A Systematic Review of Simulation Models to Track and Address the Opioid Crisis

Magdalena Cerdá, Mohammad S. Jalali, Ava D. Hamilton, Catherine DiGennaro, Ayaz Hyder, Julian Santaella-Tenorio, Navdep Kaur, Christina Wang, Katherine M. Keyes

Web Table 1: Extracted Data from 88 Opioid Modeling Studies

	Model Details	Data sources	Calibration/Validation approach	Findings
Agar, 2001[1]	**Model Type:** Agent-based model **Research Question:** Report and evaluation of a preliminary Agent-based model used for a potential resource for research on heroin trends (no interventions) **Target Population:** 100 agents; a sample of youth in Baltimore County	**Simulated Population:** Parker, Aldridge, and Measham's (1998) longitudinal study of a general youth sample in the United Kingdom, where roughly one-third were regular drug users, one-third were experimenting on the way to regular use or on the way out, and one-third were abstinent. **Interventions:** N/A	**Calibration:** N/A **Validation:** N/A	**Results:** Key elements of the explanation of experimentation can be modeled and the outcomes show potential use in intervention as well as validation of the anthropological research. **Conclusion:** Same as results.
Agar, 2002[2]	**Model Type:** Agent-based model **Research Question:** What are some potential reasons for the unexpected arrival and speed of onset of illicit drug epidemics? **Target Population:** 500 agents; a sample of youth in Baltimore County	**Simulated Population:** N/A **Interventions:** N/A	**Calibration:** N/A **Validation:** N/A	**Results:** (1) Heroin reputation is sufficient to generate epidemiologic curves similar to those in actual illicit drug epidemics. (2) Variation in outcomes is striking under the same initial conditions. (3) Although the number of addicts increases with the number who have ever used, it is not a simple linear relationship. (4) There is a dampening effect of increased social connections on lifetime heroin use and heroin addiction. **Conclusion:** Same as results**.**
Alistar, 2011[3]	**Model Type:** Dynamic compartmental model **Research Question:** The Cost-effectiveness of increasing number of methadone maintenance treatment (MMT) slots versus expanding access to antiretroviral therapy (ART) versus both **Target Population:** 1,000,000 individuals aged 15-49, segmented by drug usage status, HIV disease stage, and ART access	**Simulated Population:** Ukraine county-level data **Interventions:** Studies on (1) effect on transmission probability via sexual contact, progression rate from HIV to AIDS, and AIDS mortality for ART and (2) effectiveness of buprenorphine pilot programs (no data available for effectiveness of MMT in Ukraine)	**Calibration:** The model was calibrated against registered total prevalence trends. **Validation:** Study compared (1) model results with recorded demographic trends in Ukraine and (2) predicted outputs after initializing the model with epidemic and behavioral data from mid-2005 with reported data.	**Results:** MMT was the most cost-effective (Add 76000 QALYs at $530/QALY) and expanded ART and MMT was the second most effective (Add 105000 QALYs at $1120/QALY). **Conclusion:** MMT is highly cost-effective. A strategy expanding both MMT and ART is the most effective intervention and very cost-effective by WHO criteria.
Alistar, 2014[4]	**Model Type:** Dynamic compartmental model **Research Question: T**he Cost-effectiveness of oral pre-exposure prophylaxis (PrEP) in various combinations with MMT ART **Target Population:** 1,000,000 individuals aged 15-49, segmented by HIV/AIDS status, injection drug use (IDU) status, prevention status, and treatment status	**Simulated Population:** Ukraine data (Literature and estimates) **Interventions:** Interventions: Bruce et al. 2007: HIV treatment access and scaleup for delivery of opiate substitution therapy with buprenorphine for IDUs in Ukraine–program description and policy implications Connock et al. 2007: Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation	**Calibration:** The model was calibrated to match registered total HIV prevalence in Ukraine and other reported HIV epidemic data. **Validation:** Study compared model results to data from UN national report HIV/AIDS and Kruglov et al. 2008: The most severe HIV epidemic in Europe: Ukraine's national HIV prevalence estimates for 2007.	**Results:** PrEP and MMT lowered HIV prevalence the most, ART, MMT, and PrEP averted most infections (14,267). MMT was the most cost-effective ($520/QALY), MMT and ART was the next most cost-effective ($1000/QALY), and adding PrEP was also cost-effective by WHO criteria ($1700/QALY). **Conclusion:** Oral PrEP is an effective strategy for controlling HIV among IDUs, although there should be a focus on MMT and ART access when budget is limited.
Asche, 2015[5]	**Model Type:** Markov model **Research Question**: Opioid treatment with sublingual film versus tablet formulation of buprenorphine-naloxone combination through the following treatment phases: initiation, maintenance, discontinuation, off-treatment and re-initiation **Target Population**: Opioid dependent patients on Medicaid	**Simulated Population:** Truven Health Analytics, 2012: Medicaid Expansion: Profiling the Future Medicaid-Eligible Population. Truven Health Analytics **Interventions**: Truven Health MarketScan Database, NSDUH	**Calibration**: For years following the first year, incidence was calibrated based on the assumption that the number of patients in treatment remains approximately stable over time. **Validation:** N/A	**Results**: Sublingual buprenorphine-naloxone has 100% market share, costing $6.4B. sublingual film is progressively replaced by generic tablet, costing $6.464B. **Conclusion**: Using the sublingual film formulation for more patients treated with buprenorphine-naloxone is predicted to increase outpatient care costs, but it would also generate savings in emergency care and hospitalizations. Total direct medical costs for Medicaid would be lower for sublingual-film-treated patients at current drug prices.

Baia Medeiros, 2019[6]	**Model Type:** Discrete-event simulation model **Research Question:** Examine the capacity planning alternatives (increasing overall demand to the emergency department, increasing or decreasing number of emergency department visits due to substance abuse, and adjusting resource capacity to address the forecasted demand) for the emergency department of an academic hospital in Toronto. **Target Population:** Predicting the number of beds in emergency department in Toronto Western Hospital	**Simulated Population:** Data collected from the National Ambulatory Care Reporting System and the Electronic Patient Records system from University Health Network in Toronto **Interventions:** (1) Council of Academic Hospitals of Ontario, 2017: Addictions Program, Reduces Emergency Room Visits for Opioid Overdose and Improves Patient Experience across Ontario, Health Quality Ontario, Toronto, Canada. (2) T. Kula, META: PHI Dropped User Reliance on Emergency Department in Sarnia 45 Per Cent, Doctor Says, Sarnia Observer, Sarnia, Canada, 2017, (3) Rocky Mountain HIDTA 2017: Legalization of Marijuana in Colorado: Impact, Vol. 5, Rocky Mountain HIDTA, Denver, CO, USA. (4) Colorado Department of Public Health & Environment 2014: Monitoring Health Concerns Related to Marijuana in Colorado.	**Calibration:** Data from the fiscal year 2016 in Simul8, a discrete-event simulation software. Stat:Fit was used to fit statistical distributions to emergency department historical data. **Validation:** Predicted and historical data were compared for the following parameters: (1) number of arrivals for both the nonmental health and addiction and mental health and addiction group, (2) average emergency department length of stay for both nonmental health and addiction and mental health and addiction groups, and (3) emergency department length of stay for nonmental health and addiction and mental health and addiction combined average. emergency department length of stay refers to the time from triage/ registration to the time of discharge.	**Results:** (1) If resource capacity is not adjusted, emergency department length of stay will deteriorate considerably given the expected growth in demand. (2) Programs that aim to reduce the number of alcohol and/or opioid visits can greatly aid in reducing emergency department wait times. (3) The legalization of recreational use of cannabis will have minimal impact. (4) Increasing the number of Psychiatric Emergency Services Unit (PESU) beds can provide great aid in reducing emergency department pressure. **Conclusion:** Same as results.
Barbosa, 2019[7]	**Model Type:** Dynamic, Deterministic compartmental mode **Research Question**: Examine the cost-effectiveness of HCV treatment of people who inject drugs (PWID), combined with MMT and needle and syringe programs (NSP), to tackle the increasing HCV epidemic in the United States. **Target Population:** Current and ex-PWID in Perry County, Kentucky and San Francisco	**Simulated Population:** Kentucky: Social Networks Among Appalachian People cohort study; San Francisco: The UFO study **Interventions:** Levels of NSP and MMT with existing HCV care and treatment based on a series of HCV screening studies	**Calibration:** Population demographics, and fit to coverage of MMT and NSP, and the proportion of PWID at high risk in each setting **Validation:** Model projections were validated with prevalence in those injecting over 3 years and HCV incidence in Kentucky, and prevalence in those aged under 30 in San Francisco.	**Results:** Scaling up of NSP and MMT without changes to treatment combined with HCV screening and treatment for current PWID averts 1852 and 36,473 more HCV infections and increases QALYS by 3095 and 7893 in KY and SF respectively **Conclusion:** Combining HCV screening and MMT and NSP for PWID is a cost-effective strategy for reducing HCV burden in the United States.
Barnett, 2001[8]	**Model Type:** Dynamic compartmental model **Research Question:** Cost-effectiveness of adding buprenorphine maintenance to current opiate dependence treatment system **Target Population:** Nine mutually exclusive groups based on HIV status (uninfected, asymptomatic HIV positive, AIDS) and drug use status (injection drug user, user in maintenance therapy and non- user)	**Simulated Population:** Data from studies following injection users in treatment **Interventions:** Study modeling effect of adding buprenorphine maintenance therapy on total health-care costs and outcomes over 10-year time horizon	**Calibration:** The model was calibrated so, in the absence of buprenorphine treatment, its projections agreed with recent trends in the HIV epidemic. **Validation:** N/A	**Results:** (1) If people entering buprenorphine maintenance treatment increases by 10%, cost-effectiveness ratio is <$45000/QALY for all prices. (2) If people entering buprenorphine maintenance treatment increases by 10%, with half being IDU newly entering and half being people switching from methadone, the cost-effectiveness ratio is <$45000/QALY for $5 and $15/dose, and >$65000/QALY for $30/dose. **Conclusion:** (1) At $5/dose, buprenorphine maintenance is cost-effective under all scenarios. (2) At $15/dose, buprenorphine maintenance is cost-effective if it doesn't lead to net decline in methadone use**.**
Barnett, 1999[9]	**Model Type:** Two-state Markov model **Research Question:** Cost-effectiveness of methadone maintenance **Target Population:** Cohort of 25 y/o heroin users	**Simulated Population:** Data from studies of heroin and opioid addicts **Interventions:** Literature review of the effect of methadone treatment on the rate of mortality associated with opiate addiction	**Calibration:** N/A **Validation:** N/A	**Results:** Providing opiate addicts with access to methadone maintenance has an incremental cost-effectiveness ratio of $5915 per life-year gained. **Conclusion:** Methadone maintenance treatment cost-effective and comparable to many common medical therapies**.**

Battista, 2019[10]	**Model Type:** Deterministic compartmental model **Research Question:** Develop a mathematical model for prescription drug addiction and treatment **Target Population:** 4 population classes: susceptibles, prescribed users, addicted individuals, and individuals in treatment for addiction	**Simulated Population:** (1) NSDUH, 2015 (2) CDC WONDER **Interventions:** (1) Prescription Opioid Addiction Treatment Study, (2) Study of 164 inpatient opioid detoxification patients	**Calibration:** N/A **Validation:** The model was validated against national data for prescription opioid deaths between 1999 and 2016.	**Results:** No addiction-free equilibrium can exist without stringent control over how opioids are administered/prescribed. **Conclusion:** Necessary measures to combat opioid epidemic include lowering number/duration of medically prescribed painkillers, more successful treatment regimens, and increasing availability/ease/motivation for opioid addicts to enter treatment.
Bayoumi, 2008[11]	**Model Type:** Dynamic Compartmental Model **Research Question**: Estimate the impact of the only supervised injection facility on survival, rates of HIV and HCV infection, referral to methadone maintenance treatment and associated costs **Target Population:** Vancouver, British Columbia population	**Simulated Population:** Statistics Canada, 2006 and Vancouver Injection Drug Users Study **Interventions:** Kerr et al. 2005: Safer injection facility use and syringe sharing in injection drug users	**Calibration:** Population demographics and to Vancouver population data, and calibrated the number of injections to to the first year of the model when the Safe Injection Facility was operative **Validation:** N/A	**Results:** When looking at effects of decreased needle sharing, increase use of safe injection practices and increased referral to methadone maintenance treatment the incremental net savings was more than $18 million and the number of life-years gained 1175 **Conclusion**: Vancouver's supervised injection site is associated with improved health and cost savings,
Benneyan, 2017[12]	**Model Type:** Agent-based model, ODE model **Research Question:** Model/replicate 17 years of the growth of the opioid and heroin epidemic at town, county, state level. Develop and use several simulation models to test changes in opioid prescribing patterns, social interventions, and addiction treatment capacity expansion **Target Population:** Massachusetts counties and Barnstable, MA towns	**Simulated Population:** (1) CDC WONDER (2) National Center for Health Statistics **Interventions:** Literature review of effects of treatment capacity expansion and reduced pain prescribing	**Calibration:** Study combined expert input with statistical fitting to state mortality data to maximize model-vs-empirical agreement. input sensitivity analysis was carried out and experiment with various search algorithms (evolutionary, swarm, tunneling, annealing). **Validation:** Logic and assumption reviews with panel experts were carried out, as well as scenario testing across multiple settings and directional verification. Agent-based modeling results produced face-validity to match historical data.	**Results:** A potential 50-75% reduction in opioid mortality rates among high school students and young adults was found. **Conclusion:** A combination of increased addiction treatment and restricting acute pain prescribing has the greatest impact to reduce opioid overdose deaths drug abusers.
Bernard, 2016[13]	**Model Type:** Dynamic compartmental model **Research Question:** Evaluate the cost-effectiveness of (1) PrEP alone, (2) PrEP with frequent screening, and (3) PrEP+screen with enhanced provision of ART for individuals who become infected **Target Population:** Adult U.S. people who inject drugs	**Simulated Population:** (1) Tempalski et al. 2013: Trends in the population prevalence of people who inject drugs in US metropolitan areas 1992-2007, (2) CDC. HIV infection and HIV-associated behaviors among injecting drug users - 20 cities, United States, 2009. **Interventions:** MacArthuer et al. 2012: Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis	**Calibration:** The study calibrated the model to CDC estimates of HIV prevalence, incidence, and infection awareness by risk group using existing literature. **Validation:** N/A	**Results:** PrEP, screen, and ART averts 26,700 infections and reduces HIV prevalence among PWID by 14%. Costs of $253000/QALY are gained. **Conclusion:** PrEP with frequent screening and prompt treatment can reduce HIV burden among PWID and provide health benefits for the entire U.S. population. However, at current drug prices, it remains an expensive intervention both in absolute terms and in cost per QALY gained.

