (WHO) introduce targets to eliminate HCV as a public health threat, aiming to reduce HCV incidence by 80% and HCV-related mortality by 65% by 2030 [6]. There is no vaccine for HCV, but traditional harm reduction interventions such as needle and syringe programs (NSP) and opiate agonist therapy (OAT) are effective at preventing the acquisition of HCV among PWID [7]. However, theoretical models have shown these are insufficient to dramatically reduce HCV incidence in isolation [8]. Recent development of short duration and highly tolerable direct-acting antiviral (DAA) therapy for HCV can result in cure in >90% of individuals [9]. In addition to the individual benefits of treatment, HCV treatment for those at risk of transmission could also act as a means of prevention [1]. However, few individuals are diagnosed (an estimated 20% worldwide) and even fewer diagnosed are treated [1, 10]. This varies widely between settings where an estimated 8% of people infected with HCV are diagnosed in low- and middle-income country (LMIC) settings compared to 43% in high-income settings [11]. In this dissertation introduction, we provide an overview of the WHO viral

hepatitis elimination targets, the natural history of HCV, review the global epidemiology of HCV, examine current HCV screening, diagnostics, and interventions, discuss how epidemic and economic modeling has been used to assess the impact and cost-effectiveness of HCV treatment and prevention strategies, highlighting those which have been shown to inform HCV elimination strategies and lastly, present the proposed aims for this dissertation.

WHO viral hepatitis elimination targets

In 2016, in an effort to focus resources on the global elimination of viral hepatitis as a public health threat, WHO set 15-year elimination targets, to be achieved between 2015 and 2030 [6]. For HCV, these targets included an 80% reduction of HCV incidence, equating to a reduction from 6-10 million cases to 0.9 million cases, and 65% reduction in liver-related mortality by 2030, reducing annual deaths from 1.4 million to 0.5 million [1]. As a part of this elimination strategy, WHO had helped over 84 countries develop and establish viral hepatitis control programs by 2017 [11]. A global HCV elimination modeling study showed that achieving global elimination will be dependent on the success of a multifaceted approach including prevention interventions, outreach screening, and progress within key countries which have high-burden populations driving this epidemic, such as India, China, and Pakistan [12]. To achieve these goals, countries will likely require setting-specific modeling to estimate what level and mixture of interventions are required to ensure the WHO targets are met in the most effective and cost-effective manner. As HCV epidemics are highly heterogenous by country and setting, the WHO elimination goals are more likely to be met through the development and implementation of programs tailored to setting-specific HCV epidemics and rolled out among those identified key populations. This is a focus of this dissertation. However, with this ambitious set of goals, and the armory of traditional prevention interventions combined with new, highly effective HCV therapy, HCV elimination may move from dream to reality. Achieving these goals likely requires improvement in HCV diagnosis, treatment, and prevention, as discussed in the following sections.

Natural history of HCV

Initial exposure to HCV leads to a brief period of acute infection, lasting approximately 6 months [13, 14]. An estimated 70-80% of people with acute HCV are asymptomatic [15], and as a result, most individuals infected with HCV remain unaware of their status. Approximately 15-45% of HCV-infected individuals clear their acute infection on their own (termed “spontaneous clearance”) within 6-12 months without treatment [16]. For those who do not spontaneously clear the acute HCV infection, the remainder progress to chronic infection [2]. If left untreated, chronic infection can slowly lead to progressive liver fibrosis, cirrhosis, liver cancer, and/or death, with an estimated 20-30% developing cirrhosis, 5-10% developing end-stage liver disease, and 4-8% dying from liver-related causes within 15-25 years [3, 16]. Of those with chronic HCV infections, approximately 470,000 people worldwide die each year from HCV, 399,000 of which die from end-stage HCV infection, due to cirrhosis and hepatocellular carcinoma [1].

Global epidemiology of HCV

Globally, an estimated 2.5% (177.5 million) individuals showed evidence of past or current HCV infection in 2015 [17]. In 2015, the World Health Organization (WHO) estimated the global prevalence of chronic HCV infection to be 1% or 71 million individuals [1], with as many as 90% of chronically infected individuals living in LMICs [18]. Additionally, WHO estimated 1.75 million new HCV infections were diagnosed that same year [1]. In the past 10 years, there have been increases in HCV morbidity and mortality, with the highest burden (accounting for 80% of global burden [18]) occurring in low- and middle-income countries (LMICs) [17-19].

Key populations at risk for HCV infection

HCV is a bloodborne disease that is transmitted by parenteral contact with infected blood [20]. The most common routes of transmission include injection drug use, unsafe medical injection practices, transmission within health care settings, transfusion of unscreened blood or blood products, organ and tissue transplant, and mother-to-child transmission [20, 21].

However, high risk populations for HCV infection can vary dramatically by setting, even among LMICs or within a single country. For example, the contribution of HCV transmission attributed to injection drug use among people who inject drugs (PWID) is greater in high income settings (79%; 95% CI: 57-97), compared to LMIC settings (38%; 95% CI: 24-64) [22]. Sub-Saharan Africa (14%; 95% CI: 2-43%) and south Asia (14%; 95% CI: 4-31%) are among the countries with the lowest population attributable fraction of HCV transmission attributed to injection drug use whereas North America (77%; 95% CI: 56-100%), eastern (96%; 95% CI: 69-99) and western Europe (83%; 95% CI: 53-94), and Latin America (71%; 95% CI: 49-98) were among the highest [22]. In 2015, WHO estimated about 5% of healthcare-related injections were unsafe, globally [1]. In many resource-limited countries, healthcare workers and recipients of donated blood or organs are at risk through contact with contaminated needles or inadequately screened blood products. Vertical HCV transmission can occur when an infected mother passes the virus to her child but is rare among women with HCV monoinfection, occurring at a transmission rate of 5.8% (95% CI: 4.2-7.8%) [23] although there is an increased risk among HIV-infected women (11-25%) [23, 24]. While it has been documented among HIV-infected men who have sex with men [25, 26], there is a low risk of spreading HCV via sexual contact [27], and thus not considered a major transmission route for HCV. This thesis focuses on two of the key populations at risk for HCV transmission: PWID and HIV-infected individuals. Below, we briefly describe the epidemiology of HCV among these groups.

HCV among PWID: Globally, PWID are one of the populations most impacted by HCV. Current PWID are one of the main risk groups for HCV transmission because of behaviors such as syringe sharing, which contributes greatly to HCV incidence worldwide [22]. In 2015, approximately 15.6 million people (95% Uncertainty Interval [UI]: 10.2-23.7) between 15-64 years old injected drugs globally (in the past 12 months), with the largest PWID populations existing in east and southeast Asia (4.0 million), eastern Europe (3.0 million), and North America (2.6 million) [4]. This study estimated that the seroprevalence, or those with a history of

HCV infection, was 52% among current PWID globally (8.2 million; 95% UI:4.7-12.4 million) and found high heterogeneity in prevalence, ranging from 2% to 89% across 81 countries [4]. Additionally, an estimated 43% of incident HCV infections could be prevented from 2018-2030 if the risks of unsafe injecting practices were removed [22].

HCV among HIV-infected individuals: Due to common transmission routes, HCV is also a highly prevalent (6.2%; 95% CI: 3.4-11.9) co-infection among HIV-infected individuals globally, equating to approximately 2.28 million individuals (IQR: 1.28-4.42 million) estimated to be HCV/HIV-seropositive [5]. The highest burden of HCV/HIV co-infection occurs among PWID worldwide, with 82.4% (95% CI: 55.2-88.5) of HIV-infected PWID estimated to be co-infected, compared to 6.4% (95% CI: 3.2-10.0) in men who have sex with men, and 2.4% (IQR: 0.8-5.8) within the general population [5]. Additionally, compared to HIV-uninfected individuals, HIV-infected individuals are 6 times (OR: 5.8; 95% CI: 4.5-7.4) more likely to become infected with HCV [5]. HCV/HIV co-infection rates up to 96% have been reported in east Asia, in a population with an estimated 20% of HIV-infected individuals also being PWID [5]. While successful scale-up of antiretroviral therapy (ART) among HIV-infected individuals has dramatically increased life expectancy, HCV has now emerged as a major contributor to morbidity and mortality within this population. Compared to HIV monoinfected individuals, HCV/HIV coinfection was significantly associated with increased risk of liver-related mortality (adjusted Rate Ratio (aRR) 6.2; 95% CI: 3.3-11.6)) and increased all-cause mortality (aRR 1.4; 95% CI: 1.2-1.8) [28]. Furthermore, HCV/HIV co-infection has been associated with decreased rates of spontaneous clearance of HCV [29, 30] and accelerated HCV-liver disease compared to HIV-monoinfection [31-33], thus early diagnosis and HCV treatment is important in this population.

HCV screening & diagnosis

While HCV screening methods exist, implementation of appropriately targeted and widespread screening programs remains a challenge. One of the critical gaps in HCV detection is inaccessible testing, due to a multitude of challenges including high cost, lack of diagnostic

infrastructure, poor awareness of testing facilities, lack of HCV awareness among patients and healthcare providers, and stigma and discrimination [34-38]. As a result, globally, as few as 20% of individuals living with HCV were aware of their status as of 2015 [39]. Furthermore, many LMICs have low diagnosis rates (10%) [11], resulting in most chronic HCV cases remaining undiagnosed until they manifest into more advanced stages of liver disease [40]. With the WHO global elimination efforts underway, the landscape is constantly changing. However, a few key barriers to testing access and uptake remain in LMICs including (1) high levels of stigma and discrimination, particularly among PWID, (2) limited healthcare infrastructure for HCV testing, (3) poor laboratory capacity including limited staff and testing materials, (4) costs of diagnostics, particularly HCV RNA testing, (5) limited HCV surveillance programs, and (6) in some countries a lack of guidance for testing or absence of national HCV testing strategies and funding [41]. Aside from these factors, and while this is changing, low level of awareness about HCV, HCV risk, testing and treatment remain major factors among key populations such as PWID, globally [42, 43].

HCV treatment

Historically, interferon-based HCV drug therapy was associated with a long treatment duration (6-12 months), severe side effects, and cured only about half of HCV monoinfected individuals, with lower cure rates among HCV/HIV-infected individuals [44, 45]. Within the past decade, however, new HCV antiviral therapies has revolutionized the field of HCV treatment globally, and are now curative in the majority of individuals. In 2011, first generation direct-acting antivirals (DAAs) were available in combination with interferon and ribavirin, which increased cure rates to about 60% but were still long in duration and associated with serious side effects [46, 47]. Around 2014, the second generation of all-oral DAAs had minimal side effects, shorter courses of therapy (8-12 weeks), and are associated with cure rates of over 90% in clinical and real-world studies in both HCV monoinfected and HCV/HIV co-infected

individuals [48-50]. Despite these higher cure rates achieved with newer DAA therapy, reinfection is still possible [51], as treatment does not induce immunity to HCV infection.

However, with initial costs per DAA treatment course at >$80,000 in the US, price was an immediate barrier for access. While costs have been lowered in recent years (~$24,000 in the US [52]), to nearly a quarter of the price when DAAs came to market in the US, treatment cost still remains a significant challenge to access. Even with treatments offered at lower prices in many low or lower-middle income country settings (such as $84 in Egypt, $60 in Rwanda, and $39 in India for 12-week course) [53, 54], the resources required for diagnosis, treatment and monitoring remain a huge barrier for healthcare systems in resource-rich and resource-limited countries alike.

As a result, worldwide, only 7% of those diagnosed (1.1 million) were started on treatment in 2015 [1]. Of those who started treatment in 2015, about half received DAAs [1]. Due to low treatment rates, the number of new HCV infections was greater than the number of HCV-infected individuals who initiated treatment in 2015 [1]. In 2017, an estimated 19% of people living with HCV (approximately 13.1 million) were aware of their status and 5 million people diagnosed with HCV were treated using DAAs [55].

Prevention strategies among PWID

Among PWID, the main prevention strategies include harm reduction interventions, such as opiate agonist therapy (OAT) and needle and syringe exchange programs (NSP). OAT is an evidence-based, biomedical approach using medication-assisted therapy, such as methadone or buprenorphine, to treat those who are dependent on opioids [56]. OAT has been shown to reduce the risk of fatal overdose by as much as 70% [57] and bloodborne disease transmission such as HCV by 50% (RR=0.50, 95% CI: 0.40-0.63) [7] and HIV by 54% (RR=0.46, 95% CI: 0.32 to 0.67) [58].

NSPs provide a multi-pronged approach to reduce the use of contaminated injection equipment with the intention of reducing the risk of transmission of bloodborne diseases including HCV and HIV. At its core, NSPs provide sterile needles and syringes and other injection equipment [59]. In addition to needles and syringes, NSPs may also provide condoms, medications, educational materials on overdose prevention, HCV, sexually transmitted infections and more [60]. NSPs may provide a range of services including but not limited to education, care for abscesses, drug treatment (OAT), and HIV testing and counseling [59]. Additional services such as linkage to care and treatment for HIV and other illnesses, access to healthcare services and legal and social support may also be available [59]. In addition to OAT, NSPs are effective in reducing HCV transmission among PWID [7]. For example, a systematic review showed weaker evidence that high NSP coverage (receiving ≥1 sterile syringe per injection) was found to reduce HCV acquisition by approximately 23% (RR=0.77, 95% CI: 0.38-1.54), as this estimate straddled the null [7]. However, the impact of NSP has been shown to vary by region, with high NSP coverage in Europe associated with a 56% reduction in HCV acquisition risk (RR=0.44, 95% CI: 0.24-0.80) [7]. When combining high coverage of both NSP and OAT interventions, the risk of acquiring HCV was reduced by an estimated 71% (RR=0.29, 95% CI: 0.13-0.65) [7]. While scale-up of current harm reduction interventions have been shown to be successful, modeling studies have indicated that harm reduction alone is unlikely to eliminate or substantially reduce HCV incidence among PWID [8].

Recent studies have proposed the additional use of HCV treatment as a means of prevention among PWID and other populations at risk of transmission [61-63]. The theoretical basis for this originated from the extensive body of clinical trial [64, 65], theoretical modeling [66], and ecological analyses [67] examining the potential impact for ART to be used for HIV prevention. It has been argued that due to the finite duration and curative ability of HCV antivirals, HCV treatment as prevention would be expected to show similar if not stronger success rates in transmission reductions. This optimism is hampered by concerns about the risk

of HCV reinfection. One of the primary challenges includes the lack of empirical data evaluating the prevention benefit of antivirals [68]. However, there is theoretical evidence of HCV treatment as prevention benefits from epidemic modeling [62, 69, 70] which we discuss in the next section.

Role of epidemic modeling in public health

Epidemic models are mechanistic models which simulate disease transmission within a population. The development of modern models of communicable disease dynamics have been credited largely to Kermack and McKendrick in the late 1920s whose initial work was centered on describing why epidemics spread through a population without infecting the entire population [71]. These epidemic models often use compartmental models, which distinguish specific subgroups or compartments of a given population and follow the transition of individuals between these compartments over time [72]. For example, for many diseases, the population can be split into four main compartments including susceptible, exposed (infected, not infectious), infectious, and removed (recovered and immune, death, vaccinated). Within each compartment, individuals are assumed to be homogenous [72]. Numerous versions and adaptations of these compartmental epidemic models have been utilized to study a wide range of diseases to predict the potential future epidemic trajectory and impact of interventions. These types of epidemic models have utility in comparing the effectiveness of prevention and control programs. For example, some early models compared screening, contact tracing, and vaccination to compare a variety of control strategies against gonorrhea [73] as well as sought to identify ideal age groups to receive influenza vaccination in order to reduce cost and fatalities [74].

Mathematical epidemic models simulate disease epidemic trajectories over time and can help negotiate effective and impactful programmatic and policy changes. There are numerous benefits to using epidemic models to analyze infectious disease transmission, progression, and intervention. These models can be used to predict the impact of intervention implementation

and scale-up on disease prevalence and incidence over time, and are particularly valuable when clinical trials are unfeasible due to time or resource required.

HCV modeling

A number of epidemic models have been used to explore HCV transmission patterns, with many of these early models used to model HCV prevention focused among PWID [61, 63, 69]. Thus, these models focused on evaluating the impact of harm reduction interventions or overall reduction in risk of HCV transmission. However, modeling has shown that while scale-up of traditional primary prevention (such as harm reduction interventions) could have success in certain settings, they would not be able to reduce HCV to very low levels [69]. More recently, models have evaluated the impact of HCV treatment scale-up used as a tool for prevention to reduce HCV incidence, alone and in combination with harm reduction [12]. Among PWID, these studies have shown that treatment scale-up may play a key role in HCV epidemic control among PWID, and furthermore HCV treatment along with the use of harm reduction scale-up and treatment as prevention has shown a significant impact on HCV transmission [63, 69]. Additionally, a small amount of treatment may have large impacts in reducing HCV prevalence, particularly when coupled with harm reduction interventions such as OAT and NSP [61-63]. Few modeling studies have been used to evaluate HCV elimination strategies among other key populations, such as HIV-infected individuals, particularly outside of high-income settings [75]. However, there are few studies which have modeled the impact of these programs, particularly within the context of HCV elimination, in LMIC settings [76]. A few studies have examined country-level elimination strategies among HCV monoinfected individuals, such as in Pakistan [76], which also highlight the benefit of prioritization of PWID and of concomitant scale-up of harm reduction on achieving elimination. A key gap in this research is the absence of studies modeling the impact HCV treatment and prevention strategies required to achieve HCV elimination in LMIC settings. This thesis addresses this gap by evaluating various HCV

treatment and harm reduction strategies, scaled-up alone and in combination among PWID in Tijuana, Mexico.

Role of cost-effectiveness analysis in HCV programs

A key secondary question for policymakers in addition to whether an intervention is effective is whether it is cost-effective. Cost-effectiveness evaluation compares the costs and outcomes of two different courses or interventions, often comparing the current intervention to a new intervention to determine which provides the best value for cost [77]. As a result, cost-effectiveness evaluation is a demonstrated and valuable tool to help inform policymakers on how to best allocate scarce resources. The determination of whether a public health intervention is cost-effective depends on whether it falls above or below what is known as the willingness-to-pay (WTP) threshold. Interventions that cost more than the defined WTP are not cost-effective, whereas interventions that cost less than the WTP are considered cost-effective. There is greater uncertainty in the determination of the WTP threshold, however. According to WHO guidelines, the WTP is defined based on the per capita gross domestic product (GDP) of the country in which the intervention takes place. If the intervention is less than three-times the per capita GDP of the country, it is considered cost-effective, and if it is less than one-time the per capita GDP, it is highly cost-effective. However, this is not the only WTP threshold that is used to determine cost-effectiveness. As an alternative to the WHO definition, using cost-effectiveness thresholds based on the purchasing power parity (PPP)-adjusted GDP has been suggested [78]. WTP thresholds based on PPP suggest that the WHO estimates are often too high and would not be recommended to determine the necessary allocation of resources [78]. Yet, further investigation of PPP-adjusted GDP in lieu of the per capita GDP is needed to determine which WTP should be more widely recommended. Yet, regardless of method, these thresholds exist as recommendations, arising from both the financial value of an intervention as well as its estimated health benefits, within a specified setting, and thus are not intended to be

used as the sole determining factor in deciding whether or not to implement a given intervention [79].

Cost-effectiveness evaluation has played a key role in HCV research. For example, a number of economic evaluations have assessed the cost-effectiveness of HCV treatment for an individual, generally finding DAAs cost-effective in HCV monoinfection compared to interferon-based treatments or no treatment in high income settings like the US [80] and Europe [81, 82]. HCV treatment with DAA-containing regimens among HCV monoinfected individuals has been shown to be cost-effective in Egypt [83] and in India [84, 85] compared to no treatment, yet studies evaluating this in LMIC settings are limited, and these studies did not utilize programmatic treatment delivery or outcome data. Similarly, HCV treatment with interferon-based regimens among HCV/HIV co-infected individuals was also found to be cost-effective in an urban cohort in the US [86], with the cost-effectiveness of DAAs among HCV/HIV co-infected individuals being highly dependent on the cost of therapies [87]. Furthermore, early screening and treatment using DAAs has also shown to be cost-effective in high-income settings, such as among HIV-infected men who have sex with men in the Netherlands [88] and among PWID in Germany [89] and in the US [90, 91]. To our knowledge, no studies have assessed the cost-effectiveness of real-world, HCV treatment programs using DAAs in an LMIC setting among HCV/HIV coinfected individuals. This thesis addresses this gap by using real-world programmatic data to assess the cost-effectiveness of HCV screening and treatment among HIV-infected individuals in Myanmar, a LMIC setting.

In addition to evaluating the cost-effectiveness of HCV screening and treatment programs, economic evaluations are increasingly being applied to determine the most cost-effective strategy for achieving HCV elimination. These studies compare various intervention portfolios to assess the most efficient way to achieve elimination goals, such as the WHO goal of reducing HCV incidence by 80%. For example, while numerous studies have shown that HCV treatment [80], OAT, and NSP [92] are cost-effective in the United States, the most cost-

effective scale-up strategy for reaching the WHO elimination goal remains unclear. Increasingly, dynamic models are being developed to address this question. Whereas standard cost-effectiveness analyses evaluating HCV treatment, even those focusing on treatment for PWID, traditionally focus solely on individual benefits of HCV treatment, newer dynamic transmission models include the possible population prevention benefits of treatment [93-97]. Only a handful of studies have assessed the most cost-effective elimination strategies, with a study in Pakistan finding that using an HCV point-of-care test to detect and inform treatment response could be cost-saving by 2030 and feasible to achieve elimination [98] and similarly a study in Greece finding that implementing a population-based HCV screening and awareness campaign, which could achieve HCV elimination, could be highly cost-effective by 2035 [99]. Furthermore, cost-effectiveness of tailored HCV prevention and intervention programs is critical to achieving HCV elimination, particularly in LMIC settings where there have been few studies assessing the cost-effectiveness of elimination strategies. This thesis addresses this gap by using dynamic economic modeling to assess what intervention portfolios are required to achieve HCV elimination among PWID in Tijuana, Mexico, and the most cost-effective intervention strategy.

Dissertation aims and structure

The goal of this dissertation is to determine effective and cost-effective strategies to treat and prevent HCV among high-risk groups including PWID and HIV-infected individuals in LMICs.

Chapter 2 focuses on using dynamic modeling to determine what intervention scale-up is required to achieve HCV elimination goals among people who inject drugs in Tijuana, Mexico. With Mexico announcing its strategy for HCV elimination in 2019, it became the first country in Latin America to take action against HCV [100, 101]. Yet the intervention scale-up required to achieve the WHO elimination targets among PWID is unknown, particularly in settings with very high HCV prevalence and limited harm reduction as in Mexico. The documented high prevalence of HCV among PWID in Tijuana (>90% [102]), where evidence-based harm

reduction interventions are limited, underscores the need to identify the potential impact of intervention scale-up and what is required to achieve WHO elimination targets in Tijuana. The dynamic modeling analysis in Chapter 2 identifies what combination portfolios of harm reduction and treatment can achieve the HCV elimination goals in Tijuana.

Just as important as the identification of effective HCV eliminations strategies, is the need to understand the cost-effectiveness of these proposed strategies. Only one cost-effectiveness analysis of HCV treatment was performed in Mexico in the pre-DAA era, in 2005 [103], but none have been performed since. Now, with HCV elimination goals in focus, solely understanding which intervention packages may be the most effective in achieving the HCV incidence and mortality reductions among PWID in Tijuana is not sufficient. In order for policymakers and programmatic changes to be considered and henceforth implemented, cost-effectiveness of these proposed interventions is critically needed. Chapter 3 evaluates the cost-effectiveness of scale-up of various HCV elimination strategies needed to reach the WHO HCV incidence elimination goal among PWID in Tijuana, Mexico.

Few studies have evaluated the cost-effectiveness of HCV treatment in LMIC settings where health care management of liver disease and costs of providing DAA treatment differ dramatically from high-income countries. Existing evaluations have been limited to theoretical analyses of DAA-containing regimens for HCV monoinfection in in Egypt [83], India [84, 85], Pakistan [76], and Thailand [104]; and have not evaluated real-world program implementation costs or cost-effectiveness, nor have they addressed HIV-infected individuals. Evaluating real-world HCV treatment programs in low-income settings is critical to designing and implementing effective and cost-effective HCV treatment programs to achieve the global HCV elimination targets set by the World Health Organization [6]. Chapter 4 uses real-world data to assess the cost and cost-effectiveness of HCV treatment among HIV-infected individuals in Dawei, Myanmar. Findings from these studies can be used to inform policymakers as to the most

effective and cost-effective strategies for HCV prevention and treatment required for HCV elimination in LMIC settings.

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CHAPTER 2: Is hepatitis C virus (HCV) elimination achievable among people who inject drugs in Tijuana, Mexico? A modeling analysis

ABSTRACT

Background: In 2019, Mexico became the first Latin American country committed to hepatitis C virus (HCV) elimination, but the amount of intervention scale-up required is unclear. In Tijuana, HCV among people who inject drugs (PWID) is high; yet there is minimal and intermittent harm reduction, and involuntary exposure to compulsory abstinence programs (CAP) occurs which is associated with increased HCV risk. We determined what combination intervention scale-up can achieve HCV elimination among current and former PWID in Tijuana.

Methods: We constructed a dynamic, deterministic model of HCV transmission, disease progression, and harm reduction among current and former PWID parameterized to Tijuana (~10,000 current PWID, 90% HCV seropositive, minimal opiate agonist therapy [OAT] or high coverage needle/syringe programs [HCNSP]). We evaluated the number of direct-acting antiviral (DAA) treatments needed from 2019 to achieve elimination targets (80% incidence reduction, 65% mortality reduction by 2030) with: (a) DAAs alone, (b) DAAs plus scale-up of OAT+HCNSP (up to 50% coverage of OAT and HCNSP separately, producing 25% of PWID receiving both), (c) DAAs plus CAP scale-up to 50%. Scenarios examined the number of DAAs required if prioritized to current PWID or provided regardless of current injection status, and impact of harm reduction interruptions.

Results: Modeling suggests among ~30,000 current and former PWID in Tijuana, 16,160 (95%CI: 12,770-21,610) have chronic HCV. DAA scale-up can achieve the incidence target, requiring 770 treatments/year (95%CI: 640-970) if prioritized to current PWID. 40% fewer DAAs are required with OAT+HCNSP scale-up to 50% among PWID, whereas more are required with involuntary CAP scale-up. Both targets can only be achieved through treating both current and former PWID (1,710 treatments/year), and impact is reduced with harm reduction interruptions.

Conclusions: Elimination targets are achievable in Tijuana through scale-up of harm reduction and DAA therapy, whereas involuntary CAP and harm reduction interruptions hamper elimination.

Keywords: Hepatitis C elimination, people who inject drugs, modeling

INTRODUCTION

Hepatitis C virus (HCV) is a blood-borne infection which, if untreated, can result in cirrhosis, liver cancer, and death. Of the estimated 71 million chronic HCV infections globally, 80% occur in low to middle income countries (LMIC) [1-3]. Globally, people who inject drugs (PWID) are a main group at risk for HCV transmission, with an estimated 52% of all PWID having a history of HCV infection [4]. In addition, an estimated 43% of incident HCV infections could be prevented from 2018-2030 if the risks of unsafe injecting practices were removed [5]. In 2016, in an effort to focus resources on reducing the high global burden of HCV and aim for global elimination, the World Health Organization (WHO) set elimination targets to be achieved by 2030 [6]. These elimination targets include an 80% reduction in HCV incidence and 65% reduction in HCV-related mortality in 2030 compared to 2015 [6]. In 2019, Mexico became the first country in Latin America to launch an HCV elimination strategy, with the first phase including purchase of 12,500 direct-acting antiviral (DAA) treatments, among an estimated 450-550,000 people with HCV infection in Mexico [7,8]. Yet the intervention scale-up required to achieve the WHO elimination targets among PWID is unknown, particularly in settings with very high HCV prevalence and limited harm reduction as in Mexico.

Tijuana, Mexico, a border city with the United States, is situated on a major drug trafficking route. Within Mexico, Tijuana has had the highest rates of illicit drug use and the most recent estimate suggests that approximately 10,000 current PWID reside there [9]. HCV is highly prevalent among PWID in Mexico, with HCV seroprevalence being reported among PWID as high as 92% in Ciudad Juarez and 79% in San Luis Rio Colorado [10]. In Tijuana,

seroprevalence exceeds 90% [10,11]. Despite this, access to harm reduction is minimal. After a brief increase in needle and syringe exchange program (NSP) services resulting from the Global Fund support in 2011-2013, withdrawal of this funder has severely limited NSP provision [12,13] and there is no access to High Coverage NSP [HCNSP] (as defined as receiving one or more sterile needles/syringes for each injection, [14]) in Tijuana. These services are critical given the evidence they reduce recent HIV transmission [15], and could reduce HCV transmission, particularly if provided in combination with opiate agonist therapy (OAT) [14]. Access to evidence-based OAT among PWID is <5% [16]. Instead, beginning in 2014, government funds in Tijuana were allocated to compulsory drug abstinence programs (CAP), which remain the main type of drug rehabilitation program available [17]. In Tijuana, CAPs entail involuntary physical restraint of individuals in non-medically supervised centers for approximately 3-6 months, with non-evidence-based detoxification and abstinence interventions [18]. PWID who had been brought involuntarily by friends/family or police to CAP were more likely to engage in receptive syringe sharing, which if this association is causal, could mean involuntary exposure to CAPs fuel HIV transmission, and therefore could serve to disseminate HCV and hamper elimination progress [19].

