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

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Abstract

Background and Aims—In Latin America, Mexico was first to launch a hepatitis C virus (HCV) elimination strategy, where people who inject drugs (PWID) are a main risk group for transmission. In Tijuana, HCV seroprevalence among PWID is >90% with minimal harm reduction (HR). We evaluated cost-effectiveness of strategies to achieve the incidence elimination target among PWID in Tijuana.

Methods—Modelling study using a dynamic, cost-effectiveness model of HCV transmission and progression among active and former 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 compared with 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 with one-time per capita GDP (\$9,698 in 2019) and purchasing power parity-adjusted per capita GDP (\$4,842–13,557) willingness-to-pay (WTP) thresholds.

Results—DAAs alone were the least costly elimination strategy (\$173M [95%CI 126M–238M]), but accrued fewer health benefits compared with strategies with HR. DAAs+50% HR coverage among PWID averted the most DALYs, but cost \$265M [95%CI 210M–335M]. The optimal

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strategy was DAAs+50% HR (ICER \$6743/DALY averted compared to DAAs only) under the one-time per capita GDP WTP (\$9,698).

Conclusions—A combination of high-coverage harm reduction and hepatitis C virus (HCV) treatment is the optimal cost-effective strategy to achieve the HCV incidence elimination goal in Mexico.

Keywords

HCV; people who inject drugs; cost-effectiveness; prevention; harm reduction; modeling

INTRODUCTION

People who inject drugs (PWID) are a main risk group 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 (HR) 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 direct-acting antivirals (DAAs) can cure >90% of PWID (7), and are cost-effective among the general population in several LMICs such as Egypt and India (8, 9). In addition to 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 become more affordable 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 (11–13).

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 (14, 15). Among PWID in Tijuana, Mexico (a city along the United States border) the seroprevalence of HCV is high (>90%), and HR coverage is low (<5%)(16, 17). Our previous analyses have shown that the HCV elimination goals are achievable in Tijuana, particularly when scaling up HR interventions in combination with DAAs (18); however, the most cost-effective elimination strategy is unknown. One recent U.S. economic evaluation found combination HR and HCV treatment scale-up cost-effective in two U.S. settings (19), but no study has compared the cost-effectiveness of potential elimination strategies incorporating HR.

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 HR 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 HR intervention costs. Our analysis used a dynamic model incorporating 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 (Figure S1) (18). 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 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 R2018b (The Mathworks, Natick, MA).

Model parameterization

The model was parameterized to an estimated 10,000 current PWID in Tijuana, Mexico (20), with a 90% HCV seroprevalence based on a 2017/18 cross-sectional survey (16). Data on HR access, average duration of injecting, and PWID mortality were obtained from a longitudinal cohort of PWID (Table 1) (17, 21–23). At baseline, we assumed no coverage (0%) of HR interventions or HCV treatment due to very low coverage 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%) were obtained from published data for PWID (7, 26). OAT and HCNSP efficacy were obtained from a Cochrane systematic review and meta-analysis (5). For OAT, we assumed OAT reduced the risk of acquiring HCV by 50% (RR=0.50, 95% CI: 0.40–0.63)(5). For HCNSP, we assumed HCNSP reduced HCV acquisition by 23% (RR=0.77, 95% CI: 0.38–1.54) and that combined, high coverage of both HCNSP and OAT reduce the risk of acquiring HCV by 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)(27).

Model calibration and probabilistic uncertainty analysis

To account for uncertainty in parameters, we sampled 1000 parameter sets from their respective parameter uncertainty distributions shown in Table 1. For each sampled parameter set, the model was calibrated to the HCV prevalence among PWID in Tijuana by varying the 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 (28, 29).