Bernard, 2017[14]	**Model Type:** Dynamic compartmental model **Research Question:** Compare cost-effectiveness of combinations of opioid substitution therapy (OST) and NSPs, HIV testing/treatment, and oral HIV PrEP **Target Population:** The U.S. adult population aged 18 to 64 years, stratified by HIV infection and awareness status, CD4 count, ART status, OST status, and risk group	**Simulated Population:** US epidemiological data **Interventions:** (1) Studies on injection reduction, HIV screening rates, IDU cessation, and cost/benefit analysis for PWID receiving OST, (2) Studies on equipment sharing reduction and cost-effectiveness of NSPs, (3) Studies on cost-effectiveness and engagement levels of HIV testing/treatment, and (4) Studies on cost-effectiveness of HIV PrEP	**Calibration:** The study used random search algorithm to repeatedly sample from estimated distributions for each model input, then empirically fit model to US epidemiological data. **Validation:** N/A	**Results:** Scaling OST coverage up to 50%, NSP coverage to 50%, Test & Treat coverage to 50% was cost-effective, with each expansion resulting in <$50000/QALY gained. **Conclusion:** OST, NSPs, and Test & Treat implemented individually or in combination are most cost-effective in preventing HIV in US people who inject drugs. HIV PrEP is likely not cost-effective.
Birger, 2017[15]	**Model Type:** Deterministic compartmental ODE model **Research Question:** Use a mathematical model of HIV, HCV and injecting drug use in Ho Chi Minh City to predict the impact of MMT coverage scale-up (50%), ART coverage scale-up (80%), and HCV treatment coverage **Target Population:** High HIV-HCV prevalence population	**Simulated Population:** Various studies on substance users in Vietnam. **Interventions:** Various studies on patients receiving DAAs	**Calibration:** The model was calibrated to data on HIV and HCV prevalence using Maximum Likelihood Estimation (MLE) with a binomial likelihood function. **Validation:** N/A	**Results:** (1) Scale-up of ART impacts HIV but not HCV burden. (2) Scale-up of MMT impacts both, and (3) HCV treatment roll-out increases multifold mortality reductions afforded by ART/MMT scale-ups alone. **Conclusion:** HCV treatment roll-out has long-lasting effects on averting PWID deaths on top of ART/MMT scale-up
Bobashev, 2014[16]	**Model Type:** Agent-based model **Research Question:** Propose a polydrug Agent-based model to describe drug users interconnected in a network to explain drug users to switch between primary drugs of choice (no interventions) **Target Population:** 10,000 patients, 70 non-patient drug dealers, 30 physicians, 10 emergency departments, and 10 pharmacies; intended to be reflective of certain populations in a town community	**Simulated Population:** Ethnographic data **Interventions:** N/A	**Calibration:** N/A **Validation:** N/A	**Results:** After the market locally stabilizes, law enforcement leads to an increase in consequences of the local meth market, which leads to reduction in meth use and increase in other reinforcements available in social network. Because heroin has a higher addictive potential than "other" reinforcements, it eventually wins over the community with a temporary dominance of other reinforcements. **Conclusion:** Same as results.
Bobashev, 2018[17]	**Model Type:** Agent-based model **Research Question:** Evaluate effects of physician prescription drug monitoring program compliance, pharmacy use of tamper-resistant pills, reduced initial doses of opioids, and increased naloxone available at local level **Target Population:** 10,000 patients, 70 non-patient drug dealers, 30 physicians, 10 emergency departments, and 10 pharmacies	**Simulated Population:** N/A **Interventions:** N/A	**Calibration:** N/A **Validation:** N/A	**Results:** There were strong effects of naloxone use, marginal short-term effects of prescription drug monitoring program compliance, and few to no positive effects of tamper-resistant medications on non-child opioid use trajectories. **Conclusion:** Same as results.
Borquez, 2018[18]	**Model Type:** Deterministic compartmental model **Research Question:** Assess the past and future effect of narcomenudeo reform (depanelized possession of small amounts of selected drugs for personal consumption) on HIV incidence in PWID in Tijuana, Mexico **Target Population:** PWID in Tijuana, Mexico	**Simulated Population:** El Cuete IV cohort study **Interventions:** El Cuete IV cohort study	**Calibration:** HIV incidence and prevalence by sex and incarceration history among PWID in Tijuana from 2005–15 **Validation:** N/A	**Results:** Implementation reform averted 2% of new HIV infections in PWID between 2012-2017. If implementation reduced incarceration in PWID by 80% after 1018, 9% of HIV infections could be averted, and 21% of people were sent to OST instead of prison. **Conclusion:** Appropriate implementation of narcomenudeo reform could have a strong effect on reducing HIV incidence especially if linked to OST instead

Carter, 2017[19]	**Model Type:** Markov chain model **Research Question:** Evaluate cost-effectiveness of subdermal implantable buprenorphine versus sublingual buprenorphine **Target Population:** Simulated subdermal implantable buprenorphine and sublingual buprenorphine cohorts transitioning through four mutually-exclusive health state for 12 months: 1) on treatment + not relapsed, 2) on treatment + relapsed, 3) off treatment + relapsed, 4) dead	**Simulated Population:** Health technology assessment guidelines and similar cost-effectiveness analyses. **Interventions:** Rosenthal et al. 2016: Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial	**Calibration:** N/A **Validation:** N/A	**Results: S**ubdermal implantable buprenorphine was associated with lower total costs (-$4,386), more QALYs (+0.031), and favorable incremental net-monetary-benefit at all willingness-to-pay thresholds considered. **Conclusion: S**ubdermal implantable buprenorphine was preferred over sublingual buprenorphine from a health-economic perspective for treatment of opioid use disorder in clinically-stable adults.
Caulkins, 2007[20]	**Model Type:** Dynamic compartmental model **Research Question:** Model for illicit drug use, injection users in Australia. The pre-drought (of heroin) data is used to reflect what would have happened in the absence of the drought **Target Population:** Injection users. Five compartments characterized both by type of drug and route of administration	**Simulated Population:** 1998 Australian National Drug Strategy Household Survey. **Interventions:** N/A	**Calibration:** Calibration was done comparing the model estimates with data from the 1998 Australian National Drug Strategy Household Survey, reproducing trends in Australian illicit drug use through 2000. **Validation:** N/A	**Results:** IDU would have grown by 3.5%/year had the heroin drought not occurred. **Conclusion:** The model did a reasonable job of reproducing trends in Australian illicit drug use through 2000.
Cepeda, 2018[21]	**Model Type:** Dynamic Compartmental Model **Research Question:** Assess the effects of scaling up harm reduction (use of OST and coverage of NSPs) and use of ART might have on HIV incidence and the frequency of fatal overdoses among PWID in two cities **Target Population:** PWID in two Russian cities, Omsk and Ekaterinburg	**Simulated Population:** Samples from Global Fund to Fight AIDS, Tuberculosis, and Malaria and US Centers for Disease Control and Prevention and surveillance studies from WHO and regional AIDS centers **Interventions:** Coverage levels of OST, NSPs, and ART use from WHO targets and other global settings using survey data.	**Calibration:** HIV prevalence based on research studies supported by the Global Fund and the US Centers for Disease Control and Prevention and surveillance studies from WHO and regional AIDS centers. **Validation:** N/A	**Results:** Scaling up OST coverage for 2 years could prevent HIV infections and HIV-related deaths in Omsk and Ekaterinburg, as well as prevent 33% of overdose deaths over 10 years. Scaling up of NSPs and OST and tripling recruitment to ART could prevent more than half of HIV infections and HIV-related deaths and a third of opioid overdose deaths. **Conclusion:** Legalization of OST and increased use of ART and NSPs for PWID are needed to prevent fatal overdose and HIV among PWID in Russia
Chalmers, 2012[22]	**Model Type:** System dynamics model **Research Question:** Examine the current costs nor the future predicted costs if government subsidized dispensing fees of pharmacotherapy maintenance programs **Target Population:** 93,546 Injecting Drug users, including new users, those in treatment, those getting MOUDs	**Simulated Population:** Australian Institute of Health and Welfare, 2007 **Interventions:** Costs calculated from: National Evaluation of Pharmacotherapies for Opioid Dependence from Late 1990s	**Calibration:** The model was calibrated to reflect a stable system: That is, a stable number of people entering and leaving the opioid pharmacotherapy system over time. **Validation:** N/A	**Results:** If the government provided dispensing fee relief for methadone maintenance patients, it would be a costly exercise. However, these additional costs are offset by the social and health gains achieved from the methadone maintenance program. **Conclusion:** Same as results.

Chalmers, 2009[23]	**Model Type:** System dynamics model **Research Question:** The development of an interactive quantitative model of the treatment service system in order to explore the implications of policy options (e.g., pharmacotherapy treatment) designed to address issues of affordability, availability and accessibility of treatment **Target Population:** Australian opioid-dependent people	**Simulated Population:** (1) National Drug Strategy Household Survey, (2) Australian Bureau of Statistics data on opioid overdose deaths, (3) National Hospital Morbidity Database, (4) National Dataset of Ambulance Attendance at Non-fatal Opioid Overdoses, (5) Australian Crime Commission, (6) National Notifiable Diseases Surveillance System, (7) Needle and Syringes Program, (8) Heroin Overdose Study, (9) Alcohol and Other Drug Treatment Services National Minimum Data Set **Interventions:** National Drug Strategy Household Survey	**Calibration:** The model was calibrated to reflect a stable system: That is, a stable number of people entering and leaving the opioid pharmacotherapy system over time. **Validation:** N/A	**Results:** (1) It would take a 50% increase in the rate of inflow to opioid dependence to match the impact on in-treatment numbers of 20% decrease in the length of stay between treatment, (2) whereas a 25% increase in individual goal attainment of all opioid-dependent people (in- and between-treatment) could be achieved with a small cost-saving to the government (prescribing costs alone) with low-threshold model. It would take a 31% increase in costs to achieve 50% increase in overall individual goal attainment under high-threshold model. **Conclusion:** The first system dynamics model of opioid pharmacotherapy treatment in Australia can be used to as means to explore potential costs associated with policies.
Chen, 2019[24]	**Model Type:** System dynamics model **Research Question:** Project the impact of interventions on lowering prescription opioid misuse on opioid overdose deaths from 2016 to 2025 **Target Population:** Projected US opioid overdose deaths from 2016-2025	**Simulated Population:** CDC WONDER, NSDUH, and Cicero et al. 2017 **Interventions:** NSDUH	**Calibration:** Calibrated parameters using approaches from (1) Stout et. al 2009. Calibration methods were used in cancer simulation models and suggested reporting guidelines from (2) Kong et al 2009. Calibration of disease simulation model was done using an engineering approach from (3) Taylor et al, 2010. Methods of model calibration included observations from a mathematical model of cervical cancer. **Validation:** Model-projected overdose deaths from prescription opioids and from illicit opioids closely replicated the outcomes reported by the CDC during 2002 to 2015.	**Results:** Across all interventions tested, further lowering the incidence of prescription opioid misuse from 2015 levels is projected to decrease overdose deaths by only 3.0% to 5.3%. **Conclusion:** Interventions targeting prescription opioid misuse such as prescription monitoring programs may have a modest effect, at best, on the number of opioid overdose deaths.
Cipriano, 2018[25]	**Model Type:** Decision-analytic model **Research Question:** Develop a decision-analytic model to evaluate the costs, benefits, and cost-effectiveness of placing naloxone in high schools, relative to relying on existing emergency and public health resources **Target Population:** Canada	**Simulated Population:** (1) Weiner et al 2017. One-year mortality of opioid overdose victims who received naloxone by emergency medical services and (2) Mathers et al 2013. Mortality among people who inject drugs: a systematic review and meta-analysis. **Interventions:** Degenhardt et al 2011. Mortality among regular or dependent users of heroin and other opioids: a systematic review and meta-analysis of cohort studies	**Calibration:** N/A **Validation:** N/A	**Results:** A school naloxone program likely costs <CAD$50,000/QALY gained if the overdose frequency is at least once each year and reduces opioid poisoning mortality by at least 40% (from 10% to<6.0%) or if the overdose frequency is at least two per year and the program reduces mortality by at least 20% (from 10% to<8.0%). **Conclusion:** School naloxone programs are relatively inexpensive, but that does not ensure that they are a cost-effective use of resources**.**

Cipriano, 2012[26]	**Model Type:** Dynamic Compartmental Model **Research Question:** Estimate the cost, effectiveness, and cost effectiveness of HIV and HCV screening of IDUs in OST. **Target Population:** US urban center with a population of 2.5 million PWID and people who do not inject drugs	**Simulated Population:** Collaborative Injection Drug Users Study **Interventions:** Reports on HIV and HCV screening strategies.	**Calibration:** Fit estimates of HIV and HCV prevalence and incidence in IDUs and general population **Validation:** Model projections were validated against credible intervals of HIV and HCV prevalence and incidence	**Results:** Adding HIV and HCV viral RNA testing to antibody testing averts 14.8–30.3 HIV and 3.7–7.7 HCV infections in a screened population of 26,100 IDUs entering OST over 20 years, depending on screening frequency. Screening for HIV antibodies every 6 months costs $30,700/QALY gained. Screening for HIV antibodies and viral RNA every 6 months has an incremental a cost-effectiveness ratio of $65,900/QALY gained. Strategies including HCV testing have incremental a cost-effectiveness ratios exceeding $100,000/QALY gained unless awareness of HCV-infection status results in a substantial reduction in needle-sharing behavior. **Conclusion:** Screening individuals in OST every 3–6 months for HIV infection using both antibody and viral RNA technologies and initiating ART for acute HIV infection appears cost effective.
Coffin, 2013(I)[27]	**Model Type:** Markov chain model **Research Question:** Evaluate the cost-effectiveness of distributing naloxone to illicit opioid users for lay overdose reversal in Russian cities **Target Population:** Russian cities	**Simulated Population:** Studies on impact of interventions on sustained drug injection cessation + overdose risk **Interventions:** Reports + study on naloxone distribution activities and cost-effectiveness	**Calibration:** The model was calibrated to parallel findings from epidemiologic studies from Russia where available and international sites if no other sources were available. **Validation:** Model results were consistent with literature estimates on the percentage of witnessed overdose resulting in death, median age of overdose death, percent of overdose deaths that received medical attention, and percent chance of naloxone kit being used for overdose reversal.	**Results:** (1) For each 20% of heroin users reached with naloxone distribution, there was a 13.4% reduction in overdose deaths in 5 years and 7.6% over lifetime. (2) Naloxone distribution was cost-effective in all deterministic/probabilistic sensitivity analyses, with an incremental cost of $94/QALY gained. **Conclusion:** Naloxone distribution to heroin users for lay overdose reversal is highly likely to reduce overdose deaths in target communities and is robustly cost-effective.
Coffin, 2013(II)[28]	**Model Type:** Markov chain model **Research Question:** Evaluate the cost-effectiveness analysis comparing the distribution of naloxone to 20% of heroin users with no distribution **Target Population:** Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses	**Simulated Population:** Published literature calibrated to epidemiologic data **Interventions:** Published literature calibrated to epidemiologic data	**Calibration:** The calibrated model was consistent with conservative estimates of overdose, mortality, naloxone use, and drug use cessation from epidemiologic studies. **Validation:** N/A	**Results:** 6% of overdose deaths were prevented with naloxone distribution, 1 death was prevented and 227 naloxone kits were distributed. Naloxone distribution increased costs by $53 and QALYs by 0.119 for an incremental cost-effectiveness ratio of $438. **Conclusion:** Naloxone distribution to heroin users likely to reduce overdose deaths and is cost-effective, even under conservative assumptions.