Previous mathematical models of HCV transmission amongst PWID found modest scale-up of HCV antiviral treatment, especially coupled with harm reduction interventions such as OAT and HCNSP could be used as prevention [20, 21]. Yet only a few modeling studies have examined what combination intervention scale-up is required to achieve the WHO elimination targets among PWID, and these were limited to high income settings [22]. We used dynamic modeling to determine the level of combination intervention scale-up necessary to achieve WHO hepatitis C virus elimination goals of 80% incidence reduction and 65% mortality reduction by 2030 among PWID in Tijuana, and to assess the potential impact of involuntary CAP expansion or interruptions to harm reduction services.

METHODS

Mathematical model

We constructed a dynamic, deterministic model of HCV transmission and progression among current and former (permanently cessated) PWID. We assumed transmission only occurs among current PWID, but continue to track HCV disease progression and mortality among former PWID. We used this model to evaluate changes in prevalence, incidence, and mortality with varying levels of scale-up of DAA treatment and harm reduction interventions (**Figure 2.1**). We modeled an open population where individuals continually enter due to initiation of drug use and exit the model due to death. Additionally, we assumed random mixing among PWID and that PWID continuously transition between evidence-based harm reduction intervention compartments: (a) no intervention, (b) OAT only, (c) HCNSP only, and (d) OAT + HCNSP simultaneously. A proportion of PWID may become chronically infected with HCV, with their risk being proportional to the background prevalence of disease and to their intervention exposure. Those with chronic infection who remain untreated can progress to decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and death. Individuals with chronic infection can receive DAAs. For those who received DAAs, a proportion may fail treatment and remain chronically infected, and progress through the natural history of disease stages. PWID who are successfully treated, progress to the previously infected compartment, where they are at risk of re-infection. After permanent injecting cessation, former PWID are tracked in our model for disease progression. For the baseline scenario, we assumed that PWID with DC or HCC are not provided DAA treatment as this is unlikely to occur currently given health services in Tijuana. We assumed no coverage of HCV treatment at baseline given the lack of availability in Mexico. At baseline, we also assume no coverage of harm reduction (OAT or HCNSP), as <5% of PWID in Tijuana report recent access to OAT, and there is no access to HCNSP. For an alternative scenario analysis, we redefine the OAT compartment to represent involuntary receipt of CAP, and parameterize the relative risks accordingly to examine the impact of scale-up of CAP

instead of OAT. Analyses were conducted in Matlab version R2018b (The Mathworks, Inc., Natick, MA).

Model parameterization

The model was parameterized to Tijuana, Mexico, with an estimated 10,000 current PWID [9]. Model parameters were obtained from published literature and data from cross-sectional and longitudinal cohorts of PWID in Tijuana (**Table 2.1)**. HCV seroprevalence (90%) was obtained from PWID recruited from drug consumption sites in Tijuana between 2017-18 [10]. Similar to other modeling analyses [20], we estimate chronic prevalence from seroprevalence, based on a 26% spontaneous clearance rate (95% CI: 0.22-0.30) from a systematic review of longitudinal studies [23], consistent with other studies evaluating spontaneous clearance among PWID [24] as well as region-specific viremic rates (74% for Latin America) [25]. Data including proportion of individuals accessing harm reduction interventions (OAT, HCNSP), the average duration of injecting, and PWID mortality rate were obtained from the El Cuete IV study in Tijuana [16,19, 26]. Average duration of injecting by sex was obtained from the El Cuete IV study and weighted by the distribution of PWID in Tijuana by sex (85% males, 15% females, [27], as women were oversampled in El Cuete IV.

Intervention effect estimates: HCV DAA sustained virological response (SVR) rates (approximately 95%) were obtained from published data for PWID [28, 29]. Effectiveness of evidence-based OAT and HCNSP (defined as receiving one or more sterile syringe per each injection) on reducing HCV acquisition was obtained from a Cochrane systematic review and meta-analysis, with OAT reducing the risk of HCV transmission by 50% (sampled from the 95% confidence interval (95%CI) of the relative risk (RR): 0.40-0.63), and with HCNSP reducing the risk of HCV transmission by 23% (sampled from the 95%CI of the RR 0.38-1.54) [14]. In combination, both HCNSP and OAT reduce the risk of acquiring HCV by an estimated 71% (sampled from the 95%CI of the RR: 0.13-0.65) [14]. Data from El Cuete IV cohort among PWID in Tijuana indicate that, compared to PWID never exposed to involuntary CAP, PWID with a

history of involuntary CAP had an elevated relative risk of recent receptive syringe sharing (RR 1.14 [95%CI: 1.00-1.30]) [19]. We note that it is unclear from the epidemiological data whether this elevation in syringe sharing occurs during and/or after CAP exposure, or whether this association is truly causal. However, evidence from other custodial settings (such as prisons) where injecting drug use is prohibited indicates that although a lower proportion of PWID continue to inject drugs while detained, injecting risk is greatly enhanced due to elevated rates of syringe sharing [30, 31]. Accordingly, we implemented the effect of CAP exposure in the model by assuming a 14% increase (varying from 0 to 30%) in receptive syringe sharing among PWID while in CAP. As such, our model neglects any potential negative effects of syringe sharing on CAP after release.

Model calibration

To account for uncertainty in these model parameters, we sampled 1000 parameter sets from each parameter's associated uncertainty distribution (**Table 2.1**). For each parameter set, the model was calibrated to HCV chronic prevalence among PWID in Tijuana in 2018, through varying the HCV transmission rate (calibrated fits shown in **Supplementary Figure S2.1**). Since historic estimates show stable HCV prevalence among PWID in Tijuana [10, 11, 32], we assumed HCV is at steady-state. We then calibrated fixed recruitment rates onto OAT and HCNSP starting in 2019 required to achieve scale-up to 20%, 40%, and 50% coverage by 2030 of each intervention among PWID for each intervention scenario (producing 10%, 20%, and 25% of PWID receiving both OAT and HCNSP). Model calibration was achieved by minimizing the least squares fit to the prevalence data using a global optimization solver (*lsqnonlin* with *multistart* in MATLAB).

Intervention scenarios

We evaluated various strategies to achieve the previously-referenced WHO HCV elimination goals. We examined the impact on incidence, chronic prevalence, and HCV-related mortality of the following intervention scenarios:

1) Status quo: no treatment or harm reduction.
2) DAAs only: DAA treatment scale-up only beginning in 2019 to achieve the elimination goals.
3) DAAs combined with evidence-based harm reduction: DAA treatment scale-up in combination with scaled-up OAT+HCNSP from 2019 to reach 20%, 40%, or 50% coverage levels of each intervention among PWID by 2030 (producing 10%, 20%, and 25% of PWID receiving both OAT and HCNSP). **Supplementary Figure S2.2** shows coverage scale-up over time.
4) DAAs combined with involuntary CAP: DAA treatment scale-up in combination with scaled-up CAP to 50% among PWID beginning in 2019.

Additionally, to evaluate the potential impact of interruptions in harm reduction coverage as historically observed, we examined the impact of scale-up of combination prevention required to achieve the incidence target (DAAs and 50% OAT+HCNSP among PWID) but interruption/removal of harm reduction from 2025-2030.

Sensitivity analyses

Due to parameter uncertainty, we performed sensitivity analyses examining the impact on numbers of treatments (inclusive of retreatments of reinfection) required to achieve both elimination goals if DAAs are allocated to both current and former PWID with the following scenarios: lower or higher number of current PWID (5,000 or 15,000 compared to 10,000 at baseline), lower chronic prevalence among current PWID (50%, compared to 67% at baseline), lower SVR (90% vs 95% at baseline), and differing injecting duration (5 years or 25 years, compared to 17.5 at baseline).

RESULTS

Model calibration

The calibrated model estimated 10,000 current PWID, with an associated 19,500 former PWID, (95% CI: 12,700-30,200) in Tijuana. Among the approximately 30,000 individuals with a history of injection drug use (IDU), we estimated there were 16,160 (95% CI: 12,770-21,610) chronic HCV infections in 2019. In 2019, HCV incidence among PWID was estimated to be 20 per 100 person years (/100py) (95% CI: 14-29/100py), equating to 650 new infections per year (95% CI: 510-850). An estimated 430 current PWID (95% CI: 310-560) and 1,350 former PWID (95% CI: 910-1,970) had decompensated cirrhosis and approximately 100 current PWID (95% CI: 60-160) and 280 former PWID (95% CI: 150-500) had hepatocellular carcinoma. Among both current and former PWID, there were an estimated 330 (95% CI: 250-440) HCV-related deaths in 2019.

WHO Goal: Achieving 80% incidence reduction among PWID by 2030

Combination intervention strategies needed to achieve 80% incidence reduction (from 20/100py to 4/100py) in Tijuana among PWID by 2030 are shown in **Figure 2.2.** Without any DAA treatment, harm reduction alone was unable to achieve the 80% incidence target **(Supplementary Figures S1.3-S1.4).** If DAAs were prioritized to PWID, DAAs alone, at a median rate of 770 annually [95% CI: 640-970] (equivalent to 11% of chronic infections among PWID being treated the first year) could achieve the HCV incidence target by 2030. Moderate scale-up of OAT+HCNSP to coverage levels of 20% or 40% among PWID, in addition to DAA scale-up, reduced the annual number DAAs needed to 670 PWID annually (95%CI: 540-850) or 540 PWID annually (95% CI: 410-750), respectively. Scaling up OAT+HCNSP to 50% coverage among PWID reduced the DAAs required by 40% (460 PWID annually [95% CI: 310-690]). Conversely, if involuntary exposure to CAP were scaled-up to 50% coverage among PWID, 7% more DAAs would be required compared to DAAs alone because of the increase in syringe sharing (and therefore HCV) associated with CAP (830 annually [95% CI: 670-1080]).

If DAAs were provided without regard to injecting status, nearly double the DAA treatment numbers would be required to achieve the incidence target, compared to if DAAs were prioritized to current PWID (1,480/year [95%CI: 1,150-2,150], **Figure 2.2**). Without DAA prioritization, combination scale-up of OAT+HCNSP to current PWID could substantially reduce the DAAs required by 30% if harm reduction was scaled-up to 50% coverage among current PWID. As before, scale-up of CAP to 50% coverage would require more DAAs to achieve the WHO target (**Figure 2.2**).

Achieving both 80% incidence reduction and 65% HCV-related mortality reduction by 2030

To achieve the 65% HCV-related mortality reduction, total HCV-related deaths among both current and former PWID would need to decrease from an estimated 330/year in 2018 to <110/year by 2030. More DAAs would be required to reach both WHO targets compared to the incidence target alone (**Figure 2.3**). To achieve the HCV-related mortality target, treatment must also be provided to former PWID. Even if current PWID were treated each year, HCV-related mortality could only be reduced by a maximum of 55% by 2030. If DAAs were provided to current and former PWID, approximately 1,710 (95%CI: 1,310-2,430) would need to be treated annually to reach both targets (13% greater than the incidence target). Scaling up evidence-based harm reduction reduces DAAs required compared to giving DAAs only; scaled-up OAT+HCNSP to 50% coverage among PWID requires 15% fewer treatments per year to reach both targets (1,450 [95%CI: 1,090-2,060]).

Impact of interruptions in harm reduction coverage

Even if combination intervention scale-up is achieved from 2020-2025, HCV incidence can rebound if harm reduction (OAT+HCNSP) availability is stopped at 2025 increasing by a mean relative 18% from 2025-2030 (**Figure 2.4)**.

Sensitivity analysis

Sensitivity analyses evaluating the numbers of DAAs required to achieve both elimination goals when allocated randomly are shown for various scenarios in **Supplementary Figure S1.5**. For both elimination goals, more treatments (median to reach incidence: 1,590 [95%CI: 1,230-2,300]; median to reach mortality: 1,870 [95%CI: 1,420-2,700]) were required with a lower SVR rate (90%), and more (median to reach incidence: 1,850 [95%CI: 1,350-2,910]; median to reach mortality: 2,170 [95%CI: 1,560-3,310]) were required when the average duration of injection was short (5 years). Fewer treatments were also needed if the baseline chronic prevalence was 50% (median to reach incidence: 970 [95%CI: 800-1,320]; median to reach mortality: 1,150 [95%CI: 920-1,610]) and the average duration of injection was longer (25 years; median to reach incidence: 600 [95%CI: 440-910]; median to reach mortality: 720 [95%CI: 520-1,070]). Estimates of numbers of treatments required scaled linearly with analyses assuming greater (50% more; median: 2,220-2,570) or fewer (50% fewer; median: 740-860) PWID.

DISCUSSION

There is a high burden of HCV among people with a history of IDU in Tijuana, Mexico, where harm reduction and HCV treatment access is low. Our modeling indicates that even in very high burden settings such as Tijuana, HCV elimination could be achieved provided the forthcoming DAAs are widely available, scaled-up among both current and former PWID, and there is concomitant scale-up of harm reduction services. The incidence target could be achieved through treating approximately 770 (95%CI: 640-970) current PWID annually, but 40% fewer would be required if combination harm reduction is scaled-up among 50% of PWID. If DAAs were allocated at the same level needed to achieve the WHO elimination goals using treatment alone, the goals could be met earlier if combination harm reduction is scaled-up. Over double the number of treatments (median 1,710) would be required to achieve both the

incidence and mortality targets, and these would need to reach both current and former PWID. Allocation of the currently purchased 12,500 DAAs across Mexico is unclear, but if allocated in proportion to estimated burden, then approximately 355-600 total treatments would be allocated to Tijuana, indicating treatment investment needs to be increased for WHO elimination. However, the incidence target may be achievable with expansion of harm reduction. As such, our findings highlight the critical role harm reduction can play in achieving elimination and reducing the number of DAAs required, and that sustained harm reduction is important to maintaining elimination. Furthermore, there are multiple sites in Mexico with concentrated HCV epidemics among PWID, including in other U.S. border cities of Ciudad Juarez and San Luis Rio Colorado [10], further highlighting the need for DAAs to be allocated to the PWID within these communities to halt transmission.

There are numerous challenges which curtail the possibility of achieving HCV elimination in Tijuana. Despite indication that HCV treatment will become available under the Mexican public health care system, and that it will be available or PWID, DAAS are not currently available for PWID in Tijuana. Additionally, even if technically available, many PWID do not access or receive basic health care [33, 34], in part due to negative experiences and stigma [35,36], both internalized and expressed by healthcare providers [37, 38]. Additionally, PWID often lack the documentation required to register for Mexico's national health care system. Compounding this lack of access is also a lack of awareness of HCV. Estimates of the proportion of HCV-infected individuals who are diagnosed in Tijuana are unknown, but in a recent cross-sectional survey among PWID in treatment centers in Tijuana, despite the vast majority of PWID harboring HCV infection, only 25% of all respondents self-reported having ever been diagnosed with HCV, and none had received treatment (unpublished data from [10]). However, once diagnosed and initiated on treatment, other studies have found high HCV treatment adherence rates among PWID, which supports feasibility of implementing these interventions in Tijuana [28].

In addition to barriers to treatment scale-up, expansion of evidence-based harm reduction is challenging in Tijuana. Existing OAT provision is expensive, and unaffordable for most PWID [39]. Capacity is also a considerable issue, as OAT is only offered by a few providers, so expansion of providers would be required. As mentioned, government funding has been provided for CAPs, which based on our model should be reoriented towards evidence-based treatment, including OAT provision to enhance HCV elimination strategies. Expansion in the quantity of HCNSPs and their provision is also urgently needed, particularly as the withdrawal of the Global Fund in late 2013 resulted in a dramatic reduction in the number of syringes and ancillary harm reduction components provided, as well as the geographical scope of the service, leading to increases in syringe sharing [12]. The intermittent and fluctuating provision of harm reduction and recent cut to harm reduction funding in Mexico will hamper efforts to control HCV [40]; our simulations indicate that even if scaled-up to achieve WHO targets, removal of these programs after 2030 will allow HCV infections to rebound to their pre-treatment levels. We recognize that within government administrations, there is uncertainty in securing, directing, and continuing funding for such programs, spanning all levels from municipal, state, to federal, particularly with frequent turnover of elected officials. Our analyses support the need to provide long-term funding opportunities as to prevent a rebound in HCV transmission both before and after HCV elimination goals have been met. Importantly, there are additional benefits of implementing the proposed harm reduction strategies which are not represented in this model which might have a broader impact on the health of the PWID community in Tijuana. For example, improved harm reduction coverage could additionally reduce HIV transmission [15], fatal overdoses [41] and reincarceration [42], which itself is associated with HIV and HCV risk [43].

Strengths and limitations

To our knowledge this is the first modeling analysis to project the level of combination interventions required to achieve the WHO HCV global elimination goals among PWID in a low-

middle income setting. Other studies have examined country-level elimination strategies, such as in Pakistan, which also highlight the benefit of prioritization of PWID and of concomitant scale-up of harm reduction on achieving elimination [44]. Our results also support findings from other studies that combination harm reduction and treatment strategies are a key component of HCV epidemic control [45, 46]. Additionally, our results support literature showing that scaling-up harm reduction interventions reduces the number of treatments required and is cost-effective in the United States [22]. Finally, this analysis supports our previous modeling work indicating that scale-up of involuntary exposure to CAP could increase infectious diseases among PWID, such as HIV [19].

Our modeling study has a number of limitations, most notably related to uncertainty in parameterization. To account for these, we incorporated these uncertainties in our analysis and performed additional sensitivity analyses. First, there is substantial uncertainty in the number of PWID in Tijuana, with the estimate of 10,000 PWID arising from a Centro Nacional para la Prevención y Control del VIH/SIDA (CENSIDA) cross-sectional survey of 35 zones in Tijuana [9]. Our sensitivity analyses indicate uncertainty could strongly impact the number of DAAs needed. More robust, current estimates of PWID population sizes in Tijuana would help improve intervention planning and resource allocation.

Second, there is always considerable uncertainty in the average duration of injecting until final cessation as injecting drug use is a chronic relapsing condition. Cohort estimates of average duration of injection are often used to infer average time to cessation, yet these data are both right censored (participants have not cessated yet) and left censored (people who inject for a very brief period of time are unlikely to be captured by the cohort). As such, we used Tijuana data to inform this estimate but account for wide uncertainty in this parameter within our analyses. More generally, we note that our analysis characterizes the PWID population between those who have permanently cessated from injecting and those who have not, and as such do not explicitly simulate periods of temporary cessation. Thus, the current PWID prioritization

strategies we examine incorporate prioritization to PWID who may be in a period of temporary cessation (such as those receiving OAT), but who are at high risk of relapse, and therefore future transmission.

Third, as HCV treatment is unavailable in Tijuana, we were unable to obtain local estimates of SVR rates and relied on estimates from other populations. However, studies of PWID indicate SVR among those with a history of IDU or who continue to inject after treatment, are high and exceed 90% [29].

Fourth, we assumed exposure to involuntary CAP is causally associated with increased receptive syringe sharing while exposed to CAP, however causality has not been established and even if causal it is unclear when syringe sharing is elevated. It is possible that PWID who are involuntarily brought to CAPs may represent a population with higher baseline injecting risk. Alternatively, the observed increased odds in syringe sharing could potentially result from poor mental health and consequences of diminished self-care following physical or psychological abuse occurring in CAPs [19]. Additionally, it is possible individuals who relapse after CAP release may share more to avoid being caught in trying to obtain clean syringes. Further, even if exposure to CAP causes syringe sharing it is unclear whether risk is elevated during and/or after exposure. Indeed, recent incarceration has been associated with elevated HIV and HCV incidence, but there is evidence this effect persists long-term [43]. As duration in CAP is relatively short (6-12 months) compared to an overall injecting career, if there is a long-term excess risk associated with CAP these would not be included in our results, and would mean CAP has even more of a negative effect than we predict. Future work examining causal pathways and periods of heightened risk associated with CAP is warranted.

Furthermore, we neglected to account for HIV among PWID in Tijuana in our model as previous studies have shown it to be relatively low (3-7%) compared to HCV prevalence [10, 27]. HIV infection would act as a competing risk for death; however, the same intensity of

interventions would be required to reach the same relative reduction in HCV related mortality regardless of HIV status.

Finally, our analyses explored DAA provision to PWID with chronic infection, as the current published strategy highlights PWID as a priority population, and does not restrict by disease stage. Yet, we recognize that given the current health system reform in Mexico, the prioritization and allocation of treatment may change in the future, which would merit further modeling to assess the population impact and cost-effectiveness of these strategies. As the current strategy focuses highlights PWID and prisoners (many of whom are PWID) as priority populations, strategies to improve case finding and linkage to care among these groups will be an important focus. Future studies should examine these issues in further detail.

CONCLUSION

In conclusion, WHO global elimination goals can be achieved by 2030 in Tijuana, Mexico, through combination scale-up of evidence-based harm reduction and DAA treatment. Access to affordable HCV treatment and sustained evidence-based harm reduction is critical to achieving these goals, and existing compulsory abstinence programs could hamper elimination efforts.

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Chapter 2, in full, is a reprint of the material as it appears in the International Journal for Drug Policy 2020. Marquez, Lara K; Cepeda, Javier A; Bórquez, Annick; Strathdee, Steffanie A; Gonzalez-Zúñiga, Patricia E; Fleiz, Clara; Rafful, Claudia; Garfein, Richard S; Kiene, Susan M; Brodine, Stephanie; Martin, Natasha K. The dissertation author was the primary investigator and author of this paper.

FIGURES

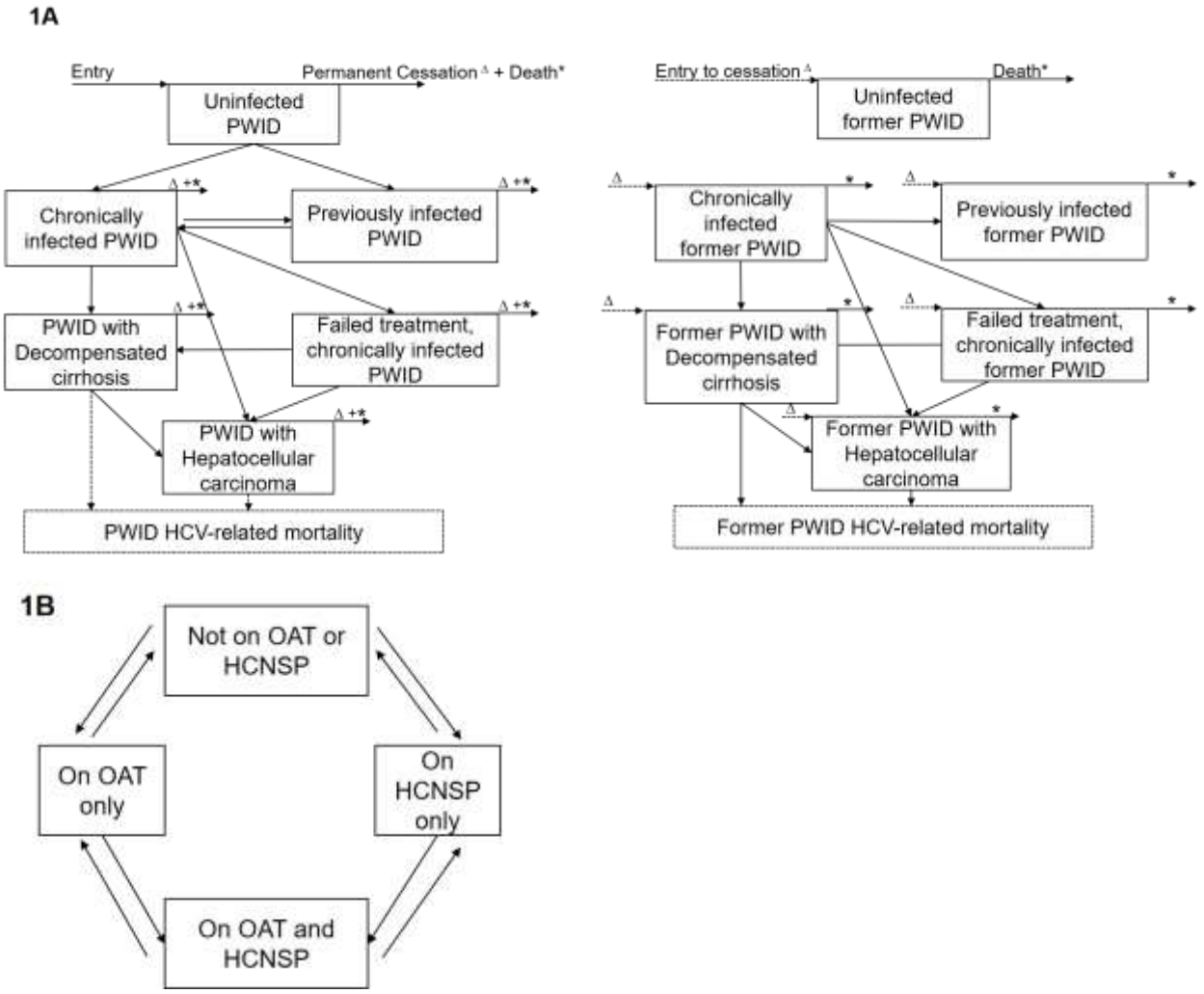

Figure 2.1 Model schematics showing (A) HCV disease progression by liver disease states and (B) stratification by harm reduction interventions. PWID: People who inject drugs; OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection). *PWID exiting the model due to death; ΔCurrent PWID transitioning to former PWID model, resulting from permanent cessation.

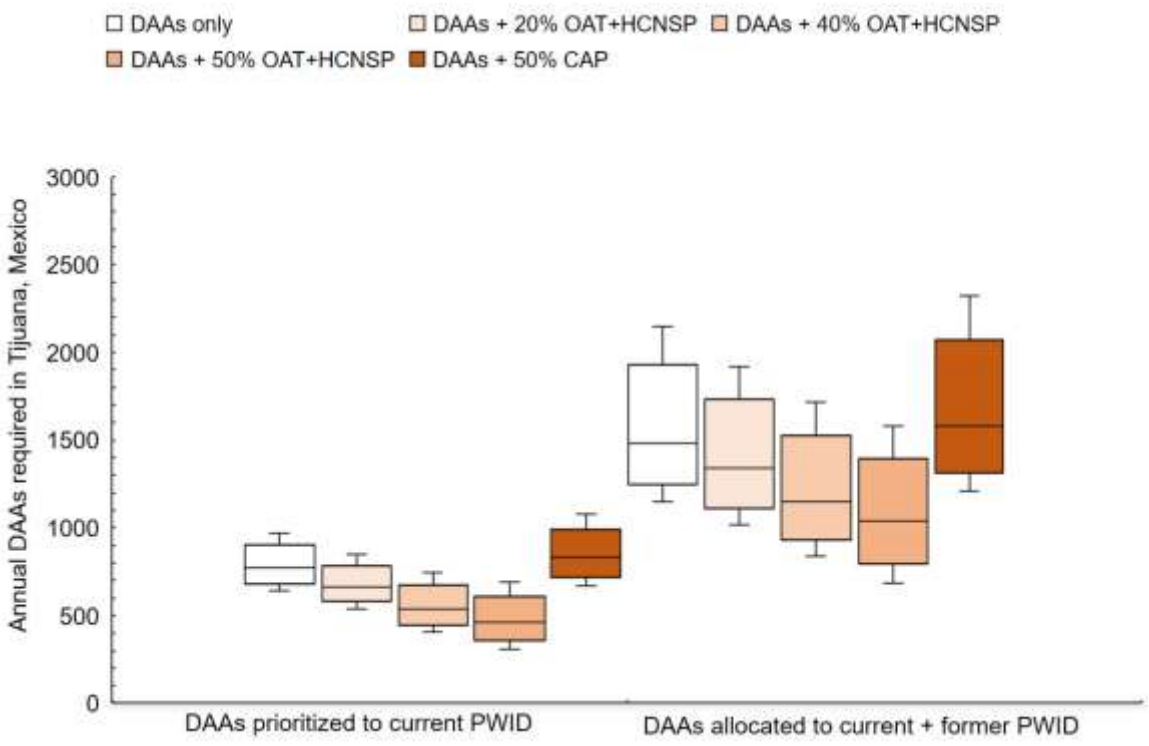

Figure 2.2 Annual DAA treatment numbers (B) required (with or without combination scale-up) to achieve an 80% incidence reduction among PWID by 2030 in Tijuana, Mexico, if treatment is prioritized to current PWID or allocated to current and former PWID. Scenarios examine combination scale-up of DAAs with evidence-based harm reduction (OAT+HCNSP) or involuntary exposure to compulsory drug abstinence programs (CAP). DAAs: HCV direct-acting antiviral treatment; OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection).