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 (18). Based on these previously published findings, we considered the following intervention scenarios:

- **Baseline status quo:** no coverage of HR or HCV treatment
- **Elimination with DAAs only:** Implementing the number of DAAs required to achieve the 80% incidence reduction, without HR scale-up (770 annually [95% CI: 640–970], as calculated in (18)).
- **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 (18)) to achieve the 80% incidence reduction with a concomitant scale-up of combination HR (OAT+HCNSP) to 20% coverage of each intervention among PWID (10% of PWID on HCNSP or OAT only with an additional 10% of PWID on both).
- **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 (18)) to achieve the 80% incidence reduction with a concomitant scale-up of combination HR to 40% coverage of each intervention among PWID (20% of PWID on HCNSP or OAT only with an additional 20% of PWID on both).
- **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 (18)) to achieve the 80% incidence reduction with a concomitant scale-up of combination HR to 50% coverage of each intervention among PWID (25% of PWID on HCNSP or OAT only with an additional 25% of PWID on both).

Costs and health outcomes

Costs were attached to each disease stage and intervention in 2019 US\$ (Table 1). Costs of OAT (\$2,148/year) (30) and HCNSP (\$228/year) (31) were obtained from recent Tijuana studies. Mexico-specific costs for HCV testing, DAA drugs (\$4,000)(32) and advanced liver disease (DC and HCC) were obtained (33). Cost of DC and HCC include estimated direct

annual medical costs based on an institutional resource utilization questionnaire from an expert panel at the Mexican Institute of Social Security (33). 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 and based on supportive care costs for individuals with chronic HCV as observed in from Peru, Colombia, Brazil (34), and the UK (35). 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 ((36) submitted). Screening (HCV rapid antibody test cost \$1.75/per test) and diagnostic costs (HCV RNA confirmatory testing cost \$69.30/test) were included (see supplementary information for more details) and obtained from unit prices provided by Gilead Sciences from a 2017–18 study evaluating HCV prevalence among PWID in Tijuana (16).

Health disutilities in disability adjusted life years (DALYs) were attached to each disease stage (Table 1). The use of DALYs is recommended by the World Health Organization for cost-effectiveness evaluations and commonly used in LMICs; further, QALY measures were not available for liver disease in Mexico. Health disutilities were obtained from the Global Burden of Disease for decompensated cirrhosis, hepatocellular carcinoma, and current PWID states (37). As there was no specific GBD estimate for chronic HCV, we calculated the midpoint value of mild abdominopelvic problem and compensated cirrhosis (37). Based on evidence of quality of life improvements for those on OAT (38), 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 through an incremental analysis, ranking each intervention in terms of cost, removing dominated (and weakly dominated) strategies, and calculating the mean incremental cost-effectiveness ratios (ICER, \$/DALY averted, calculated through dividing the mean differences in costs by the mean differences in DALYs between each intervention and its next least costly non-dominated comparator). Results were plotted on a cost-effectiveness plane (showing incremental costs and incremental DALYs compared to the status quo), and cost-effectiveness acceptability curves were generated (39). Per WHO benchmarks, cost-effectiveness was assessed against a willingness-to-pay (WTP) threshold equal to one-time the 2019 per capita GDP of Mexico (\$9,698) (40). 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) (41). The optimal strategy was one that achieved the greatest health benefits with an ICER below the WTP threshold.

Sensitivity analysis

In addition to the probabilistic uncertainty analysis, we additionally performed several one-way sensitivity analyses (where individual parameters were varied for each of the 1,000 simulations), 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, [36]) 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.

Our primary research question and analysis plan were not pre-registered and thus the results should be considered to be exploratory.

RESULTS

Cost-effectiveness analysis

An elimination strategy using DAAs alone to achieve the 80% incidence reduction goal was cost-effective (Table 2), with a mean ICER of \$1,931 per DALY averted compared to the status quo. 100% of the simulations fell under both the per capita GDP willingness-to-pay (WTP) threshold for Mexico (\$9,698), and the PPP-adjusted GDP WTP range (\$4,842–13,557), see Figure 2a. This strategy resulted in total costs of \$173 million (95% CI \$126–238 million), with an incremental cost of \$58 million (95% CI \$49–64 million) compared to the status quo (Figure 1, Table 2).