Degenhardt, 2010[29]	**Model Type:** Deterministic compartmental model **Research Question:** Model the effect of increased coverage and a combination of these three approaches on HIV transmission and prevalence in injecting drug users **Target Population:** global injection drug user population	**Simulated Population:** N/A **Interventions:** Kaplan 1989: Needles that kill: modeling human immune deficiency virus transmission via shared drug injection equipment in shooting galleries. Kaplan & Heimer 1992: A model-based estimate of HIV infectivity via needle sharing.	**Calibration:** N/A **Validation:** N/A	**Results:** Model projections suggest high coverage of ART, OST, and NSPs in combination are important for reduction of incidence of HIV infection in IDUs by more than 50%; very high intensity and coverage of single interventions is necessary to achieve similar effects; short-term, small-scale, single interventions are unlikely to be effective **Conclusion:** Social and structural changes are a potentially important element in a combination intervention approach to HIV prevention, especially in situations for which scale-up is difficult or when HIV transmission and injecting risk behavior are not diminished as expected.
Dray, 2008[30]	**Model Type:** Agent-based model **Research Question:** How street-level drug markets adapt to a macro-level disruption to the supply of heroin under drug law enforcement: Random patrol, hot-spot policing and problem-orientated policing **Target Population:** 150 dealers, 3000 problematic heroin users in Melbourne, Australia	**Simulated Population:** (1) Australian Bureau of Statistics (High Court and Magistrate Court orders), (2) the Ambulance Service Records (attended overdoses) **Interventions:** (1) Australian Institute of Health and Welfare, (2) the Australian Crime Commission, (3) the Australian Institute of Criminology, (4) the National Drug and Alcohol Centre	**Calibration:** The number of heroin users and probability of overdose was calibrated to match fatal/non-fatal overdose in Melbourne. **Validation:** The study compared results to outcomes from earlier versions of models.	**Results:** Macro-level disruptions to drug supply have limited impact on street-level market dynamics when there is already a replacement drug. Street-level police interventions vary in impact. Problem-oriented policing has been shown to be an optimal strategy. **Conclusion:** Same as results.
Enns, 2016[31]	**Model Type:** Dynamic compartmental model **Research Question:** Estimate the cost-effectiveness of establishing one or more supervised injection facilities in Toronto and Ottawa and project optimal number of facilities **Target Population:** Populations of 15-64 y/o in Toronto and Ottawa divided into compartments based on sexual behavior, drug use, and HIV/HCV infection	**Simulated Population:** Published literature, secondary analyses of self-reported survey responses from I-Track, and administrative health record data sets. **Interventions:** Bayoumi et al. 2008: The cost-effectiveness of Vancouver's supervised injection facility.	**Calibration:** The model was calibrated to match projected population growth, projected overall HIV incidence, HIV incidence among men who have sex with men and the estimated fraction of new HIV infections attributable to injection drug use in each city. **Validation:** N/A	**Results:** Facilities in Toronto and Ottawa had incremental a cost-effectiveness ratios of $10763/QALY and $6127QALY respectively. **Conclusion:** At a $50,000/QALY threshold, 3 facilities in Ottawa and 2 in Ottawa would be cost-effective**.**
Fraser, 2018 (rural)[32]	**Model Type:** ODE Transmission Model **Research Question:** Determine the required scale-up of HCV treatment with or without scale-up of HCV prevention interventions to achieve a 90% reduction in HCV chronic prevalence or incidence by 2025 and 2030 in a rural US setting. **Target Population:** PWID in Scott County, Indiana	**Simulated Population:** People identified in contact tracing effort during the 2014-15 HIV outbreak in Scott County, Indiana **Interventions:** Cochrane review of OST and NSP effectiveness, meta-analysis of methadone maintenance treatment retention.	**Calibration:** Fit to to a sampled estimate for the PWID population size in 2015, increase in PWID population throughout 2008–13, chronic prevalence in 2015 and four- to seven- fold increase in annual incident infections throughout 2010–14 **Validation:** Model projections were validated against observed HIV incidence and prevalence in target population.	**Results:** To achieve a 90% reduction in incidence and prevalence by 2030, without MMT and NSP scale-up, 159 per 1000 PWID need to be HCV-treated annually. However, with MMT and NSP scaled-up, treatment rates are halved (89 per 1000 annually or 14.5%). To reach the same target by 2025 with MMT and NSP scaled-up, 121 per 1000 PWID (19.9%) need treatment annually. These treatment requirements are threefold higher than if the epidemic was stable, and the impact targets are unattainable without retreatment. **Conclusion:** Combined scale-up of hepatitis C virus treatment and prevention interventions is needed to decrease the increasing burden of hepatitis C virus incidence and prevalence in rural Indiana, USA, by 90% by 2025/30.

Fraser, 2018 (Europe)[33]	**Model Type:** Dynamic Compartmental Model **Research Question:** Estimate the impact of current and scaled-up HCV treatment with and without scaling up OST and needle and syringe programs (NSPs) across Europe over 10 years **Target Population:** PWID across 11 sites in Europe	**Simulated Population:** PWID **Interventions:** Scaling up OST and NSP access	**Calibration:** Fit to the PWID population size, to OST and NSP coverage levels, and to either the chronic or antibody HCV prevalence at a site-specific time point **Validation:** Model projections were validated using past measurements of HCV incidence.	**Results:** Scaling-up OST and NSP to 80% coverage with current treatment rates using DAAs could achieve observable reductions in HCV prevalence (18–79%) in all sites. **Conclusion:** The scale-up of HCV treatment and other interventions is needed in most settings to minimize HCV transmission among PWID in Europe.
Fraser, 2018 (Scotland)[34]	**Model Type:** ODE Transmission Model **Research Question:** Determine whether observed decreases in HCV incidence post-2008 can be attributed to OST and NSP intervention scale-up **Target Population:** Scotland, UK	**Simulated Population:** PWID **Interventions:** Scaling up OST and NSP access	**Calibration:** Fit to Scottish HCV prevalence and incidence data for 2008/09 **Validation:** Model projections were fit to (1) rate PWID initiate injecting by fitting to the sampled PWID population size; (2 and 3) time-varying recruitment rates onto OST and NSP by fitting to the sampled OST and high coverage NSP coverage for specified years (1985, 2005, 2008 and 2013/14 for OST and 1990, 2008 and 2011/12 for NSP); and (4) proportion high-risk when initiating injecting and transition rates from low to high- risk by fitting to the sampled proportion high-risk for specified years (1990, 2005, 2008 and 2013/14)	**Results:** Scale-up of interventions (OST + NSP + HCV treatment) and decreases in high-risk behavior from 2008 to 2015 resulted in a 33.9% (23.8–44.6%) decrease in incidence, with the remainder [27.4% (17.6–37.0%)] explained by historical changes in OST + NSP coverage and risk pre-2008. Projections suggest that scaling-up of all interventions post-2008 averted 1492 (657–2646) infections over 7 years, with 1016 (308–1996), 404 (150–836) and 72 (27–137) due to scale-up of OST + NSP, decreases in high-risk behavior and HCV treatment, respectively. **Conclusion:** Most of the decline in hepatitis C virus (HCV) incidence in Scotland between 2008 and 2015 appears to be attributable to intervention scale-up (opioid substitution therapy and needle and syringe provision) due to government strategies on HCV and drugs.
Gicquelais, 2019[35]	**Model Type:** ODE transmission model **Research Question:** Interrupt transmission and decrease HCV prevalence in young PWID via primary prevention (reduced injection initiation), secondary prevention (behavioral initiatives), and tertiary initiatives (HCV treatment) **Target Population:** 15–29 y/o in Michigan during 2000–2016	**Simulated Population:** Number of newly identified acute and chronic HCV cases per year during 2000–2016 **Interventions:** Selected the best-fitting 10% of parameter sets to simulate the potential impact of interventions on acute and chronic HCV in Michigan during the period 2017–2030, scaled one or more parameters in each parameter set during the period 2017–2030	**Calibration:** Non-PWID (Zi) begin injecting drugs (transition to Si) at an estimated injection initiation rate (θi) calibrated to fit acute case data. **Validation:** N/A	**Results:** Treating 3 per 100 PWID per year could reduce chronic HCV by 27.3% and acute HCV by 23.6%. By 2030, if 90% are cured, reducing the number of syringe sharing partners per year by 10% was predicted to reduce chronic HCV by 15.7% and acute cases by 21.4% among PWID. In simulations of combinations of interventions, reducing injection initiation, syringe sharing, and relapse rates each by 10% while increasing cessation rates by 10% predicted a 27.7% reduction in chronic HCV and a 38.4% reduction in acute HCV. **Conclusion:** This study highlights the need for HCV treatment among current and former PWID and the scale up of primary and secondary interventions to reduce HCV prevalence.
Goedel, 2019[36]	**Model Type:** Agent-based model **Research Question:** Estimate the relative benefits of pre-existing and reactive NSP implementation on HIV transmission within a virtual population representative of a rural county in the United States. **Target Population:** 24,110 residents of rural Scott County, Indiana in the United States	**Simulated Population:** (1) 2006-2010 cycle of American Community Survey by US Census Bureau, (2) Contact tracing investigation data in Scott County. **Interventions:** Patel et al. 2018: Reduction of injection-related risk behaviors after emergency implementation of a syringe services program during an HIV outbreak.	**Calibration:** The study sought to replicate the Scott County outbreak by introducing a single HIV infection in the injection-related network without adjusting demographic or behavioral characteristics, allowing for the natural dynamics of HIV transmission to evolve as the model progressed. **Validation:** N/A	**Results:** Proactive implementation averted 154 infections and decreased incidence by 90.3%. Reactive implementation averted 107 infections and decreased incidence by 60.8%. **Conclusion:** Proactive implementation of an NSP in Scott County had the potential to avert more HIV infections than reactive implementation after the detection of an outbreak.

Heard, 2014[37]	**Model Type:** Agent-based model **Research Question:** Explore techniques for reducing the complexity of an Agent-based model on increased police presence for a 24-hour period during which a number of street dealers are arrested and removed from the market (returning an average of 20 days later once they are released) **Target Population:** 200 customers, 20 street dealers, 25 street brokers, 25 private dealers, 100 homeless, and 1 police office - Larimer open-air heroin market in Denver, Colorado	**Simulated Population:** Ethnographic data **Interventions:** Ethnographic data	**Calibration:** N/A **Validation:** Study compare results among full and reduced models.	**Results:** A reduced model was created that performs equivalently to the full model. **Conclusion:** Same as results.
Hoffer & Alam, 2013[38]	**Model Type:** Agent-based model **Research Question:** Understand how brokering and heroin package resizing influence heroin consumption costs **Target Population:** 500 customers, 100 street dealers - Larimer open-air heroin market in Denver, Colorado	**Simulated Population:** Ethnographic data **Interventions:** Ethnographic data	**Calibration:** N/A **Validation:** N/A	**Results:** Quality-adjusted price of heroin is greater than the retail price in all conditions. **Conclusion:** Increased competition in heroin markets does not lower costs.
Hoffer, 2009[39]	**Model Type:** Agent-based model **Research Question:** Apply agent-based modeling techniques to better understand the operation, organization, and structure of a local heroin market (no interventions) **Target Population:** 200 customers, 20 street dealers, 25 street brokers, 25 private dealers, 100 homeless, and 1 police officer - Larimer open-air heroin market in Denver, Colorado	**Simulated Population:** Ethnographic data **Interventions:** N/A	**Calibration:** Calibration of parameters was conducted to match known marginal values. **Validation:** N/A	**Results:** Concept and findings from this study remain experimental. These methods represent a novel way in which to understand illicit drug markets. **Conclusion:** Same as results.
Hoffer, 2012[40]	**Model Type:** Agent-based model **Research Question:** How can the social structure of the heroin market impact the physiology of heroin addiction and how can heterogeneity of addiction patterns can be shaped by market dynamics? (no interventions) **Target Population:** 200 customers, 20 street dealers, 25 street brokers, 25 private dealers, 100 homeless, and 1 police officer - Larimer open-air heroin market in Denver, Colorado	**Simulated Population:** Ethnographic data **Interventions:** N/A	**Calibration:** Windfall and seeking money processes are calibrated to represent the frequency with which a user is able to acquire drugs. **Validation:** N/A	**Results:** "Binge/crash" (customers trying to overcome their tolerance rapidly, but run out of money to consistently maintain such a high addiction level), "stepped" (addiction levels increase for 1 month, followed by a plateau period, then followed by another increase. The pattern then repeated as the addiction level decreases.), and "stable" (Heroin users with considerable experience with their addiction show remarkable resilience in maintaining affordable and manageable levels of use) patterns in customer addiction levels **Conclusion:** Same as results

Hoffer, 2013[41]	**Model Type:** Agent-based model **Research Question: (**1) What if instead of using numerical values to inform a model, it be better to develop concepts in the field then observe how they generate quantified outcomes? (2) Why are heroin prices inelastic to demand compared to some studies of marijuana and cocaine prices? (no interventions) **Target Population:** 500 agents	**Simulated Population:** Ethnographic data **Interventions:** N/A	**Calibration:** N/A **Validation:** N/A	**Results:** (1) There are lessons on working on an anthropological as opposed to epidemiological agent-based models. (2) The "tax" and improved deal values from brokering buffer effects of price changes by efficiently and rapidly distributing cost. The actual cost of heroin in real heroin markets is greater than its retail price suggests, implying price increases have much less of effect on consumption because most people are already paying higher prices through taxes and downsizing, they just don't know. **Conclusion:** N/A
Irvine, 2018[42]	**Model Type:** Markov chain model **Research Question:** Estimate impact of the take-home naloxone program in terms of number of deaths averted over the study period **Target Population:** Population of people who use drugs in one of three states: 1) at risk of overdose 2) not at risk of overdose 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl overdose	**Simulated Population:** The Centre for Global Public Health 2016: Estimation of key population size of PWID, men who have sex with men and sex workers who are at risk of acquiring HIV and hepatitis C in the five health regions of the Province of British Columbia **Interventions:** Take-home kit program data on monthly number of kits distributed and number of kits replaced due to an overdose event	**Calibration:** The study used the Bayesian inference approach (expert opinion and previous estimates of parameter informed model calibration and produced a final model fit with error that included both parameter and model uncertainty). **Validation:** The cross-validation scheme (each of the four data sources was left out of model-fitting process, various predicted values were then compared with the original data source that had been removed) was used.	**Results:** 298 deaths were averted by take-home naloxone program in the study period. An earlier scale-up of program could have averted an additional 118 deaths. **Conclusion:** Earlier adoption and distribution of take-home naloxone intervention might have had greater impact on overdose deaths.
Irvine, 2019[43]	**Model Type:** Markov process model **Research Question:** Measure the combined impact of large-scale interventions a.k.a. take-home naloxone kits, overdose prevention/supervised consumption sites, and OST implemented in British Columbia, Canada on the number of deaths averted **Target Population:** Overdose events and overdose-related deaths in British Columbia from January 2012 to December 2017	**Simulated Population:** (1) BC Coroner's Service, (2) BC Ambulance Service (3) The Centre for Global Public Health 2016: Estimation of Key Population Size of PWID, Men who Have Sex with Men and Sex Workers who are At Risk of Acquiring HIV and Hepatitis C in the Five Health Regions of the Province of British Columbia **Interventions:** (1) Provincial take-home naloxone programs (2) Opioid prevention service sites (3) Provincial Health Officer Report & Pharmanet	**Calibration:** The likelihood used for calibration was a composition of, at the regional level, monthly ambulance-attended overdoses, monthly fentanyl/non-fentanyl overdose deaths, monthly take-home naloxone kits used and provincial monthly ambulance call-out survey data and monthly urinalysis **Validation:** Model validation was assessed using root mean squared error of prediction and mean absolute error of prediction. Cross-validation was performed on the full model. Data for coroner-confirmed deaths, ambulance-attended overdoses, and take-home naloxone kits returned were removed for a region.	**Results:** An estimated 3030 deaths were averted by all interventions combined (1580 by take-home naloxone, 230 by overdose prevention services, and 590 from OST). **Conclusion:** The combined intervention approach has been effective in averting overdose deaths during BC's opioid overdose crisis.
Jackson, 2015[44]	**Model Type:** Markov chain model **Research Question:** Estimate the cost-effectiveness of injectable extended-release naltrexone compared with MMT and buprenorphine maintenance treatment **Target Population:** Simulated cohort of adult males aged 18–65 in the United States initiating pharmacotherapy for opioid dependence over a 6-month period	**Simulated Population:** (1) Mattick et al. 2014: Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence, (2) Krupitsky et al. 2011: Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicenter randomized trial **Interventions:** Same as for simulated population	**Calibration:** N/A **Validation:** N/A	**Results:** Extended-release naltrexone more effective and costly than methadone/buprenorphine, with incremental cost per opioid-free day gained relative to next most effective MMT of $72 **Conclusion:** Extended-release naltrexone is predicted to be more effective and more costly than methadone or buprenorphine in target population, extended-release naltrexone is a cost-effective medication for treating opioid dependence if state addiction treatment payers are willing to pay at least $72 per opioid-free day