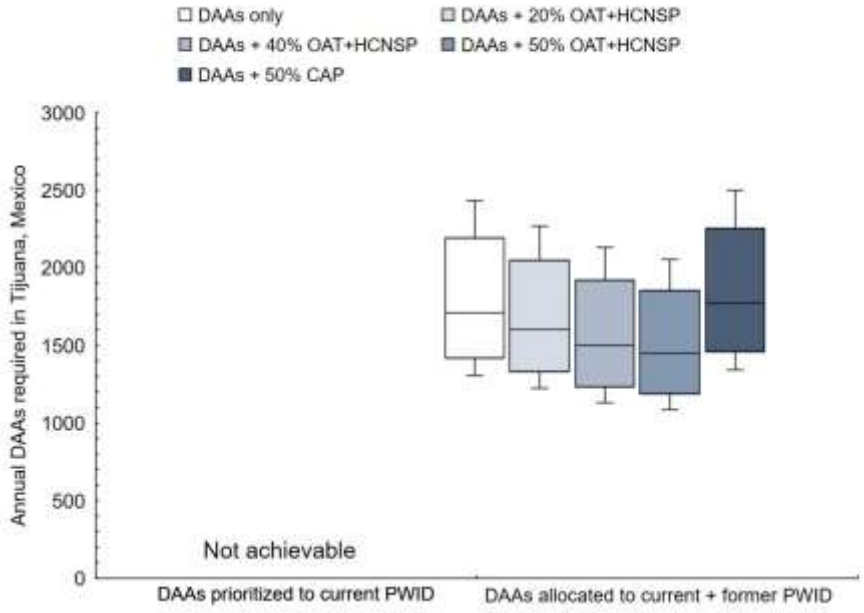

Figure 2.3 Annual DAA treatment numbers required (with or without combination scale-up) to achieve both WHO targets (80% incidence reduction and 65% reduction in HCV-related mortality) by 2030 in Tijuana, Mexico, if treatment is prioritized to current PWID or allocated to current and former PWID. Scenarios examine combination scale-up of DAAs with evidence-based harm reduction (opiate agonist therapy and high coverage needle/syringe programs, OAT+HCNSP) or involuntary exposure to compulsory drug abstinence programs (CAP). DAAs: HCV direct-acting antiviral treatment; OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection). ****Treating only current PWID cannot achieve the 65% mortality goal by 2030.

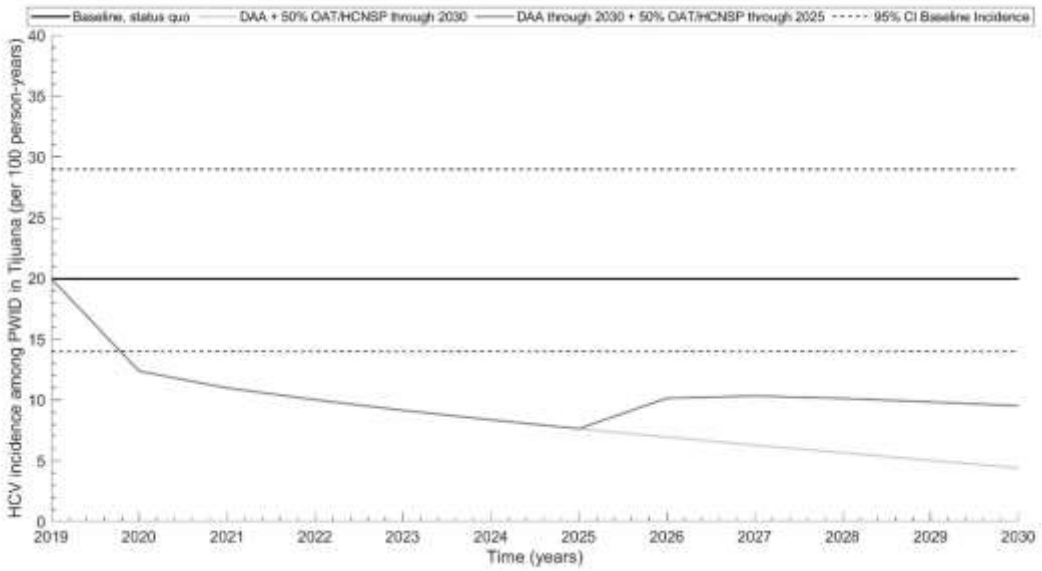

Figure 2.4 Future projections of HCV incidence among PWID in Tijuana with: status quo scenario, combination harm reduction elimination scenario (DAAs plus OAT+HCNSP at 50% coverage), and combination intervention but harm reduction removal in 2025. Lines present mean values from 1,000 simulations. Dashed lines show 2.5 and 97.5% centile predictions from the baseline scenario. DAA: Direct-acting antiviral treatment; OAT: Opiate agonist therapy; HCNSP: Needle/syringe exchange program.

TABLES

Table 2.1 Model parameters and their distributions. Distribution ranges: Uniform: minimum, maximum; Beta: alpha, beta; Lognormal: shape, scale. DC: decompensated cirrhosis; HCC: Hepatocellular carcinoma; OAT: Opiate agonist therapy; HCNSP: High coverage needle and syringe program.

Definition	Mean sampled value (95% CI)	Sample distribution	Unit	Reference
Rate of new PWID initiations	Fit to 10,000 PWID	-	Individuals per year	--
Rate of infection	Fit to HCV chronic prevalence among current PWID		Per year	
HCV seroprevalence among current PWID	0.90 (0.85- 0.95)	Beta (alpha= 141.74, Beta=14.48);	--	[10]
Proportion of infections that spontaneously clear	0.26 (0.22-0.30)	Uniform (min=0.22, max=0.30)	--	[23]
Sustained viral response	0.95 (0.91-0.99)	Uniform (min=0.903, max=0.998)	--	[28,29]
Average duration of injecting until permanent cessation	17.5	Uniform (min=11, max=24)	Years	Weighted average assumed (15% female; 85% male) [19, 27])
Mortality rate among PWID	0.02 (0.016, 0.024)	Uniform (min=0.016, max=0.024)	Per year	[19]
OAT recruitment rate	Varied to fit to target proportion PWID on OAT	-	Per year	--
Leaving rate from OAT	1.5	Uniform (min=1, max=2)	Per year	[20, 47, 48]
HCNSP recruitment	Varied to fit to target proportion on HCNSP	-	Per year	--
Leaving rate from HCNSP	Assumed to be the same as OAT (1.5)	Uniform (min=1, max=2)	Per year	Assumed same as OAT [21]
Relative risk of HCV transmission on OAT only compared to no OAT	0.50 (0.39, 0.64)	Lognormal (ln(0.50), 95%CI: 0.40-0.63)	--	[14]
Relative risk of HCV transmission on HCNSP only compared to no HCNSP	0.79 (0.38, 1.60)	Lognormal (ln(0.79), 95% CI: 0.39-1.61)	--	[14]
Relative risk of HCV acquisition on OAT and HCNSP compared to none	0.23 (0.09, 0.62)	Lognormal (ln(0.24), 95% CI: 0.09-0.62)	--	[14]
Relative risk of HCV transmission on involuntary CAP compared to not on involuntary CAP	1.14 (1-1.3)	Lognormal (mean 1.14, 95% CI: 1.0-1.3)	--	Implemented through a relative change in syringe sharing as in [19]

Table 2.1 Model parameters and their distributions, Continued. Distribution ranges: Uniform: minimum, maximum; Beta: alpha, beta; Lognormal: shape, scale. DC: decompensated cirrhosis; HCC: Hepatocellular carcinoma; OAT: Opiate agonist therapy; HCNSP: High coverage needle and syringe program.

Definition	Mean sampled value (95% CI)	Sample distribution	Unit	Reference
Disease transition probabilities				
Chronic – DC	0.016 (0.013, 0.019)	Uniform (min=0.0128, max=0.0192)	Per year	Calculated from fibrosis progression rates in [49]
Chronic—HCC	0.009 (0.007, 0.01)	Uniform (min=0.0072, max=0.0108)	Per year	Calculated from fibrosis progression rates in [49]
DC – HCC	0.012 (0.002, 0.04)	Beta (alpha=1.193, beta=136.107)	Per year	[50]
Excess HCV-related mortality rate from DC	0.14 (0.11, 0.17)	Uniform (min=0.11, max=0.17)	Per year	[50]
Excess HCV-related mortality rate from HCC	0.55 (0.31, 0.79)	Uniform (min=0.3, max=0.8)	Per year	[50, 51]

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SUPPLEMENTARY MATERIAL FOR CHAPTER 2

Included in the supplementary information, we present the model structure and equations, followed by supplementary figures presenting the model fit of our estimated baseline HCV prevalence compared to the HCV prevalence point estimate (**Supplementary Figure S2.1)** and show OAT and HCNSP recruitment and coverage rates over time (**Supplementary Figure S2.2**). We show the 11-year relative reduction in (1) HCV incidence and (2) HCV-related mortality resulting from harm reduction intervention scale-up alone, in the absence of DAAs, shown in **Supplementary Figures S1.3** and **Supplementary Figure S2.4**. Lastly, we consider various scenarios including variations in current PWID population, HCV chronic prevalence, SVR rate, and average duration of injecting, in our sensitivity analyses to determine the percent relative difference from baseline on the treatment numbers required to achieve both HCV elimination goals (**Supplementary Figure S1.5**).

Model equations

Model equations are presented below. The model includes compartments for uninfected PWID ($X_{i,j}$), chronically infected PWID ($C_{i,j}$), previously infected PWID ($P_{i,j}$), chronically infected PWID who failed HCV treatment ($Z_{i,j}$), PWID with decompensated cirrhosis ($D_{i,j}$), and PWID with hepatocellular carcinoma ($H_{i,j}$). For current PWID, the subscript notation *i,j* denotes intervention status, presented as opiate agonist therapy (OAT) status (*i*=0 Not on OAT, *i*=1 On OAT) and high coverage needle and syringe program (HCNSP) status (*j*=0 Not on HCNSP, *j*=1 On HCNSP). Additional compartments represent former PWID in these aforementioned HCV disease stages (denoted as *XF, CF, PF, ZF, DF,* and *HF*, respectively).

Uninfected PWID enter the model at a rate, θ. Susceptible PWID can become infected with HCV (a dynamic process, proportional to the infection rate, chronic prevalence among PWID, and intervention coverage). A proportion progress to chronic infection $(1-\delta)$, whereas the remainder spontaneously clear their HCV infection (δ). For those who become chronically

infected, a fixed number will be treated each year (at a rate $\Phi(\mathrm{t})$ individuals per year), which is allocated proportional to chronic infection group size depending on the treatment prioritization strategy examined, either to current PWID or to both current and former PWID. When the total number of eligible infected individuals was less than the number of possible treatments per year, all individuals were treated. A proportion of those treated achieve a sustained virologic response (SVR) (α) whereas others will not achieve SVR (proportion $(1-\alpha)$). Current PWID who were previously infected with HCV, can become reinfected at the same rate of infection as primary infection, and will then move back into the chronically infected compartment. Those who are chronically infected (treatment naïve or who have failed treatment) can progress to more advanced stages of liver disease including decompensated cirrhosis (at a rate, β_1), or develop hepatocellular carcinoma (at a rate, β_2). Those who have decompensated cirrhosis can progress to hepatocellular carcinoma (at a rate, ρ). Finally, those who are in advanced stages of liver disease (decompensated cirrhosis or hepatocellular carcinoma) die from HCV-related mortality at rates, μ_3 and μ_4, respectively. Current PWID may also transition from current injecting to permanent cessation from all disease stages at a rate, μ_1. Both current and former (those who permanently cessated) PWID die from non-HCV-related death at a rate, μ_2, from any disease stage. Current PWID can be recruited on to OAT (rate $\gamma(t)$) or HCNSP (rate $\eta(t)$).

Force of infection equations for the model are detailed following the model equations. Here, π is defined by the HCV transmission rate within the PWID population. We assumed PWID on OAT or HCNSP experience reduced transmission and acquisition (at a relative risk Γ for on HCNSP, Π on OAT, B on both OAT and HCNSP, and Ψ for on involuntary CAP, each compared to no intervention). Leaving rates from OAT and HCNSP are κ and ε, respectively. We assumed that those on involuntary CAP were at increased risk of HCV transmission due to increased receptive syringe use (RR: 1.14 [95%CI: 1.00-1.30]) (Borquez et al., 2018). For our CAP scenario, we implemented the intervention using the OAT compartment and replaced the

sampled RR of HCV transmission on OAT only (RR: 0.50 [95% CI: 0.40-0.63]; (Platt et al., 2018)) with the sampled CAP RR stated above. We assume former PWID are no longer at risk for infection/reinfection.

Model Equations for PWID not on OAT and not on HCNSP:

(1.1) $\frac{dX_{0,0}}{dt} = \theta - (1-\delta)X_{0,0}\lambda_{0,0} - \delta X_{0,0}\lambda_{0,0} + \kappa X_{1,0} + \varepsilon X_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))X_{0,0}$

(2.1) $\frac{dC_{0,0}}{dt} = (1-\delta)X_{0,0}\lambda_{0,0} - \phi_{0,0}(\mathrm{t}) + (1-\delta)P_{0,0}\lambda_{0,0} - (\beta_1+\beta_2)C_{0,0} + \kappa C_{1,0} + \varepsilon C_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))C_{0,0}$

(3.1) $\frac{dP_{0,0}}{dt} = \delta X_{0,0}\lambda_{0,0} + \alpha\phi_{0,0}(\mathrm{t}) - (1-\delta)P_{0,0}\lambda_{0,0} + \kappa P_{1,0} + \varepsilon P_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))P_{0,0}$

(4.1) $\frac{dZ_{0,0}}{dt} = (1-\alpha)\phi_{0,0}(\mathrm{t}) - (\beta_1+\beta_2)Z_{0,0} + \kappa Z_{1,0} + \varepsilon Z_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))Z_{0,0}$

(5.1) $\frac{dD_{0,0}}{dt} = \beta_1(C_{0,0} + Z_{0,0}) - \rho D_{0,0} + \kappa D_{1,0} + \varepsilon D_{0,1} - (\mu_1 + \mu_2 + \mu_3 + \gamma(t) + \eta(t))D_{0,0}$

(6.1) $\frac{dH_{0,0}}{dt} = \beta_2(C_{0,0} + Z_{0,0}) + \rho D_{0,0} + \kappa H_{1,0} + \varepsilon H_{0,1} - (\mu_1 + \mu_2 + \mu_4 + \gamma(t) + \eta(t))H_{0,0}$

Model Equations for PWID on OAT and not on HCNSP:

(1.2) $\frac{dX_{1,0}}{dt} = -(1-\delta)X_{1,0}\lambda_{1,0} - \delta X_{1,0}\lambda_{1,0} + \varepsilon X_{1,1} + \gamma(t)X_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))X_{1,0}$

(2.2) $\frac{dC_{1,0}}{dt} = (1-\delta)X_{1,0}\lambda_{1,0} - \phi_{1,0}(\mathrm{t}) + (1-\delta)P_{1,0}\lambda_{1,0} - C_{1,0}(\beta_1+\beta_2) + \varepsilon C_{1,1} + \gamma(t)C_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))C_{1,0}$

(3.2) $\frac{dP_{1,0}}{dt} = \delta X_{1,0}\lambda_{1,0} + \alpha\phi_{1,0}(\mathrm{t}) - (1-\delta)P_{1,0}\lambda_{1,0} + \varepsilon P_{1,1} + \gamma(t)P_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))P_{1,0}$

(4.2) $\frac{dZ_{1,0}}{dt} = (1-\alpha)\phi_{1,0}(\mathrm{t}) - (\beta_1+\beta_2)\ Z_{1,0} + \varepsilon Z_{1,1} + \gamma(t)Z_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))Z_{1,0}$

(5.2) $\frac{dD_{1,0}}{dt} = \beta_1(C_{1,0} + Z_{1,0}) - \rho D_{1,0} + \varepsilon D_{1,1} + \gamma(t)D_{0,0} - (\mu_1 + \mu_2 + \mu_3 + \kappa + \eta(t))D_{1,0}$

(6.2) $\frac{dH_{1,0}}{dt} = \beta_2(C_{1,0} + Z_{1,0}) + \rho D_{1,0} + \varepsilon H_{1,1} + \gamma(t)H_{0,0} - (\mu_1 + \mu_2 + \mu_4 + \kappa + \eta(t))H_{1,0}$

Model Equations for PWID not on OAT and on HCNSP:

(1.3) $\frac{dX_{0,1}}{dt} = -(1-\delta)X_{0,1}\lambda_{0,1} - \delta X_{0,1}\lambda_{0,1} + \kappa X_{1,1} + \eta(t)X_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))X_{0,1}$

(2.3) $\frac{dC_{0,1}}{dt} = (1-\delta)X_{0,1}\lambda_{0,1} - \phi_{0,1}(\mathrm{t}) + (1-\delta)P_{0,1}\lambda_{0,1} - (\beta_1+\beta_2)C_{0,1} + \kappa C_{1,1} + \eta(t)C_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))C_{0,1}$

(3.3) $\frac{dP_{0,1}}{dt} = \delta X_{0,1}\lambda_{0,1} + \alpha\phi_{0,1}(\mathrm{t}) - (1-\delta)P_{0,1}\lambda_{0,1} + \kappa P_{1,1} + \eta(t)P_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))P_{0,1}$

(4.3) $\frac{dZ_{0,1}}{dt} = (1-\alpha)\phi_{0,1}(\mathrm{t}) - \beta_1 Z_{0,1} - \beta_2 Z_{0,1} + \kappa Z_{1,1} + \eta(t)Z_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))Z_{0,1}$

(5.3) $\frac{dD_{0,1}}{dt} = \beta_1(C_{0,1} + Z_{0,1}) - \rho D_{0,1} + \kappa D_{1,1} + \eta(t)D_{0,0} - (\mu_1 + \mu_2 + \mu_3 + \varepsilon + \gamma(t))D_{0,1}$

(6.3) $\frac{dH_{0,1}}{dt} = \beta_2(C_{0,1} + Z_{0,1}) + \rho D_{0,1} + \kappa H_{1,1} + \eta(t)H_{0,0} - (\mu_1 + \mu_2 + \mu_4 + \varepsilon + \gamma(t))H_{0,1}$

Model Equations for PWID on OAT and on HCNSP:

(1.4) $\frac{dX_{1,1}}{dt} = -(1-\delta)X_{1,1}\lambda_{1,1} - \delta X_{1,1}\lambda_{1,1} + \eta(t)X_{1,0} + \gamma(t)X_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)X_{1,1}$

(2.4) $\frac{dC_{1,1}}{dt} = (1-\delta)X_{1,1}\lambda_{1,1} - \phi_{1,1}(\mathrm{t}) + (1-\delta)P_{1,1}\lambda_{1,1} - (\beta_1+\beta_2)C_{1,1} + \eta(t)C_{1,0} + \gamma(t)C_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)C_{1,1}$

(3.4) $\frac{dP_{1,1}}{dt} = \delta X_{1,1}\lambda_{1,1} + \alpha\phi_{1,1}(\mathrm{t}) - (1-\delta)P_{1,1}\lambda_{1,1} + \eta(t)P_{1,0} + \gamma(t)P_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)P_{1,1}$

(4.4) $\frac{dZ_{1,1}}{dt} = (1-\alpha)\phi_{1,1}(\mathrm{t}) - (\beta_1+\beta_2)\ Z_{1,1} + \eta(t)Z_{1,0} + \gamma(t)Z_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)Z_{1,1}$

(5.4) $\frac{dD_{1,1}}{dt} = \beta_1(C_{1,1} + Z_{1,1}) - \rho D_{1,1} + \eta(t)D_{1,0} + \gamma(t)D_{0,1} - (\mu_1 + \mu_2 + \mu_3 + \kappa + \varepsilon)D_{1,1}$

(6.4) $\frac{dH_{1,1}}{dt} = \beta_2(C_{1,1} + Z_{1,1}) + \rho D_{1,1} + \eta(t)H_{1,0} + \gamma(t)H_{0,1} - (\mu_1 + \mu_2 + \mu_4 + \kappa + \varepsilon)H_{1,1}$

Model Equations for Former PWID:

(1.5) $\frac{dXF}{dt} = \mu_1(X_{0,0} + X_{1,0} + X_{0,1} + X_{1,1}) - \mu_2 XF$

(2.5) $\frac{dCF}{dt} = \mu_1(C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1}) - \phi_{CF}(\mathrm{t}) - CF(\beta_1+\beta_2) - \mu_2 CF$

(3.5) $\frac{dPF}{dt} = \mu_1(P_{0,0} + P_{1,0} + P_{0,1} + P_{1,1}) + \alpha\phi_{CF}(\mathrm{t}) - \mu_2 \mathrm{PF}$

(4.5) $\frac{dZF}{dt} = \mu_1(Z_{0,0} + Z_{1,0} + Z_{0,1} + Z_{1,1}) + (1-\alpha)\phi_{CF}(\mathrm{t}) - (\beta_1+\beta_2)ZF - \mu_2 ZF$

(5.5) $\frac{dDF}{dt} = \mu_1(D_{0,0} + D_{1,0} + D_{0,1} + D_{1,1}) + \beta_1(CF + ZF) - \rho DF - (\mu_2 + \mu_3)DF$

$$(6.5)\ \frac{dHF}{dt} = \mu_1\left(H_{0,0} + H_{1,0} + H_{0,1} + H_{1,1}\right) + \beta_2(CF + ZF) + \rho DF - (\mu_2 + \mu_4)HF$$

where the force of infection equations are below:

$$\lambda_{0,0} = \pi \frac{(\Omega_{0,0} + \Gamma(\Omega_{0,1}) + \Pi(\Omega_{1,0}) + \mathrm{B}(\Omega_{1,1}))}{(\Omega_{0,0} + \Lambda_{0,0}) + \Gamma(\Omega_{0,1} + \Lambda_{0,1}) + \Pi(\Omega_{1,0} + \Lambda_{1,0}) + \mathrm{B}(\Omega_{1,1} + \Lambda_{1,1})}$$

$$\lambda_{0,1} = \Gamma\lambda_{0,0}$$

$$\lambda_{1,0} = \Pi\lambda_{0,0}$$

$$\lambda_{1,1} = \mathrm{B}\lambda_{0,0}$$

where

$$\Omega_{i,j} = \mathrm{C}_{i,j} + \mathrm{Z}_{i,j} + \mathrm{D}_{i,j} + \mathrm{H}_{i,j}$$

and

$$\Lambda_{i,j} = \mathrm{P}_{i,j} + \mathrm{X}_{i,j}$$

Note that when involuntary CAP is implemented in the model, Π (RR of HCV transmission on OAT) is replaced with Ψ (RR of HCV transmission on involuntary CAP), and joint risk multiplied ($\mathrm{B} = \Gamma * \Psi$).

When treatment is allocated to all PWID and former PWID:

If t<2019

$$\phi_{i,j}(\mathrm{t}) = \phi_{CF}(\mathrm{t}) = 0$$

and if t>= 2019,

$$\phi_{i,j}(\mathrm{t}) = \Phi * \frac{C_{i,j}}{C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1} + CF}$$

and

$$\phi_{CF}(\mathrm{t}) = \Phi * \frac{CF}{C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1} + CF}.$$

When treatment is only allocated to PWID:

If t<2019

$$\phi_{i,j}(\mathrm{t}) = \phi_{CF}(\mathrm{t}) = 0$$

and if t>= 2019,

$$\phi_{i,j}(\mathrm{t}) = \Phi * \frac{C_{i,j}}{C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1}}$$

and

$$\phi_{CF}(\mathrm{t}) = 0.$$

SUPPLEMENTARY FIGURES

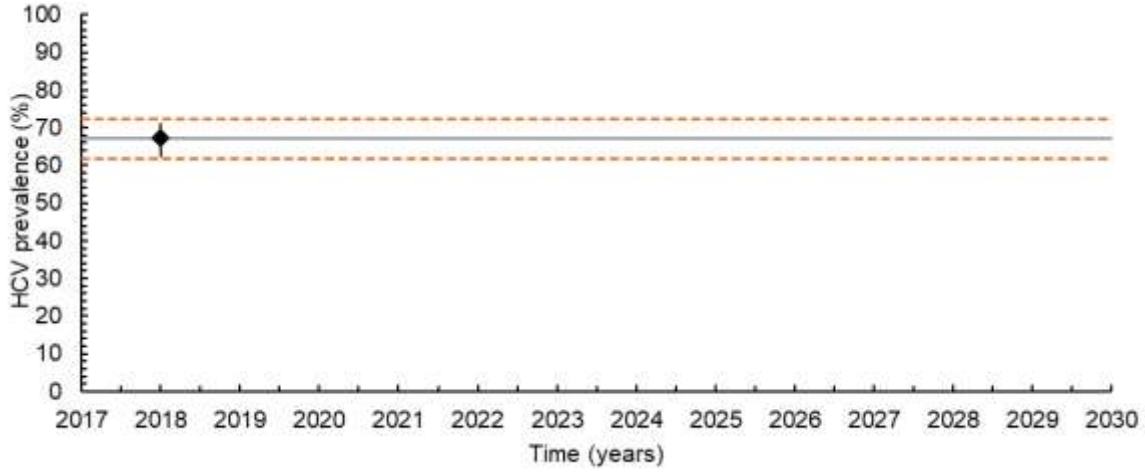

Figure S2.1 Model fit of baseline HCV prevalence among PWID (%) compared to HCV prevalence point estimate and corresponding 95% confidence interval (diamond represents the point estimate, line indicates the 95% CI).

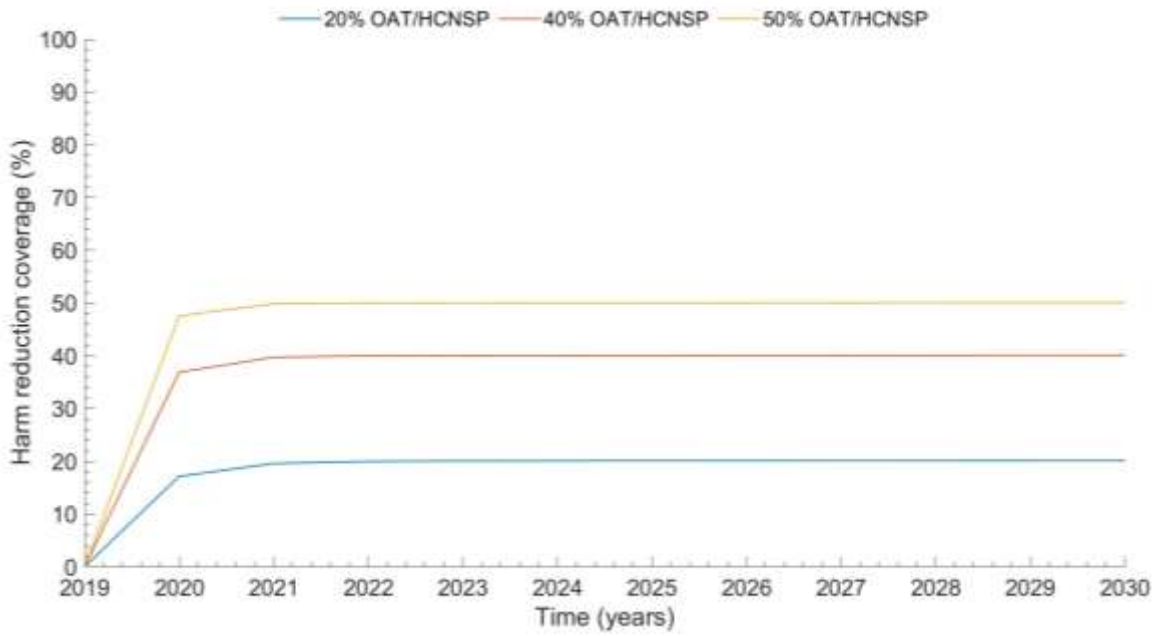

Figure S2.2 OAT and HCNSP recruitment and coverage rates over time (2019-2030) among PWID in Tijuana. OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program.

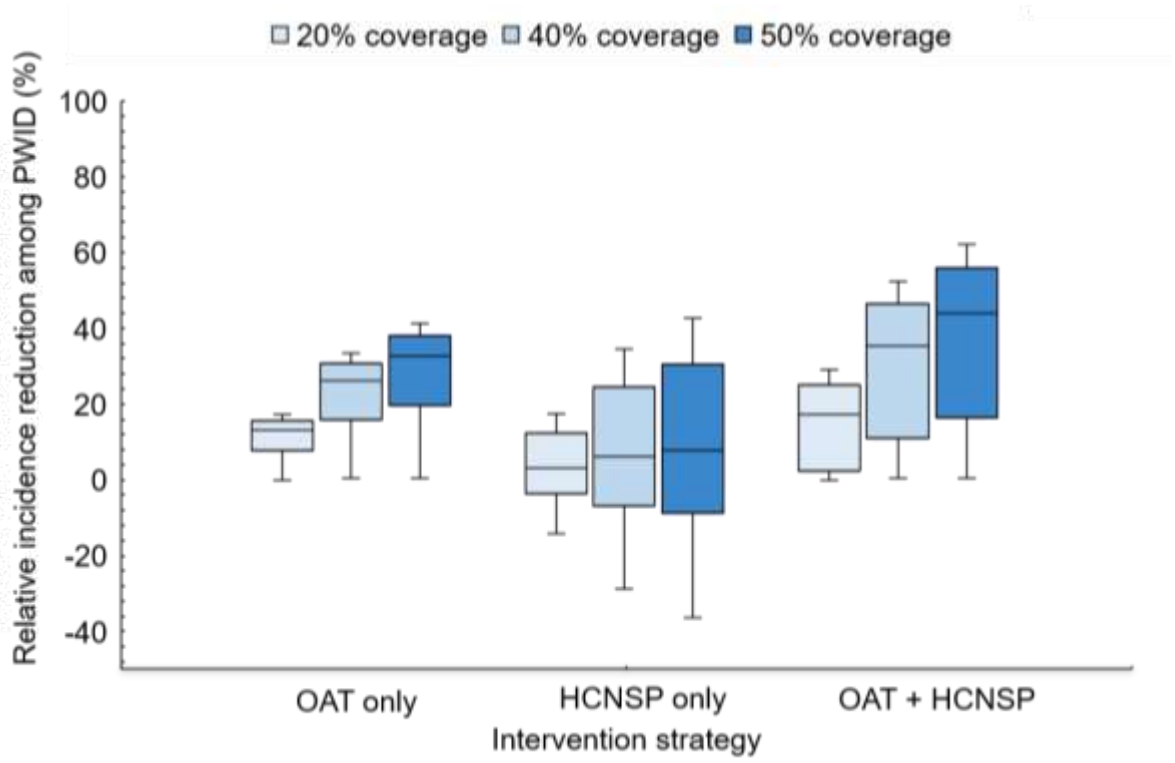

Figure S2.3 Impact of harm reduction intervention scale-up alone on relative incidence reduction over 11-year period (2019-2030) among current PWID in Tijuana, Mexico. PWID: People who inject drugs; OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program.