Strategies that incorporated HR scale-up combined with DAAs accrued additional health benefits (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 HR provision (Table S1). Strategies with low or moderate levels of HR (DAAs+20% HR and DAAs+40% HR) were weakly dominated by DAAs+50% HR (Table 2). The DAAs+50% HR strategy achieved the greatest health benefits but also the greatest total costs (\$265 million [95% CI \$210–335 million]). Compared to DAAs alone, the DAAs+50% HR strategy yielded a mean ICER of \$6743/DALY averted. Therefore, the DAAs+50%HR is the optimal elimination strategy using the per capita GDP WTP threshold for Mexico (\$9,698), with 100% of simulations falling under the WTP (Figure 2b). Only if the WTP is <\$7,000 does the DAA alone strategy become optimal (>50% of DAA+50% HR simulations exceeding the WTP).

Sensitivity analysis

The DAAs+50% HR strategy remained optimal under the per capita GDP WTP (\$9,698) even with a higher discount rate, doubled DAA costs, and fewer (5%) PWID accessing care (Table S2). 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), and removing screening and diagnostic costs. Under a shorter time horizon (20 years), all strategies were weakly dominated by the DAAs+50% HR strategy 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). In this case, the DAAs+50%HR ICER was \$10,258/DALY averted, just exceeding the one-time GDP WTP threshold, but still falling below the upper bound of the PPP threshold.

DISCUSSION

Main findings

Our analysis indicates that strategies to achieve the HCV incidence elimination target are cost-effective in Tijuana, Mexico, and that the optimal strategy is to scale-up 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. This combination strategy accrued more health benefits due to prevention of HCV and overdose, in addition to broader benefits not explicitly included in our analysis, and also required fewer DAA treatments compared to strategies using DAAs alone. 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 (\$4,000/treatment for DAA therapies and roughly as much in addition for treatment delivery) compared to harm reduction (~\$2,000/year for OST).

With the commitment from Mexico to achieve HCV elimination by 2030 and allocation of 12,500 DAA treatments nationwide (15, 32), there is need to determine cost-effective and achievable elimination strategies. Tijuana is a high prevalence HCV setting, where >90% of PWID have history of HCV infection (16), yet evidence-based harm reduction interventions are limited. Furthermore, Tijuana is not alone. There are several other concentrated HCV epidemics among PWID along the US border in San Luis Rio Colorado and Ciudad Juarez (16, 28). 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 DAA allocations in Mexico, combination interventions such as DAAs plus expansion of OAT and high coverage NSP to 50% coverage among PWID may also serve as the most feasible option for implementation. However, provision of HCNSP and OAT has currently and historically been limited in Tijuana, as a result of funding lapses or terminations (31, 42). Despite the limited provision of these evidence-based harm reduction strategies, PWID in Tijuana have reported a high need for addiction treatment programs (43). While future funding of these harm reduction programs is unclear, our analyses indicate that their expansion would be cost-effective, reducing HCV as well as preventing fatal overdose (27) as well as HIV transmission among PWID (5, 44) 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, stigma within the healthcare system is prevalent and hinders accessibility (45–48). Additionally, many PWID do not even have access to basic health care (49, 50), let alone specialized treatment and care for more advanced diseases.

Strengths and limitations of study

This study is novel in that it is the first study to evaluate cost-effectiveness of combination HCV elimination strategies in Latin America. Importantly however, our study has several

limitations. As with all modeling studies, there is uncertainty within the model parameters. First, there is uncertainty in the proportion of PWID accessing liver-related care in Tijuana, 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). However, our sensitivity analyses indicated the 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, thus 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, as QALY measures were unavailable for liver disease in Mexico, we used DALYs as recommended by the World Health Organization for cost-effectiveness evaluations and commonly used in LMICs. However, future studies should collect health utility data for liver disease in LMIC settings for comparison.