Javanbakht, 2014[45]	**Model Type:** Decision-analytical Markov model **Research Question:** Determine the long-term effectiveness of MMT in prevention of HCV infection among IDUs **Target Population:** 1000 IDUs	**Simulated Population:** Self-reported data from 259 IDUs in seven governmental MMT centers in Shiraz, south of Iran. **Interventions:** Alavian et al. 2013: Effectiveness of Methadone Maintenance Treatment in Prevention of Hepatitis C Virus Transmission among Injecting Drug Users.	**Calibration:** N/A **Validation:** N/A	**Results:** The total discounted life years and QALYs saved in a cohort of 1000 IDUs in MMT are 1790 and 1590. **Conclusion:** It is necessary to develop MMT centers at regional and national levels when considering high prevalence of illicit injecting drug use in Iran and MMT effectiveness in prevention of HCV infection.
Keane, 2018[46]	**Model Type:** Agent-based model **Research Question:** Use an Agent-based model to improve understanding of effective community-based naloxone distribution to laypersons to reverse opioid overdose (no interventions) **Target Population:** 10,000 agents with opioid use disorder in Allegheny County	**Simulated Population:** Qualitative data **Interventions:** N/A	**Calibration:** N/A **Validation:** N/A	**Results:** Adding secondary distribution via social networks to a single distribution site resulted in 42.5% fewer overdose deaths relative to baseline, and a 39.9% decrease associated with tenfold increase in number of sites (sites distributing 10 kits/visit). **Conclusion:** Optimal distribution methods are secondary distribution so that the person who picks up naloxone kits can enable others in the community to administer naloxone, as well as targeting naloxone distribution to sites where individuals at high-risk for opioid overdose death are likely to visit. (ex: syringe-exchange programs)
Khan, 2018[47]	**Model Type:** Agent-based Model **Research Question:** Model the effect of combining direct acting antiviral treatment with Syringe access/MMT participation **Target Population:** PWID in NYC, US	**Simulated Population:** National HIV Behavioral Surveillance **Interventions:** Literature including Lawitz et al. 2013: Sofosbuvir for previously untreated chronic hepatitis C infection. New England Journal of Medicine. Turner et al. 2011: The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. Addiction.	**Calibration:** Prevalence estimates set to match current population level outcomes in NYC based on National HIV Behavioral Surveillance data **Validation:** Simulations of the baseline settings over 15 year were compared to historical trend data from NYC to ensure the simulation would converge at a relatively steady state that matched the known population rate of PWID in NYC	**Results:** Syringe access/MMT by itself has small effects on HCV prevalence; direct acting antiviral treatment by itself can lower both HCV and HCV-related advanced liver disease prevalence; combined strategies at sufficient levels can dramatically reduce HCV incidence. **Conclusion:** Combining interventions of Syringe access /MMT with direct acting antiviral treatment can play a critical role in reducing the long-term consequences of ongoing HCV infection.
King, 2016[48]	**Model Type:** Markov chain model **Research Question:** Compare the cost-effectiveness of flexible-dose clinic-based MMT and flexible-dose office-based buprenorphine maintenance therapy from the perspective of third-party payers in the US **Target Population:** Simulated cohort of 1000 adult, opioid-dependent patients with no history of treatment within 30 days	**Simulated Population:** Literature search for studies that compared MMT and buprenorphine maintenance therapy, in the US, used flexible dosage regimens, examined patients entering opioid maintenance therapy, and included retention in treatment and percentage of opioid negative urine drug screens **Interventions:** Same as for simulated population	**Calibration:** N/A **Validation:** N/A	**Results:** MMT is more costly and effective ($4,613 vs. $4,155, 20.3% vs. 15.9%), had an incremental cost-effectiveness ratio of $10,437/additional patient retained in treatment and $8,515 per opioid abuse-free week gained. **Conclusion:** MMT is more cost-effective than buprenorphine maintenance therapy (more effective in terms of retention in treatment at 1 year and opioid abuse-free weeks. Cost/week had the largest impact on retention-in-treatment outcome).

Krebs, 2018[49]	**Model Type:** Semi-Markov cohort model **Research Question:** Determine the cost-effectiveness of opioid agonist treatment for all treatment recipients compared with the observed standard of care for patients presenting with opioid use disorder to California's publicly funded treatment facilities **Target Population:** Patients presenting with opioid use disorder to publicly funded treatment facilities in California	**Simulated Population:** (1) Department of Justice, (2) California Department of Corrections and Rehabilitation, (3) National Death Index, (4) Linked data on all individuals admitted for the first time for publicly funded treatment for opioid use disorder in California (2006 to 2010) with linked mortality and criminal justice data (Krebs et al. 2018: Estimating state transitions for opioid use disorders). **Interventions:** Zarkin GA, Dunlap LJ, Hicks KA, Mamo D. 2005: Benefits and costs of methadone treatment: results from a lifetime simulation model. Health Econ;14:1133-50	**Calibration:** N/A **Validation:** The study assessed the model's internal and external validity by comparing projected mortality, HIV incidence, and the proportion of time spent in treatment with observed outcomes**.**	**Results:** Immediate access to OST for all treatment recipients costs less (by $78,257), with patients accumulating more QALYs (by 0.42) than with the observed standard of care, total lifetime savings for this cohort could be as high as $3.8 billion. **Conclusion:** The value of publicly funded treatment of opioid use disorder in California maximized when OST was delivered to all patients presenting for treatment. There are greater health benefits to cost savings than the observed standard of care.
Langham, 2018[50]	**Model Type:** Markov chain model **Research Question:** Replicate the US economic model developed by Coffin & Sullivan 2013 (Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal) and adapt it to the United Kingdom to assess the cost-effectiveness of distributing naloxone to adults at risk of heroin overdose for use by nonmedical responders (i.e., heroin users, family, friends, and caretakers) **Target Population:** Adults at risk for heroin overdose in United Kingdom	**Simulated Population:** (1) Population Mortality: UK - Office for National Statistics, National Life Tables, 1982-2014, (2) European Monitoring Centre for Drugs and Drug Addiction. **Interventions:** (1) T Bennett, K Holloway, Evaluation of the take home naloxone demonstration project - Welsh Assembly Government Social Research, 2011, (2) The NTA overdose and naloxone training program for families and caretakers. National Treatment Agency for Substance Misuse. National Treatment Agency, UK, 2011, (3) British National Formulary list price for Prenoxad® (Martindale Pharmaceuticals Ltd., Buckinghamshire, United Kingdom)	**Calibration:** N/A **Validation:** The model was validated by building it in Microsoft Excel 2016 and reproducing it in R version 3.3.2	**Results:** Distribution of intramuscular naloxone would decrease overdose deaths by around 6.6%. In a population of 200,000 heroin users, prevention of 2,500 premature deaths at an incremental cost QALY gained of £899. **Conclusion:** Implementation of new take-home naloxone programs/expanding existing ones will have measurable positive impact on lives saved
Levin, 1972[51]	**Model Type:** System dynamics model **Research Question:** Describe the flow of numbers of people in a community through various drug use statuses: potential users, soft drug users, heroin users, addicts in the community, addicts in community care, addicts in custody + impact of methadone programs and community rehabilitation **Target Population:** Ethnically/economically heterogenous geographic area of 8 square miles with population of about 180,000 people in NYC	**Simulated Population:** A critical review of the literature, an area study of an urban community, and interviews with treatment program directors, addicts, ex-addicts, research scientists, teachers, parole officers and other informant groups **Interventions:** Same as simulated population	**Calibration:** N/A **Validation:** N/A	**Results:** I) There is a need for a balanced set of programs to cope with a community narcotics problem. A total program for dealing with the problem should include sub-programs for rehabilitation, education, and police work directed at reducing heroin supply. Intensive application of any one of these programs will not be nearly as effective as the balanced use of all of them. The community must perceive addiction at least in part as a social and medical problem in order for rehabilitation programs to be successfully implemented. Community education programs are required toward this end. **Conclusion:** Same as results**.**

Mabileau, 2018[52]	**Model Type:** Deterministic compartmental model **Research Question:** Evaluate effectiveness and cost-effectiveness of interventions (NSPs, OST, HCV/HIV diagnosis, ART, and/or HCV treatment) targeting HCV/HIV infections among PWID in Eastern Europe/Central Asia **Target Population:** PWID moving between injecting statuses (non-PWID; PWID using neither NSP nor OST; PWID using NSP but not OST; and PWID using OST) in Eastern Europe/Central Asia	**Simulated Population:** International literature and data collections initiated by teams on HIV/HCV prevalence, and injecting/sexual behavior in Belarus, Georgia, Kazakhstan, Republic of Moldova, and Tajikistan **Interventions:** Same as simulated population	**Calibration:** N/A **Validation:** N/A	**Results:** Increasing NSP + OST led to a 42% of HCV infections averted in Tajikistan and 55% in Republic of Moldova. 30% of HIV infections were averted in Belarus and 61% in Kazakhstan over 20 years. Increasing coverage for all interventions is the most effective strategy, and is cost-effective in Belarus and in Kazakhstan (incremental a cost-effectiveness ratio = $12,960 and $21830/YLS). **Conclusion:** Increasing NSP and OST coverage, in addition to ART and HIV diagnosis, was very effective and cost-effective/cost-saving.
Martin, 2013 (1)[53]	**Model Type:** Dynamic deterministic compartmental model **Research Question:** Project the impact of combining OST, high-coverage needle and syringe programs (HCNSP), and antiviral treatment on hepatitis C virus (HCV) prevalence/incidence among PWID **Target Population:** People who inject drugs in the UK	**Simulated Population:** N/A **Interventions:** pooled analysis of UK data	**Calibration:** N/A **Validation:** N/A	**Results:** Large reductions (>45%) in HCV chronic prevalence over 10 years require HCV antiviral treatment. Scaling up OST and HCNSP substantially reduces the treatment rate required to achieve specific HCV prevalence reductions. If OST and HCNSP coverage were increased to 40% each (no coverage at baseline), then annually treating 10, 23, or 42 per 1000 PWID over 10 years would halve prevalence for 20%, 40%, or 60% baseline chronic HCV prevalence, respectively. Approximately 30% fewer treatments are necessary with new direct-acting antivirals. If coverage of OST and HCNSP is 50% at baseline, similar prevalence reductions require higher treatment rates for the same OST and HCNSP coverage. **Conclusion:** Combining antiviral treatment with OST with HCNSP is critical for achieving substantial reductions (>50%) in HCV chronic prevalence over 10 years.
Martin, 2013 (2)[54]	**Model Type:** Dynamic deterministic compartmental model **Research Question:** Project the potential impact of direct-acting antiviral therapy on HCV prevalence in three international settings (Edinburgh, UK; Melbourne, Australia; and Vancouver, Canada) with varied prevalence **Target Population:** People who inject drugs in Edinburgh, UK; Melbourne, Australia; and Vancouver, Canada	**Simulated Population:** Edinburgh: Data from the University of Glasgow Centre for Drug Misuse Research and Health Protection Scotland Melbourne: Australian Needle and Syringe Program National Data Report 2007-2011, Illicit Drug Reporting System (IDRS) Vancouver: McInnes et al. 2009: HIV/AIDS in Vancouver, British Columbia: a growing epidemic. **Interventions:** Edinburgh: The Needle Exchange Surveillance Initiative (NESI) Melbourne: Australian Needle and Syringe Program National Data Report 2007-2011, Illicit Drug Reporting System (IDRS) Vancouver: Urban Health Research Initiative of the British Columbia Centre for Excellence in HIV/AIDS	**Calibration:** Model was calibrated to the sampled HCV chronic prevalence in 2012 and proportion on opiate substitution therapy/high risk **Validation:** N/A	**Results:** Current HCV treatment rates may have a minimal impact on prevalence in Melbourne and Vancouver (<2% relative reductions) but could reduce prevalence by 26% in 15 years in Edinburgh. Prevalence could halve within 15 years with treatment scale-up to 15, 40, or 76 per 1,000 PWID annually in Edinburgh, Melbourne, or Vancouver, respectively (2-, 13-, and 15-fold increases, respectively). Scale-up to 22, 54, or 98 per 1,000 PWID annually could reduce prevalence by three-quarters within 15 years. **Conclusion:** Interferon-free direct-acting antivirals could enable increased HCV treatment uptake among PWID, which could have a major preventative impact