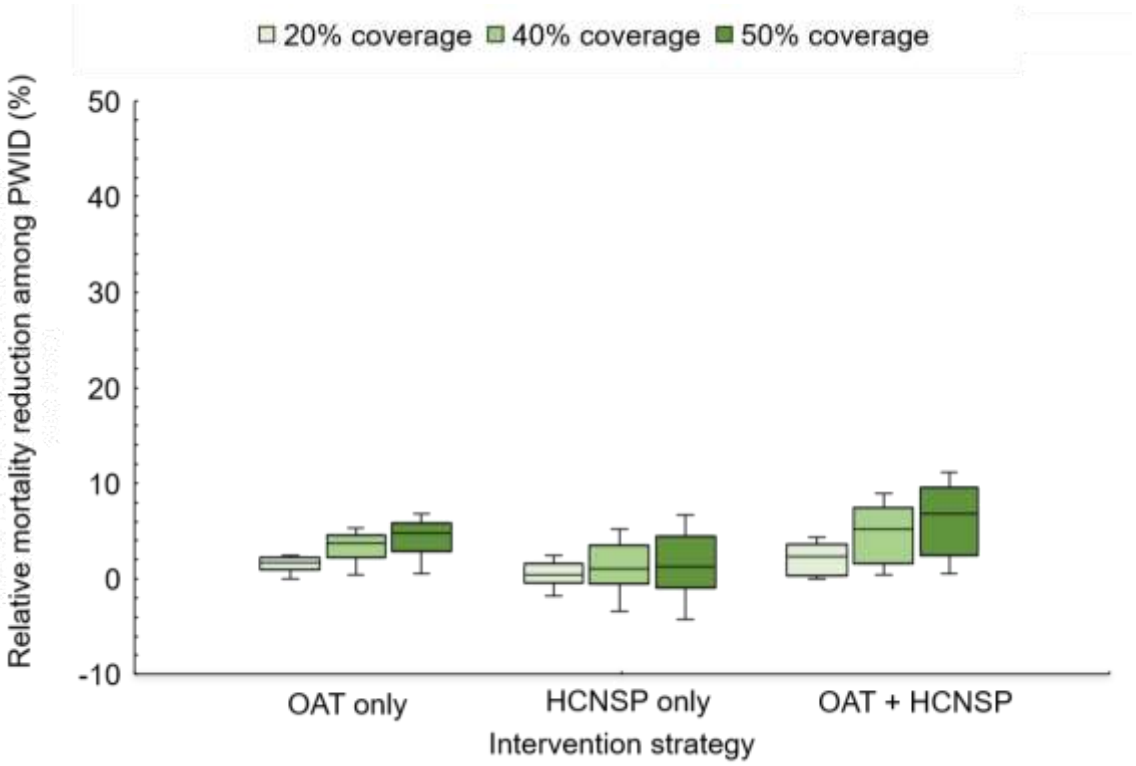

Figure S2.4 Impact of harm reduction intervention scale-up alone on relative HCV-related mortality reduction over 11-year period (2019-2030) among current PWID in Tijuana, Mexico. PWID: People who inject drugs; OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program.

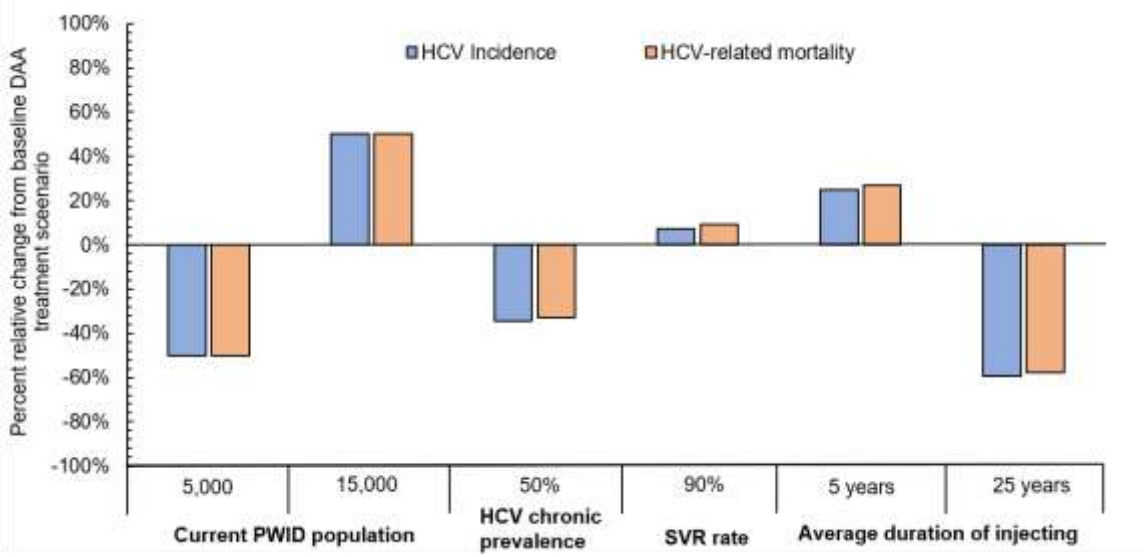

Figure S2.5 Sensitivity analysis on treatment numbers required (percent relative change compared to baseline) to achieve both HCV incidence and HCV-related mortality elimination goals in Tijuana, if DAAs are allocated regardless of injecting status. PWID: People who inject drugs; SVR: Sustained virological response.

CHAPTER 3. Cost-effectiveness of hepatitis C virus (HCV) elimination strategies among people who inject drugs (PWID) in Tijuana, Mexico

Background: Mexico was the first country in Latin America to launch an HCV elimination strategy, where the main risk group for transmission are people who inject drugs (PWID). In the city of Tijuana, HCV seroprevalence among PWID is >90% with minimal harm reduction (HR). We evaluated the cost-effectiveness of strategies to achieve the incidence elimination target (80% reduction by 2030) among PWID in Tijuana.

Methods: We developed a dynamic, cost-effectiveness model of HCV transmission and progression among former and active PWID in Tijuana, to assess the cost-effectiveness of incidence elimination strategies from a healthcare provider perspective. The model incorporated PWID transitions between HR stages (no HR, only opioid agonist therapy, only high coverage needle-syringe programs, both). Four strategies that could achieve the incidence target (80% reduction by 2030) were each compared to the status quo (no intervention). The strategies incorporated the number of direct-acting antiviral (DAA) treatments required with: 1) no HR scale-up, 2) HR scale-up from 2019 to 20% coverage among PWID, 3) HR to 40% coverage 4) HR to 50% coverage. Costs (2019 US$) and health outcomes (disability-adjusted life years [DALYs]) were discounted 3%/year. Mean incremental cost-effectiveness ratios ([ICER] $/DALY averted) were compared to willingness-to-pay thresholds of one-time per capita GDP ($9,698 in 2019) and PPP-adjusted per capita GDP ($4,842-13,557).

Results: All elimination strategies were cost-effective (ICER <$4,000/DALY averted) under both thresholds. DAAs alone were the least costly ($173M [95%CI 126M-238M]), but accrued fewer health benefits compared to a combination strategy. DAAs with 50% HR coverage averted the most DALYs, but could cost $265M [95%CI 210M-335M].

Conclusions: Combination harm reduction and treatment HCV elimination strategies are cost-effective in Mexico. Although combination prevention strategies are more costly,

initiating and sustaining harm reduction would provide more health benefits, and are critical components to reducing HCV, HIV and overdose in Mexico.

INTRODUCTION

People who inject drugs (PWID) remain one of the main risk groups for hepatitis C virus (HCV) transmission, among whom over half have ever been infected globally [1], with the majority residing in low- and middle-income countries (LMICs) [2-4]. Harm reduction interventions, such as needle and syringe exchange programs (NSP) and opioid agonist therapy (OAT) are effective at preventing the acquisition of HCV infection among PWID [5], yet <5% of PWID reside in countries with high coverage of both these interventions [6]. Recent development of short duration and highly tolerable direct-acting antivirals (DAAs) can cure >90% of PWID [7], and have been shown to be cost-effective among the general population in several LMICs such as Egypt and India compared to no treatment [8, 9]. In addition to the individual benefits of treatment, HCV treatment for PWID at risk of transmission could also act as a means of prevention at a population level [10]. However, while HCV treatment costs have been negotiated to more affordable prices in some LMICs, HCV screening and treatment remains inaccessible for many PWID for numerous reasons. These include structural barriers such as location and access to testing and treatment facilities, and socio-cultural barriers including stigma and discrimination [11-14].

In 2019, Mexico became the first Latin American country to commit to the World Health Organization's (WHO) 2016 HCV elimination goals of achieving 80% HCV incidence reduction and 65% HCV-related mortality reduction by 2030 [15, 16]. Among PWID in Tijuana, Mexico a city along the United States border, the seroprevalence of HCV is high (>90%), and harm reduction intervention coverage is low (<5%) [17, 18]. Our previous analyses have shown that the HCV elimination goals are achievable in Tijuana, particularly when scaling up harm

reduction interventions in combination with DAAs [19]; however, the most cost-effective elimination strategy is unknown. One recent U.S. economic evaluation found combination harm reduction and HCV treatment scale-up cost-effective in two U.S. settings [20], but no study has compared the cost-effectiveness of potential elimination strategies incorporating harm reduction.

To address this gap and inform elimination policymaking, we assessed the cost-effectiveness of various elimination strategies (scale-up HCV treatment with DAA provision among PWID, with or without harm reduction expansion) needed to achieve the WHO HCV incidence elimination goal among PWID in Tijuana.

METHODS

Overview

We assessed the cost-effectiveness of four HCV elimination strategies among PWID in Tijuana, Mexico, from a health care provider perspective. Our analysis incorporates costs of HCV disease stages, HCV screening, testing, and treatment delivery, as well as harm reduction intervention costs. Our analysis used a dynamic model that incorporated the transmission benefits of treatment and prevention interventions.

Model description and structure

We developed a dynamic, deterministic, compartmental model of HCV transmission among current and former PWID (**Supplementary Figure 2.1**) [19]. We simulated an open population where individuals enter due to initiation of injection drug use, and remain at risk of HCV transmission until permanent cessation, whereby they transition to former PWID. All individuals can exit the model due to death, with excess mortality among current PWID. We assumed PWID can transition between harm reduction (HR) intervention compartments: (a) no HR, (b) on OAT only, (c) on high coverage needle and syringe program (HCNSP; receiving ≥1 sterile syringe per injection) only, and (d) on both OAT+HCNSP simultaneously. PWID can become chronically infected with HCV, with a risk related to the background prevalence of

disease and their intervention exposure. Untreated individuals can progress to decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), whereby they experienced HCV-related mortality. For those who received direct-acting antiviral treatment (DAAs), a small proportion fail treatment and progress through the natural history of disease. PWID who were successfully treated move to the previously infected compartment, where they remain at risk of re-infection. Analyses were conducted in Matlab version R2018b (The Mathworks, Inc., Natick, MA).

Model parameterization

The model was parameterized to an estimated 10,000 current PWID in Tijuana, Mexico [21], with a 90% HCV seroprevalence based on a 2017/18 cross-sectional survey [17]. Data on harm reduction access, average duration of injecting, and PWID mortality were obtained from a longitudinal cohort of PWID in the El Cuete IV study (**Table 3.1**) [18, 22-24]. At baseline, we assumed no coverage (0%) of harm reduction interventions (OAT/HCNSP) or HCV treatment due to the very low coverage rates of OAT (<5%) and HCNSP (0%) in Tijuana, and because DAAs have only recently become available in Mexico. DAA sustained virologic response (SVR) rates (~95%), defined as undetectable levels of HCV RNA 12 or more weeks following completion of treatment with HCV antiviral therapy [25, 26], were obtained from published data for PWID [7, 27]. OAT and HCNSP efficacy were obtained from published data from a Cochrane systematic review and meta-analysis [5]. For OAT efficacy, we assumed OAT reduced the risk of acquiring HCV by 50% (RR=0.50, 95% CI: 0.40-0.63) [5]. For HCNSP efficacy, we assumed that HCNSP reduced HCV acquisition by approximately 23% (RR=0.77, 95% CI: 0.38-1.54) and that combined, high coverage of both HCNSP and OAT will reduce the risk of acquiring HCV by an estimated 71% (RR=0.29, 95% CI: 0.13-0.65) [5]. Based on systematic review data, current PWID on OAT additionally experienced a reduced all-cause mortality (excluding HCV-related) by 75% (RR=0.25, 95% CI: 0.18-0.36) [28].

Model calibration

To account for uncertainty in the parameter estimates, we sampled 1000 parameter sets from their respective parameter uncertainty distributions shown in **Table 3.1**. For each parameter set, the model was calibrated to the HCV prevalence among PWID in Tijuana by varying the HCV transmission rate. Based on historic HCV seroprevalence estimates among PWID in Tijuana, we assumed the HCV epidemic among PWID was at a steady, state equilibrium [29, 30].

Intervention scenarios

We simulated an 11-year (2019-2030) intervention implementation, and assessed long-term costs and health outcomes among individuals using a 50-year time horizon (2019-2069). Our previously published modeling analysis determined the scale-up of DAAs (alone, or in combination with various levels of harm reduction scale-up) that could achieve the 80% incidence reduction targets by 2030 [19]. Based on these previously published findings, we considered the following intervention scenarios:

- **Baseline status quo:** no coverage of harm reduction or HCV treatment
- **Elimination with DAAs only:** Implementing the number of DAAs required to achieve the 80% incidence reduction, without harm reduction scale-up (770 annually [95% CI: 640-970], as calculated in [19]).
- **Elimination with DAAs and 20% harm reduction coverage (DAAs+20%HR)**: implementing the number of DAAs required (665 PWID annually [95%CI: 540-850], as calculated in [19]) to achieve the 80% incidence reduction with a concomitant scale-up of combination harm reduction (OAT+HCNSP) to 20% each among PWID (therefore 10% are on both OAT and HCNSP).
- **Elimination with DAAs and 40% harm reduction coverage (DAAs+40%HR)**: **:** implementing the number of DAAs required (540 PWID annually [95% CI: 405-745], as

calculated in [19]) to achieve the 80% incidence reduction with a concomitant scale-up of combination harm reduction to 40% each among PWID (20% on both OAT and HCNSP).

- **Elimination with DAAs and 50% harm reduction coverage (DAAs+50%HR)**: **:** implementing the number of DAAs required (460 PWID annually [95% CI: 310-690], as calculated in [19]) to achieve the 80% incidence reduction with a concomitant scale-up of combination harm reduction to 50% each among PWID (25% on both OAT and HCNSP).

Costs and health outcomes

Costs were attached to each disease stage and intervention in 2019 US$ (**Table 3.1**). Costs of OAT ($2,148/year) [31] and HCNSP ($228/year) [32] per PWID receiving each harm reduction service, were obtained from recent (2017) Tijuana studies. Mexico-specific costs for HCV testing, DAA drugs ($4,000) [33] and advanced liver disease (DC and HCC) were obtained [34]. Cost of HCV management for untreated chronic HCV (prior to DC and HCC) were unavailable, so we assumed the same fraction of costs compared to DC as observed in from Peru, Colombia, Brazil [35], and the UK [36]. The cost of DAA treatment delivery, including routine lab tests, clinical monitoring, and hospital referral costs were unavailable for Mexico, so we obtained costs from a recent micro-costing study in Cambodia, adjusted by per capita GDP, and inflated to 2019 values ([37] submitted). Screening (HCV rapid antibody test cost $1.75/per test) and diagnostic costs (HCV RNA confirmatory testing cost $69.30/test) were included and obtained from unit prices provided by Gilead Sciences from a 2017-18 study evaluating HCV prevalence among PWID in Tijuana [17].

Health disutilities in disability adjusted life years (DALYs) were attached to each disease stage (**Table 3.1**). Health disutilities were obtained from the Global Burden of Disease for decompensated cirrhosis, hepatocellular carcinoma, and current PWID states [38]. As there was no specific GBD estimate for chronic HCV, we calculated the midpoint value of mild

abdominopelvic problem and compensated cirrhosis [38]. Based on evidence of quality of life improvements for those on OAT [39], we applied a disutility improvement (of 0.05) to all PWID on OAT. All costs and utilities were discounted 3% annually.

Cost-effectiveness analysis

Cost-effectiveness of intervention strategies were evaluated using an incremental cost-effectiveness ratio (ICER) analysis, where potential elimination strategies were compared to the status quo (no intervention) by dividing the mean differences in costs by the mean differences in DALYs. Results were additionally plotted on a cost-effectiveness plane (showing incremental costs and incremental DALYs compared to the status quo) [40]. Per WHO benchmarks, cost-effectiveness was assessed against a willingness-to-pay threshold equal to one-time the 2019 per capita GDP of Mexico ($9,698) [41]. We also compare the ICER to the purchasing power parity (PPP)-adjusted GDP per capita for Mexico in 2019 ($4,842-13,557 depending on elasticity estimate) [42].

Sensitivity analysis

We additionally performed several one-way sensitivity analyses including varying the proportion accessing care for their HCV disease (from 5% to 100%, compared to 25% at baseline), discount rate (0% and 6% compared to 3% at baseline), time horizon (20 years compared to 50 years at baseline), reduced HCV treatment delivery costs using a simplified model of care from Cambodia ($220 vs $685, ([37], submitted) see supplement for details), increased DAA costs ($8,000 vs $4,000), halved harm reduction costs (for both HCNSP and OAT), and excluding HCV screening and diagnostic costs.

RESULTS

Cost-effectiveness analysis

Compared to no intervention (status quo), all strategies that could achieve the 80% incidence reduction elimination goal were cost-effective (**Table 3.2**), with mean ICERs falling

under both the per capita GDP willingness-to-pay (WTP) threshold for Mexico ($9,698), and the PPP-adjusted GDP WTP ($4,842-13,557). Achieving the incidence target with DAAs alone was the least costly, resulting in total incremental costs of $58.1 million (95% CI $48.7-63.6 million), and averting 30,076 DALYs (95% CI 27,659-31,526) compared to the status quo (**Figure 3.1, Table 3.2**). Overall, the strategy of DAAs alone resulted in a mean ICER of $1,931 per DALY averted compared to the status quo.

Strategies that incorporated harm reduction scale-up combined with DAAs accrued additional health benefits (in terms of DALYs averted), compared to the DAA only strategy. However, these strategies also accrued additional costs, as although they required fewer DAA treatments (and therefore savings in DAA costs), these savings were offset by costs of harm reduction provision (**Supplementary Table S3.1**). Overall, the greatest health benefits (and greatest costs) were achieved through harm reduction scale-up to the highest level examined (DAAs+50%HR), averting 41,121 DALYs (95% CI 39,413-44,001) compared to the status quo (**Figure 3.1, Table 3.2**). However, this was also the most expensive elimination strategy, resulting in incremental costs of $149.8 million (95%CI $146.1-150.2 million) compared to the status quo. Nonetheless, the DAAs+50% HR strategy was highly cost-effective (mean ICER $3,474/DALY averted) under one-time per capita GDP WTP threshold and cost-effective under the PPP WTP threshold.

Sensitivity analysis

Nearly all elimination strategies remained cost-effective (ICERs < $6,000) compared to the status quo even with a higher discount rate, doubled DAA costs, and fewer (5%) PWID accessing care (**Supplementary Table S3.2**). All strategies became more cost-effective with a lower discount rate, halved OAT+HCNSP costs, with reduced HCV treatment delivery costs using a simplified treatment protocol, if a greater proportion or all PWID accessed care for liver-related problems (**Figure 3.2**), and removing screening and diagnostic costs. Under a shorter time horizon (20 years), the elimination strategies exceeded the one-time GDP WTP threshold,

but were below both the 3 times per capita GDP of Mexico, thus still considered cost-effective according to WHO recommendations, as well as the upper bound of the PPP threshold (ICERs $10,500-13,500/DALY averted). Notably, the only scenario that changed the relative cost-effectiveness of the strategies was with a shorter time horizon. The highest level of harm reduction (DAAs+50% HR) was the most cost-effective scenario, due to immediate prevention benefits of harm reduction and lack of full accrual of mortality benefit for treated infections (which required a longer time horizon).

DISCUSSION

Main findings

Our analysis indicates that achieving the HCV incidence elimination target are cost-effective in Tijuana, Mexico. Scale-up of combination harm reduction programs (opioid agonist therapy and high coverage needle and syringe programs) with 50% coverage among PWID along with scale-up of DAAs, resulted in the most health benefits, required fewer DAA treatments compared to strategies using DAAs alone, and was cost-effective. This strategy was slightly more expensive than a strategy of DAAs alone, but accrued more health benefits due to prevention of HCV and overdose, in addition to broader benefits not explicitly included in our analysis. We were surprised that combination prevention was more expensive despite reducing the number of treatments required, but this was due to the relatively low cost of DAAs ($4000/treatment for DAA therapies and roughly as much in addition for treatment delivery) compared to harm reduction (~$2000/year for OST). Indeed, we found the ICER of combination strategies approached that of the DAA-only strategy if treatment costs were increased or harm reduction costs reduced, indicating that in other settings with higher DAA prices or lower harm reduction costs the combination preventions strategies may be more cost-effective or less costly compared to treatment alone. Indeed, we note that existing harm reduction provision is extremely limited in Tijuana, and as such the expansion of these services could lead to

efficiencies in delivery which could reduce costs and alter relative cost-effectiveness. Nevertheless, even with the costs presented, combination prevention elimination strategies were cost-effective, and provided the greatest health benefits.

With the new commitment from Mexico to achieve HCV elimination by 2030 within the country and forthcoming allocation of 12,500 DAA treatments nationwide [15, 33], there is immediate need to understand and evaluate cost-effective and achievable intervention strategies. Tijuana, is a high prevalence HCV setting, where over 90% of PWID are expected to have ever been HCV-infected [17], yet availability of evidence-based harm reduction interventions are limited. Given the current, government-led HCV elimination efforts in Mexico, coupled with the critical needs of HCV-infected PWID in Tijuana, proposing effective and cost-effective interventions to achieve these goals is pertinent. Furthermore, Tijuana is not alone. There are several other concentrated HCV epidemics among PWID along the US border in San Luis Rio Colorado (79.1%) and in Ciudad Juarez (91.7%) [17]. The rampant HCV epidemics among PWID in Mexico further highlights the immediate need to prioritize these communities and for prompt rollout of tailored HCV intervention strategies, as achieving HCV elimination in Mexico will not be possible without treating PWID.

Due to limited, forthcoming DAA allocations in Mexico, and that all interventions were cost-effective, combination interventions such as DAAs + 50% OAT+HCNSP, which was determined to be cost-effective under the one-time per capita GDP WTP threshold, may also serve as the most feasible option for implementation. HCV treatment adherence among PWID has been reported as high as 95% (ranging from 80-95%) in other settings [27]. Thus, it is possible that adherence rates similar to these could be achieved among other PWID communities, such as those in Tijuana. However, among the numerous challenges which remain is the provision of HCNSP and OAT which has currently and historically been limited in Tijuana, as a primary result of funding lapses or terminations [32, 43]. Despite the limited provision of these evidence-based harm reduction strategies, PWIDs in Tijuana have self-

reported a high-level need for addiction treatment programs [44]. While future funding of these harm reduction programs is unclear, our analyses indicate that their implementation, even scaling to levels as high as 50% for both OAT and HCNSP, would be cost-effective and otherwise beneficial to the PWID in Tijuana, reducing HCV as well as preventing and fatal overdose [28] as well as HIV transmission among PWID [5, 45] and perhaps the broader community.

For PWID in Tijuana, accessing healthcare remains another critical obstacle. However, despite expressing the desire to access care in Tijuana, as in other settings, stigma within the healthcare system is rampant and greatly hinders accessibility [46-49]. Additionally, many PWID do not even have access to basic health care [50, 51], let alone specialized treatment and care for more advanced diseases. Thus, there is a concern that despite the recent allocation of 12,500 DAAs to Mexico for HCV elimination, allocation to Tijuana and prioritizing PWID to receive these allotted treatments are unclear, as in other literature, which show that when public healthcare resources are limited, PWID are less likely to be prioritized [52].

Strengths and limitations of study

Given limited resources, there is a need to determine achievable interventions that can support the efforts towards HCV elimination within Tijuana, and in Mexico overall, which will not be achieved without implementing evidence-based interventions that prioritize high-risk, high HCV prevalence groups such as PWID. This study is novel in that it is, to our knowledge, the first study to evaluate cost-effectiveness of combination HCV elimination strategies in Latin America, thus contributing to a significant gap in knowledge and much needed evidence to better recommend impactful interventions among PWID in Tijuana and in Mexico.

Our study has several limitations. As with all modeling studies, there is uncertainty within the model parameters. First, there is substantial uncertainty in the proportion of PWID accessing liver-related care in Tijuana (with our estimate based on a limited sample of survey respondents), as well as the costs of care for these disease stages (with our estimates either

using older estimates from Mexico or extrapolating relative costs from other settings), but our sensitivity analyses indicated the model results were robust to assumptions of very low access to care, indicating the cost of disease stages were not a main driver of the results. Second, costs of HCV treatment delivery were unavailable for Mexico, so we adjusted costs from a recent micro-costing study in Cambodia. It is unclear as to whether these costs are generalizable to Mexico, yet our sensitivity analyses indicated the results were robust to this uncertainty. Third, due to a lack of data suggesting otherwise, we assume that all individuals are equally likely to accept our interventions (HCV treatment or harm reduction). It is possible there may be heterogeneity in willingness to accept OAT or DAAs, such that higher risk PWID may be less willing to accept harm reduction or HCV treatment, which could reduce the impact of prevention efforts. More studies are warranted to assess willingness to access HCV interventions and implications on elimination efforts. Fourth, we assume fixed costs for all interventions (treatment or harm reduction). We would not expect harm reduction costs to vary depending on stage of HCV elimination, however we acknowledge that current harm reduction provision is very limited in Tijuana, and if scaled-up to the coverages examined could achieve economies of scale which would reduce costs over time. Regarding HCV treatment, we incorporate increased screening costs required to diagnose individuals for treatment as prevalence declines, but assume the cost of treatment delivery remains unchanged. On one hand, as more people are treated, we may observe efficiencies which could reduce treatment delivery costs. Alternatively, those who remain untreated until the end could reflect a harder to engage population which may require additional efforts (and associated costs) to engage them with treatment. As treatment programs expand, they will provide the required data on how treatment delivery costs evolve through the elimination process. Fifth, there is uncertainty in the effect estimates for harm reduction impact on HCV transmission, particularly for high coverage NSP. Our effect estimates were obtained from a recent global Cochrane systematic review and meta-analysis, but there were no studies from Latin America, and as such it is unclear whether

these estimates are generalizable to Mexico [5]. In particular, the global effect estimate for the HCNSP effect estimate was uncertain and straddled the null, whereas a much stronger effect was observed in Europe. Further studies are required to determine the impact of harm reduction on prevention of HCV among PWID in Mexico and other similar Latin American settings.

CONCLUSION

HCV elimination is cost-effective in Tijuana, and the greatest health benefits can be achieved through a combination strategy that includes scale-up of harm reduction and DAA provision. Implementation of a combination prevention strategy will not only prevent new HCV infections and re-infections, but also accrue additional benefits in prevention of HIV transmission and mortality from fatal overdose. Provision of harm reduction and HCV treatment for people who inject drugs is urgently needed in Tijuana, and Mexico more broadly.

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FIGURES

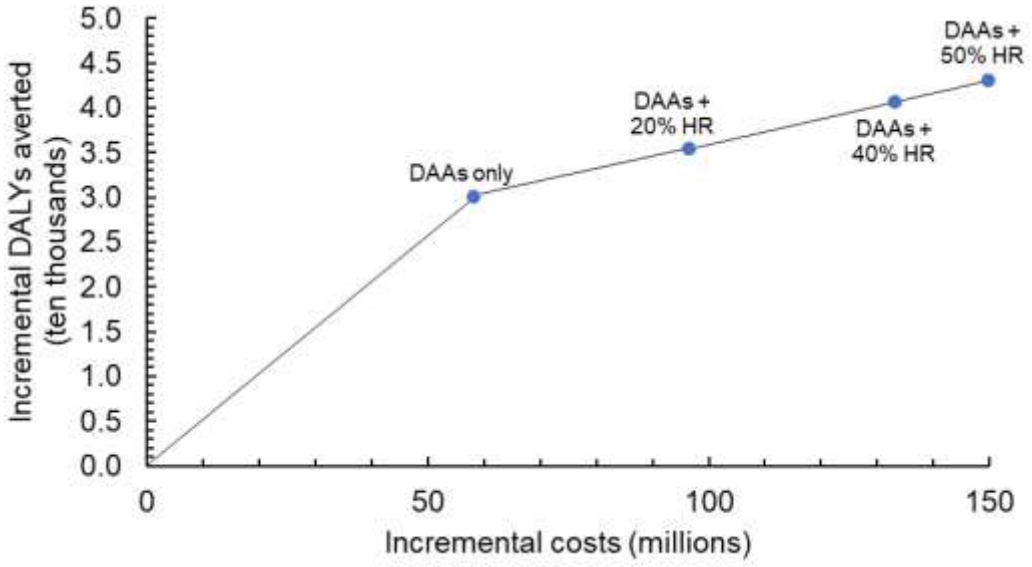

Figure 3.1 Incremental costs and DALYs averted for various HCV elimination strategies to achieve 80% HCV incidence reduction by 2030 compared to status quo in Tijuana, Mexico. DAA: Direct-acting antiviral treatment. HR: Harm reduction includes (1) OAT: Opioid agonist therapy and (2) HCNSP: High coverage needle/syringe program (receiving ≥1 sterile syringes per injection).