Fourth, due to a lack of data suggesting otherwise, we assume 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.

Fifth, 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.

Sixth, there may be additional costs required to generate engagement and demand for testing and treatment among PWID not included in our analysis. These demand generation programs may need to overcome barriers that are both logistical (e.g., location and distance of services) as well as psychosocial (experiences of stigma from healthcare providers) (45–48, 50).

Seventh, 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 HCNISP 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.

Finally, we adopted a healthcare provider perspective as societal costs such as the impact of HCV infection on employment, and data on costs related to HCV treatment and care (such as transportation and childcare) were unavailable. Further studies assessing and incorporating these broader costs are warranted.

CONCLUSION

HCV elimination is cost-effective in Tijuana, and the optimal approach is a combination strategy including 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *The Lancet Global health*. 2017;5(12):e11192–e207. [PubMed: 29074409]
2. Polaris Observatory HCVC. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. *Lancet Gastroenterol Hepatol*. 2017;2(3):161–76. [PubMed: 28404132]
3. Graham CS, Swan T. A path to eradication of hepatitis C in low- and middle-income countries. *Antiviral Research*. 2015;119:89–96. [PubMed: 25615583]
4. Mohd Hanafiah K, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology (Baltimore, Md)*. 2013;57(4):1333–42.
5. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, et al. Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis. *Addiction (Abingdon, England)*. 2018;113(3):545–63.

6. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. *Lancet Glob Health*. 2017;5(12):e1208–e20. [PubMed: 29074410]
7. Grebely J, Dalgard O, Conway B, Cunningham EB, Bruggmann P, Hajarizadeh B, et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. *Lancet Gastroenterol Hepatol*. 2018;3(3):153–61. [PubMed: 29310928]
8. Kim DD, Hutton DW, Raouf AA, Salama M, Hablas A, Seifeldin IA, et al. Cost-effectiveness model for hepatitis C screening and treatment: Implications for Egypt and other countries with high prevalence. *Glob Public Health*. 2015;10(3):296–317. [PubMed: 25469976]
9. Aggarwal R, Chen Q, Goel A, Seguy N, Pendse R, Ayer T, et al. Cost-effectiveness of hepatitis C treatment using generic direct-acting antivirals available in India. *PLoS One*. 2017;12(5):e0176503. [PubMed: 28520728]
10. Martin NK, Vickerman P, Dore GJ, Hickman M. The hepatitis C virus epidemics in key populations (including people who inject drugs, prisoners and MSM): the use of direct-acting antivirals as treatment for prevention. *Curr Opin HIV AIDS*. 2015;10(5):374–80. [PubMed: 26248124]