Masson, 2004[55]	**Model Type:** Two-state Markov model **Research Question:** To compare the cost and cost-effectiveness of methadone maintenance treatment and 180-day methadone detoxification enriched with psychosocial services **Target Population:** 179 adults with diagnosed opioid dependence	**Simulated Population:** 179 adults with opioid dependence recruited from research clinic in established drug treatment program in San Francisco **Interventions:** (1) Luce et al., 1996: Estimating cost in cost-effectiveness analysis. (2) Gold et al., 1996: Cost-Effectiveness in Health and Medicine, pp. 25–53. New York: Oxford University Press	**Calibration:** N/A **Validation:** N/A	**Results:** Total health-care costs and study costs are greater for maintenance than detoxification treatment ($7564 vs $6687, $4739 vs $2855). Detoxification patients incurred significantly higher costs for substance abuse and mental health than for care received outside the study. cost per life-year gained for methadone maintenance was $16,967. **Conclusion:** Methadone maintenance was more effective with cost-effectiveness ratio within range of many accepted medical interventions and may provide a survival advantage.
McGregor, 2019[56]	**Model Type:** System dynamics model **Research Question:** Identify the role of chiropractic care and opioid therapy in the management of chronic, nonmalignant pain. **Target Population:** 184,600 opioid dependent patients receiving chiropractic therapy, opioid therapy, both therapies, and those who received opioid therapy and developed opioid use disorder in Canada	**Simulated Population:** Canadian population-based data from online nationwide statistical sources and published literature. **Interventions:** Wakeland et al. 2011: System dynamics modeling as a potentially useful tool in analyzing mitigation strategies to reduce overdose deaths associated with pharmaceutical opioid treatment of chronic pain.	**Calibration:** N/A **Validation:** N/A	**Results:** Diverting patients early with collaborative care resulted in a significant decrease in dependence (z=65.25, z=59.39). Diverting patients early resulted in a significant drop in number of deaths (z=6.38). **Conclusion:** A future clinical study diverting patients with non-malignant musculoskeletal pain early to chiropractic stream of care could be most effective.
Morozova, 2019[57]	**Model Type:** Deterministic compartmental model **Research Question:** Evaluate the cost-effectiveness of a range of plausible OST scale-up strategies (allocating treatment slots to specialty and primary care clinics) in Kyiv, Mykolaiv, and Lviv in Ukraine **Target Population:** People at risk of and with opioid use disorder in Ukraine	**Simulated Population:** Aside from official demographic and administrative opioid agonist treatment data, most parameter estimates obtained from (1) a pilot study of integrating opioid agonist treatment into primary care settings and a large, cross-sectional survey among opioid-dependent PWID in Ukraine ad (2) two routine opioid agonist treatment patient data management systems in Ukraine **Interventions:** Same as simulated population	**Calibration:** The model was calibrated using empirical data from recent studies in Ukraine and literature. **Validation:** N/A	**Results:** There was an estimated 12.2-fold, 2.4-fold, and 13.4-fold OST capacity increase over 2016 baseline capacity in Kyiv, Mykolaiv, and Lviv, which would be cost-effective. **Conclusion:** Substantial increased in opioid agonist treatment capacity in 3 Ukrainian cities would be cost-effective for a wide range of willingness-to-pay thresholds
Nielsen, 2012[58]	**Model Type:** System dynamics model **Research Question:** Develop a system dynamics model of the medical use of pharmaceutical opioids and the associated diversion and nonmedical use of these drugs. Identify points of high leverage for policy interventions to reduce the adverse consequences associated with the epidemic of nonmedical use **Target Population:** Not provided in paper	**Simulated Population:** (1) CDC WONDER data for overdose/opioid use disorder rates and mortality rates, (2) CONSORT for overdose/opioid use disorder rates, (3) WHO for chronic pain. **Interventions:** (1) US population mortality data, (2) panel consensus, (3) Potter, M., et al. 2001. "Opioids for Chronic Nonmalignant Pain: Attitudes and Practices of Primary Care Physicians in the UCSF/Stanford Collaborative Research Network." Journal of Family Practice, 50(2):145-51, (4) Gureje, O., Simon, G. E., and Von Korff, M. 2001."A Cross-National Study of the Course of Persistent Pain in Primary Care." Pain, 92: 195-200.	**Calibration:** Model outputs were compared with reference data for the historical period (1995 to 2008) where these data were available. **Validation:** Model outputs were compared with reference data for the historical period (1995 to 2008) where these data were available.	**Results:** Principal findings were that the introduction of a tamper resistant formulation unexpectedly increased total overdose deaths. This was due to increased prescribing which counteracted the drop in the death rate. **Conclusion:** It is important to choose metrics carefully. A system dynamic modeling approach can help evaluate interventions intended to ameliorate adverse outcomes associated with opioids for treating pain.

Nielsen, 2013[59]	**Model Type:** System dynamics model **Research Question:** Evaluate the progress of a system dynamics model of the complex system surrounding the initiation and nonmedical use of pharmaceutical opioids in the US **Target Population:** Not provided in paper, assumed to be the U.S. population	**Simulated Population:** NSDUH **Interventions:** NSDUH	**Calibration:** Most parameters were calibrated to fit three time series from the NSDUH for the years 1995-2005: Total past year nonmedical opioid users, total past year initiates of opioid use, total past year opioid users who meet the criteria for opioid abuse or addiction. To build confidence in the model concept, model outputs were tested for fit against 2006-2011 data. **Validation:** N/A	**Results:** Preliminary findings indicate that interventions which reduce the perceived attractiveness of opioids for recreational use may significantly reduce initiation and nonmedical use most significantly, while supply restriction effected through drug take back days and prescribing changes may have more modest effects. **Conclusion:** System dynamics is an effective approach for evaluating potential interventions for use of pharmaceutical opioids to treat pain.
Nosyk, 2012[60]	**Model Type:** Semi-Markov cohort model **Research Question:** Compare the cost-effectiveness of diacetylmorphine and methadone maintenance treatment for chronic opioid dependence refractory to treatment **Target Population:** A cohort of patients assigned the baseline characteristics of the participants in the North American Opiate Medication Initiative (25+ y/o, regular opioid injection, minimum 5 years opioid use, at least 2 attempts at substitution treatment)	**Simulated Population:** North American Opiate Medication Initiative (NAOMI), randomized controlled trial conducted in Vancouver, British Columbia and Montreal, Quebec **Interventions:** North American Opiate Medication Initiative (NAOMI) and British Columbia Methadone Maintenance Treatment Outcome Study	**Calibration:** N/A **Validation:** Study compared baseline model results to reported trial data from NAOMI trial and compared overall annual mortality rate in MMT arm to estimates from the study by Bargagli et al.	**Results:** People receiving methadone gained 7.46 discounted QALYs on average and generated a societal cost of $1.14 million, those receiving diacetylmorphine gained 7.92 discounted QALYs on average and generated $1.10 million. **Conclusion:** Diacetylmorphine may be more effective and less costly than methadone among people with chronic opioid dependence refractory to treatment.
Nosyk, 2014[61]	**Model Type:** Multi-state Markov models **Research Question:** Characterize longitudinal patterns of drug use careers and identify determinants of drug use frequency across cohorts of primary heroin, methamphetamine and cocaine users in community, criminal justice and drug treatment settings in California, USA **Target Population:** Primary users of heroin (N= 629), cocaine (N= 694) and methamphetamine (N= 474) in California	**Simulated Population:** Subjects who reported a primary drug problem of heroin, cocaine, or methamphetamine use from several studies **Interventions:** Literature on the cumulative effect of drug treatment on drug use patterns	**Calibration:** N/A **Validation:** N/A	**Results:** Across primary drug use types, PH frailty models demonstrated durations of daily use diminished in successive episodes over time. Multi-state Markov models revealed that primarily stimulant users had more erratic longitudinal patterns of drug use, transitioning more rapidly between periods of treatment, abstinence, non-daily and daily use. Methamphetamine users exhibited relatively longer durations of high-frequency use. Criminal engagement had a destabilizing effect on health state durations across drug types. Longer incarceration histories were associated with delayed transitions toward cessation. **Conclusion:** PH frailty and Multi-state Markov modeling techniques provide complementary info on longitudinal patterns of drug abuse, and can inform clinical practice and policy and be used in health economic simulation models to inform resource allocation decisions

Nosyk, 2017[62]	**Model Type:** Deterministic compartmental model **Research Question:** Isolate independent effects of harm reduction services (OST uptake and needle distribution volumes) and ART on HIV transmission via needle sharing in British Columbia, Canada **Target Population:** Adult population (15-64 y/o) of HIV-infected people in British Columbia from 1996 to 2013, compartmentalized based on HIV risk behavior, screening status, and HIV infection status	**Simulated Population:** Comprehensive linked individual health administrative and registry data in British Columbia, Canada **Interventions:** Same as simulated population	**Calibration:** The model was calibrated to replicate true number of people living with HIV on ART in British Columbia at annual midpoint. **Validation:** The model was validated to ensure key epidemiological parameters were approximated to known or externally-estimated figures**.**	**Results:** 3204 incident HIV cases were averted in 1996-2013 due to the impact of expansion of harm reduction services and ART coverage on HIV transmission via needle sharing. Assuming ART had zero effect on transmission through needle sharing, it is estimated that harm reduction services alone would have accounted for 77% of averted HIV incidence. Assuming harm reduction services remained at 1996 levels, it is estimated that ART alone would have accounted for 44% of averted HIV incidence. **Conclusion:** ART could have a great effect on incident cases of HIV transmission through needle sharing averted than that of harm reduction.
Pitt, 2018[63]	**Model Type:** System dynamics model **Research Question:** Project addiction-related deaths, life years, and quality-adjusted life years from 2016 to 2025 for 11 policy responses related to increasing naloxone availability, needle exchange, medication-for opioid use disorder, and psychosocial treatment to the opioid epidemic **Target Population:** Not provided in paper	**Simulated Population:** (1) 2008, 2014 CDC Multiple Cause of Death files, (2) NSDUH, 2002-2011, (3) 2012–2013 NESARC-III, (4) nationwide Survey of Key Informants' Patients (SKIP), (5) Vital Statistics, (6) Injection Drug Users in the UFO Study, San Francisco, California, 1997–2007 **Interventions:** (1) Evidence-based review of 79 studies on the development of abuse/addiction and aberrant drug related behaviors (ADRBs) in chronic pain patients with nonmalignant pain on exposure to opioid addiction treatment, (2) systematic review of 38 studies of chronic pain and opioid misuse, (3) systematic review of 26 studies of clinical effectiveness and cost-effectiveness studies	**Calibration:** Study used model calibration (1) so that chronic pain prevalence is constant over the model time horizon, (2) to approximate the probability of "Chronic pain nonuser" beginning prescription opioid use, (3) to arrive at monthly chance of escalation among the "severe opioid use disorder without Rx" population, (4) and to select enrollment and dropout rates that yield increasing prevalence of medication-for opioid use disorder among the prescription opioid-addicted and constant treatment prevalence among heroin addicts under the status quo. **Validation:** N/A	**Results:** Over 5 years, increasing naloxone availability, promoting needle exchange, expanding medications for opioid use disorder, and increasing psychosocial treatment increased life years and QALYs and reduced deaths. Other policies reduced opioid prescription supply and related deaths but increased heroin-related deaths. Over a longer horizon, some such policies may avert enough new addiction to outweigh the harms. No single policy likely to substantially reduce deaths over 5 to 10 years **Conclusion:** Policies focused on services for addicted people improve population health without harming any groups. Policies that reduce the prescription opioid supply may increase heroin use and reduce quality of life in the short term, but in the long term could generate positive health benefits.

Rhodes, 2010[64]	**Model Type:** Deterministic compartmental model **Research Question:** Simulate the transmission of HIV in an injection drug user population model **Target Population:** Injection drug users in Russia	**Simulated Population:** Hickman et al 2007: Hepatitis C virus (HCV) prevalence, and injecting risk behaviour in multiple sites in England in 2004. Nordt & Stohler 2006: Incidence of heroin use in Zurich, Switzerland: a treatment case register analysis. Sweeting et al 2008: Estimating the prevalence of ex-injecting drug use in the population. **Interventions:** Gowing et al 2008: Substitution treatment of injecting opioid users for prevention of HIV infection. Van den Berg et al 2007: Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus: evidence from the Amsterdam cohort studies among drug users. Des Jarlais et al 2007: Reducing HIV infection among new injecting drug users in the China-Vietnam Cross Border Project. Foss et al 2007: Could the CARE-SHAKTI intervention for injecting drug users be maintaining the low HIV prevalence in Dhaka, Bangladesh?	**Calibration:** N/A **Validation:** N/A	**Results:** Current coverage of syringe distribution programs in Russia (10%) is unlikely to reduce HIV incidence among injecting drug users by more than 15% over five years. Conversely, increasing the coverage of opioid substitution treatment from 0% to 10%, 25%, or 50% could decrease incidence by 21% (90% confidence interval 14% to 34%), 34% (23% to 51%), or 55% (40% to 71%), respectively. **Conclusion:** Russia could substantially reduce the incidence of HIV infection if it permitted the use of opioid substitution treatment.
Rhodes, 2015[65]	**Model Type:** Deterministic compartmental model **Research Question**: Explore the expectations of the effects of implementing methadone in Kenya as well as to project its potential HIV transmission impact **Target Population**: People who inject drugs in Nairobi, Kenya	**Simulated Population:** Test and Linkage to Care Kenya Study **Interventions:** Brinkhof et al 2009: Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality Johansson et al 2010: Further benefits by early start of HIV treatment in low-income countries: survival estimates of early versus deferred antiretroviral therapy. Mills et al 2011: Mortality by baseline CD4 cell count among HIV patients initiating antiretroviral therapy: evidence from a large cohort in Uganda. Carrico 2011: Substance use and HIV disease progression in the HAART era: implications for the primary prevention of HIV	**Calibration:** The current yearly sexual HIV incidence among PWID is estimated by calibrating a constant force of infection model to the possible HIV prevalence achieved among newly initiated PWID before they start injecting. The injecting HIV transmission probability is calibrated to give a 20% HIV prevalence among PWID in 2014, as found in recent respondent-driven sampling surveys in Nairobi. **Validation**: N/A	**Results:** The modelled impact of OST shows relatively slight reductions in HIV incidence (5–10%) and prevalence (2–4%) over 5 years at coverage levels (around 10%) anticipated in the planned roll-out of OST. However, there is a higher impact with increased coverage, with 40% coverage producing a 20% reduction in HIV incidence, even when accounting for relatively high sexual transmissions. **Conclusion:** Methadone offers HIV prevention potential, but there is a need to better model the effects of sexual HIV transmission in mediating the impact of OST among PWID in settings characterized by a combination of generalized and concentrated epidemics.

Ritter, 2016[66]	**Model Type:** Microsimulation model **Research Question:** Detail the development of an microsimulation model for heroin use which can be used to assess net social benefit of current heroin treatment strategies, such that the final model can be used to compare different combinations of treatment alternatives (detoxification, residential rehabilitation, opioid substitution treatment, counselling only, prison w/o treatment, and prison w/ OST) **Target Population:** Individuals who have ever used heroin (including those currently abstinent, in treatment groups, and in prison) in New South Wales, Australia	**Simulated Population:** (1) Australian Treatment Outcome Study data, (2) Shand, F. L. et al. 2014. Hepatitis C testing and status among opioid substitution treatment clients in New South Wales. Australian and New Zealand Journal of Public Health, 38(2), 160-164., (3) The Kirby Institute, (4) Linked dataset of the Pharmaceutical Drugs of Addiction System and the Bureau of Crime Statistics and Research Re-offending Database **Interventions:** (1) Systematic review of heroin treatment outcome literature, (2) Australian administrative treatment data, (3) Australian Treatment Outcome Study data	**Calibration:** Study (1) Verified coding of conceptual logic by randomly selecting 100 individuals in the model and matching traced behavior against conceptual logic. The transition summary from the model for these 100 individuals was manually compared against the expected transition summary, (2) Mortality rate, imprisonment rate, and transitions to community states from the model compared to rates used in input, (3) Verifications on the population aging, costs, benefits, HIV and HCV infections and the associated illness progressions. **Validation:** MIX dataset (Victorian cohort of 688 people who inject drugs) and data from published research on mortality rates were used for model validation. Monte Carlo simulation (running the model 100 times given the tight confidence intervals) was used.	**Results:** The final model represented 42 years of a heroin use career for a cohort based on Australian data. Individuals cycle into and out of heroin using states (including abstinence), as well as treatment and prison states. We were able to build a stable, tractable model and verified all parameters. High validity. **Conclusion:** Same as results.
Rossi, 2002[67]	**Model Type:** System dynamics model **Research Question:** Propose an SD model to reflect the spread of drug use in a population **Target Population:** Not provided in paper	**Simulated Population:** (1) Consensus Conference on AIDS (Italy, 1998), (2) EMCDDA (European Monitoring Centre for Drugs and Drug Addiction),1999 **Interventions:** EMCDDA (European Monitoring Centre for Drugs and Drug Addiction), 1999	**Calibration:** N/A **Validation:** N/A	**Results:** Qualitative and quantitative results apply to any kind of epidemic of drug use, even involving new drugs, at least from a qualitative point of view. In particular, the qualitative evaluation of the effectiveness of different types of intervention over the course of the epidemic is valid for any epidemic of problematic drug use. **Conclusion:** Same as results.
Schackman, 2012[68]	**Model Type:** Decision-analytic model **Research Question**: Evaluate effectiveness of long-term office-based buprenorphine-naloxone versus no treatment for clinically stable opioid-dependent patients **Population**: Clinically stable patients with opioid-dependence who already completed 6 months of office-based buprenorphine-naloxone treatment	**Simulated Population**: Published cohort study that includes treatment retention, opioid use, and costs for this population. **Interventions**: Multiple published cohort studies	**Calibration**: Model parameters were derived from a cohort sample of 53 long-term opioid users treated with office-based buprenorphine-naloxone treatment in a primary care setting, and a previous cost study. **Validation:** N/A	**Results**: Office-based buprenorphine-naloxone treatment for clinically stable patients has a cost-effectiveness ratio of $35,100/QALY compared to no treatment after 24 months, with 64% probability of being < $100,000/QALY. **Conclusion**: office-based buprenorphine-naloxone treatment for this set of patients can be a cost-effective alternative to no treatment at an accepted threshold of $100,000/QALY.
Sheerin, 2004[69]	**Model Type:** Markov chain model **Research Question:** Cost-effectiveness of treatment for HCV infection is investigated for Maori and non-Maori IDUs on MMT and anti-viral therapy in New Zealand **Target Population:** Injection drug users in New Zealand	**Simulated Population:** N/A **Interventions:** N/A	**Calibration:** N/A **Validation:** N/A	**Results:** Cost-effectiveness of MMT alone is $25,397/life year saved for non-Maori men and $25,035 for non-Maori women IDUs. Cost-effectiveness of providing conventional combination therapy is similar to MMT and costs/life year saved lower for Maori for men and women. Cost-effectiveness of new treatment with pegylated interferon and ribavirin is similar to that of conventional combination therapy. **Conclusion:** HCV treatment has a cost/ life year saved that compares favorably with other treatments that are currently funded in New Zealand**.**