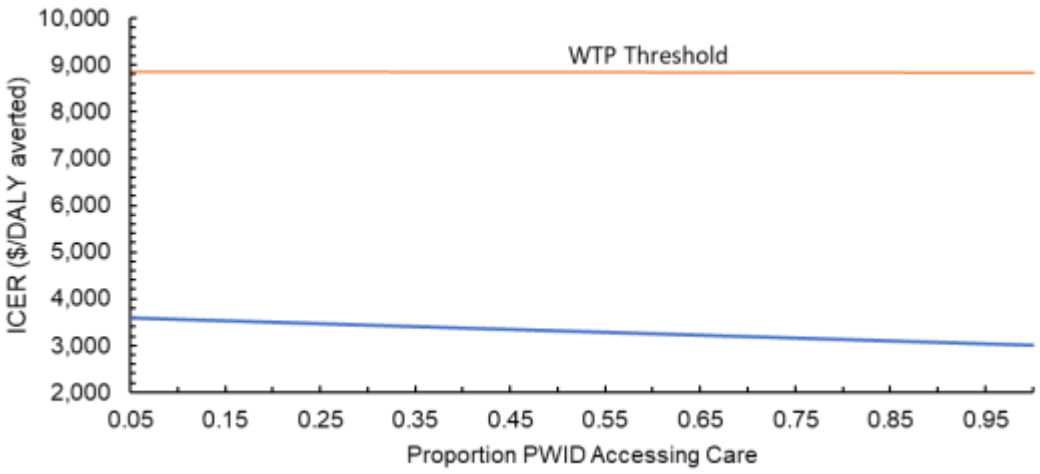

Figure 3.2 Incremental cost-effectiveness ratio (ICER) of DAAs+50%HR strategy compared to status quo, with varying proportions of HCV-infected accessing care in Tijuana, Mexico. OAT: Opioid agonist therapy; HCNSP: High coverage needle/syringe program (receiving ≥1 sterile syringes per injection); DAA: Direct-acting antiviral treatment.

TABLES

Table 3.1 Model parameters and their distributions. Distribution ranges: Uniform: minimum, maximum; Beta: alpha, beta; Lognormal: shape, scale. DC: decompensated cirrhosis; HCC: Hepatocellular carcinoma; OAT: Opioid agonist therapy; NSP: Needle/syringe program; HCNSP: High-coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection).

Definition	Mean sampled value (95% CI)	Sample distribution	Unit	Reference
Number of current PWID	10,000	Not sampled		[21]
HCV seroprevalence among current PWID (2017/18)	0.90 (0.85-0.95)	Beta	--	[17]
Proportion of infections that spontaneously clear	0.26 (0.22-0.30)	Uniform	--	[53]
HCV sustained viral response rates	0.95 (0.91-0.99)	Uniform	--	[7, 27]
Average duration of injecting	17.5 (11.3-23.6)	Uniform	Years	Weighted average assumed (15% female; 85% male) [22, 23, 54]
Mortality rate among PWID	0.02 (0.016, 0.024)	Uniform	Per year	[23, 24]
Relative reduction of all-cause (excluding HCV) mortality for current PWID on OAT compared to off OAT	0.25 (0.18, 0.36)	Lognormal		[28]
OAT recruitment rate	Varied to fit to target proportion PWID on OAT	-	Per year	--
Leaving rate from OAT	1.5 (1.0-2.0)	Uniform	Per year	[55-57]
HCNSP recruitment	Varied to fit to target proportion on HCNSP	-	Per year	--
Leaving rate from HCNSP	1.5 (1.0-2.0)		Per year	Assumed same as OAT [58]
Relative risk of HCV transmission on OAT only compared to no OAT	0.50 (0.39, 0.64)	Lognormal	--	[5]
Relative risk of HCV transmission on HCNSP only compared to no HCNSP	0.79 (0.38, 1.60)	Lognormal	--	[5]
Relative risk of HCV acquisition on OAT and HCNSP compared to none	0.23 (0.09, 0.62)	Lognormal	--	[5]

Table 3.1 Model parameters and their distributions, Continued. Distribution ranges: Uniform: minimum, maximum; Beta: alpha, beta; Lognormal: shape, scale. DC: decompensated cirrhosis; HCC: Hepatocellular carcinoma; OAT: Opioid agonist therapy; NSP: Needle/syringe program; HCNSP: High-coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection).

Definition	Mean sampled value (95% CI)	Sample distribution	Unit	Reference
Disease transition probabilities				
Chronic – DC	0.016 (0.013, 0.019)	Uniform	Per year	Calculated from fibrosis progression rates in [59]
Chronic—HCC	0.009 (0.007, 0.01)	Uniform	Per year	Calculated from fibrosis progression rates in [59]
DC – HCC	0.012 (0.002, 0.04)	Beta	Per year	[60]
HCV-related mortality rate from DC	0.14 (0.11, 0.17)	Uniform	Per year	[60]
HCV-related mortality rate from HCC	0.55 (0.31, 0.79)	Uniform	Per year	[60, 61]
HCV-related costs (in 2019 US$)				
HCV antibody test	$1.75		Per test	[17]
HCV RNA test	$69.30		Per test	[17]
DAA drugs	$4,000	--	Per treatment	[33, 62]
HCV treatment delivery	$4,812	--	Per treatment	Costs from HCV treatment program in Cambodia, adjusted by GDP ratio (2017 Mexico/2017 Cambodia GDP). Then, inflated to 2019 costs.([37], submitted)
OAT in Tijuana or Mexico	$2,148 (1,749-2,565)	Uniform +/- 20% point estimate	Per year	[31]
NSP in Tijuana or Mexico	$228 (184-272)	Uniform +/- 20% point estimate	Per year	[32]
Chronic HCV (no treatment)	$749.69 (395.90-1,094.36)	1/13*DC estimate	Per year	No Mexico estimates available. Assumed to be 1/13th of the DC estimate based on data from Peru, Colombia, Brazil [35], and the UK [36].
DC	$9,509.94 (5,090.88-14,132.67)	Uniform +/- 50% point estimate	Per year	Based on the 2005 estimate for cirrhosis [34]; published cost not specified for decompensation: $1944. Inflated to 2019 prices
HCC	$9,662.56 (4,977.47-14,199.51)	Uniform +/- 50% point estimate	Per year	Based on the 2005 estimate: $5523 [34]; Inflated to 2019 prices

Table 3.1 Model parameters and their distributions, Continued. Distribution ranges: Uniform: minimum, maximum; Beta: alpha, beta; Lognormal: shape, scale. DC: decompensated cirrhosis; HCC: Hepatocellular carcinoma; OAT: Opioid agonist therapy; NSP: Needle/syringe program; HCNSP: High-coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection).

Definition	Mean sampled value (95% CI)	Sample distribution	Unit	Reference
Health disutility values for HCV disease stages				
Uninfected		Beta		[38]
Ex/non-PWID	0			
Active PWID	0.333 (0.202-0.467)			
Hepatitis C Virus Stage decrement				
Chronic HCV	0.063	--		No GBD estimate for moderate chronic HCV, took midpoint value of mild abdominopelvic problem and compensated cirrhosis [38]
Decompensated cirrhosis	0.178 (0.123-0.250)	Beta		[38]
Hepatocellular carcinoma	0.569 (0.389-0.727)	Beta		[38]
OAT disutility improvement	0.05 (0.03-0.07)	Uniform		[39]

Table 3.2 Cost-effectiveness of strategies to reach the 80% HCV incidence reduction target by 2030 among PWID in Tijuana compared to no intervention (status quo). ICER: Incremental cost-effectiveness ratio; DAAs: Direct-acting antiviral treatment; HR: harm reduction. *compared to status quo.

	Mean cost (millions)		Mean DALYs		
Intervention Scenario	**Total (95% CI)**	**Incremental***	**Total (95% CI)**	**Incremental***	**ICER ($ per DALY averted) compared to status quo**
No Intervention (status quo)	114.90 (62.50, 188.90)	--	553,330 (448,310, 700,400)	--	--
DAA only strategy	173.0 (126.10, 237.60)	58.10 (48.70, 63.60)	523,250 (420,650, 668,870)	-30,080 (-27,660, -31,530)	1,931
DAAs+ 20%HR coverage strategy	211.40 (163.60, 280.70)	96.50 (91.80, 101.10)	517,850 (416,070, 663,260)	-35,480 (-32,250, -37,140)	2,719
DAAs+ 40% HR coverage strategy	248.0 (196.90, 317.10)	133.10 (128.20, 134.40)	512,640 (411,410, 658,500)	-40,690 (-36,900, -41,900)	3,272
DAAs + 50% HR coverage strategy	264.70 (209.90, 335.0)	149.80 (146.10, 150.20)	510,210 (408,900, 656,400)	-43,120 (-39,410, -44,000)	3,474

SUPPLEMENTARY INFORMATION FOR CHAPTER 3

Included in the supplementary information, we provide additional details about some of the parameters we selected to include in our model, present the model structure and equations, followed by supplementary figures presenting the model schematic (**Supplementary Figure S2.1)** and the total number of DAA treatments estimated to achieve the 80% HCV incidence reduction goal by 2030 by harm reduction intervention strategy (**Supplementary Figure S2.2**). Additionally, we detail the breakdown of each intervention scenario by cost component (**Supplementary Table S3.1)**. Lastly, in our sensitivity analyses, we consider various scenarios including variations in cost of harm reduction, DAAs, and treatment delivery, to examine the impact of these alternative scenarios on the cost-effectiveness of the presented interventions (**Supplementary Table S3.2**).

Description of simplified model of care

The simplified model of care differed from the full model of care in the: (1) point of care tests for HCV diagnosis (SD Bioline rapid HCV antibody test, GeneXpert) instead of ELISA/PCR utilized in the full model of care, (2) reduced the number of nurse-counsellor visits throughout treatment (from 10 to 2 visits), (3) eliminated HCV genotyping and several monitoring blood tests, (4) required 50% fewer patient visits during treatment (from 8 to 4 visits), as well as (4) some task-shifting from physicians to nurses and pharmacists ([1] submitted)).

Screening and diagnostic costs

The costs of screening and diagnosis were incorporated in the model, such that the costs of diagnosing an individual for treatment increased as chronic prevalence reduced over time. Unit prices of diagnostics were obtained from unit prices provided by Gilead Sciences from a 2017-18 study evaluating HCV prevalence among PWID in Tijuana [2]. The cost in 2017-18 per HCV rapid test was $1.75 (34 Mexican pesos) and HCV RNA confirmatory test was $69.30 (1,350 Mexican pesos).

Model Equations

Model equations are presented below. The model includes compartments for uninfected PWID ($X_{i,j}$), chronically infected PWID ($C_{i,j}$), previously infected PWID ($P_{i,j}$), chronically infected PWID who failed HCV treatment ($Z_{i,j}$), PWID with decompensated cirrhosis ($D_{i,j}$), and PWID with hepatocellular carcinoma ($H_{i,j}$). For current PWID, the subscript notation *i,j* denotes intervention status, presented as opiate agonist therapy (OAT) status (*i*=0 Not on OAT, *i*=1 On OAT) and high coverage needle and syringe program (HCNSP) status (*j*=0 Not on HCNSP, *j*=1 On HCNSP). Additional compartments represent former PWID in these aforementioned HCV disease stages (denoted as *XF, CF, PF, ZF, DF,* and *HF*, respectively).

Uninfected PWID enter the model at a rate, θ. Susceptible PWID can become infected with HCV (a dynamic process, proportional to the infection rate, chronic prevalence among PWID, and intervention coverage). A proportion progress to chronic infection $(1-\delta)$, whereas the remainder spontaneously clear their HCV infection (δ). For those who become chronically infected, a fixed number will be treated each year (at a rate $\Phi(\mathrm{t})$ individuals per year), which is allocated proportional to chronic infection group size depending on the treatment prioritization strategy examined, either to current PWID or to both current and former PWID. When the total number of eligible infected individuals was less than the number of possible treatments per year, all individuals were treated. A proportion of those treated achieve a sustained virologic response (SVR) (α) whereas others will not achieve SVR (proportion $(1-\alpha)$). Current PWID who were previously infected with HCV, can become reinfected at the same rate of infection as primary infection, and will then move back into the chronically infected compartment. Those who are chronically infected (treatment naïve or who have failed treatment) can progress to more advanced stages of liver disease including decompensated cirrhosis (at a rate, β_1), or develop hepatocellular carcinoma (at a rate, β_2). Those who have decompensated cirrhosis can progress to hepatocellular carcinoma (at a rate, ρ). Finally, those who are in advanced stages of

liver disease (decompensated cirrhosis or hepatocellular carcinoma) die from HCV-related mortality at rates, μ_3 and μ_4, respectively. Current PWID may also transition from current injecting to permanent cessation from all disease stages at a rate, μ_1. Both current and former (those who permanently cessated) PWID die from non-HCV-related death at a rate, μ_2, from any disease stage, due to evidence of high mortality rates among both current and former PWID in the El Cuete Cohort. Based on systematic review data, current PWID on OAT have a relative reduction in all-cause (not HCV-related) mortality (RR=0.25; 95% CI: 0.18-0.36) compared to those not on OAT [3], and thus die at a rate of μ_2*OAT_mortality. Current PWID can be recruited on to OAT (rate $\gamma(t)$) or HCNSP (rate $\eta(t)$). Force of infection equations for the model are detailed following the model equations. Here, π is defined by the HCV transmission rate within the PWID population. We assumed PWID on OAT or HCNSP experience reduced transmission and acquisition (at a relative risk Γ for on HCNSP, Π on OAT, B on both OAT and HCNSP, each compared to no intervention). Leaving rates from OAT and HCNSP are κ and ε, respectively. We assume former PWID are no longer at risk for infection/reinfection.

<u>Model Equations for PWID not on OAT and not on HCNSP:</u>

$$(1.1)\ \frac{dX_{0,0}}{dt} = \theta - (1-\delta)X_{0,0}\lambda_{0,0} - \delta X_{0,0}\lambda_{0,0} + \kappa X_{1,0} + \varepsilon X_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))X_{0,0}$$

$$(2.1)\ \frac{dC_{0,0}}{dt} = (1-\delta)X_{0,0}\lambda_{0,0} - \phi_{0,0}(\mathrm{t}) + (1-\delta)P_{0,0}\lambda_{0,0} - (\beta_1+\beta_2)C_{0,0} + \kappa C_{1,0} + \varepsilon C_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))C_{0,0}$$

$$(3.1)\ \frac{dP_{0,0}}{dt} = \delta X_{0,0}\lambda_{0,0} + \alpha\phi_{0,0}(\mathrm{t}) - (1-\delta)P_{0,0}\lambda_{0,0} + \kappa P_{1,0} + \varepsilon P_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))P_{0,0}$$

$$(4.1)\ \frac{dZ_{0,0}}{dt} = (1-\alpha)\phi_{0,0}(\mathrm{t}) - (\beta_1+\beta_2)Z_{0,0} + \kappa Z_{1,0} + \varepsilon Z_{0,1} - (\mu_1 + \mu_2 + \gamma(t) + \eta(t))Z_{0,0}$$

$$(5.1)\ \frac{dD_{0,0}}{dt} = \beta_1\left(C_{0,0} + Z_{0,0}\right) - \rho D_{0,0} + \kappa D_{1,0} + \varepsilon D_{0,1} - (\mu_1 + \mu_2 + \mu_3 + \gamma(t) + \eta(t))D_{0,0}$$

$$(6.1)\ \frac{dH_{0,0}}{dt} = \beta_2\left(C_{0,0} + Z_{0,0}\right) + \rho D_{0,0} + \kappa H_{1,0} + \varepsilon H_{0,1} - (\mu_1 + \mu_2 + \mu_4 + \gamma(t) + \eta(t))H_{0,0}$$

Model Equations for PWID on OAT and not on HCNSP:

(1.2) $\frac{dX_{1,0}}{dt} = -(1-\delta)X_{1,0}\lambda_{1,0} - \delta X_{1,0}\lambda_{1,0} + \varepsilon X_{1,1} + \gamma(t)X_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))X_{1,0}$

(2.2) $\frac{dC_{1,0}}{dt} = (1-\delta)X_{1,0}\lambda_{1,0} - \phi_{1,0}(\mathrm{t}) + (1-\delta)P_{1,0}\lambda_{1,0} - C_{1,0}(\beta_1+\beta_2) + \varepsilon C_{1,1} + \gamma(t)C_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))C_{1,0}$

(3.2) $\frac{dP_{1,0}}{dt} = \delta X_{1,0}\lambda_{1,0} + \alpha\phi_{1,0}(\mathrm{t}) - (1-\delta)P_{1,0}\lambda_{1,0} + \varepsilon P_{1,1} + \gamma(t)P_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))P_{1,0}$

(4.2) $\frac{dZ_{1,0}}{dt} = (1-\alpha)\phi_{1,0}(\mathrm{t}) - (\beta_1+\beta_2)Z_{1,0} + \varepsilon Z_{1,1} + \gamma(t)Z_{0,0} - (\mu_1 + \mu_2 + \kappa + \eta(t))Z_{1,0}$

(5.2) $\frac{dD_{1,0}}{dt} = \beta_1(C_{1,0} + Z_{1,0}) - \rho D_{1,0} + \varepsilon D_{1,1} + \gamma(t)D_{0,0} - (\mu_1 + \mu_2 + \mu_3 + \kappa + \eta(t))D_{1,0}$

(6.2) $\frac{dH_{1,0}}{dt} = \beta_2(C_{1,0} + Z_{1,0}) + \rho D_{1,0} + \varepsilon H_{1,1} + \gamma(t)H_{0,0} - (\mu_1 + \mu_2 + \mu_4 + \kappa + \eta(t))H_{1,0}$

Model Equations for PWID not on OAT and on HCNSP:

(1.3) $\frac{dX_{0,1}}{dt} = -(1-\delta)X_{0,1}\lambda_{0,1} - \delta X_{0,1}\lambda_{0,1} + \kappa X_{1,1} + \eta(t)X_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))X_{0,1}$

(2.3) $\frac{dC_{0,1}}{dt} = (1-\delta)X_{0,1}\lambda_{0,1} - \phi_{0,1}(\mathrm{t}) + (1-\delta)P_{0,1}\lambda_{0,1} - (\beta_1+\beta_2)C_{0,1} + \kappa C_{1,1} + \eta(t)C_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))C_{0,1}$

(3.3) $\frac{dP_{0,1}}{dt} = \delta X_{0,1}\lambda_{0,1} + \alpha\phi_{0,1}(\mathrm{t}) - (1-\delta)P_{0,1}\lambda_{0,1} + \kappa P_{1,1} + \eta(t)P_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))P_{0,1}$

(4.3) $\frac{dZ_{0,1}}{dt} = (1-\alpha)\phi_{0,1}(\mathrm{t}) - \beta_1 Z_{0,1} - \beta_2 Z_{0,1} + \kappa Z_{1,1} + \eta(t)Z_{0,0} - (\mu_1 + \mu_2 + \varepsilon + \gamma(t))Z_{0,1}$

(5.3) $\frac{dD_{0,1}}{dt} = \beta_1(C_{0,1} + Z_{0,1}) - \rho D_{0,1} + \kappa D_{1,1} + \eta(t)D_{0,0} - (\mu_1 + \mu_2 + \mu_3 + \varepsilon + \gamma(t))D_{0,1}$

(6.3) $\frac{dH_{0,1}}{dt} = \beta_2(C_{0,1} + Z_{0,1}) + \rho D_{0,1} + \kappa H_{1,1} + \eta(t)H_{0,0} - (\mu_1 + \mu_2 + \mu_4 + \varepsilon + \gamma(t))H_{0,1}$

Model Equations for PWID on OAT and on HCNSP:

(1.4) $\frac{dX_{1,1}}{dt} = -(1-\delta)X_{1,1}\lambda_{1,1} - \delta X_{1,1}\lambda_{1,1} + \eta(t)X_{1,0} + \gamma(t)X_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)X_{1,1}$

(2.4) $\frac{dC_{1,1}}{dt} = (1-\delta)X_{1,1}\lambda_{1,1} - \phi_{1,1}(\mathrm{t}) + (1-\delta)P_{1,1}\lambda_{1,1} - (\beta_1+\beta_2)C_{1,1} + \eta(t)C_{1,0} + \gamma(t)C_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)C_{1,1}$

(3.4) $\frac{dP_{1,1}}{dt} = \delta X_{1,1}\lambda_{1,1} + \alpha\phi_{1,1}(\mathrm{t}) - (1-\delta)P_{1,1}\lambda_{1,1} + \eta(t)P_{1,0} + \gamma(t)P_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)P_{1,1}$

(4.4) $\frac{dZ_{1,1}}{dt} = (1-\alpha)\phi_{1,1}(\mathrm{t}) - (\beta_1+\beta_2)\ Z_{1,1} + \eta(t)Z_{1,0} + \gamma(t)Z_{0,1} - (\mu_1 + \mu_2 + \kappa + \varepsilon)Z_{1,1}$

(5.4) $\frac{dD_{1,1}}{dt} = \beta_1(C_{1,1} + Z_{1,1}) - \rho D_{1,1} + \eta(t)D_{1,0} + \gamma(t)D_{0,1} - (\mu_1 + \mu_2 + \mu_3 + \kappa + \varepsilon)D_{1,1}$

(6.4) $\frac{dH_{1,1}}{dt} = \beta_2(C_{1,1} + Z_{1,1}) + \rho D_{1,1} + \eta(t)H_{1,0} + \gamma(t)H_{0,1} - (\mu_1 + \mu_2 + \mu_4 + \kappa + \varepsilon)H_{1,1}$

Model Equations for Former PWID:

(1.5) $\frac{dXF}{dt} = \mu_1(X_{0,0} + X_{1,0} + X_{0,1} + X_{1,1}) - \mu_2 XF$

(2.5) $\frac{dCF}{dt} = \mu_1(C_{0,0} + C_{1,0} + C_{0,1} + C_{1,1}) - \phi_{CF}(\mathrm{t}) - CF(\beta_1+\beta_2) - \mu_2 CF$

(3.5) $\frac{dPF}{dt} = \mu_1(P_{0,0} + P_{1,0} + P_{0,1} + P_{1,1}) + \alpha\phi_{CF}(\mathrm{t}) - \mu_2 \mathrm{PF}$

(4.5) $\frac{dZF}{dt} = \mu_1(Z_{0,0} + Z_{1,0} + Z_{0,1} + Z_{1,1}) + (1-\alpha)\phi_{CF}(\mathrm{t}) - (\beta_1+\beta_2)ZF - \mu_2 ZF$

(5.5) $\frac{dDF}{dt} = \mu_1(D_{0,0} + D_{1,0} + D_{0,1} + D_{1,1}) + \beta_1(CF + ZF) - \rho DF - (\mu_2 + \mu_3)DF$

(6.5) $\frac{dHF}{dt} = \mu_1(H_{0,0} + H_{1,0} + H_{0,1} + H_{1,1}) + \beta_2(CF + ZF) + \rho DF - (\mu_2 + \mu_4)HF$

where the force of infection equations are below:

$$\lambda_{0,0} = \pi \frac{(\Omega_{0,0} + \Gamma(\Omega_{0,1}) + \Pi(\Omega_{1,0}) + \mathrm{B}(\Omega_{1,1}))}{(\Omega_{0,0} + \Lambda_{0,0}) + \Gamma(\Omega_{0,1} + \Lambda_{0,1}) + \Pi(\Omega_{1,0} + \Lambda_{1,0}) + \mathrm{B}(\Omega_{1,1} + \Lambda_{1,1})}$$

$\lambda_{0,1} = \Gamma\lambda_{0,0}$

$\lambda_{1,0} = \Pi\lambda_{0,0}$

$\lambda_{1,1} = \mathrm{B}\lambda_{0,0}$

where

$\Omega_{i,j} = \mathrm{C}_{i,j} + \mathrm{Z}_{i,j} + \mathrm{D}_{i,j} + \mathrm{H}_{i,j}$

and

$$\Lambda_{i,j} = \mathrm{P}_{i,j} + \mathrm{X}_{i,j}$$

SUPPLEMENTARY FIGURES

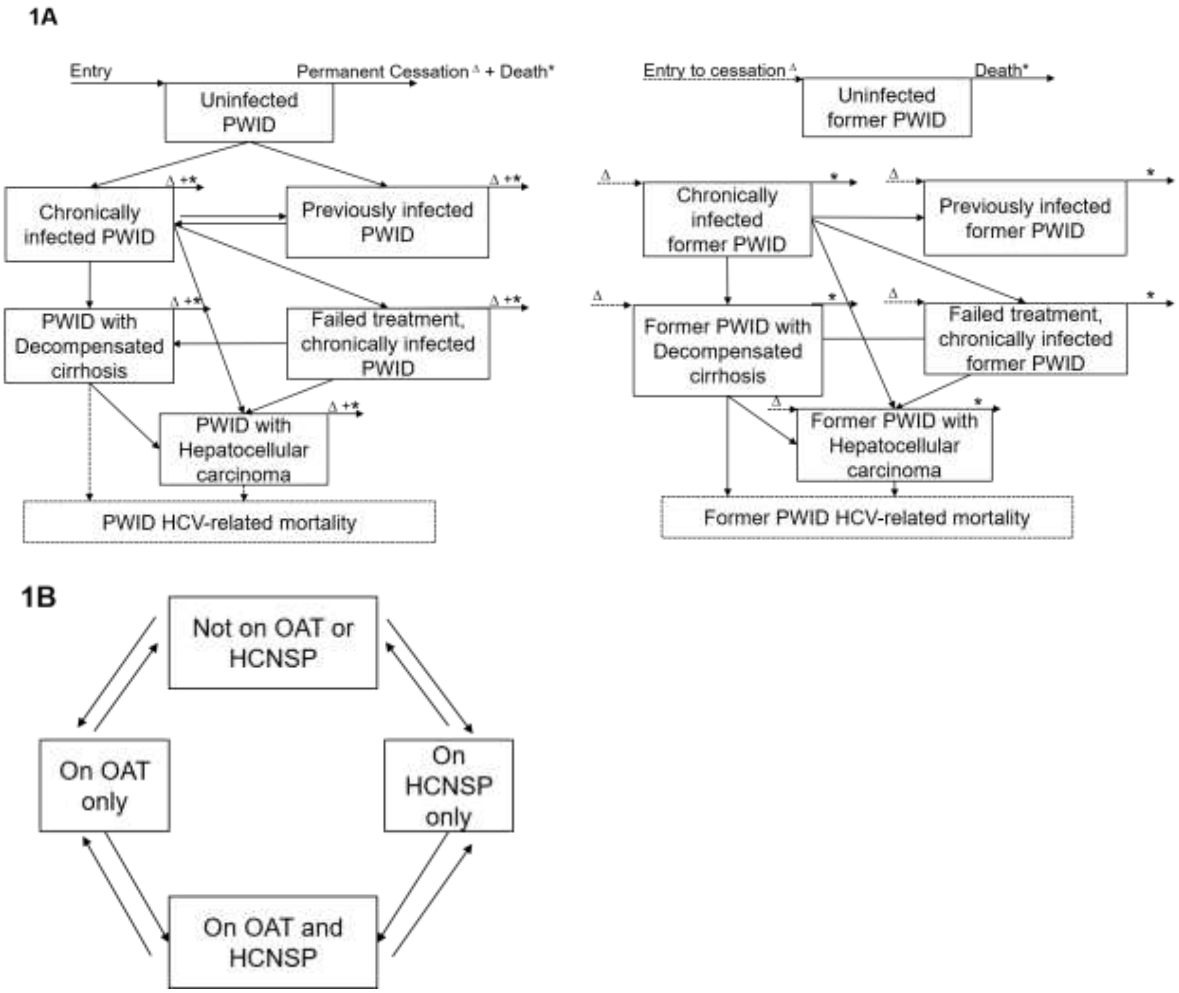

Figure S3.1 Model schematics showing (A) HCV disease progression by liver disease states and (B) stratification by harm reduction interventions. PWID: People who inject drugs; OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection). *PWID exiting the model due to death; ΔCurrent PWID transitioning to former PWID model, resulting from permanent cessation.