11. Swan D, Long J, Carr O, Flanagan J, Irish H, Keating S, et al. Barriers to and facilitators of hepatitis C testing, management, and treatment among current and former injecting drug users: a qualitative exploration. *AIDS Patient Care STDS*. 2010;24(12):753–62. [PubMed: 21138381]
12. Lally MA, Montstream-Quas SA, Tanaka S, Tedeschi SK, Morrow KM. A qualitative study among injection drug using women in Rhode Island: attitudes toward testing, treatment, and vaccination for hepatitis and HIV. *AIDS Patient Care STDS*. 2008;22(1):53–64. [PubMed: 18095839]
13. Barocas JA, Brennan MB, Hull SJ, Stokes S, Fangman JJ, Westergaard RP. Barriers and facilitators of hepatitis C screening among people who inject drugs: a multi-city, mixed-methods study. *Harm Reduct J*. 2014;11:1. [PubMed: 24422784]
14. WHO. Global Health Sector Strategy on Viral Hepatitis 2016–2021. 2016.
15. Ochoa MMéxico se compromete a eliminar la Hepatitis C para 20302019
[Available from: <https://www.unotv.com/noticias/portal/nacional/detalle/mxico-se-compromete-eliminar-hepatitis-c-609911/>].
16. Fleiz C, Domínguez Mario, Villatoro Velazquez Jorge, Quiroz Vázquez, , Fabiola ZM, Eduardo Sánchez Ramos, Rodrigo Escobar, Esbehidy, Bustos Gamiño Marycarmen. Cuqueando la Chiva: Contextos del consumo de heroína en la frontera norte de México. . 2019.
17. Robertson AM, Garfein RS, Wagner KD, Mehta SR, Magis-Rodriguez C, Cuevas-Mota J, et al. Evaluating the impact of Mexico's drug policy reforms on people who inject drugs in Tijuana, B.C., Mexico, and San Diego, CA, United States: a binational mixed methods research agenda. *Harm Reduct J*. 2014;11:4. [PubMed: 24520885]
18. Marquez LK, Cepeda JA, Bórquez A, Strathdee SA, Gonzalez-Zúñiga PE, Fleiz C, et al. Is hepatitis C virus (HCV) elimination achievable among people who inject drugs in Tijuana, Mexico? A modeling analysis. *Int J Drug Policy*. 2019.
19. Barbosa C, Fraser H, Hoerger TJ, Leib A, Havens JR, Young A, et al. Cost-effectiveness of scaling-up HCV prevention and treatment in the United States for people who inject drugs. *Addiction*. 2019;114(12):2267–78. [PubMed: 31307116]
20. Magis-Rodriguez C, Brouwer KC, Morales S, Gayet C, Lozada R, Ortiz-Mondragon R, et al. HIV prevalence and correlates of receptive needle sharing among injection drug users in the Mexican-U.S. border city of Tijuana. *Journal of psychoactive drugs*. 2005;37(3):333–9. [PubMed: 16295018]
21. Strathdee SA, Lozada R, Pollini RA, Brouwer KC, Mantsios A, Abramovitz DA, et al. Individual, social, and environmental influences associated with HIV infection among injection drug users in Tijuana, Mexico. *J Acquir Immune Defic Syndr*. 2008;47(3):369–76. [PubMed: 18176320]
22. Borquez A, Beletsky L, Nosyk B, Strathdee SA, Madrazo A, Abramovitz D, et al. The effect of public health-oriented drug law reform on HIV incidence in people who inject drugs in Tijuana,