Su, 2019[70]	**Model Type:** Monte Carlo simulation **Research Question:** Estimate the trend of heroin-only, synthetic drug-only and polydrug (heroin/synthetic drug) use during 2000–2030 period in China using existing data (No interventions modeled) **Target Population:** Not provided in paper, assumed to be the Chinese population	**Simulated Population:** Annual Report on Drug Control in China and peer-reviewed publications. **Interventions:** No interventions were modeled.	**Calibration:** Using a stepwise approach, the model with the fewest required parameters without significant reduction in its fitness is chosen as the calibrated model. **Validation:** N/A	**Results:** Synthetic drug use will become dominant in drug users in China, but polydrug use of both heroin and synthetic drugs will remain substantial. **Conclusion:** Same as results.
Sweeney, 2019[71]	**Model Type:** Deterministic compartmental model **Research Question:** Evaluate the cost-effectiveness of NSPs compared with no NSPs on hepatitis C virus (HCV) transmission in the United Kingdom **Target Population:** PWID in cities in the United Kingdom (Dundee, Walsall, Bristol)	**Simulated Population:** (1) Jones H. E et al. 2015. Problem drug use prevalence estimation revisited: heterogeneity in capture–recapture and the role of external evidence, (2) King R.et al. 2013.Injecting drug users in Scotland, 2006: listing, number, demography, and opiate-related death-rates. **Interventions:** Platt L et al. 2017. Assessing the impact and cost-effectiveness of needle/syringe provision on hepatitis C transmission among people who inject drugs in the United Kingdom: analysis of pooled datasets and economic modeling.	**Calibration:** The model was parameterized for each city using context-specific survey data and data from literature and calibrated using intervention coverage/HCV prevalence data. **Validation:** Additional HCV prevalence and incidence data were used to validate the model projections**.**	**Results:** NSPs are highly cost-effective over 50 years and decreased the number of HCV incident infections. The mean incremental cost-effectiveness ratio was cost-saving in Dundee and Bristol, and £596 per QALY gained in Walsall, with 78, 46 and 40% of simulations being cost-saving in each city, respectively, with differences driven by coverage of NSP and HCV prevalence (lowest in Walsall). **Conclusion:** NSPs are a highly cost-effective, low-cost intervention to reduce HCV transmission, and in some settings are cost-saving.
Townsend, 2020[72]	**Model Type:** Decision-analytic model **Research Question:** Compare the cost-effectiveness of 8 strategies of naloxone distribution that encompass combinations of low and high distribution to laypeople, police/firefighters, emergency medical services personnel, and combinations **Target Population:** (1) People likely to witness or experience overdose ("laypeople"); (2) police and firefighters; (3) emergency medical services personnel; and (4) combinations of these groups, assumed to be in the U.S.	**Simulated Population:** NSDUH, 2016 **Interventions:** Peter J. Neumann et al. JAMA, 2016: Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses Second Panel on Cost-Effectiveness in Health and Medicine Gillian D. Sanders	**Calibration:** Two steps were carried out: (1) The adjustment of annual probability of overdose (given no prior overdoses) such that 50-60% of those surviving at 10-20 years after initiation would have a lifetime history of overdose, (2) as well as the adjustment of several parameters (probability of subsequent overdose mortality rates of first and subsequent overdoses, etc.) to approximate the estimated 47,600 opioid overdose deaths nationwide in 2017. **Validation:** Two steps were carried out: (1) Checked that lifetime percentage of overdose deaths averted in the high laypeople /low emergency medical services personnel/low police/firefighters strategy was similar to that in two modeling studies of lay naloxone distribution, and (2) compared the percentage of lay naloxone kits used with that in three empirical studies.	**Results:** High distribution to all three groups maximized net monetary benefit and minimized fatal overdoses, averted 21% of overdose deaths compared to minimum distribution. High distribution to laypeople and one of the other groups comprised the second and third best strategies. The majority of health gains resulted from increased lay distribution. In the societal analysis, every strategy was cost-saving compared to its next-best alternative; cost savings were greatest in the maximum distribution strategy. **Conclusion:** Increasing naloxone distribution to laypeople and first responder groups would maximize health gains and be cost-effective. If feasible, communities should distribute naloxone to all groups. Otherwise, distribution to laypeople and one of the first responder groups should be emphasized.

Uyei, 2017[73]	**Model Type:** Decision-analytic Markov model **Research Question:** Perform a cost-effectiveness modeling study on the effects of naloxone distribution alone or in combination with addiction treatment with or without pre-exposure prophylaxis for HIV prevention in people who inject drugs **Target Population:** Simulate opioid overdose, HIV incidence, overdose-related deaths, and HIV-related deaths in PWID in Connecticut, U.S.	**Simulated Population:** Parameters developed + selected from published sources in consultation with program implementation and policy experts at Connecticut Department of Public Health and with addiction/HIV experts who are knowledgeable about service delivery for people who use drugs in Connecticut. **Interventions:** Cost based on data from the consortium of hospital and community-based HIV care sites in the USA.	**Calibration:** N/A **Validation:** The fit of the model was evaluated by comparing model generated estimates for a no intervention scenario to published epidemiologic studies for 4 targets: 5-year mortality, 10-year mortality, HIV incidence, and HIV prevalence**.**	**Results:** Naloxone distribution strategy yielded incremental cost-effectiveness ratio of $323/QALY. The most efficient strategies were naloxone distribution combined with linkage to addiction treatment (cost saving), and naloxone distribution combined with PrEP and linkage to addiction treatment (incremental a cost-effectiveness ratio = $95337/QALY) at a willingness-to-pay threshold of $100000. **Conclusion:** Naloxone distribution through syringe service programs combined with linkage to addiction treatment is cost-saving compared with no additional services. Combining naloxone distribution, PrEP, and linkage to addiction treatment results in greater health benefits in people who inject drugs and is also cost-effective**.**
Vickerman, 2012[74]	**Model Type:** Dynamic Compartmental Model **Research Question:** Investigate the impact of scaling-up OST and high coverage needle and syringe programs **Target Population:** UK	**Simulated Population:** PWID **Interventions:** Scaling up OST and NSP access	**Calibration:** Fit to specific NSP and OST coverage levels **Validation:** N/A	**Results:** In the United Kingdom, without current coverage levels of OST and 100% NSP the chronic HCV prevalence could be 65% instead of 40%. When increasing OST and 100% NSP coverage further is unlikely to reduce chronic prevalence to less than 30% over 10 years unless coverage becomes 80%. **Conclusion:** Scaling-up OST and high coverage NSP can reduce HCV prevalence among PWID, but reductions can be modest and require long-term sustained intervention coverage. In high coverage settings, other interventions are needed to further decrease HCV prevalence. In low coverage settings, sustained scale-up of both interventions is needed.
Vickerman, 2014[75]	**Model Type:** Dynamic Compartmental Model **Research Question:** Model the potential impact on HIV incidence and prevalence of OST, NSP and ART in three illustrative epidemic scenarios: Russia (St. Petersburg); Estonia (Tallinn) and Tajikistan (Dushanbe). **Target Population:** people who inject drugs in St. Petersburg, Russia; Tallinn, Estonia; and Dushanbe, Tajikistan	**Simulated Population:** Uuskula et al 2011: Expanded syringe exchange programs and reduced HIV infection among new injection drug users in Tallinn, Estonia. Platt et al. 2006: High HIV prevalence among injecting drug users in Estonia: Implications for understanding the risk environment. Beyrer et al. 2009: Characterization of the emerging HIV type 1 and HCV epidemics among injecting drug users in Dushanbe, Tajikistan. Niccolai et al 2010: High HIV prevalence, suboptimal HIV testing, and low knowledge of HIV-positive serostatus among injection drug users in St. Petersburg, Russia. **Interventions**: Aspinall et al 2014: Are needle and syringe programs associated with are duction in HIV transmission among people who inject drugs: A systematic review and meta-analysis. Uuskula et al 2011: Expanded syringe exchange programs and reduced HIV infection among new injection drug users in Tallinn, Estonia. Turner et al 2011: The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: Pooling of UK evidence.	**Calibration:** The model was first fit to available HIV prevalence and incidence data assuming all HIV transmission in St. Petersburg is injection related by varying the injection related infection rate, the seeding prevalence in 1996 and the duration of injecting. Then, because a large body of evidence suggest there could be considerable sexual HIV transmission occurring among PWID in St. Petersburg, we then calibrated the level of sexual HIV trans-mission in the model to produce the level of sexual HIV prevalence(7%) estimated to be occurring among PWID in St. Petersburg from a recent detailed modeling analysis. The injecting related infection rate was then adjusted to re-calibrate the model to the HIV epidemiological data. The same model fitting method used in St. Petersburg was then used to fit the model to the HIV prevalence and incidence data available in Dushanbe and Tallinn. **Validation**: N/A	**Results:** For St. Petersburg, when OST, NSP and ART are combined, only 14% coverage of each intervention is required to achieve a 30% reduction in HIV incidence over 10 years. Similar findings are obtained for Tallinn and Dushanbe. In order to achieve the same reductions in HIV prevalence over 10 years, over double the coverage level is required relative to what was needed to achieve the same reduction in HIV incidence in that setting. To either reduce HIV incidence to less than 1% or HIV prevalence to less than 10% over 20 years, with all interventions combined, projections suggest that very high coverage levels of 74–85% are generally required for the higher prevalence settings of Tallinn and St. Petersburg, whereas lower coverage levels (23–34%) are needed in Dushanbe. Coverage requirements are robust to increased sexual HIV transmission, risk heterogeneity and like-with-like mixing, as well as to assuming a lower HIV acute phase cofactor or different injecting cessation rate. **Conclusion**: High but achievable coverage levels of NSP can result in large decreases (30%) in HIV incidence in settings with high HIV prevalence among PWID. Required coverage levels are much lower when interventions are combined or in lower prevalence settings. However, even when all three interventions are combined, the targets of reducing HIV incidence to less than 1% or prevalence to less than 10% in 20 years may be hard to achieve except in lower prevalence settings.

Wakeland, 2011[76]	**Model Type:** System dynamics model **Research Question:** Evaluate mitigation strategies (making available drug formulations with increased tamper-resistance, prescriber education programs, programs that reduce rates of medical user-related abuse and addiction) to address the rise in abuse, addiction, and overdose deaths associated with prescription opioids (POs) to treat chronic pain **Target Population:** Not provided in paper	**Simulated Population:** (1) CDC WONDER and CONSORT for overdose/opioid use disorder rates, (2) CDC WONDER for mortality rates, (3) WHO for chronic pain. **Interventions:** Not discussed in the paper.	**Calibration:** N/A **Validation:** The model was tested to ensure that its behavior remained plausible when subjected to tests involving extreme conditions (i.e., abnormal parameter values)**.**	**Results:** Tamper-resistant drug products will likely reduce overdose death rates but may not reduce overall deaths if there is increased prescribing. Prescriber education would likely reduce deaths through a reduction in patient access to pharmaceutical opioid analgesics. **Conclusion:** The system dynamics approach may have potential for opioid-related policy evaluation, but metrics must be carefully selected and trade-offs may be involved.
Wakeland, 2013[77]	**Model Type:** System dynamics model **Research Question:** Evaluate the potential impacts of three educational interventions on opioid overdose: (1) Prescriber education program, (2) patient education program that halved the rate medical users with chronic pain developed abuse or addiction, (3) popularity intervention that simulated an education program targeted at nonmedical users halved rate of initiation and also the level of perceived popularity of opioids for nonmedical use **Target Population:** Not provided in paper	**Simulated Population:** (1) CDC WONDER and CONSORT for overdose/opioid use disorder rates, (2) CDC WONDER for mortality rates, (3) WHO for chronic pain. **Interventions:** NSDUH	**Calibration:** Model outputs were compared with reference data for the historical period (1995 to 2008) where these data were available. **Validation:** The model was tested in detail to determine its robustness and ability to endogenously match simulated data against historical data.	**Results:** (1) Prescriber education intervention reduced total overdose deaths in the model and reduced total # who receive opioid analgesic therapy. (2) Medical user education reduced overdose deaths among medical users but increased deaths from nonmedical use. (3) "Popularity" intervention sharply reduced overdose deaths among nonmedical users while having no effect on medical use. **Conclusion:** System dynamics modeling shows promise for evaluating potential interventions to ameliorate the adverse outcomes associated with the complex system surrounding the use of opioid analgesics to treat pain**.**
Wakeland, 2015[78]	**Model Type:** System dynamics model **Research Question:** Explain historical behaviors of interest, including various populations of nonmedical opioid users and accidental overdose mortality within those populations and explore policy interventions (Tamper resistant drug formulations, reducing medicine sharing via patient education or smaller prescription sizes, and implementing drug take-back days) **Target Population:** Population of people who initiate nonmedical prescription opioid analgesics (POA) usage	**Simulated Population:** NSDUH, Monitoring the Future, Treatment Episode Data Set, CDC. **Interventions:** Prescription drug monitoring program Center of Excellence 2011, NSDUH	**Calibration:** (1) Interviews were conducted with our expert advisory panel of four researchers and practitioners. (2) Literature review was conducted to locate sources of empirical support for the relationships represented in the model, and research from the large body of published literature was synthesized to estimate parameter values. **Validation:** Model results were compared to NSDUH data on POA users, use disorder, heroin users and deaths.	**Results:** (1) The model is able to replicate patterns seen in historical data for each user population and associated overdose deaths. (2) Policy analysis showed tamper resistant formulations and interventions to reduce informal sharing could significantly reduce nonmedical user populations and overdose deaths in the long term. **Conclusion:** Creating a theory/model that can explain system behaviors at a systems level scale is feasible and facilitates thorough evaluation of policy interventions.
Wakeland, 2016[79]	**Model Type:** System dynamics model **Research Question:** Study the impact of three types of policy interventions to reduce adverse pain medicine outcomes: (1) 50% reduction via prescription drug monitoring programs in fraudulent prescriptions obtained by traffickers through doctor shopping and prescription forgery, (2) tamper resistant drug formulation, (3) reduction in the popularity of opioids for nonmedical use by 50% **Target Population:** (1) People prescribed opioids, (2) people prescribed opioids w/ abuse or addiction, (3) nonmedical opioid users	**Simulated Population: NSDUH,** Monitoring the Future, Treatment Episode Data Set, CDC. **Interventions:** Prescription drug monitoring program Center of Excellence 2011, NSDUH	**Calibration:** (1) Interviews were conducted with our expert advisory panel of four researchers and practitioners, (2) literature review was conducted to locate sources of empirical support for the relationships represented in the model, and research from the large body of published literature was synthesized to estimate parameter values. **Validation:** Model results were compared to NSDUH data on prescription opioid analgesics (POA) users, use disorder, heroin users and deaths**.**	**Results:** (1) Prescription drug monitoring programs reduced nonmedical overdoses through supply restriction, (2) intervention to reduce popularity of nonmedical usage reduced nonmedical overdoses by curtailing demand, and (3) tamper-resistant drug formulation intervention resulted in decreased risk to individuals but increased overdose deaths. **Conclusion:** Key policy insights are that supply and demand must be carefully considered. The feedback loops, which created the problem, can help to identify solutions. The outcome metrics must be carefully chosen.