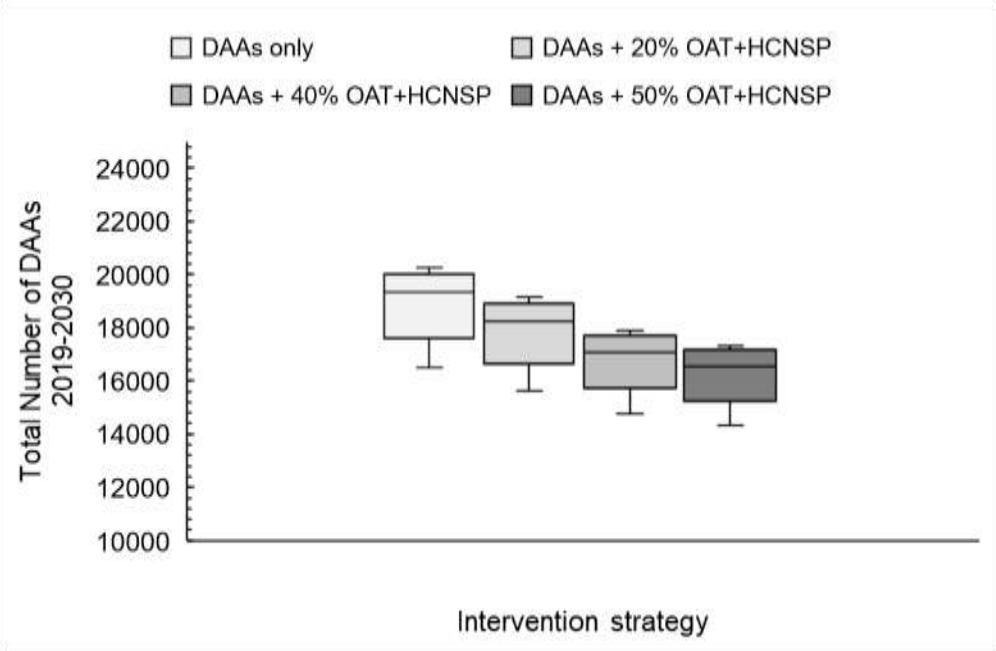

Figure S2.2 Total number of DAA treatments estimated to achieve the 80% HCV incidence reduction goal by 2030 by harm reduction intervention strategy. DAA: Direct-acting antiviral treatment; OAT: Opiate agonist therapy; HCNSP: High coverage needle/syringe exchange program (receiving ≥1 sterile syringes per injection).

SUPPLEMENTARY TABLES

Table S3.1 Intervention scenario by cost component. Treatment costs include DAA costs (US$4,000) and cost of treatment delivery (US$4,812). Harm reduction costs include cost of OAT (US$2,148/year) and HCNSP (US$228/year) in Tijuana. DAA: Direct-acting antiviral treatment; HR: Harm reduction includes (1) OAT: Opiate agonist therapy and (2) HCNSP: High coverage needle/syringe program (receiving ≥1 sterile syringes per injection).

	Disease stage costs (95%CI)	**Screening & diagnostic costs (95%CI)**	**Treatment costs (95%CI)**	**Harm reduction costs (95%CI)**	**Total cost (95%CI)**
No intervention (status quo)	114.90 (62.50-188.88)	0	0	0	114.90 (62.50-188.88)
DAAs only	107.94 (60.88-171.36)	0.97 (0.85-1.0)	64.07 (59.59-64.25)	0	172.98 (126.09-237.63)
DAAs+20% HR	108.22 (60.74-172.24)	0.85 (0.77-0.95)	57.45 (55.48-59.75)	44.84 (37.14-52.49)	211.36 (163.63-280.65)
DAAs+40% HR	108.31 (60.39-173.10)	0.69 (0.63-0.77)	49.04 (37.98-61.39)	90.0 (74.53-105.27)	248.04 (196.94-317.11)
DAAs+50%HR	108.28 (60.50-174.02)	0.58 (0.51-0.66)	43.11 (28.43-55.62)	112.72 (93.29-131.90)	264.69 (209.91-335.01)

Table S3.2 Sensitivity analyses of alternative intervention scenarios showing ICER of each scenario compared to no intervention (status quo). DALY: Disability-adjusted life years; CI: Confidence interval; ICER: Incremental cost-effectiveness ratio; HR: Harm reduction; DAA: Direct-acting antiviral treatment; HCV: Hepatitis C virus.

	Mean cost (millions)	Mean DALYs (hundred thousand)	
Intervention Scenario	**Total (95% CI)**	**Total (95% CI)**	**ICER ($ per DALY averted) compared to status quo**
Reduced HR cost by half			
No Intervention (status quo)	114.90 (62.50-188.88)	5.53 (4.48-7.00)	--
DAA only	172.98 (126.09-237.63)	5.23 (4.21-6.69)	1,931
DAAs+ 20%HR	188.94 (141.21-256.17)	5.18 (4.16-6.63)	2,087
DAAs+ 40% HR	203.04 (154.68-270.65)	5.13 (4.11-6.59)	2,166
DAAs + 50% HR	208.33 (159.69-276.90)	5.10 (4.09-6.56)	2,167
Double DAAs cost ($8,000)			
No Intervention (status quo)	114.90 (62.50-188.88)	5.53 (4.48-7.00)	--
DAA only	202.06 (155.26-266.19)	5.23 (4.21-6.69)	2,898
DAAs+ 20%HR	237.44 (189.34-307.00)	5.18 (4.16-6.63)	3,454
DAAs+ 40% HR	270.30 (219.22-339.42)	5.13 (4.11-6.59)	3,819
DAAs + 50% HR	284.26 (229.49-354.59)	5.10 (4.09-6.56)	3,928
5% HCV-infected PWID accessing care			
No Intervention (status quo)	22.98 (12.50-37.78)	5.53 (4.48-7.00)	--
DAA only	86.63 (77.00-99.84)	5.23 (4.21-6.69)	2,116
DAAs+ 20%HR	124.79 (110.21-141.89)	5.18 (4.16-6.63)	2,869
DAAs+ 40% HR	161.39 (140.97-182.92)	5.13 (4.11-6.59)	3,402
DAAs + 50% HR	178.06 (153.86-202.82)	5.10 (4.09-6.56)	3,597
100% HCV-infected PWID accessing care			
No Intervention (status quo)	459.59 (250.01-755.53)	5.53 (4.48-7.00)	--
DAA only	496.78 (308.72-750.70)	5.23 (4.21-6.69)	1,237
DAAs+ 20%HR	536.03 (347.01-798.02)	5.18 (4.16-6.63)	2,154
DAAs+ 40% HR	572.97 (382.75-838.89)	5.13 (4.11-6.59)	2,787
DAAs + 50% HR	589.54 (397.69-858.60)	5.10 (4.09-6.56)	3,014
Discount rate (0%)			
No Intervention (status quo)	219.98 (119.66-361.62)	13.31 (10.82-16.93)	--
DAA only	279.41 (189.82-402.63)	12.51 (10.03-16.11)	744
DAAs+ 20%HR	326.99 (236.89-455.26)	12.42 (9.96-16.02)	1,205
DAAs+ 40% HR	372.21 (280.12-503.72)	12.34 (9.88-15.93)	1,568
DAAs + 50% HR	392.59 (296.77-524.16)	12.30 (9.85-15.89)	1,713

Table S3.2 Sensitivity analyses of alternative intervention scenarios showing ICER of each scenario compared to no intervention (status quo), Continued. DALY: Disability-adjusted life years; CI: Confidence interval; ICER: Incremental cost-effectiveness ratio; HR: Harm reduction; DAA: Direct-acting antiviral treatment; HCV: Hepatitis C virus.

	Mean cost (millions)	Mean DALYs (hundred thousand)	
Intervention Scenario	**Total (95% CI)**	**Total (95% CI)**	**ICER ($ per DALY averted) compared to status quo**
Discount rate (6%)			
No Intervention (status quo)	71.43 (38.85-117.42)	2.73 (2.22-3.43)	--
DAA only	125.11 (95.58-165.90)	2.61 (2.10-3.30)	4,238
DAAs+ 20%HR	156.78 (126.19-200.90)	2.57 (2.07-3.27)	5,240
DAAs+ 40% HR	187.16 (152.31-231.22)	2.53 (2.04-3.23)	5,828
DAAs + 50% HR	201.05 (162.71-246.72)	2.52 (2.02-3.21)	6,004
Time horizon (20 years)			
No Intervention (status quo)	66.44 (38.85-117.42)	1.82 (1.46-2.27)	--
DAA only	129.86 (102.19-167.61)	1.77 (1.42-2.21)	13,587
DAAs+ 20%HR	167.70 (137.72-209.02)	1.73 (1.38-2.18)	11,736
DAAs+ 40% HR	203.89 (168.45-246.13)	1.69 (1.34-2.13)	10,885
DAAs + 50% HR	220.32 (182.01-264.77)	1.67 (1.32-2.11)	10,514
Simplified model of care costs			
No Intervention (status quo)	114.90 (62.50-188.88)	5.53 (4.48-7.00)	--
DAA only	149.22 (102.27-213.76)	5.23 (4.21-6.69)	1,141
DAAs+ 20%HR	190.06 (142.88-259.25)	5.18 (4.16-6.63)	2,118
DAAs+ 40% HR	229.85 (178.71-298.89)	5.13 (4.11-6.59)	2,825
DAAs + 50% HR	248.70 (193.91-319.01)	5.10 (4.09-6.56)	3,103
No screening and diagnostic costs			
No Intervention (status quo)	114.90 (62.50-188.88)	5.53 (4.48-7.00)	--
DAA only	172.01 (125.12-236.67)	5.23 (4.21-6.69)	1,899
DAAs+ 20%HR	210.51 (162.81-279.79)	5.18 (4.16-6.63)	2,695
DAAs+ 40% HR	247.35 (196.26-316.46)	5.13 (4.11-6.59)	3,255
DAAs + 50% HR	264.11 (209.36-334.39)	5.10 (4.09-6.56)	3,460

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CHAPTER 4. Cost and cost-effectiveness of a real-world HCV treatment program among HIV-infected individuals in Myanmar

ABSTRACT

Background: Over half of those coinfected with hepatitis C virus (HCV) and HIV live in low- and middle-income countries (LMICs), and many remain undiagnosed or untreated. In 2016, Médecins Sans Frontières (MSF) established a direct-acting antiviral (DAA) treatment program for people co-infected with HCV and HIV in Myanmar. We evaluated the real-world cost and cost-effectiveness of this program.

Methods: Costs (patient-level micro-costing) and treatment outcomes were collected from the MSF prospective cohort study in Dawei, Myanmar. A Markov model was used to assess cost-effectiveness of the program compared to no HCV treatment from a health provider perspective. Estimated lifetime and healthcare costs (in 2017 US$) and health outcomes (in disability-adjusted life-years [DALYs]) were simulated to calculate the incremental cost-effectiveness ratio (ICER), compared to a willingness-to-pay threshold of the per capita GDP in Myanmar ($1,250). We additionally evaluated potential cost-effectiveness with updated quality-assured generic DAA prices, or with a proposed simplified treatment protocol with updated DAA prices, implemented by the Ministry of Health (task shifting, fewer visits, local staff, no coordination).

Results: From 11/2016 to 10/2017, 122 HCV/HIV coinfected patients were treated with DAAs (46% cirrhotic), 96% (n=117) achieved sustained virologic response (SVR). Mean treatment costs were $1,229 (non-cirrhotic) and $1,971 (cirrhotic), with DAA drug as the largest contributor to cost. Compared to no treatment, the program was cost-effective (ICER $634/DALY averted); even more so with updated prices for quality-assured generic DAAs (ICER $488/DALY averted). A simplified protocol delivered by the Ministry of Health could be cost-effective if associated with similar outcomes (ICER $316/DALY averted).

Conclusions: DAA treatment for HCV infection among HIV-coinfected individuals is cost-effective in Myanmar, and even more so with recently updated DAA prices. A simplified treatment protocol could enhance cost-effectiveness if further rollout demonstrates it is not associated with worse treatment outcomes.

Lay summary: We evaluated the real-world cost and cost-effectiveness of HCV direct-acting antiviral treatment for HCV/HIV-coinfected individuals in Myanmar. We found the program cost-effective. A simplified treatment protocol could enhance cost-effectiveness if not associated with worse treatment outcomes.

INTRODUCTION

Among people living with hepatitis C virus (HCV) infection, coinfection with HIV can lead to accelerated liver cirrhosis, liver cancer, and death compared to those with HCV monoinfection [1-3]. Globally, an estimated 6.2% of people living with HIV show serologic evidence of HCV antibody (2.3 million individuals), the majority residing in low-middle income countries (LMICs) [4]. In Myanmar, an estimated 5.3% of the 222,000 HIV-infected individuals are HCV-seropositive [5-7], but in the Southern township of Dawei, Myanmar, HCV seroprevalence rises to 8% among people living with HIV (data unpublished), and as high as 23% among male HIV-infected fisherman [8].

Promisingly, HCV treatment with new direct-acting antivirals (DAAs) is highly effective among HCV/HIV-coinfected individuals (>90% cure rate) [9]. Yet the previous high cost of DAAs restricted many individuals in LMICs settings from accessing treatment in these highest burdened areas [10]. Few studies have evaluated the cost-effectiveness of HCV treatment in LMIC settings where health care management of liver disease and costs of providing DAA treatment differ dramatically from high-income countries. Existing evaluations are limited to theoretical analyses of DAA-containing regimens for HCV monoinfection in Egypt, India, Pakistan, and Thailand; and have not evaluated real-world program implementation costs or cost-effectiveness [11-14]. Evaluating real-world HCV treatment programs in low-income settings is critical to designing and implementing cost-effective HCV treatment programs to achieve the global HCV elimination targets set by the World Health Organization as it provides real data of current programs which allows a better understanding of which components are driving cost and where cost savings can be made [15].

In 2016, Médecins sans Frontières (MSF) began a UNITAID-funded HCV treatment program within an HIV cohort in Dawei, Myanmar using interferon-free DAA-based regimens, and in 2018, obtained updated prices for quality-assured generic DAAs [16]. With programmatic

experience treating HCV/HIV coinfected patients in Dawei, MSF subsequently proposed a simplified HCV treatment protocol as a potential HCV model of care that aligns with the 2017 Myanmar Ministry of Health (MoH) National Hepatitis Guidelines.

In this study, we evaluate the cost of providing DAA treatment in the MSF program and assess the cost-effectiveness of the program compared to no treatment among HCV/HIV coinfected patients in Myanmar. We additionally evaluate the potential cost-effectiveness of HCV treatment using generic DAAs and the proposed simplified treatment protocol. To our knowledge, this is the first study to conduct a full costing and cost-effectiveness analysis of a real-world HCV treatment program for HIV-infected individuals in a LMIC.

METHODS

Setting and model of care

The MSF-Dawei HIV clinic was established in 2004, targeting patients in Dawei and the entire Thanintharyi Division in Southern Myanmar. In 2014, MSF began screening for HCV within the MSF-Dawei HIV clinic, initially providing interferon-based treatment. In late 2016, a UNITAID-funded prospective cohort study evaluating interferon-free HCV regimens with DAAs was initiated in the clinic. Within the MSF-Dawei clinic, there were 73 local staff members and 2 expatriate staff. Data including patient characteristics, outcomes, and costs were collected from this UNITAID study, which was part of a larger multi-center cohort study to evaluate the effectiveness and cost-effectiveness of HCV screening and treatment programs in LMIC [17].

We assessed costs and outcome data among chronically HCV-infected (HCV RNA-positive) patients from the MSF-Dawei HIV cohort initiated on interferon-free DAA treatment between November 2016 and October 2017. There were no restrictions on treatment eligibility by HCV disease stage or substance use criteria. Prior to initiation, patients underwent liver disease staging and testing for co-morbidities. Patients were classified by METAVIR stage (F0,

F1, F2, F3, F4) based on transient elastography with those classified as having cirrhosis (F4) if they had a liver stiffness measure of ≥11kPa. Decompensated cirrhosis was defined as liver stiffness ≥11kPa and Child-Pugh score ≥6 based on values for HCV/HIV coinfected patients [18]. All patients were screened for hepatocellular carcinoma (HCC) via abdominal ultrasound. Patients were treated with sofosbuvir+daclatasvir (SOF+DAC) without or with ribavirin (RBV) as per the 2015 European Association for the Study of the Liver (EASL) recommendations [19]. During treatment, patients returned every 2-4 weeks (or more frequently, if necessary) for routine clinical monitoring and biological testing (**Figure 4.1**). Patients were evaluated for sustained virologic response (SVR), defined as a negative HCV RNA test 12 or more weeks after the end of treatment. Patients were considered as lost to follow-up if they did not return within two months after a scheduled appointment and were not noted as dead or transferred out. Intention-to-treat SVR rates were calculated that included patients who were lost to follow-up or died.

Costing methods

Overall costing approach: We performed a patient-level micro-costing analysis of HCV treatment delivery from a program provider's perspective, incremental to the standard twice-yearly HIV visits. Data on costs were obtained from MSF's financial records, receipts, and price lists from a 12-month period (January 2017-December 2017), when the majority of the HCV-related costs were incurred. Records prior to 2017 were used to allocate a proportion of capital equipment costs obtained in previous years based on expected service lives estimated by interviewing local staff. Using an ingredients approach, patient-level resource use (in terms of type and frequency of visit) was combined with cost information for each patient interaction type. Patient-level data on number and type of visits, clinical examinations, laboratory investigations, treatment regimens, and treatment outcomes were extracted from electronic medical records [20]. Resources were valued from MSF financial records, invoices, price lists and additionally

informed through interviews with key staff (finance, logistics, pharmacy manager, medical activity manager). We present costs stratified by HCV-related visit components, HCV-related lab costs, DAA costs, and coordination costs, as described below. Results are presented in 2017 US dollars.

HCV-related visit components: HCV-related visits were classified as: (1) *pre*-treatment (2) *on*-treatment, and (3) *post*-treatment as per the MSF protocol (**Figure 4.1**). All HCV-related labs costs were excluded from visit costs and costed separately (see below). Each HCV visit included personnel time specific to the visit (patient-interacting and administrative time, determined by staff diaries), space/materials depending on which area of the clinic was utilized (laboratory, medical, counseling, pharmacy), and proportion of usage for HCV treatment. For each location, the visit cost incorporated recurrent costs (general personnel costs, medicines (excluding HCV), medical and laboratory supplies, non-medical supplies, transport operating costs, building rental and insurance, maintenance, utilities and bills, freight and clearance, travel, and training) and capital costs (buildings, vehicles, medical equipment including Fibroscan transient elastography machine, laboratory equipment including GeneXpert real-time PCR system, cold chain equipment, non-medical equipment, construction and rehabilitation, and furniture). Building space for each location visit was determined through site maps and visual inspection and allocated as HCV-related by determining the proportion of all consultations which were HCV-related from records. Personnel effort by visit type was determined by general staff category (coordination, nursing, medical doctor, individual counselling, pharmacy, registration, human resources, support staff), involvement in HCV-related activities and allocated to proportion of staff, budget, floor space, or consultations. Group counselling for HCV treatment, in which patients shared HCV treatment experiences and served as a discussion group for treatment preparation (including counselling on HCV infection, transmission,

encouragement for family testing, lifestyle, treatment, and monitoring plan) was costed separately.

HCV-related laboratory costs: Costs of HCV-related laboratory investigations as per the MSF protocol (**Figure 4.1**) were obtained from invoices and price lists.

DAA costs: Unit costs were determined from MSF invoices (**Supplementary Table S4.1**). Patient-specific DAA costs were calculated based on observed length of treatment and treatment regimen.

Coordination costs: Per visit MSF coordination costs were included from the local coordination site (Dawei) and country coordination (Yangon) using a top-down method. (see supplementary material). For Dawei, HCV-related coordination costs were estimated through obtaining the remaining personnel, recurrent and capital costs associated with the HCV program, after extracting specific costs attributable to direct HCV visits by type. For Yangon, coordination costs included the proportion of personnel effort attributed to the Dawei program by staff type and non-personnel costs (e.g. all HCV-related activities) and were allocated as a proportion of the total budget.

Cost-effectiveness methods

Disease progression model: We developed a compartmental, deterministic Markov model of liver disease progression in a closed cohort of diagnosed HCV/HIV coinfected adults (**Supplementary Figure S4.1**), based on the liver disease distribution in the MSF cohort (**Supplementary Table S4.2**). We simulated disease progression through each stage of HCV-related hepatic fibrosis (METAVIR stages F0, F1, F2, F3), compensated cirrhosis (CC, METAVIR F4), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC). Liver-related mortality was assumed to only occur from DC or HCC. The model did not include liver transplantation, as this is not commonly performed in Myanmar. The model was additionally stratified by treatment history and outcome (untreated, treated and cured, or treated and failed).

Individuals with F3 or milder liver disease who were treated and achieved SVR were assumed not to have further liver fibrosis progression. Those with CC, DC, or HCC who were treated and achieved SVR could progress to more severe liver disease states or liver-related death but at reduced rates. We assumed those who achieved SVR cannot be re-infected. The model was developed in Matlab R2018a.

Disease progression rates and mortality: Liver disease state transition probabilities (**Supplementary Table S4.3**) were based on previous studies among HCV/HIV coinfected individuals which suggests faster acceleration to more advanced hepatic fibrosis stages and mortality among HCV/HIV co-infected individuals off ART compared to HCV/HIV co-infected individuals on ART [1, 21-26]. Background (non-HCV related) mortality rates were estimated given the CD4 count distribution, ART status of the cohort, and estimated life expectancy based on mean age of the cohort weighted by sex ([27] see supplement).

Costs: HCV treatment and routine HIV care and treatment costs were obtained through our patient-level analyses. Due to a lack of information available on patient access to care for advanced liver disease associated with HCV outside of the HIV Clinic, for the baseline analysis we utilize estimates of HCV related disease management costs from similar income settings (Cambodia), adjusted for Gross Domestic Product (GDP; **Supplementary Table S4.3**).

Health utilities: Health outcomes were evaluated in disability-adjusted life-years (DALYs). Health disutilities for HIV and liver disease stages were obtained from the Global Burden of Disease (**Supplementary Table S3**) [28] and coinfection disutility values calculated as: [1-((1-HIV disability weight)x(1-HCV disability weight)] [26].

Cost-effectiveness analyses: We evaluated the cost-effectiveness of HCV treatment for HCV/HIV infected individuals compared to no HCV treatment. We evaluated the following treatment protocol scenarios:

- "Observed MSF": Data from observed full MSF protocol from the implemented UNITAID HCV DAA study in 2016/17, utilizing 2017 DAA prices.
- "MSF updated DAA cost": Costs estimated from full MSF protocol, but with updated DAA prices based on the outcomes of the MSF HCV tender for quality-assured generic DAAs (reduces 12-weeks SOF+DAC from US$493 to US$120) negotiated after the study in 2018.
- "Simplified MoH": We estimate costs of a simplified treatment protocol (as proposed by MSF to the Myanmar MoH after the study in 2018, **Figure 4.1**) if implemented by the MoH. The simplified protocol reduced the number of visits and laboratory measurements and incorporated partial task-shifting from doctors to nurses. To represent implementation by the MoH, we also use local staff costs (26% less expensive than current staff costs), no MSF coordination costs, quality-assured generic DAA prices, and updated HCV test costs (previously OraQuick rapid test, and now SD Bioline HCV rapid test resulting in a ~US$5 reduction per test). We simulate cost-effectiveness of the proposed simplified protocol assuming the same SVR as observed with the full protocol.

The model was run for 100 years, with cost and utilities discounted at 3%/year. To account for parameter uncertainty, we performed a probabilistic sensitivity analysis, sampling 1000 parameter sets from parameter distributions (**Supplementary Table S4.3**). We calculated the mean incremental cost-effectiveness ratio (ICER, mean incremental costs divided by mean incremental DALYs averted) for the intervention compared to no treatment. Interventions with an ICER less than a willingness-to-pay (WTP) threshold of one-times per capita GDP of Myanmar (US$1250 in 2017) were considered cost-effective [29, 30].

One-way sensitivity analyses: We performed several one-way sensitivity analyses on the ICER for each of the “Observed MSF”, “MSF updated DAA cost”, and “Simplified MoH” strategies compared to no treatment. We varied the discount rate (0% and 6% compared to 3% at baseline), time horizon (20 and 50 years versus 100 years at baseline), SVR rate (90% and 98% versus 96% at baseline), initial distribution of fibrosis stage (30% and 60% patients with cirrhosis versus 46% at baseline), HCV/HIV coinfection disutility values (lower and upper bounds versus mean values at baseline), transient elastography costs (cost in Cambodia observed with higher volume of use compared to Dawei: $4 compared to $115), reinfection among those who achieved SVR (5%/year versus 0% at baseline), no cost for care for all hepatic fibrosis stages (versus F0:$0; F1: $35; F2: $80; F3: $137; F4: $207; DC: $314; HCC: $378 at baseline), no coordination cost (versus $98 for patients without cirrhosis and $142 for patients with cirrhosis at baseline), and accelerated liver disease progression among patients with GT3 (HR:1.31 for cirrhosis [95% CI 1.22-1.39]; HR: 1.80 for HCC [95% CI 1.61—2.03] [31]; among 56% of patients). Additionally, for the “Simplified MoH” strategy we examine task shifting to nurse-led care only during treatment, reducing overall physician interactions by 56% (9 visits vs 4; and nurse interaction by 66% from 6 interactions to 2).

HCV screening and treatment sensitivity analyses: Because screening occurred several years prior to the UNITAID intervention, our base case evaluates the cost-effectiveness of the DAA treatment program only. For a sensitivity analysis, we explored the cost-effectiveness of a combined screening and treatment program for the “Simplified MoH” scenario compared to no screening and treatment across various HCV seroprevalences (0.5%-10%), reflecting likely geographical heterogeneity across Myanmar. We estimated associated screening costs based on testing yields for each prevalence scenario, assuming HCV antibody testing using the SD Bioline HCV rapid test (US$2.33) and GeneXpert HCV RNA test (US$21.09) with staff costs included.

This study was approved by the MSF Ethical Review Board and the Ethical Review Committee of the Department of Medical Research (Lower Myanmar).

RESULTS

Treatment outcomes

From November 2016 to October 2017, 122 HIV-infected patients (mean age 43) were treated with DAAs (56/122 (46%) with cirrhosis [CC or DC]). No HCC was detected among those treated or untreated. Roughly half of the treated cohort were genotype (GT) 3 (51%), followed by GT1 (46%), and GT6 (3%). Of these, 96% (n=117) achieved SVR. The majority of patients with cirrhosis (n=50; 89%) were treated with 24 weeks of SOF+DAC, but 6 were treated with 12 weeks of SOF+DAC+RBV resulting in lower costs (All 6 patients achieved SVR; GT1:n=1; GT3: n=4; GT6: n=1). Of those who did not achieve SVR (n=5), 1 died, 1 did not complete treatment, and 3 completed treatment. There was no difference in SVR by liver fibrosis stage (**Supplementary Table S4.2)**.

Treatment delivery cost

The average cost of HCV treatment per patient was $1,229 (95%CI $848-1,829) for patients without cirrhosis and $1,971 (95%CI $1,307-2,686) for patients with cirrhosis (**Supplementary Figure S4.2**). Variations in cost were predominantly due to differences in durations of treatment and drug regimens, with minor differences in monitoring. DAA drug cost was the largest cost component, and main driver of difference in cost by liver disease stage (without cirrhosis: $524 vs with cirrhosis: $1,122; **Table 4.1**). The second largest driver of cost was laboratory costs, with minimal difference by liver disease stage (without cirrhosis: $421 vs with cirrhosis: $437). Of these laboratory costs, transient elastography costs comprised $115, which was high because of the initial purchase price (~US$49,037) and relatively low usage

(159 measurements in 2017). Visit costs were the third largest contributor to cost (breakdown by visit type in **Supplementary Table S4.4)**. Within the personnel component of visit costs, 61% of the personnel costs were due to physician costs (3 local, 1 foreign), as the protocol incorporated physician-led treatment. Coordination costs were on average $98 per treatment for patients without cirrhosis and $142 per treatment for patients with cirrhosis (45% from Dawei, and 55% from Yangon; see supplement for details).

Updated quality-assured generic DAA costs were obtained after the end of our study ($120 for 12 weeks of SOF/DAC before MSF-overhead charges (**Supplementary Table S4.1**). With these updated costs, the total estimated DAA costs when incorporating RBV (included in 54% of treatments) were $184 for 12 weeks, $453 for 24 weeks, reflecting variations in dose). With these costs, based on the observed treatment protocol, the total cost per treatment would be $889 for patients without cirrhosis and $1,302 for patients with cirrhosis (**Table 4.1**)**.** In this scenario, the highest contributors to overall cost would be the laboratory and monitoring costs.

Cost-effectiveness of HCV treatment among HIV-infected Individuals

The “Observed MSF” treatment program (mean treatment costs: $1,229 (patients without cirrhosis), $1,971 (patients with cirrhosis)) resulted in an average incremental cost of $2,121 per patient treated including annual HIV care costs (**Supplementary Table S3.5**), and 3.35 DALYs averted per patient. This led to a mean ICER of $634/DALY averted compared to no treatment, cost-effective compared to a WTP threshold of one-times the per capita GDP of Myanmar ($1,250) (**Table 4.2**). In this analysis, 100% of the simulations fell under the WTP threshold.

The “MSF updated DAA cost” analysis (with updated DAA prices, mean treatment cost $889 (patients without cirrhosis), $1,302 (patients with cirrhosis)) produced a mean ICER of $488/DALY averted compared to no treatment, cost-effective under the WTP threshold (all simulations fell under the WTP threshold).

Finally, a “Simplified MoH” strategy (also with cheaper drugs) could result in substantial reductions in treatment cost (patients without cirrhosis: $417, patients with cirrhosis: $601), and if resulting in equal treatment outcomes, could be highly cost effective (mean ICER $316 DALY averted compared to no treatment, all simulations fell under the WTP threshold).

One-way sensitivity analyses

The “Observed MSF” treatment program remained cost-effective across all scenarios, if the discount rate was reduced to 0% or increased to 6%, there were no cost of care for hepatic fibrosis stages, coordination costs were excluded, GT3 patients were assumed to have accelerated liver disease progression, transient elastography costs were decreased, there was a time horizon of 20 or 50 years, they achieved a reduced SVR rate, there was different disutility estimates were used, cirrhosis prevalence varied, or reinfection rate was 5%/year (**Figure 4.2**).