- Mexico: an epidemic modelling study. *The Lancet Public health*. 2018;3(9):e429–e37. [PubMed: 30122559]
23. West BS, Abramovitz DA, Gonzalez-Zuniga P, Rangel G, Werb D, Cepeda J, et al. Drugs, discipline and death: Causes and predictors of mortality among people who inject drugs in Tijuana, 2011–2018. *Int J Drug Policy*. 2019;75:102601. [PubMed: 31775080]
 24. Ghany MG, Strader DB, Thomas DL, Seeff LB, American Association for the Study of Liver D. Diagnosis, management, and treatment of hepatitis C: an update. *Hepatology*. 2009;49(4):1335–74. [PubMed: 19330875]
 25. Lindsay KL. Introduction to therapy of hepatitis C. *Hepatology*. 2002;36(5 Suppl 1):S114–[PubMed: 12407584]
 26. Dore GJ, Altice F, Litwin AH, Dalgard O, Gane EJ, Shibolet O, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. *Ann Intern Med*. 2016;165(9):625–34. [PubMed: 27537841]
 27. Sordo L, Barrio G, Bravo MJ, Indave BI, Degenhardt L, Wiessing L, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. *BMJ (Clinical research ed)*. 2017;357:j1550.
 28. White EF, Garfein RS, Brouwer KC, Lozada R, Ramos R, Firestone-Cruz M, et al. Prevalence of hepatitis C virus and HIV infection among injection drug users in two Mexican cities bordering the U.S. *Salud publica de Mexico*. 2007;49(3):165–72. [PubMed: 17589770]
 29. Frost SD, Brouwer KC, Firestone Cruz MA, Ramos R, Ramos ME, Lozada RM, et al. Respondent-driven sampling of injection drug users in two U.S.-Mexico border cities: recruitment dynamics and impact on estimates of HIV and syphilis prevalence. *Journal of urban health : bulletin of the New York Academy of Medicine*. 2006;83(6 Suppl):i83–97. [PubMed: 17072761]
 30. Burgos JL, Cepeda JA, Kahn JG, Mittal ML, Meza E, Lazos RRP, et al. Cost of provision of opioid substitution therapy provision in Tijuana, Mexico. *Harm reduction journal*. 2018;15(1):28. [PubMed: 29792191]
 31. Cepeda JA, Burgos JL, Kahn JG, Padilla R, Meza Martinez PE, Segovia LA, et al. Evaluating the impact of global fund withdrawal on needle and syringe provision, cost and use among people who inject drugs in Tijuana, Mexico: a costing analysis. *BMJ open*. 2019;9(1):e026298.
 32. México establecerá una estrategia de tratamiento y eliminación de la hepatitis C [press release]. 2019.
 33. Garcia-Contreras F, Nevarez-Sida A, Constantino-Casas P, Abud-Bastida F, Garduno-Espinosa J. Cost-effectiveness of chronic hepatitis C treatment with thymosin alpha-1. *Arch Med Res*. 2006;37(5):663–73. [PubMed: 16740439]
 34. Chhatwal J, Chen Q, Bethea ED, Ladd MA, Mueller PP, Hutin Y, et al. Hep C Calculator: an online tool for cost-effectiveness analysis of DAAs. *Lancet Gastroenterol Hepatol*. 2018;3(12):819. [PubMed: 30507463]
 35. Martin NK, Vickerman P, Miners A, Foster GR, Hutchinson SJ, Goldberg DJ, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology*. 2012;55(1):49–57. [PubMed: 21898506]
 36. Walker JG, Mafirakureva N, Iwamoto M, et al. Cost and cost-effectiveness of a simplified treatment model with direct-acting antivirals for chronic hepatitis C in Cambodia. *Liver Int*. 2020;40(10):2356–2366. doi:10.1111/liv.14550 [PubMed: 32475010]
 37. Salomon JA, Haagsma JA, Davis A, de Noordhout CM, Polinder S, Havelaar AH, et al. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health*. 2015;3(11):e712–23. [PubMed: 26475018]
 38. Nosyk B, Marsh DC, Sun H, Schechter MT, Anis AH. Trends in methadone maintenance treatment participation, retention, and compliance to dosing guidelines in British Columbia, Canada: 1996–2006. *J Subst Abuse Treat*. 2010;39(1):22–31. [PubMed: 20418051]
 39. Alistar SS, Owens DK, Brandeau ML. Effectiveness and cost effectiveness of oral pre-exposure prophylaxis in a portfolio of prevention programs for injection drug users in mixed HIV epidemics. *PLoS One*. 2014;9(1):e86584. [PubMed: 24489747]
 40. Bank W. GDP per capita, Mexico 2019 [Available from: <https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=MX>.