White, 2007[80]	**Model Type:** Compartmental ODE Model **Research Question:** Identify parameters of interest for further study to assist policy-makers in targeting prevention and treatment resources for maximum effectiveness **Target Population:** Irish population	**Simulated Population:** Research Outcome Study in Ireland (ROSIE) **Interventions:** N/A	**Calibration:** Fit characteristics of the drug-using career to a susceptible-infectious disease model **Validation:** N/A	**Results**: An equation for reproduction rate - defined as the probability of becoming addicted to drugs multiplied by the mean amount of time spent using drugs without treatment. **Conclusion:** When the probability of becoming a drug user is greater than the sum of the cessation probabilities, prevalence will rise. The probability of becoming a drug user, is the most useful parameter to target for the reduction of reproduction rate**.**
Wilson, 2003[81]	**Model Type:** Dynamic compartmental model **Research Question:** Estimate the allocation of a $1 million budget between MM and SO that averts the greatest number of HIV infections in both IDUs and their sex partners **Target Population:** Simulated 10,000 heterosexual IDUs, 7,500 males and 2,500 females, and 5,000 heterosexual female non-IDU sex partners of male IDUs in San Francisco, California, and New York City for periods from the mid-1980s to the mid-1990s	**Simulated Population:** (1) Lewis DK, et al. 1994. Sexual risk behavior among heterosexual intravenous drug users: ethnic and gender variations, (2) Cohen JB, et al. 1989 Women and IV drugs: parenteral and heterosexual transmission of human immunodeficiency virus, (3) Friedland GH, et al. 1987. Transmission of the human immunodeficiency virus. N Engl J Med. 1987, (4) Friedman SR, et al. 1989. AIDS and the new drug injector, (5) Des Jarlais DC, et al. Intravenous drug use and the heterosexual transmission of the human immunodeficiency virus. Current trends in New York City **Interventions:** Existing literature on methadone maintenance treatment and street outreach programs	**Calibration:** N/A **Validation:** N/A	**Results:** Best allocation nearly always involves spending as much as possible on street outreach **Conclusion:** Even though prevention works better in higher risk scenarios, the choice of intervention mix is more important in the lower risk scenarios
Wisløff, 2018[82]	**Model Type**: Dynamic compartmental model **Research Question**: Analyze the impact of screening to increase HCV treatment and harm reduction initiatives on reducing the incidence of new infection among people who inject drugs **Target Population**: Norwegian population	**Simulated Population:** PWID in addiction treatment institutions, NSPs, OST. **Interventions:** SIRUS (Ellen Amundsen) and Turner et al 2011: The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence.	**Calibration:** N/A **Validation:** N/A	**Results:** The most cost-effective strategy for increasing hepatitis C treatment uptake was screening by general practitioners while allowing for all infected people to be treated (Reduces incidence of hepatitis C by 2030 by 63%). The 2 harm reduction strategies both reduced the incidence of hepatitis C by about 70%. Combining an increase in NSPs with OST was most cost-effective, and can reduce incidence of hepatitis C by 80% compared with the current incidence by 2030. **Conclusion:** Interventions to reduce burden and spread of hepatitis C are cost-effective. Reaching WHO target of 90% reduction in hepatitis C incidence by 2030 may be difficult without combining different initiatives**.**
Yenikomshian, 2017[83]	**Model Type:** Markov process model **Research Question:** Estimate the healthcare resource utilization, associated costs, and number needed to harm from a physician's decision to prescribe extended release non-abuse-deterrent opioids (non-ADO) as compared to ER ADOs in a chronic pain population. **Target Population:** 10,000 extended-release opioid appropriate patients	**Simulated Population:** (1) Roland et al. 2013 and Palmer et al. 2015 for commercial population, (2) Oderda et al. 2015 for Medicare population, (3) McAdam-Marx et al. 2010 for Medicaid population, and (4) Baser et al. 2013 for VA population **Interventions:** (1) Human abuse liability studies on extended release ADO morphine and real-world rates of non-medical use of prescription drugs, (2) data quantifying association between positive subjective endpoints and non-medical use rates from White et al. study	**Calibration:** N/A **Validation:** N/A	**Results:** Prescribing extended release ADOs was associated with fewer misuse and/or abuse-related events and reduced associated costs per patient in commercial, VA, Medicaid, and Medicare populations. **Conclusion:** A physician's decision to prescribe extended release ADOs could lead to large reductions in misuse and/or abuse-related events and associated costs across patient populations**.**

Zaric, 2000(I)[84]	**Model Type:** Dynamic compartmental model **Research Question:** Assess the cost-effectiveness of maintenance treatment for heroin addiction, with emphasis on its role in preventing HIV infection **Target Population:** Adults ages 18-44 divided into nine compartments according to HIV infection status (uninfected, infected without AIDS, and AIDS) and risk group (injection drug users not in treatment, IDUs in treatment, and non-IDUs)	**Simulated Population:** (1) For some parameters (e.g., number of injections, death rates among IDUs), data estimated based on information from a number of sources, chose a value near the middle of the reported range, (2) For other parameters (e.g., QALYs lived by IDUs, knowledge of HIV status), adapted information on closely related quantities or selected parameter values based on the best available information that would lead to reasonable projections by the model **Interventions:** Same as simulated population	**Calibration:** N/A **Validation:** The base cases were validated by projecting the epidemic forward for 10 years and comparing our model's projections with recent growth of the HIV epidemic**.**	**Results:** Incremental expansion of methadone maintenance programs was found to have a cost-effectiveness ratio of between $9,700 and $17,200 per life year gained, and between $6,300 and $10,900 per QALY gained. **Conclusion:** Expanding existing methadone maintenance programs is a cost-effective health-care intervention that can play an important role in slowing the spread of HIV and improving the length and quality of life for injection drug users (IDUs). Such expansion is cost-effective even in populations with low HIV prevalence among IDUs**.**
Zaric, 2000(II)[85]	**Model Type:** Dynamic compartmental model **Research Question:** Determine the cost-effectiveness of expanding methadone maintenance treatment for heroin addiction, particularly its effect on the HIV epidemic **Target Population:** Constructed 2 models: (1) 40% HIV prevalence among injection drug users characteristic of a community such as NYC, and (2) 5% HIV prevalence among injection drug users, characteristic of a community such as Los Angeles	**Simulated Population:** (1) For some parameters (e.g., number of injections, death rates among IDUs), data estimated based on information from a number of sources, chose a value near the middle of the reported range, (2) For other parameters (e.g., QALYs lived by IDUs, knowledge of HIV status), adapted information on closely related quantities or selected parameter values based on the best available information that would lead to reasonable projections by the model **Interventions:** Same as simulated population	**Calibration:** N/A **Validation:** The base cases were validated by projecting the epidemic forward for 10 years and comparing our model's projections with recent growth of the HIV epidemic**.**	**Results:** Additional methadone maintenance capacity costs $8200 per QALY gained in the high-prevalence community and $10 900 per QALY gained in the low-prevalence community. More than half of the benefits are gained by individuals who do not inject drugs. Even if the benefits realized by treated and untreated injection drug users are ignored, methadone maintenance expansion costs between $14100 and $15 200 per QALY gained. **Conclusion:** Expansion of methadone maintenance is cost-effective on the basis of commonly accepted criteria for medical interventions**.**
Zarkin, 2005[86]	**Model Type:** Monte Carlo simulation **Research Question:** Evaluate benefits and costs of population-level heroin use and methadone treatment over a lifetime and model 3 scenarios: (1) Increase in probability of going to treatment, (2) increase in treatment length of stay, (3) drug treatment unavailable **Target Population:** 1 million 18-60 y/o, representative of U.S.	**Simulated Population:** 1998 National Household Survey on Drug Abuse. **Interventions:** 1998 National Household Survey on Drug Abuse.	**Calibration:** The model was Calibrated to match NHSDA data. **Validation:** N/A	**Results:** Increasing access to treatment significantly increased treatment benefits and costs: an additional $1 spent on increasing treatment yields $76 in discounted lifetime benefits. Increasing length of stay in treatment did not increase benefits. **Conclusion:** Increasing access to treatment significantly increased treatment benefits and costs.
Zeiler, 2010[87]	**Model Type:** Deterministic compartmental model **Research Question:** Use mathematical modeling to explore an effective policy for Hepatitis C virus (HCV) treatment in Australia in the context of MMT **Target Population:** Australian IDU population	**Simulated Population:** Australian clinical trials **Interventions:** Australian clinical trials	**Calibration:** N/A **Validation:** N/A	**Results:** Over 84% of HCV treatment should be allocated to those not in MMT. Only if adherence to HCV therapy in non-MMT patients falls below 44% of that in MMT should treatment then be preferentially directed to those in MMT. **Conclusion:** The majority of therapy should be allocated to those that are still actively injecting due to rates of reinfection and high turnover of individuals in MMT. Higher adherence to HCV therapy in MMT would need to be achieved before this changed.

Zou, 2018[88]	**Model Type:** System dynamics model **Research Question:** Compare and optimize HIV and HCV control strategies in the MMT system: interventions to reduce misconceptions about MMT, unprotected sexual intercourse, drug use, injection drug use and needle sharing behaviors in China and to improve the proportion of ART and HCV treatment **Target Population:** All participants of 13 MMT clinics in Guangdong Province, China, from 2006 to 2013	**Simulated Population:** Collected information on the MMT clinics (number of MMT participants, number of MMT clinics, new entrants to MMT, etc.) and the participants (daily doses, drug use, injection drug use, needle sharing behaviors, HIV/HCV testing and results, etc. **Interventions:** Literature review and interviews with physicians and nurses in MMT clinics.	**Calibration:** The model was calibrated using HIV and HCV prevalence data collected in 13 MMT clinics in Guangdong Province from 2006 to 2013. **Validation:** Model was validated using survey data.	**Results:** (1) Condom promotion is the most effective way to reduce HIV infection (2013-2020: 2.86% to 1.76%) in MMT setting. (2) Psychological counseling (2013-2020: 7.54% to 2.42%) and contingency management (2013-2020: 7.54% to 2.96%) had been shown to be the most effective interventions to reduce HCV incidence among MMT participants. **Conclusion:** The Study underscores importance of promoting condom use in MMT clinics and integrating psychosocial interventions to reduce HIV/HCV**.**

Abbreviations:

ART – Antiretroviral therapy
HCV – Hepatitis C Virus
IDU - Injection drug use
MMT – Methadone maintenance treatment
NSDUH – National Survey on Drug Use and Health
NSP – Needle and syringe programs
OST – Opioid substitution therapy
PrEP – Oral HIV pre-exposure prophylaxis
PWID – People who inject drugs
QALY – Quality-adjusted life year

Web Table 2: Calibrated model parameters standardized across articles

Parameter (unit)	Value	Range	Prior	Source	Target population
*Injection Drug Use (IDU) Development (%/people*year)*					
Annual transition from POUD to IDU	0.071	0.054 - 0.088		Chen, 2019[24]	Projected US opioid OD deaths from 2016-2025
Annual transition from POUD to IDU α_1	0.042	0.03 - 0.054		Chen, 2019[24]	Projected US opioid OD deaths from 2016-2025
Annual transition from non-medical opioid use to IDU	0.002	0.001 - 0.002		Chen, 2019[24]	Projected US opioid OD deaths from 2016-2025
IDU initiation	0.00115	N/A		Cipriano, 2012[26]	US urban center with a population of 2.5 million PWID and people who do not inject drugs
IDU initiation	0.0003	0.0002 - 0.0004		Alistar, 2011[3]	1,000,000 individuals aged 15-49, segmented by drug usage status, HIV disease stage, and ART access
IDU initiation (15-19 yo)	2.1	0.05 - 5.0		Gicquelais, 2019[35]	15–29 y/o in Michigan during 2000–2016
IDU initiation (20-25 yo)	0.03	0.034 - 5.0		Gicquelais, 2019[35]	15–29 y/o in Michigan during 2000–2016
IDU initiation (26-29 yo)	0.54	0.034 - 10		Gicquelais, 2019[35]	15–29 y/o in Michigan during 2000–2016
IDU initiation (30-64 yo)	0.79	0.034 - 1		Gicquelais, 2019[35]	15–29 y/o in Michigan during 2000–2016
Heterosexual IDU initiation Toronto	0.03	N/A		Enns, 2016[31]	Populations of 15-64 y/o in Toronto and Ottawa divided into compartments based on sexual behavior, drug use, and HIV/HCV infection
Heterosexual IDU initiation Ottawa	0.02	N/A		Enns, 2016[31]	Populations of 15-64 y/o in Toronto and Ottawa divided into compartments based on sexual behavior, drug use, and HIV/HCV infection
Men who have sex with men IDU initiation Toronto	0.095	N/A		Enns, 2016[31]	Populations of 15-64 y/o in Toronto and Ottawa divided into compartments based on sexual behavior, drug use, and HIV/HCV infection
Men who have sex with men IDU initiation Ottawa	0.095	N/A		Enns, 2016[31]	Populations of 15-64 y/o in Toronto and Ottawa divided into compartments based on sexual behavior, drug use, and HIV/HCV infection
Population					
Population at risk	32,000	27,300 - 36,500	40,000 (22,000 - 58,000)*	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
PWUD in treatment	13,000	12,500 - 13,600	15,700 (5,750 - 31,400)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Active PWUD	27,000	26,400 - 27,600	23,100 (9,890 - 40,800)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl overdose
Drug Use Career (years)					
Average duration of IDU in Tallinn, Estonia	16	N/A		Vickerman, 2014[75]	People who inject drugs in St. Petersburg, Russia; Tallinn, Estonia; and Dushanbe, Tajikistan