The “MSF updated DAA cost” and “Simplified MoH” scenarios remained cost-effective for all sensitivity analyses (**Supplementary Figure S4.3 and S3.4)**.

Screening and treatment sensitivity analyses

A combined screening and treatment program among HIV-infected individuals implemented by the MoH using the Simplified MoH strategy could be cost-effective at the all HCV seroprevalences examined, including the lowest prevalence (0.5%; ICER: $489), below the national monoinfection estimate (2.7%), and the 8% observed among HIV-infected individuals in Dawei (ICER: $334; **Supplementary Figure S4.5**) [6].

DISCUSSION

Main findings

We used observational data from an HCV treatment study to show that DAA treatment among HCV/HIV-coinfected patients in Myanmar is cost-effective, particularly with quality-assured generic DAAs. Moreover, a simplified model of care (proposed by MSF to the Myanmar MoH, incorporating fewer visits and task shifting) implemented by the MoH with local staff could be highly cost-effective (ICER <$400/DALY averted compared to no treatment), if not associated with worse treatment outcomes, and could be cost-effective if combined with a HCV screening program among HIV-infected individuals. These findings hold even with lower than observed (90%) SVR rates and reinfection rate was 5% per year. With quality-assured generic DAAs, treatment remained cost-effective even over 20-year time horizons.

The majority of treatment costs in our study were comprised of DAA costs in 2017, which were negotiated to lower prices after the study period in 2018 by the MSF Supply Centers and MSF Access campaign ($120 for 12-week course) [16], underscoring the importance of generic competition to reduce drug prices and improve access to HCV treatment. The cost of transient elastography also contributed markedly to cost of treatment delivery because of the high purchase price and low annual use. These costs could be reduced if used in a higher volume clinic or if non-invasive methods for determining hepatic fibrosis were used (e.g., Fibrosis-4 Index for Hepatic Fibrosis (FIB-4), aspartate aminotransferase (AST)-to-platelet ratio index (APRI), or FibroSure).

Comparisons with existing literature

To our knowledge, our study is the first to evaluate the real-world costs and cost-effectiveness of DAA treatment in an implemented HCV treatment program among HIV-infected individuals in a LMIC setting. However, our study supports previous analyses indicating that HCV treatment is likely cost-effective in LMIC settings where DAAs are available at low costs.

One study in Egypt found that implementing an HCV screening program with interferon (IFN)-based DAA therapy compared to no screening would be cost-effective [11]. Compared to IFN-based therapy, IFN-free DAA therapy is superior in efficacy, shorter treatment duration, and better tolerability [32-35], yet in many settings historically more costly, though costs continue to fall [36, 37]. Similarly, two cost-effectiveness studies in India showed that implementing HCV screening and treatment with generic DAAs would be cost-saving within about a decade, but these studies did not utilize programmatic treatment delivery or outcome data [12, 38]. Importantly, none of these studies, ours included, incorporated data on access to health care, which may be low in LMIC, and therefore it is possible that treatment is less cost-effective than estimated if fewer medical costs are associated with untreated HCV infection. While our sensitivity analyses indicated that HCV treatment remained cost-effective with no cost of care for hepatic fibrosis stages, further work is warranted to assess real-world medical utilization for liver disease in LMIC.

Strengths and limitations

The main strength of our study is that it was based on real-world programmatic costs and outcome data. However, as with all modelling studies, there were numerous uncertainties in the parameter values. Nevertheless, we incorporated these uncertainties in our analysis, conducted sensitivity analyses, and our results were generally robust to most of these uncertainties. First, no patients in our cohort received additional care for HCV within the MSF-Dawei HIV clinic, but it was unknown whether they received care at other medical facilities and so was not included in our analysis. Future work in this area is warranted to refine our estimates.

Second, we utilized published data on disease progression from other settings, while it is unclear whether these are truly generalizable to Myanmar. Our baseline analysis did not simulate differential disease progression by genotype. Half our cohort was GT3, which has been

associated with accelerated liver disease progression in HCV-monoinfected individuals [31, 39, 40], yet it is unclear if this is true in HCV/HIV coinfection. A sensitivity analysis incorporating accelerated disease progression among GT3 patients improved the cost-effectiveness.

Third, reinfection rates among HIV-infected individuals in Myanmar are unknown, however we note that our analyses with quality-assured generic DAA prices indicated that treatment was cost-effective even with reinfection rates of 5%.

Fourth, although we used observational data for our main analysis ("Observed MSF"), our additional analyses examining a simplified model of care as proposed by MSF-Myanmar to the MoH. The MoH strategy assumed equal SVR rates and projected costs based on adherence to the planned visits and monitoring plan. Real-world data on costs and treatment outcomes are required to confirm these findings, although our sensitivity analyses show that treatment with generic DAA costs was cost-effective when including lower SVR and higher treatment costs, indicating that it is likely that our results would hold in other settings with worse treatment outcomes.

Finally, our study was based on data from a cohort receiving care from MSF in one setting (Dawei, Myanmar), so it is unclear whether our results are generalizable to the country or if scaled-up to the broader population of people living with HIV. Additionally, our treated cohort were all on ART with well-controlled HIV. Integrating HCV treatment into existing ART programs may be an effective strategy to reach HCV/HIV co-infected populations and should be considered.

CONCLUSION

In conclusion, treating HCV infection among HIV-infected individuals in Myanmar is cost-effective, with the potential of being even more cost-effective when utilizing a simplified protocol as long as this does not result in worse treatment outcomes. Access to affordable, quality-assured generic DAAs improved cost-effectiveness. Given our cost-effectiveness projections,

national programs in Myanmar and similar settings should no longer consider DAA cost a barrier, but rather consider these data along with simplified models of care as a means to cure people with HCV infection and progress towards WHO HCV elimination goals. While this study evaluated the current HCV treatment program implemented by MSF, these results can be informative to the MoH in Myanmar and other similar LMIC settings.

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FIGURES

Examination	Baseline (Pre-treatment)	Ongoing Monitoring (week of treatment)					Post-treatment follow-up (weeks)		
		Initiation	2	4	8	12	12	14	24
Consultation type									
Medical doctor	◆	◆	■	■	■	■	■	▲	▲
Nurse	■	■	■	▲	■	◆	■		
Counseling	◆	◆	◆	■	■	◆		▲	◆
Clinical and lab investigations									
HBsAg	◆								
CD4 count	◆					■			
HIV Viral load	◆								
ALT	◆		■	◆		■	■		
AST	◆								
Creatinine	◆		■	◆		■			
Haemoglobin	◆		■	■	■	■			
Platelets	◆								
Glucose	◆			■					
HCV Viral Load	◆					■	◆		
HCV genotype	■								
TSH	■					■			
INR	■								
Albumin	■			■		■			
Bilirubin total	■					■			
Pregnancy Test	◆			◆	■	◆	▲		
FibroScan	◆								

Legend ■ Full model of care ▲ Simplified model ◆ Both models of care

Figure 4.1 Treatment protocols for the MSF full model of care and simplified model of care for patients on a 12-week treatment regimen. Mandatory appointments shown, optional appointments excluded. ALT: Alanine aminotransferase; AST: aspartate aminotransferase; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; INR: international normalized ratio (coagulation test); TSH: thyroid stimulating hormone.

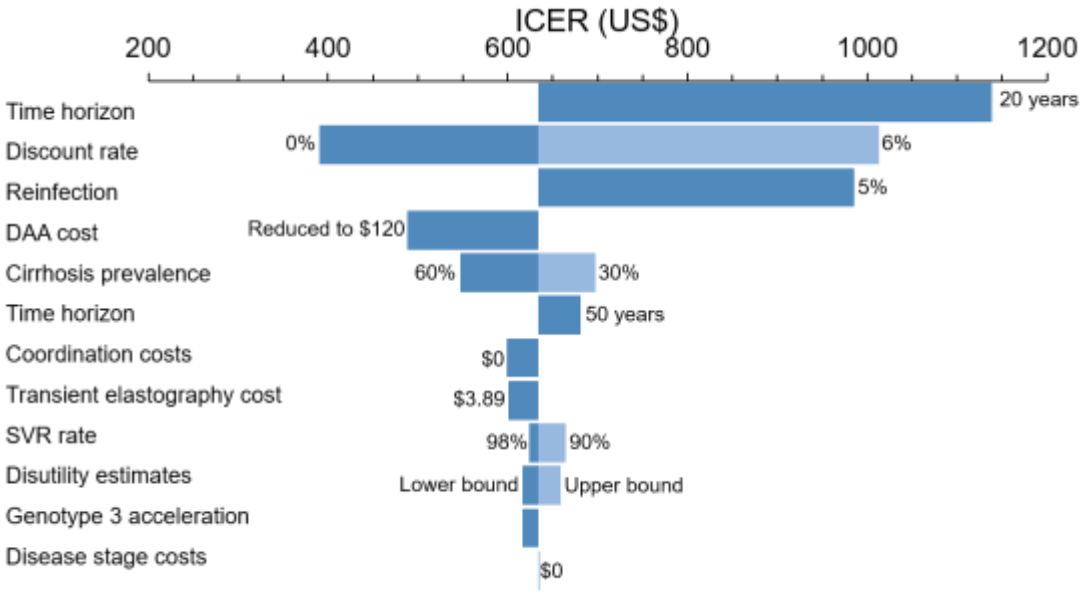

Figure 4.2 Sensitivity analysis of the cost-effectiveness of the "Observed MSF model of care with 2017 DAA costs compared to no treatment. DAA: direct-acting antiviral therapy; SVR: sustained virologic response at 12 weeks. ICER: incremental cost-effectiveness ratio. Costs shown in US dollars. The reduced fibroscan cost (US$3.89) scenario reflects the fibroscan cost estimated in similar income country setting with higher volume (GDP adjusted cost from Cambodia, US$2017; $4.31). Dark and light blue bars displayed when two values of a parameter were examined and resulted in ICER values lower and above the baseline ICER value (US$634).

TABLES

Table 4.1 Cost of HCV treatment by component type among HIV-infected individuals in Myanmar, with the "Observed MSF" treatment protocol and proposed alternative protocols. Costs in 2017 US$. [a]"Observed MSF intervention" presents summary data from observational study, including 2017 DAA prices. [b]"MSF with updated DAA costs" estimates costs with updated DAA prices for quality-assured generic DAAs negotiated in 2018. [c]"Simplified MoH" strategy estimates costs with generic DAAs and a proposed simplified protocol (Figure 1), with local staff costs and no overheads. 95% confidence intervals are presented for the observed cost data reflecting patient variations in observed costs. For estimations of costs using updated cost data or simplified strategies, patients were assumed to adhere to the exact clinical schedule (see Fig 1) and so no uncertainty is provided. Non-cirrhotic: METAVIR F0-F3, cirrhotic: F4 as measured by transient elastography.

	HCV visit costs per patient	HCV laboratory costs per patient	DAA costs per patient	HCV coordination costs per patient	Total HCV treatment costs per patient
Observed MSF intervention[a]					
Non-cirrhotic	186.60 (95%CI 158.65-292.94)	420.80 (95%CI 194.80-718.94)	523.53 (95%CI 411.60-663.81)	97.60 (95%CI 82.74-153.66)	1228.53 (95%CI 847.79-1829.35)
Cirrhotic	270.47 (95%CI 225.45-419.17)	436.73 (95%CI 251.62-697.04)	1122.01 (95%CI 711.58-1349.37)	141.84 (95%CI 118.20-220.15)	1971.05 (95%CI 1306.85-2685.72)
MSF with updated DAA costs[b]					
Non-cirrhotic	186.60	420.80	183.69	97.60	888.69
Cirrhotic	270.47	436.73	453.02	141.84	1302.06
Simplified MoH[c]					
Non-cirrhotic	80.92	216.33	120	-	417.25
Cirrhotic	89.54	271.25	240	-	600.79

Table 4.2 Incremental cost-effectiveness of HCV treatment among HIV-infected individuals in Myanmar compared to no treatment, as observed and with proposed simplified protocols and newly negotiated DAA costs. Estimates for interventions include cost of annual HIV care and treatment. [a]"Observed MSF intervention" presents summary data from observational study, including 2017 DAA prices. [b]"MSF with updated DAA costs" estimates costs with updated DAA prices for quality-assured generic DAAs negotiated in 2018. [c]"Simplified MoH" strategy estimates costs with generic DAAs and a proposed simplified protocol (Figure 1), with local staff costs and no overheads.

	Cost (US$ 2017) per capita		**DALYs per capita**		**ICER mean**
Strategy	Total mean (95%CI)	Incremental mean compared to no treatment (95%CI)	Total mean (95%CI)	Incremental mean compared to no treatment (95%CI)	$/DALY averted compared to no treatment
No treatment	3,991.71 (3,133.86, 4,955.87)	-	21.89 (20.77, 22.92)	-	-
Observed MSF treatment program[a]	6,112.72 (5,019.45, 7,170.54)	2,121.01 (1,885.59, 2,214.67)	18.54 (17.48, 19.50)	-3.35 (-3.29, -3.42)	633.60
MSF program with updated DAA costs[b]	5,624.94 (4,550.21, 6,738.39)	1,633.23 (1,416.35, 1,782.52)	18.54 (17.48, 19.50)	-3.35 (-3.29, -3.42)	487.89
Simplified MoH strategy[c]	5,050.30 (4,009.81, 6,128.90)	1,058.59 (875.95, 1,173.03)	18.54 (17.48, 19.50)	-3.35 (-3.29, -3.42)	316.23

SUPPLEMETARY INFORMATION TO CHAPTER 4

1.1 Valuation of coordination costs

Yangon coordination: To determine the proportion of the Yangon country coordination budget attributable to the HCV treatment program in Dawei, we first separated out the budget which was attributable to the full Dawei program. First, we divided the total MSF Yangon budget into personnel and non-personnel. Staff interviews were performed to determine what proportion of personnel effort was attributable to the Dawei program, by staff type. The personnel budget was allocated accordingly by multiplying the personnel costs for each staff type by their stated proportion effort attributable to Dawei. Non-personnel costs were allocated to the Dawei program as a proportion of the total budget (e.g. roughly 45% of the total budget was comprised of Dawei costs).

Among the Yangon budget estimated to be attributable to Dawei coordination, we estimated what proportion of these costs were associated with HCV-related activities based on the proportion of all consultations in Dawei which were for HCV treatment in 2017 (14%). We then divided the Dawei HCV program coordination budget estimate by the number of HCV consultations in 2017 to obtain a per HCV consultation Yangon coordination cost ($5.23/consultation).

Dawei Coordination: The Dawei HCV-related coordination costs were estimated through obtaining the remainder of the personnel, recurrent and some capital costs (shared office supplies allocated to proportion of staff) associated with the HCV program, after extracting specific costs attributable to direct HCV visits by type (e.g. laboratory visit, pharmacy visit, etc.). Some capital costs were fully allocated to coordination, such as general support items including cold chain and energy equipment, furniture, spare parts for vehicles, and construction/rehabilitation costs for building maintenance. The per HCV consultation coordination cost was obtained from dividing the total HCV-related Dawei coordination cost by the number of HCV consultations ($6.59/consultation).

1.2 Valuation of GeneXpert for HCV-related activities

GeneXpert costs were first costed separately by capital costs, personnel costs, consumables, and overheads. Since the GeneXpert was utilized to test for HIV and tuberculosis in addition to HCV, we multiplied shared costs by the proportion of HCV viral load tests performed in 2017 out of the total number of tests run on the GeneXpert for 2017. HCV viral load tests performed internally using the GeneXpert accounted for 29% of the total number of tests performed on the GeneXpert at the MSF-Dawei clinic in 2017.

1.3 Background (non-HCV related) mortality rate calculation

As all patients were on ART at HCV treatment initiation, we estimated a weighted background non-HCV related mortality rate based on the CD4 cell count distribution among the cohort at HCV treatment initiation (stratified by <200, 200-350, 350-500, >500 cells/μL, see **Supplementary Table S4**), and expected survival on ART by stage, assuming a 3-4 fold increase in lifespan if on ART [1, 2]. With this calculation, the estimated average lifespan *excluding* HCV-related mortality among the HIV infected cohort was 30 years, only slightly less (3-4 years) than the expected lifespan among the general population in Myanmar. The background death rate was then calculated as 1/weighted life expectancy.

1.4 HCV/HIV coinfection disability weights calculation

HCV/HIV coinfection disability weights were calculated as [1-((1-HIV disability weight)*(1-HCV disability weight))]. We obtained relevant disability weights from the WHO Global Burden of Disease Study 2013 [3]. For the HIV disability weight for this analysis, we use the disability weight for ART (0.078), as all were on ART in the treatment cohort. Disability weights for DC (0.178) and HCC (0.451) were obtained directly from the GBD. No disability weights were available for HCV METAVIR stages, so the weight for mild abdominopelvic problem (0.011) was used for stages F0/F1, moderate abdominopelvic problem (0.114) was used for CC, and the midpoint between these two values was used for F2 (0.063) [3, 4].

SUPPLEMENTARY FIGURES

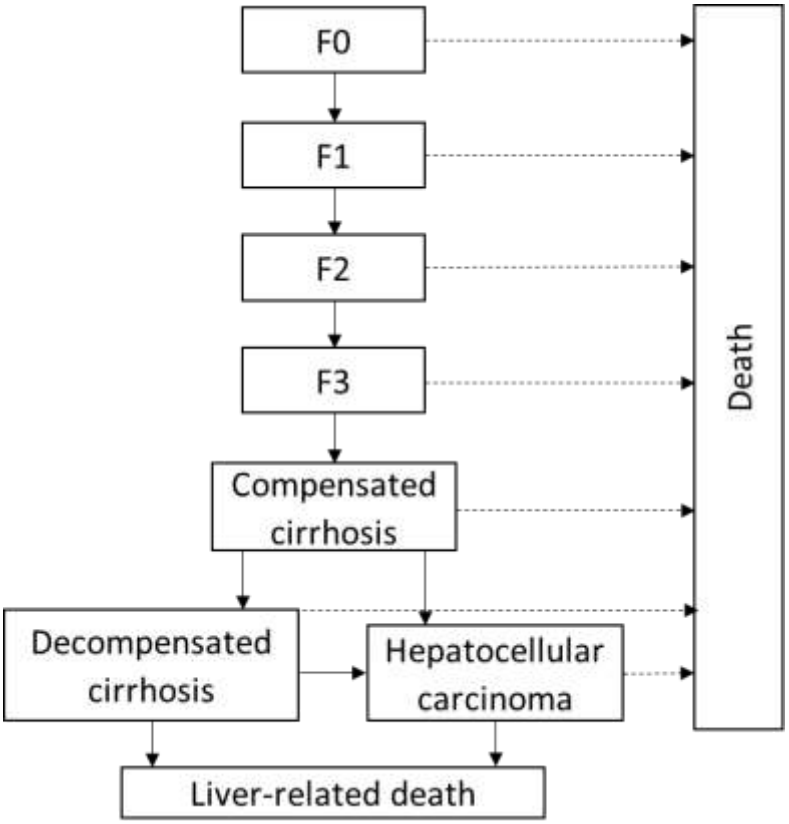

Figure S4.1 Schematic of Markov model showing natural chronic HCV disease progression by liver disease states and treatment success. For those who are cured (achieve SVR), liver disease progression is reduced. F0-F3 are METAVIR hepatic fibrosis scores determined by transient elastography (<11.0 kPa); Cirrhosis: METAVIR score≥11.0 kPa; Decompensated cirrhosis: METAVIR score≥11.0 kPa and Child-Pugh score ≥6. Hepatocellular carcinoma was determined by abdominal ultrasound.

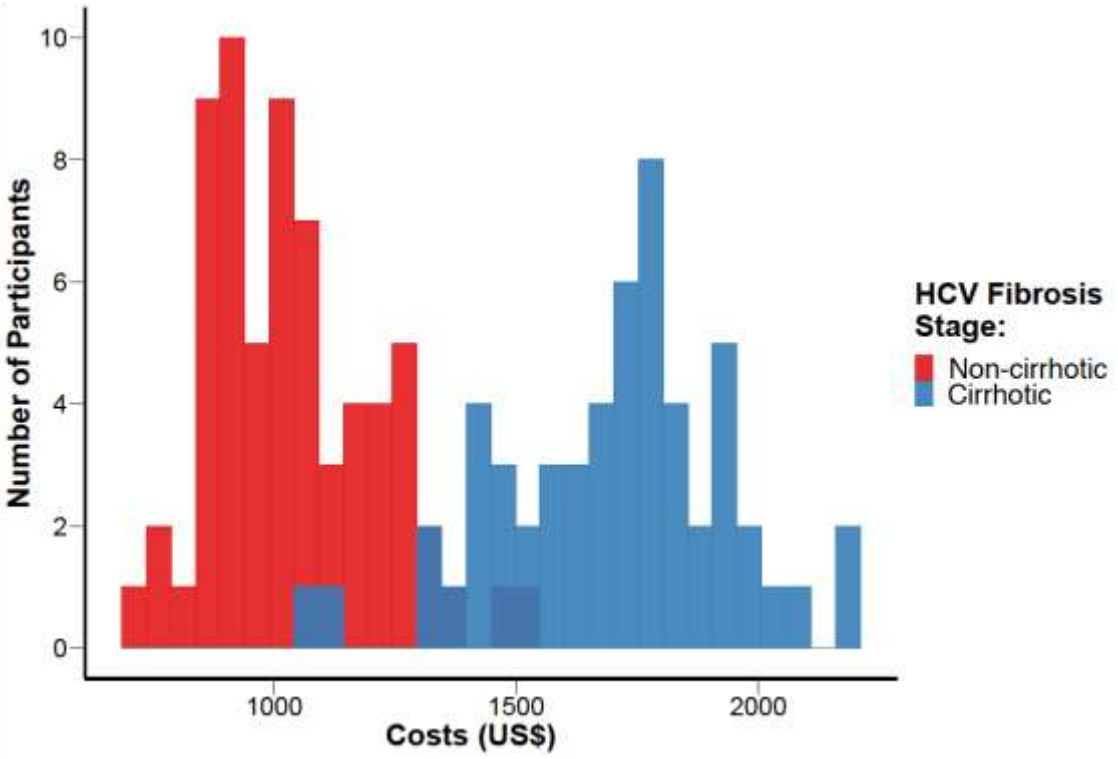

Figure S4.2 Distribution of patient-level HCV treatment costs (in 2017 US$) by liver disease stage among HIV-infected individuals in Dawei, Myanmar. Non-cirrhotic includes F0-F3, defined by METAVIR scores determined by transient elastography (<11.0 kPa); Cirrhotic includes CC: compensated cirrhosis (≥11.0 kPa); DC: decompensated cirrhosis (≥11.0 kPa and Child-Pugh score ≥6).

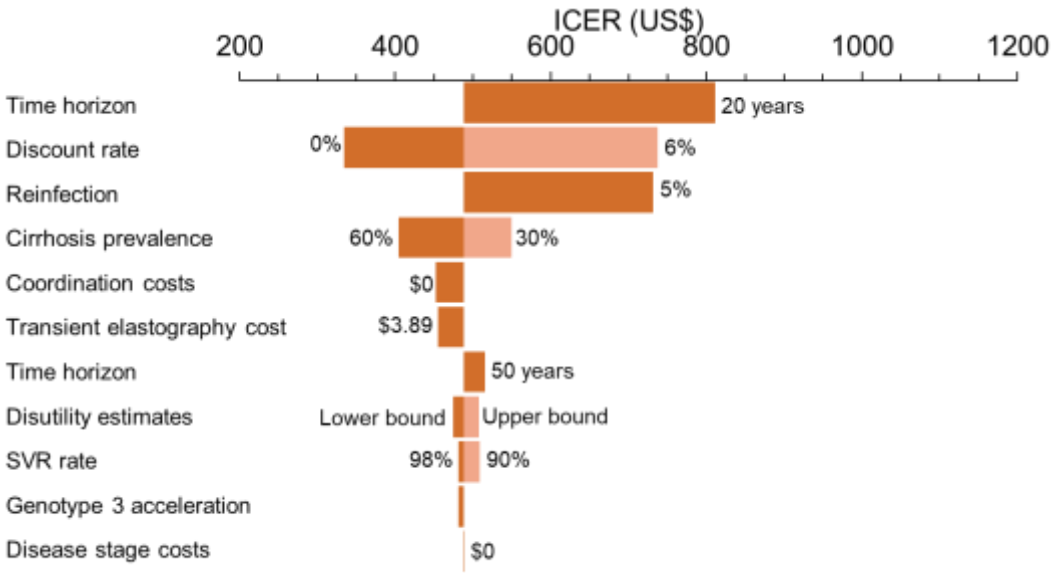

Figure S4.3 Sensitivity analysis of the cost-effectiveness of the "MSF updated DAA cost" model of care with 2018 DAA Access drug costs. 12-week Sofosbuvir/Daclatasvir treatment cost: US$120; 24-week Sofosbuvir/Daclatasvir treatment cost: US$240. DAA: direct-acting antiviral therapy; SVR: sustained virologic response at 12 weeks. Baseline parameter values are shown in Table 1. Fibroscan cost (US$3.89) reflects fibroscan cost estimated in similar setting (Cambodia, US$2017; $4.31; GDP-adjusted (Myanmar, US$1250/Cambodia, US$1385). Dark and light orange bars displayed when two values of a parameter were examined and resulted in ICER values lower and above the baseline ICER value (US$488).

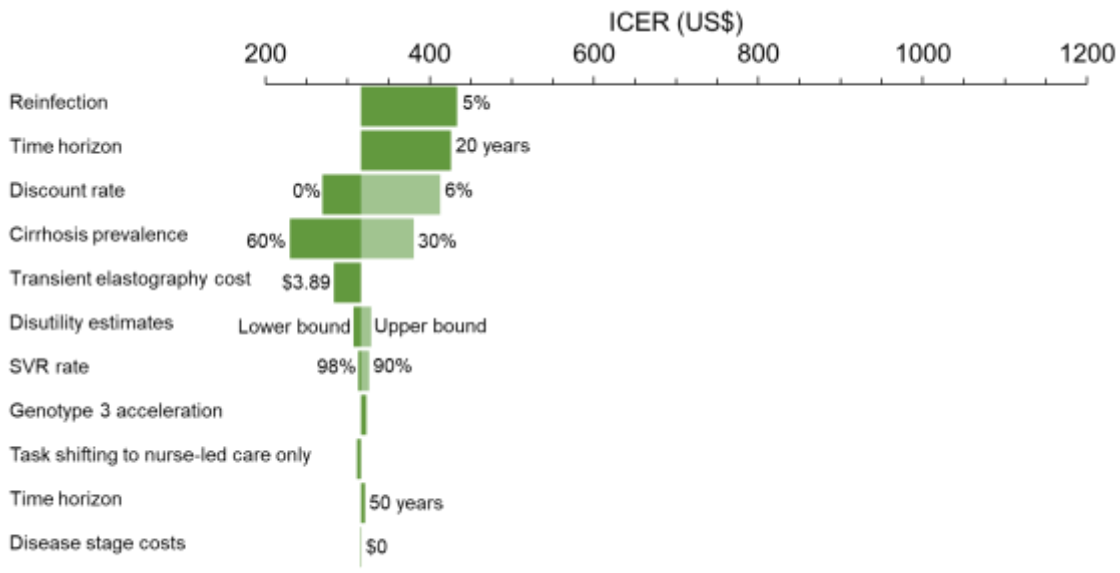

Figure S4.4 Sensitivity analysis of the cost-effectiveness of the "Simplified MoH" model of care with 2018 DAA costs. DAA: direct-acting antiviral therapy; SVR: sustained virologic response at 12 weeks. Task shifting to nurse-led care increased nurse-led consultations by 3 times. Dark and light green bars displayed when two values of a parameter were examined and resulted in ICER values lower and above the baseline ICER value (US$316).

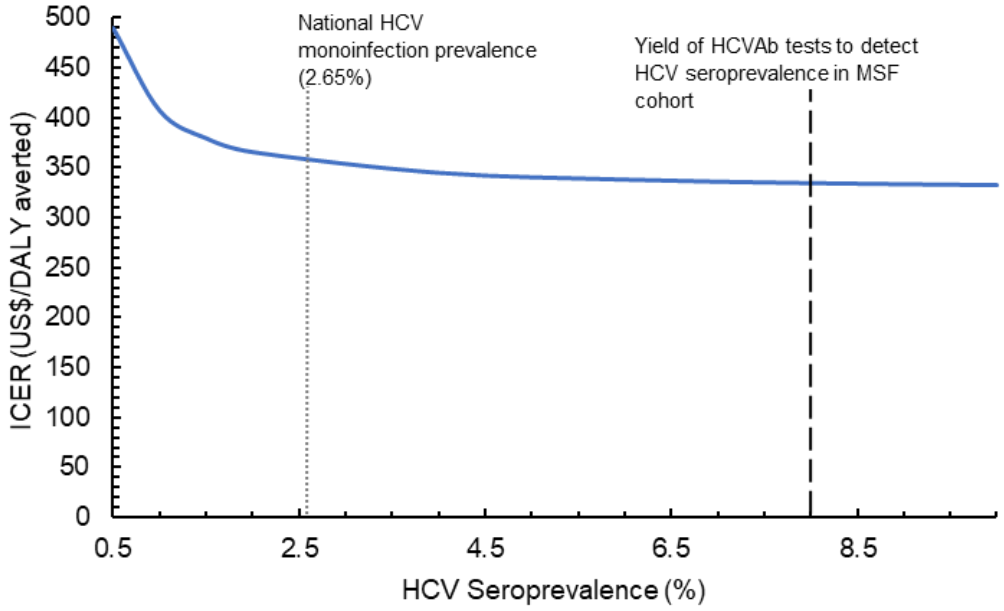

Figure S4.5 Incremental cost-effectiveness ratio (ICER) for HCV screening and treatment among HIV-infected individuals compared to no screening for various HCV seroprevalences. HCV treatment protocol examined is the proposed Myanmar Ministry of Health HCV treatment strategy. MSF cohort HCV seroprevalence (HCV Ab-positive) was 8%. ICER: incremental cost-effectiveness ratio; DALY: disability-adjusted life years; HCV: hepatitis C virus; Ab: antibody; MSF: Médecins sans Frontières.