41. Woods B, Reville P, Sculpher M, Claxton K. Country-Level Cost-Effectiveness Thresholds: Initial Estimates and the Need for Further Research. *Value in Health*. 2016;19(8):929–35. [PubMed: 27987642]
42. Thousands feared at risk after Mexico reforms HIV+ regime [press release]. Reuters 2019.
43. Werb D, Garfein R, Kerr T, Davidson P, Roux P, Jauffret-Roustide M, et al. A socio-structural approach to preventing injection drug use initiation: rationale for the PRIMER study. *Harm Reduct J*. 2016;13(1):25. [PubMed: 27629248]
44. Aspinall EJ, Nambiar D, Goldberg DJ, Hickman M, Weir A, Van Velzen E, et al. Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: a systematic review and meta-analysis. *International journal of epidemiology*. 2014;43(1):235–48. [PubMed: 24374889]
45. Biancarelli DL, Biello KB, Childs E, Drainoni M, Salhaney P, Edeza A, et al. Strategies used by people who inject drugs to avoid stigma in healthcare settings. *Drug and alcohol dependence*. 2019;198:80–6. [PubMed: 30884432]
46. von Hippel C, Brener L, Horwitz R. Implicit and explicit internalized stigma: Relationship with risky behaviors, psychosocial functioning and healthcare access among people who inject drugs. *Addictive behaviors*. 2018;76:305–11. [PubMed: 28889059]
47. Paquette CE, Syvertsen JL, Pollini RA. Stigma at every turn: Health services experiences among people who inject drugs. *The International journal on drug policy*. 2018;57:104–10. [PubMed: 29715589]
48. Brener L, Cama E, Broady T, Hopwood M, de Wit J, Treloar C. Predictors of health care workers' support for discriminatory treatment and care of people who inject drugs. *Psychology, health & medicine*. 2019;24(4):439–45.
49. Davidson PJ, Lozada R, Rosen PC, Macias A, Gallardo M, Pollini RA. Negotiating access: social barriers to purchasing syringes at pharmacies in Tijuana, Mexico. *The International journal on drug policy*. 2012;23(4):286–94. [PubMed: 22676968]
50. Smith LR, Patterson TL, Magis-Rodriguez C, Ojeda VD, Burgos JL, Rojas SA, et al. Engagement in the HIV Care Continuum among Key Populations in Tijuana, Mexico. *AIDS and behavior*. 2016;20(5):1017–25. [PubMed: 26354518]
51. Lang K, Neil J, Wright J, Dell CA, Berenbaum S, El-Aneed A. Qualitative investigation of barriers to accessing care by people who inject drugs in Saskatoon, Canada: perspectives of service providers. *Substance Abuse Treatment, Prevention, and Policy*. 2013;8(1):35.
52. Micallef JM, Kaldor JM, Dore GJ. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. *Journal of viral hepatitis*. 2006;13(1):34–41. [PubMed: 16364080]
53. Strathdee S Proyecto El Cuete phase IV.
54. Vickerman P, Martin N, Turner K, Hickman M. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings. *Addiction (Abingdon, England)*. 2012;107(11):1984–95.
55. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M. Risk of death during and after opiate substitution treatment in primary care: prospective observational study in UK General Practice Research Database. *BMJ (Clinical research ed)*. 2010;341:c5475.
56. Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2013;57 Suppl 2:S39–45. [PubMed: 23884064]
57. Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. *Hepatology (Baltimore, Md)*. 2013;58(5):1598–609.
58. Thein HH, Yi Q, Dore GJ, Krahn MD. Estimation of stage-specific fibrosis progression rates in chronic hepatitis C virus infection: a meta-analysis and meta-regression. *Hepatology (Baltimore, Md)*. 2008;48(2):418–31.

59. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alpha (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. Health technology assessment (Winchester, England). 2007;11(11):1–205, iii.
60. El-Serag HB, Siegel AB, Davila JA, Shaib YH, Cayton-Woody M, McBride R, et al. Treatment and outcomes of treating of hepatocellular carcinoma among Medicare recipients in the United States: a population-based study. Journal of hepatology. 2006;44(1):158–66. [PubMed: 16290309]
61. Acceso a tratamiento para hepatitis C, una realidad. [press release]. 02820192019.

Figure 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. Note that the DAAs+20%HR and DAAs+40% HR are weakly dominated by DAAs+ 50% HR. 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 2. Cost-effectiveness acceptability curves for (a) DAAs only compared to status quo and (b) DAAs+50%HR compared to DAAs only.

Note that the DAAs + 20%HR and DAAs + 40% HR are weakly dominated by DAAs + 50% HR. 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. Incremental cost-effectiveness ratio (ICER) of DAAs only 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.

Table 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		(20)
HCV seroprevalence among current PWID (2017/18)	0.90 (0.85–0.95)	Beta	--	(16)
Proportion of infections that spontaneously clear	0.26 (0.22–0.30)	Uniform	--	(52)
HCV sustained viral response rates	0.95 (0.91–0.99)	Uniform	--	(7, 26)
Average duration of injecting	17.5 (11.3–23.6)	Uniform	Years	Weighted average assumed (15% female; 85% male) (21, 22, 53)
Mortality rate among PWID	0.02 (0.016, 0.024)	Uniform	Per year	(22, 23)
Relative reduction of all-cause (excluding HCV) mortality for current PWID on OAT compared to off OAT	0.25 (0.18, 0.36)	Lognormal		(27)
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	(54–56)
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 (57)
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)
Proportion of PWID accessing care	0.25	--	Per year	(53) unpublished data from El Cuete IV
Disease transition probabilities				
Chronic – DC	0.016 (0.013, 0.019)	Uniform	Per year	Calculated from fibrosis progression rates in (58)
Chronic—HCC	0.009 (0.007, 0.01)	Uniform	Per year	Calculated from fibrosis progression rates in (58)
DC – HCC	0.012 (0.002, 0.04)	Beta	Per year	(59)
HCV-related mortality rate from DC	0.14 (0.11, 0.17)	Uniform	Per year	(59)
HCV-related mortality rate from HCC	0.55 (0.31, 0.79)	Uniform	Per year	(59, 60)
HCV-related costs (in 2019 US\$)				
HCV antibody test	\$1.75	--	Per test	(16)
HCV RNA test	\$69.30	--	Per test	(16)

Definition	Mean sampled value (95% CI)	Sample distribution	Unit	Reference
DAA drugs	\$4,000	--	Per treatment	(32, 61)
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. (36)
OAT in Tijuana or Mexico	\$2,148 (1,749–2,565)	Uniform +/-20% point estimate	Per year	(30)
NSP in Tijuana or Mexico	\$228 (184–272)	Uniform +/-20% point estimate	Per year	(31)
Chronic HCV (no treatment)	\$750 (396–1,094)	1/13*DC estimate	Per year	No Mexico estimate available. Assumed to be 1/13 th of the DC estimate based on data from Peru, Colombia, Brazil (34), and the UK (35).
DC	\$9,510 (5,090–14,133)	Uniform +/-50% point estimate	Per year	Based on the 2005 estimate for cirrhosis (33); published cost not specified for decompensation: \$1944. Inflated to 2019 prices
HCC	\$9,663 (4,977–14,200)	Uniform +/-50% point estimate	Per year	Based on the 2005 estimate: \$5523 (33); Inflated to 2019 prices
Health disutility values for HCV disease stages				
Uninfected				(37)
Ex/non-PWID	0			
Active PWID	0.333 (0.202–0.467)	Beta		
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 (37)
Decompensated cirrhosis	0.178 (0.123–0.250)	Beta		(37)
Hepatocellular carcinoma	0.569 (0.389–0.727)	Beta		(37)
OAT disutility improvement	0.05 (0.03–0.07)	Uniform		(38)

Table 2.
Cost-effectiveness of strategies to reach the 80% HCV incidence reduction target by 2030 among PWID in Tijuana.

ICER: Incremental cost-effectiveness ratio; DAAs: Direct-acting antiviral treatment; HR: harm reduction.
 ICER comparing to next least costly intervention scenario.

Intervention Scenario	Mean cost (millions)		Mean DALYs		ICER (\$ per DALY averted, compared to next least costly non-dominated strategy)
	Total (95% CI)	Incremental	Total (95% CI)	Incremental	
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)	--	517,850 (416,070,663,260)	--	Weakly dominated
DAAs+ 40% HR coverage strategy	248.0 (196.90, 317.10)	--	512,640 (411,410, 658,500)	--	Weakly dominated
DAAs + 50% HR coverage strategy	264.70 (209.90, 335.0)	91.70 (83.80, 97.40)	510,210 (408,900,656,400)	-13,045 (-11,755, -13,380)	6,743