SUPPLEMENTARY TABLES

Table S4.1 Unit cost in US$ of HCV therapy by drug type. 2017 drug costs are based on costs obtained from MSF invoices, which include MSF overhead charges. Updated unit drug costs from the Access campaign shown for sofosbuvir (400mg) and daclatasvir (60mg), excluding MSF overhead costs. *Ribavirin was not included in the Access campaign, but was prescribed in the “Observed MSF” intervention. Costs for Ribavirin were only included in the “Observed MSF” and “MSF with updated DAA costs” scenarios.

HCV treatment drug	2017 Cost	2018 Cost
Sofosbuvir (400mg)	3.52	1.04
Daclatasvir (60mg)	1.38	0.39
Ribavirin (200mg)	0.35	0.35*

Table S4.2 HCV treatment outcomes by liver fibrosis stage among cohort of HIV-infected patients in Dawei, Myanmar initiated on DAA treatment from 11/2016-10/2017. F0-F3 are METAVIR scores determined by transient elastography (<11.0 kPa); CC: compensated cirrhosis (≥11.0 kPa); HCV: hepatitis C virus; SVR: sustained viral response at 12 weeks; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma

HCV disease stage	N (% of total)	Number achieved SVR	SVR rate by HCV stage	Number failed treatment, lost-to-follow-up, or died
F0	39 (32%)	37	94.5%	2
F1	9 (7%)	8	88.9%	1
F2	6 (5%)	5	83.3%	1
F3	12 (10%)	11	91.7%	1
CC	54 (44%)	54	100%	0
DC	2 (2%)	2	100%	0
HCC	0 (0%)	0	-	0
Total	122 (100%)	117	95.9%	5

Table S4.3 Economic model parameters and their distributions. HCV: hepatitis C virus; SVR: sustained virologic response; ART: antiretroviral therapy; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; GDP: gross domestic product. *2017 USD$

Variable	Sampled Value mean (95%CI)	Distribution and input parameters	Source
HCV disease stage costs* (annual)			
No hepatic fibrosis – F0	0	-	[5, 6] No Myanmar data; 2017 costs from Cambodia (unpublished) for F0-CC adjusted by GDP (Myanmar GDP $1250)/ (Cambodia GDP $1385); Minimum/maximum values ±50% point estimate. Multiplier of 5.3 used from Cambodia cohort data for DC calculation; 6.5 for HCC.
Mild hepatic fibrosis– F1	34.87 (18.88, 51.85)	Uniform (min=17.64, max=52.92)	
Moderate hepatic fibrosis – F2	80.45 (41.89, 117.55)	Uniform (min=39.85, max=119.55)	
Severe hepatic fibrosis – F3	137.03 (71.72, 199.60)	Uniform (min=67.62, max=202.86)	
Compensated cirrhosis (F4, CC)	206.93 (109.23, 301.92)	Uniform (min=102.25, max=306.75)	
Decompensated cirrhosis (DC)	313.51 (161.53, 460.81)	Uniform (min=156.70, max=470.10)	
Hepatocellular carcinoma (HCC)	378.09 (202.34, 561.70)	Uniform (min=191.47, max=574.42)	
HIV care costs (annual)			
HIV care visit cost	191.70 (154.69, 227.36)	Uniform (min=152.74, max=229.12)	Dawei Cohort, including visit and ARV drug costs. See Table S4 for specific ARV costs. Bounds ±20% point estimate
Transition rates			
F0 to F1 (per year)	0.122 (0.094, 0.155)	Gamma (shape=61.95, scale=.00197)	[7]
F1 to F2 (per year)	0.115 (0.091, 0.142)	Gamma (shape=84.64, scale=0.00136)	[7]
F2 to F3 (per year)	0.124 (0.091, 0.16)	Gamma (shape=50.21, scale=0.0025)	[7]
F3 to CC (per year)	0.115 (0.096, 0.134)	Gamma (shape= 132.25, scale=0.0009)	[7]
CC to DC (per year)	0.039 (0.022, 0.062)	Beta (alpha=14.6168, beta=360.1732)	[4, 8-11] Transition probability sampled, converted to rate
CC or DC to HCC (per year)	0.015 (0.002, 0.04)	Beta (alpha=1.19326, beta=136.1074)	[4, 8-12] Transition probability sampled, converted to rate

Table S4.3 Economic model parameters and their distributions, Continued. HCV: hepatitis C virus; SVR: sustained virologic response; ART: antiretroviral therapy; CC: compensated cirrhosis; DC: decompensated cirrhosis; HCC: hepatocellular carcinoma; GDP: gross domestic product. *2017 USD$

Variable	Sampled Value mean (95%CI)	Distribution and input parameters	Source
Relative risk of CC to DC with SVR	0.078 (0.023, 0.190)	Lognormal (mean 0.07, 95%CI 0.03-0.2)	[13, 14]
Relative risk of CC/DC to HCC with SVR	0.236 (0.151, 0.352)	Lognormal (mean 0.23, 95%CI 0.16-0.35)	[15]
Background (non-HCV related) mortality	0.0336 (0.0292, 0.0378)	Uniform (min=0.029, max=0.038)	[1, 2] Weighted by CD4 status at HCV treatment initiation (Table S3), with all patients on ART as per cohort. See supplement for details.
Relative risk of DC to liver-related death in HIV/HCV coinfection compared to HCV monoinfection	2.3 (1.57, 3.38)	Lognormal (mean 2.26, 95%CI 1.51-3.38)	[4, 16-18]
DC to liver-related death for HCV monoinfection	0.130 (0.111, 0.150)	Beta (alpha=147.03, beta=983.97)	[8, 9] Transition probability sampled, converted to rate
HCC to liver-related death	0.429 (0.370, 0.482)	Beta (alpha=117.1, beta=155.23)	[4, 19-21] Transition probability sampled, converted to rate
SVR	96%	-	Dawei cohort
Discount rate	3%	-	[22]
Disability weights			
HCV/HIV coinfection (no SVR)			
F0/F1	0.088	-	Calculated as [1-((1-HIV disability weight) *(1-HCV disability weight))] using ART disability weight as all on ART in cohort. See supplement for details. [3, 4]
F2/F3	0.136	-	[4, 23]
Compensated cirrhosis (CC)	0.183	-	[3, 4]
Decompensated cirrhosis (DC)	0.242	-	[3, 4]
Hepatocellular carcinoma (HCC)	0.494	-	[3, 4]
HCV/HIV coinfection (achieved SVR)			
Disutility improvement on achieving SVR	0.045 (0.04, 0.05)	Uniform (min=0.05, max=0.05)	[24-26]

Table S4.4 Average unit cost in 2017 US$ of an HCV visit to Dawei clinic by cost category and visit component. Distribution of visit component by cost category expressed as row percentage. HCV: hepatitis C virus.

	Cost category		
Visit component	**Recurrent cost (%)**	**Personnel cost (%)**	**Capital cost (%)**
General coordination	20.31 (59.0)	13.46 (39.1)	0.66 (1.9)
HCV consultation	0.75 (65.2)	0.20 (17.7)	0.19 (17.1)
Laboratory	2.83 (90.5)	0.26 (8.4)	0.04 (1.2)
Pharmacy	0.22 (59.6)	0.13 (34.6)	0.02 (5.8)
HCV counselling	0.48 (74.2)	0.13 (20.2)	0.04 (5.6)

Table S4.5 Cost components by intervention scenario. [a]"Observed MSF intervention" presents summary data from observational study, including 2017 DAA prices. [b]"MSF with updated DAA costs" estimates costs with updated DAA prices for quality-assured generic DAAs negotiated in 2018. [c]"Simplified MoH" strategy estimates costs with generic DAAs and a proposed simplified protocol (Figure 1), with local staff costs and no overheads. HCV treatment costs are assumed to be standard for all patients ($120/12-week treatment course of sofosbuvir/daclatasvir for non-cirrhotic patients; $240/24-week treatment course of sofosbuvir/daclatasvir for cirrhotic patients). 95% confidence intervals are presented for the observed cost data reflecting patient variations in observed costs. For estimations of costs using updated cost data or simplified strategies, patients were assumed to adhere to the exact clinical schedule (see Fig 1) and so no uncertainty is provided. MSF: Médecins sans Frontières; DAA: direct-acting antiviral treatment; MoH: Ministry of Health; CI: confidence interval.

	Per patient cost (95% CI)		
Strategy	**HCV treatment**	**HIV treatment**	**HCV disease stage**
Baseline	0	2,306.63 (1,785.13, 2,868.67)	1,685.08 (1,106.88, 2,367.23)
Observed MSF treatment program[a]	1,563.92 (1,309.88, 1,855.96)	2,866.59 (2,252.05, 3,520.34)	1,682.21 (1,030.56, 2,346.50)
MSF program with updated DAA costs[b]	1,076.13 (870.05, 1,314.11)	2,866.59 (2,252.05, 3,520.34)	1,682.21 (1,030.56, 2,346.50)
Simplified MoH[c]	501.50	2,866.59 (2,252.05, 3,520.34)	1,682.21 (1,030.56, 2,346.50)

Table S4.6 HIV characteristics of study participants at baseline enrollment (n=121). WHO HIV staging categories defined as: Stage 1: Asymptomatic; Stage 2: mildly symptomatic; Stage 3: moderately symptomatic; Stage 4: severely symptomatic/AIDS [27].TDF: Tenofovir (300mg daily); 3TC: Lamivudine (300mg daily); EFV: Efavirenz (600mg daily); AZT: Zidovudine (300mg twice daily); NVP: Nevirapine (200mg twice daily); ABC: Abacavir (600mg daily); LPV/r: Kaletra/ Lopinavir/Rionavir (400mg/100mg twice daily);

Characteristic	n	%
CD4 Count (cells/μL) upon HCV treatment initiation		
<200	13	10.7
200-350	23	18.9
350-500	24	19.7
>500	62	50.8
WHO HIV staging at HIV care enrollment		
Stage 1	10	8.3
Stage 2	20	16.5
Stage 3	73	60.3
Stage 4	17	14.1
Unknown	1	0.8
HIV treatment regimen		
AZT + 3TC + NVP	19	15.7
AZT + 3TC + EFV	5	4.1
TDF + 3TC + EFV	84	69.4
ABC + 3TC + EFV	3	2.5
LPV/r + 3TC + AZT	5	4.1
TDF + 3TC + LPV/r	4	3.3
AZT + TDF + 3TC + LPV/r	1	0.8

Table S4.7 Unit cost in US$ of HIV therapy by drug type. 2017 drug costs are based on costs obtained from MSF invoices, which include MSF overhead charges. TDF: Tenofovir (300mg daily); 3TC: Lamivudine (300mg daily); EFV: Efavirenz (600mg daily); AZT: Zidovudine (300mg twice daily); NVP: Nevirapine (200mg twice daily); ABC: Abacavir (600mg daily); LPV/r: Kaletra/ Lopinavir/Rionavir (400mg/100mg twice daily)

ARV regimen	2017 Cost (Annual)
AZT+3TC+NVP	34.23
AZT+3TC+EFV	54.32
TDF+3TC+EFV	79.40
ABC+3TC+EFV	152.45
LPV/r+3TC+AZT	239.63
TDF+3TC+LPV/r	219.00
AZT+TDF+3TC+LPV/r	301.08

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CHAPTER 5: CONCLUSIONS

HCV infection is a leading cause of morbidity and mortality, globally, with the greatest burden occurring in LMICs [1-3]. However, some of the key populations for HCV transmission such as PWID and HIV-infected individuals face numerous challenges to screening, diagnosis, and treatment, thus further propagating HCV epidemics globally. Both PWID and HIV-infected individuals are marginalized populations which often face barriers to basic healthcare access, stigma and discrimination within the healthcare setting [4, 5], and a historically low level of awareness about HCV testing and treatment [6, 7]. Furthermore, in many LMICs, PWID and HIV-infected individuals face additional challenges to accessing HCV screening and treatment due to limited healthcare infrastructure for HCV testing, poor laboratory capacity including limited staff and testing materials, limited HCV surveillance programs, and in some settings, a lack of guidance for testing or absence of national HCV testing strategies and funding [8]. Currently, the WHO global HCV elimination goals aim for an 80% reduction in incidence and 65% reduction in HCV-related mortality by 2030, thus creating an ideal avenue to draw attention to the high burden of HCV in these populations, and needs of these resource-limited settings to address this public health issue. Yet the most cost-effective way to achieve the HCV elimination goals and to expand HCV treatment programs is unknown in most LMIC settings. To inform public health planning, this dissertation used infectious disease and economic modeling to further our understanding of the costs, cost-effectiveness, and population impact of HCV treatment and prevention programs in two LMIC settings (Mexico and Myanmar).

In Chapter 2, we evaluated various HCV intervention strategies including HCV treatment alone and in combination with evidence-based harm reduction interventions (OAT and HCNSP) to identify the most effective elimination strategies among PWID in Tijuana, Mexico. We used an HCV transmission and prevention model to project the impact of scaled-up combination interventions on HCV incidence and HCV-related mortality, in order to determine which levels of

scale-up of intervention and in which combination could achieve the WHO HCV global elimination goals among PWID in Tijuana. While we determined that HCV elimination among PWID in Tijuana can be achieved using treatment with DAAs alone with an estimated 770 (95% CI 640-970) treatments per year prioritized to current PWID, scaling up OAT+HCNSP in addition to DAAs decreases the total number of treatments required per year. Scale-up to 50% OAT+HCNSP+DAAs required 40% fewer treatments per year compared to DAAs alone to achieve HCV elimination. A combination intervention approach may be the most feasible option as current allocation of HCV treatment across Mexico is limited and thus a combination strategy would reduce the number of DAAs required to achieve elimination goals. Further, harm reduction interventions provide multiple other benefits such as preventing overdose [9] and HIV transmission [10, 11]. Finally, and a growing concern, is that existing compulsory abstinence programs could hamper elimination efforts by increasing syringe sharing and thus increasing the risk for HCV transmission. Our findings showed that DAAs scaled up with CAP required the greatest number of treatments per year, making it the least feasible intervention option given the resource constraints mentioned above.

In Chapter 3, we evaluated the cost-effectiveness of scale-up of various HCV elimination strategies needed to reach the WHO HCV incidence elimination goal among PWID in Tijuana, Mexico. We adapted the model developed in Chapter 2 to incorporate valuation of costs and health stages, and used this economic dynamic model to evaluate cost-effectiveness HCV portfolios which could achieve the 80% reduction in HCV incidence target by 2030. We found that all elimination portfolios were cost-effective in Tijuana. Although combination prevention strategies (incorporating treatment and harm reduction) were more costly than treatment with DAAs alone, they provided more health benefits overall, underscoring the substantial benefit combination approaches can have on improving health among PWID in Tijuana, and Mexico more broadly.

In Chapter 4, we evaluated the cost-effectiveness of a real-world HCV treatment implementation trial among HIV-infected individuals in Dawei, Myanmar. We assessed the real-world cost of treatment using micro-costing methods. We then developed an HCV treatment and disease progression model among HIV-infected individuals to assess the cost-effectiveness of DAAs for HCV/HIV-coinfected individuals compared to no treatment from a health provider perspective. We found that DAA treatment for HCV infection among HIV-coinfected individuals was cost-effective in Myanmar, even more so with recently negotiated DAA prices. We additionally found that a simplified treatment protocol as proposed to the Myanmar Ministry of Health could enhance cost-effectiveness if not associated with poorer treatment outcomes.

Dissertation strengths

To our knowledge, Chapter 2 was the first modeling study to project the level of combination interventions required to achieve the WHO HCV global elimination goals among PWID in a LMIC setting. Additionally, Chapter 3 was novel in that it was also the first study to evaluate cost-effectiveness of combination elimination strategies in Latin America, thus contributing to a significant gap in knowledge and much needed evidence to better recommend impactful interventions among PWID in Tijuana and in Mexico. As the first country in Latin America to pledge their efforts and resources to eliminate HCV, our studies aim to inform policymakers and programmatic changes to help Tijuana and Mexico accomplish these goals. Finally, Chapter 4 was the first to evaluate the cost-effectiveness of HCV DAA treatment among HIV-infected individuals in a LMIC setting. A strength of our analysis was that it was based on real-world programmatic costs and outcome data of an implemented HCV screening and treatment program in a LMIC setting.

Dissertation limitations

There are several overall limitations to this dissertation research. First, as all of our analyses involve transmission and disease progression modeling, and as with all modeling studies, there are limitations in the uncertainty of the parameters. For example, HCV seroprevalence in Tijuana and overall risk population estimates (i.e. total number of PWID in Tijuana) are highly uncertain as the populations included in the underlying epidemiological studies which formed the basis of our parameterization are transient and may be difficult to locate, may have expired from a competing illness or condition such as overdose, leaving those with high adherence, those in close proximity, and potentially neglecting those with trouble accessing and locating care and treatment, those suffering from other health conditions and disabilities and more. As a result, these studies may not capture those at highest risk for HCV transmission. However, the finding that >90% of participants show a history of HCV infection indicates that HCV transmission is widespread and the burden is extremely high, so our results are robust to this uncertainty. However, our results in terms of treatment numbers were sensitive to overall PWID population size estimates, which merits further study. Another key piece of uncertainty were costs for untreated HCV disease stages in both Mexico and in Myanmar. Given a lack of data, we adjusted costs derived from data collected in a micro-costing study in Cambodia for disease stage costs in our Myanmar analysis and for HCV treatment delivery in Mexico as this data was not available. In Mexico, disease stage costs from a 2005 HCV treatment cost-effectiveness study [12] were utilized for decompensated cirrhosis and hepatocellular carcinoma but inflated to current prices as they were similar to costs in other studies. However, for chronic HCV, our cost estimate was based on data from Peru, Colombia, Brazil [13], and the United Kingdom [14]. Overall, to address these and other uncertainties, we sampled all parameters from underlying uncertainty distributions, generating many (1000s) of parameter sets and therefore propagating this parameter uncertainty into our future modeling

projections. Additionally, we performed numerous one-way sensitivity analyses to account for variation in parameters and model assumptions. In doing so, we found that our results were robust to most uncertainties, and noted where the results were sensitive, meriting further study.

Second, we recognize there are several limitations to our models. We developed deterministic, compartmental models for our studies. These models neglect to account for networks structure and network effects, thus potentially limiting the understanding of the impact of individual behaviors, including individuals who may be more high risk than others. Our models for Tijuana neglect additional health benefits to the proposed interventions, such as the impact on harm reduction strategies on the prevention of HIV transmission and fatal overdose. Additionally, the proposed harm reduction interventions in Tijuana are limited to those with histories of injection drug use and thus do not consider the impact of transmission on other populations aside from PWID. The models also fail to consider the additional benefits of HCV prevention, such as improved economic productivity due to reduced disease burden and reduced disability-adjusted life years incurred. We suggest the development of more complex models to account for these numerous benefits as well as further research to evaluate other socio-economic benefits that could result from implementing these proposed interventions. Furthermore, our cost-effectiveness models neglect to consider costs or logistical complications that arise in developing infrastructure and strengthening health systems and capacity which is required in order to achieve the proposed intervention scale-up scenarios. Additional work is warranted here to quantify these costs, incorporate them into the model, and to re-evaluate the cost-effectiveness of the implementation of interventions under these revised details. Finally, our models are limited in that they are quantitatively driven and focused. Thus, we do not account for patient preferences towards interventions or delivery of services. We suggest that further mixed-methods and qualitative research is performed to evaluate this.

Third, our analyses were limited to LMICs and thus the results may not be generalizable to other income settings or to settings with different epidemiologic profiles (i.e. varying prevalences, type of HCV epidemic, mode of transmission, risk population). For example, our work focused on PWID and HIV-infected individuals, however, in some settings such as in Egypt, HCV epidemiology is very different in that the epidemic is highly disseminated within the general population, and a large proportion of its HCV transmission occurred between 1950 and 1980 from national treatment campaigns using unsterilized intravenous injections against schistosomiasis [15]. In settings such as Egypt, where the HCV epidemic is highly disseminated within the community or in other settings where HCV transmission largely stems from general community risks, rather than being driven by PWID, strategies required to achieve the HCV elimination goals may require focusing intervention efforts and resources on other key populations aside from those considered in our analyses. In other settings where PWID are the primary high-risk population for HCV transmission, combination DAA and harm reduction intervention scale-up are still likely to be effective in reducing the HCV transmission and burden, as has been projected in numerous countries across Europe [16]. Furthermore, our results are consistent with those modeled in other prevalence settings [16, 17], where similar treatment rates (50 per 1,000 PWID) scaled with various OAT and NSP coverage levels results in a reduction of at least 50% in under 10 years in the highest chronic prevalence settings and results in an even greater reduction in low chronic prevalence settings [16]. However, reinfection rates may vary greatly depending on prevalence and thus the threshold for treatment and harm reduction scale-up required to achieve HCV elimination may also vary as a result (i.e. higher number DAAs and scale-up needed in higher chronic prevalence, higher reinfection settings compared to lower chronic prevalence/lower reinfection settings). It is unclear if our results would apply to HCV epidemics that are not stable, as we have assumed in our model. In settings with increasing HCV epidemics, a greater number of treatments, retreatments, and

more substantial scale-up of harm reduction interventions (to levels in excess of 50%) would likely be required [18]. Conversely, in settings where the HCV epidemic is already decreasing among PWID, lower levels of interventions scale-up may be required or higher levels of intervention over a shorter period of time in order to achieve the HCV elimination goals. Another limitation to the generalizability of our findings include that HCV/HIV co-infected individuals are highly specific in that the progression to liver-related disease or mortality accelerates depending on coinfection and ART status. In Dawei, all of the HCV/HIV coinfected individuals were receiving ART therapy. However, it is unclear if our results would apply to HCV/HIV coinfected populations where ART coverage is low or zero, as there would be increased competing mortality from HIV.

Fourth, another limitation and overall challenge to cost-effectiveness research is the lack of established WTP thresholds and thus uncertainty with those defined to evaluate public health interventions. For example, a WTP of one time the per capita gross domestic product (GDP) of the corresponding country of interest, originally defined by the WHO Commission on Macroeconomics and Health, is used to provide a threshold to evaluate the cost-effectiveness of many public health interventions [19]. The rationale behind this threshold as stated by the WHO Commission on Macroeconomics and Health, was that it is if a given intervention resulted in a mean of at least one additional year of healthy life, per capita, then it was reasonable to spend the estimated value of a year of healthy life, per capita [20]. Additionally, as the per capita GDP WTP threshold was established from the following assumptions: non-health consumption, leisure time, longevity, and health-related quality of life—it is considered to be comparable to the value of statistical life and thus is representative of an individual's willingness to pay to extend their healthy life by one year [20]. Yet, these thresholds exist as recommendations, arising from both the financial value of an intervention as well as its estimated health benefits, within a specified setting, and thus are not intended to be used as the sole determining factor in deciding

whether or not to implement a given intervention [20]. More recently, this WHO definition has been criticized that (1) it may obscure the reality of implementing an intervention, ineffectively evaluating context and capacity within the given setting, (2) is seemingly arbitrary, (3) assumes that a country would pay linearly up to a valued threshold for a health benefit, and (4) neglects to sufficiently assess affordability of the proposed intervention within a given setting [21]. As an alternative to the WHO definition, using cost-effectiveness thresholds based on the purchasing power parity (PPP)-adjusted GDP has been suggested [22]. WTP thresholds based on PPP-adjusted GDP suggest that the WHO estimates are often too high and would not be recommended to determine the necessary allocation of resources [22]. As such, a true determination of cost-effectiveness is difficult. Further yet, the decision of which WTP threshold is best suited for a specific intervention may depend on whether the program funder and stakeholders are either domestic or international. Future investigation of PPP-adjusted GDP in lieu of the per capita GDP is needed to determine which WTP should be more widely recommended. Additionally, further research regarding WTP thresholds and the determination of cost-effectiveness is needed, particularly in LMICs such as Myanmar.

Public Health Implications

Overall, findings from this research can be used to advocate for evidence-based HCV screening and treatment programs among key HCV risk populations in LMICs. Our modeling indicates that even in very high burden settings such as Tijuana, HCV elimination could be achieved provided the forthcoming DAAs are widely available, scaled-up among both current and former PWID, and there is concomitant scale-up of harm reduction services. As such, our findings also highlight the need for affordable harm reduction services such as OAT, which is a major barrier in Tijuana and, emphasizes the need for continuous funding of harm reduction services including both OAT and HCNSP for PWID as disrupted funding for these programs may result in a rebound effect further hindering HCV elimination. Furthermore, there are multiple

sites in Mexico with concentrated HCV epidemics among PWID, including in other US border cities of Ciudad Juarez and San Luis Rio Colorado [23], further emphasizing the need for DAAs to be allocated to the PWID within these communities to halt HCV transmission. Additionally, implementing harm reduction interventions may result in additional benefits aside from reducing the risk of HCV transmission including reduced HIV transmission [10], fatal overdoses [9], and reincarceration [24]. Additionally, incorporating HCV screening and treatment alongside existing HIV screening and treatment services may allow for more rapidly integrated and disseminated establishment of HCV programs for HCV/HIV co-infected individuals, particularly in resource strained communities and settings. Finally, and as we have shown in both of our studies in Mexico and Myanmar, national programs in similar settings should no longer consider DAA cost a barrier, but rather consider these data along with simplified models of care as a means to cure people with HCV infection and progress towards WHO HCV elimination goals.

Future research

HCV elimination goals are achievable by 2030, even within high HCV prevalence settings, such as among PWID in Tijuana. This dissertation both identified and contributed to gaps in current literature by determining effective and cost-effective evidence-based intervention strategies that can achieve HCV elimination among PWID in a LMIC setting. Additionally, we contributed greatly to the cost literature, by performing a detailed, micro-costing study of an existing HCV treatment program among HIV-infected individuals, also in a LMIC setting. There are several suggestions for future research, building upon these analyses.

First, and critical to HCV elimination, is to examine other cities within the countries examined in our research (Mexico, Myanmar) as well as other LMIC countries facing different HCV epidemics in order to understand which interventions will be the most effective at achieving both setting-specific and overall HCV elimination. Results from these studies would improve intervention planning and resource allocation, but will need to be completed within the next few

years if the targets are going to be met on time. Second, as tailored interventions are implemented and scaled-up within key populations, additional modeling analyses will need to evaluate whether these programs are on track for HCV elimination. Similar modeling studies to that which recently evaluated the progress towards HCV elimination in Georgia, determined that current treatment rates as initially implemented through the national HCV program would not be sufficient in achieving the Georgian government's desired 90% prevalence reduction by 2020, but that Georgia is on track to achieve the WHO incidence and mortality elimination goals by 2030 [25]. Third, while the models developed in this dissertation neglected to account for heterogeneity across interventions, they are well-suited to address this. The HCV/HIV co-infected cohort in Dawei, Myanmar, included HIV-positive individuals on well-controlled antiretroviral therapy (ART), with high adherence rates. We recognize, however, that many HIV and HCV treatment programs in other settings may not have the same 'ideal' levels of adherence or may be less achievable. In order to provide a more complete picture of the impact of various levels of adherence on the scale-up of interventions proposed in this research, the current models could be adapted to examine the synergistic effects of treatment adherence levels and willingness of participants to accept a particular treatment or intervention. Results from those models would then provide levels of treatment and intervention scale-up that could extend to a variety of settings and programs. Lastly, there is an overall lack of cost data for HCV disease stages, screening, treatment, and care. Generally, detailed cost data is not collected or published which makes it difficult to evaluate current programs and propose new, cost-effective interventions. Future studies should aim to collect and publish current cost data in LMIC countries, in order to provide accurate, updated cost data to allow for future real-world costing and cost-effectiveness of these HCV elimination programs.

Conclusions

With the WHO HCV elimination goals driving the charge for HCV efforts globally, elimination cannot be met without prioritizing those within high risk communities, including PWID and HIV-infected individuals, and within high HCV burden areas, such as in LMICs. PWID and HIV-infected individuals face critical barriers to HCV screening, diagnosis, and treatment, particularly within these settings. Resources are not typically allocated for PWID, in particular, and recent funding cuts in Mexico to harm reduction interventions will hamper the HCV elimination goals among both PWID and HIV-infected individuals. Despite high prevalence of HCV among PWID in Tijuana, similar to other regions, local programs are often not tailored to the needs of their community. Among HIV-infected individuals, leveraging existing health infrastructure and HIV treatment programs to incorporate HCV treatment could further accelerate progress of disseminating HCV treatment to HCV/HIV co-infected individuals. An integrated screening and treatment approach may be a more feasible option as it would only require few additional resources, particularly in LMIC settings. Public health programs are urgently needed in these communities, implementing evidence-based, culturally appropriate programs which provide accessible and affordable screening, treatment, care, and prevention efforts. Furthermore, elimination efforts will be hindered without financial, political, and community investment in HCV programs [26].

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