Average duration of IDU in St. Petersburg, Russia	30	N/A		Vickerman, 2014[75]	People who inject drugs in St. Petersburg, Russia; Tallinn, Estonia; and Dushanbe, Tajikistan
Average duration of IDU in Dushanbe, Tajikistan	8	N/A		Vickerman, 2014[75]	People who inject drugs in St. Petersburg, Russia; Tallinn, Estonia; and Dushanbe, Tajikistan
*Treatment exit, not in remission (%/people*year)*					
Relapse rate	0.08	0.077 - 0.083	0.07 (0.05 - 0.1)*	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Rate of relapse from treatment	28.2	27.9 - 28.4	51.7 (51.5 - 52.0)*	Irvine, 2019[43]	OD events and OD-related deaths in British Columbia from January 2012 to December 2017
*Treatment entry (%/people*year)*					
Rate of increase of treatment population	0.039	0.0372 - 0.0402	0.049 (SD: 0.019)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Rate of entry into rehabilitation for those addicted	N/A	20 - 200		Battista, 2019[10]	4 population classes: susceptible individuals, prescribed users, addicted individuals, and individuals in treatment for addiction
Rate of IDUs initiating medication-based treatment for opioid use disorder	0.12	0.07 - 0.22		Cipriano, 2012[26]	US urban center with a population of 2.5 million PWID and people who do not inject drugs
Rate at which PWID initiate methadone maintenance therapy Toronto	65	N/A		Enns, 2016[31]	Populations of 15-64 y/o in Toronto and Ottawa divided into compartments based on sexual behavior, drug use, and HIV/HCV infection
Rate at which PWID initiate methadone maintenance therapy Ottawa	13	N/A		Enns, 2016[31]	Populations of 15-64 y/o in Toronto and Ottawa divided into compartments based on sexual behavior, drug use, and HIV/HCV infection
Treatment prevalence (%/people)					
Medication-based treatment coverage among PWID for 0-1 year in Scotland, 2005-2006	26.5	16.9 - 36.1		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 1-9 years in Scotland, 2005-2006	40.5	36.7 - 44.3		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 10+ years in Scotland, 2005-2006	49.5	45.3 - 53.7		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 0-1 year in Scotland, 2008-2009	29.5	20.6 - 39.7		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 1-9 years in Scotland, 2008-2009	47.9	44.1 - 54.7		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 10+ years in Scotland, 2008-2009	55.1	50.9 - 59.3		Fraser, 2018[34]	PWID in Scotland, UK

Medication-based treatment coverage among PWID for 0-1 year in Scotland, 2010	34.5	24.6 - 45.4		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 1-9 years in Scotland, 2010	56.5	52.5 - 60.3		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 10+ years in Scotland, 2010	67.6	63.6 - 71.5		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 0-1 year in Scotland, 2011-2012	40.9	26.3 - 56.8		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 1-9 years in Scotland, 2011-2012	57.8	52.9 - 62.5		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 10+ years in Scotland, 2011-2012	71.1	66.8 - 75.0		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 0-1 year in Scotland, 2013-2014	29.1	17.6 - 42.9		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 1-9 years in Scotland, 2013-2014	52.6	47.3 - 57.7		Fraser, 2018[34]	PWID in Scotland, UK
Medication-based treatment coverage among PWID for 10+ years in Scotland, 2013-2014	58.8	54.4 - 62.9		Fraser, 2018[34]	PWID in Scotland, UK
Treatment effectiveness					
Reduction in overdose risk of OST	0.11	0.09 - 0.13	0.11 (0.09 - 0.13)	Irvine, 2019[43]	OD events and OD-related deaths in British Columbia from January 2012 to December 2017
*Baseline Overdose Rate (%/people*year)*					
Baseline OD rate	10.4	10.1 - 10.6	9.7 (8.3 - 11.2)*	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Baseline OD rate	4.6	4.6 - 4.7	9.7 (8.3 - 11.3)*	Irvine, 2019[43]	OD events and OD-related deaths in British Columbia from January 2012 to December 2017
Rate of OD for active user	12.0	10.0 - 25.0*		Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses
Changes in tolerance (/month)					
Rate of regaining tolerance	0.608	0.0511 - 7.41	0.597 (0.0553 - 6.39)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Increased risk of overdose (/100,000PY)					
Increased risk of OD following relapse	179	152 - 210	181 (155 - 212)*	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed

					into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Increased rate of OD following relapse	91	90 - 92	180 (154 - 211)*	Irvine, 2019[43]	OD events and OD-related deaths in British Columbia from January 2012 to December 2017
Naloxone					
Rate of naloxone effectiveness	0.85	0.73 - 0.97	0.5 (0.025 - 0.975)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Relative risk of mortality due to naloxone administration	0.48	N/A	0.6	Townsend, 2020[72]	(1) People likely to witness or experience OD ("laypeople"); (2) police and firefighters; (3) emergency medical services personnel; and (4) combinations of these groups, assumed to be in the U.S.
Emergency medical services					
Probability of ambulance call-out after an OD	1	1 - 1	0.8 (0.78 - 0.82)	Irvine, 2019[43]	OD events and OD-related deaths in British Columbia from January 2012 to December 2017
Fentanyl in supply					
Natural log mean fentanyl in supply	0.0398	-0.0164 - 0.097	0.011 (-0.129 - 0.131)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Precision in fentanyl supply	2.42	1.62 - 3.64	0.418 (0.283 - 0.621)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
*Fentanyl OD (%/people*year)*					
Fentanyl OD rate among PWUD	66.37	65.47 – 67.32	100 (99.58 - 100)*	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Fentanyl OD rate among PWUD	62.31	61.97 – 62.70	100 (99.58 – 100)*	Irvine, 2019[43]	OD events and OD-related deaths in British Columbia from January 2012 to December 2017
OD Mortality (%)					
Likelihood of OD death without assistance	10	N/A		Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses
Reduction in survival for second OD	1.5	N/A		Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses
Reduction in survival for subsequent ODs	3	N/A		Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses
Probability of mortality due to overdose absent intervention given no prior OD	5.4	N/A	3	Townsend, 2020[72]	(1) People likely to witness or experience OD ("laypeople"); (2) police and firefighters; (3) emergency medical services personnel; and (4) combinations of these groups, assumed to be in the U.S.
Probability of mortality due to OD absent intervention given prior OD	16.4	N/A	9	Townsend, 2020[72]	(1) People likely to witness or experience OD ("laypeople"); (2) police and firefighters; (3) emergency medical services personnel; and (4) combinations of these groups, assumed to be in the U.S.

Baseline death rate (/people*year)	72.23	70.72 – 73.72	100 (0.0 - 2e10)	Irvine, 2018[42]	Population of people who use drugs in one of three states: 1) at risk of OD 2) not at risk of OD 3) recently relapsed into illicit drug use and at increased risk from fentanyl and non-fentanyl OD
Baseline death rate (/people*year)	57.16	56.10 – 58.19	100 (0.0 - 2e10)	Irvine, 2019[43]	OD events and OD-related deaths in British Columbia from January 2012 to December 2017
*All-cause Mortality (%/people*year)*					
Mortality from abstinence	0.057	0.05 - 0.056*		Ritter, 2016[66]	Individuals who have ever used heroin (including those currently abstinent, in treatment groups, and in prison) in New South Wales, Australia
Annual rate of all-cause death among active users	1.97	1.5 - 2.5*		Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses
Annual rate of all-cause death among active users <30 yo	0.98	N/A		Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses
Mortality from irregular use	0.06	0.05 - 0.056*		Ritter, 2016[66]	Individuals who have ever used heroin (including those currently abstinent, in treatment groups, and in prison) in New South Wales, Australia
Mortality from dependence w/o treatment	0.106	0.111 - 0.12*		Ritter, 2016[66]	Individuals who have ever used heroin (including those currently abstinent, in treatment groups, and in prison) in New South Wales, Australia
Law enforcement and incarceration (/population)					
Proportion of men who inject drugs incarcerated before starting injecting	0.82	0.79 - 0.92		Borquez, 2018[18]	PWID in Tijuana, Mexico
Proportion of women who inject drugs incarcerated before starting injecting	0.33	0.91 - 0.61		Borquez, 2018[18]	PWID in Tijuana, Mexico
Primary incarceration rate per year for men who inject drugs	0.018	0 - 0.047		Borquez, 2018[18]	PWID in Tijuana, Mexico
Primary incarceration rate per year for women who inject drugs	0.03	0.001 - 0.055		Borquez, 2018[18]	PWID in Tijuana, Mexico

*range from literature

<u>Abbreviations</u>:
POUD – People with OUD
IDU - Injection drug use
PWUD – People who use drugs
PWID – People who inject drugs
OD – Overdose
OST – Opioid substitution therapy

Web Table 3: Assumed model parameters

Parameter	Value	Range	Model	Target Population
Fatal or Non-fatal Overdose				
Number of opioid ODs per year among high school students	N/A	0.1 - 5.0	Cipriano, 2018[25]	Canada
Low-dose opioid death increase factor	6	N/A	McGregor, 2019[56]	184,600 opioid dependent patients receiving chiropractic therapy, opioid therapy, both therapies, and those who received opioid therapy and developed opioid use disorder in Canada
Opioid death increase factor	20.5	N/A	McGregor, 2019[56]	184,600 opioid dependent patients receiving chiropractic therapy, opioid therapy, both therapies, and those who received opioid therapy and developed opioid use disorder in Canada
Reduction in paramedics being dispatched if naloxone was used	69%	N/A	Uyei, 2017[73]	Simulate opioid OD, HIV incidence, overdose-related deaths, and HIV-related deaths in people who inject drugs in Connecticut, U.S.
Injection drug use				
Number of PWID in San Francisco	22,500	N/A	Barbosa, 2019[7]	Current and ex-PWID in Perry County, Kentucky and San Francisco
Total number of syringes exchanged in San Francisco	3,845,307	N/A	Barbosa, 2019[7]	Current and ex-PWID in Perry County, Kentucky and San Francisco
NSP coverage among PWID in urban area	84%	N/A	Barbosa, 2019[7]	Current and ex-PWID in Perry County, Kentucky and San Francisco
Average duration of injection until final cessation	20 years	5.8 - 34.2	Cepeda, 2018[21]	PWID in two Russian cities, Omsk and Ekaterinburg
Duration of injecting (yrs)	15.4 years	7.7 - 23.1	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
NSP coverage in Amsterdam	50%	35% - 65%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
NSP coverage in Denmark	50%	35% - 65%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
NSP coverage in France	N/A	40% - 60%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
NSP coverage in Norway	51%	35% - 73%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
NSP coverage in Slovenia	50%	35% - 65%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
NSP coverage in Sweden	N/A	9.8% - 32%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Ratio of opioid to methamphetamine injectors	1:1	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Duration on high coverage NSP	8 months	N/A	Fraser, 2018 (Scotland)[34]	PWID in Scotland, UK

Relative risk of street injection by users in treatment as compared to those not in treatment	0.17	0.1 - 0.25	Nosyk, 2012[60]	A cohort of patients assigned the baseline characteristics of the participants in the North American Opiate Medication Initiative (25+ y/o, regular opioid injection, minimum 5 years opioid use, at least 2 attempts at substitution treatment)
% of injection drug users that experience non-HIV related mortality when leave opioid substitution therapy	0.25%	N/A	Rhodes, 2010[64]	PWID in Russia
% of injection drug users that experience non-HIV related mortality when recruited on to opioid substitution therapy	0.25%	N/A	Rhodes, 2010[64]	PWID in Russia
Average frequency of syringe sharing per month amongst all PWID	N/A	0.3 - 10	Rhodes, 2010[64]	PWID in Russia
Degree of assortative mixing for forming syringe sharing partnerships - 0 signifies random mixing and 1 is full like with like mixing	0	N/A	Rhodes, 2010[64]	PWID in Russia
Factor difference between frequency of syringe sharing between those whose frequency of syringe sharing is above or below the median frequency per month	N/A	1 - 4	Rhodes, 2010[64]	PWID in Russia
Monthly recruitment rate of PWID on to opioid substitution therapy	N/A	1% - 10%	Rhodes, 2010[64]	PWID in Russia
Percent reduction in HIV due to scale-up of NSP from 2003-2008	40%	N/A	Vickerman, 2014[75]	PWID in St. Petersburg, Russia; Tallinn, Estonia; and Dushanbe, Tajikistan
Percent reduction in HIV risk due to scale-up of NSP to 50% coverage from 2003-2008	20%	N/A	Vickerman, 2014[75]	PWID in St. Petersburg, Russia; Tallinn, Estonia; and Dushanbe, Tajikistan
Reduction of injection activity through street outreach	30%	N/A	Wilson, 2003[81]	Simulated 10,000 heterosexual PWID, 7,500 males and 2,500 females, and 5,000 heterosexual female non-IDU sex partners of male PWID in San Francisco, California, and New York City for periods from the mid-1980s to the mid-1990s
Reduction in risky injections for PWID with AIDS	75%	N/A	Zaric, 2000 (I)[84]	Adults ages 18-44 divided into nine compartments according to HIV infection status (uninfected, infected without AIDS, and AIDS) and risk group (PWID not in treatment, PWID in treatment, and non-PWID)
MOUD Treatment				

Proportion of PWID on MMT in rural area	4.70%	N/A	Barbosa, 2019[7]	Current and ex-PWID in Perry County, Kentucky and San Francisco
Proportion of PWID on MMT in urban area	12%	N/A	Barbosa, 2019[7]	Current and ex-PWID in Perry County, Kentucky and San Francisco
Duration initial MMT phase	2 years	N/A	Birger, 2017[15]	High HIV-HCV prevalence population
Duration on OST (yr) in Amsterdam	1 year	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Duration on OST (yr) in Denmark	1 year	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Duration on OST (yr) in France	1 year	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Duration on OST (yr) in Slovenia	1 year	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Duration on OST (yr) in Sweden	1 year	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Number treated per year in Scotland	2005-2008: 60 per yr 2008-2009: 90 per yr 2009-2015: 150 per yr	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Number treated per year in Sweden	2004-2013: 45 2014: 0 2015: 70 (new DAAs)	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
OST coverage in France	80%	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
OST coverage in Slovenia	43%	30% - 56%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
OST coverage	N/A	14% - 46%	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Average long-acting treatment duration	7	N/A	Nielsen, 2012[58]	Not provided in paper
Average short-acting treatment duration	5	N/A	Nielsen, 2012[58]	Not provided in paper
Average rate leaving high coverage NSP per month	12.50%	N/A	Vickerman, 2012[74]	PWID in the UK
Proportion of cirrhosis patients who will get drug treatment	0.306	0.297 - 0.338	Wisløff, 2018[82]	Norwegian population
Relative risk of PWUD entering treatment given previous treatment history (versus users with no treatment history)	20	N/A	Zarkin, 2005[86]	1 million 18-60 y/o, representative of U.S.
Number of new drug users who have the intention to treat in MMT clinics across Guangdong Province, China	600	450 - 750	Zou, 2018[88]	All participants of 13 MMT clinics in Guangdong Province, China, from 2006 to 2013
Opioid use disorder				
Chronic substance use disorder in survivors	100%	0 - 100%	Cipriano, 2018[25]	Canada
Proportion of new chronic pain patients who go on to abuse opioids	1.30%	N/A	Nielsen, 2012[58]	Not provided in paper
Recreational prescription opioid use				

Base add opioid rate	0.125	N/A	McGregor, 2019[56]	184,600 opioid dependent patients receiving chiropractic therapy, opioid therapy, both therapies, and those who received opioid therapy and developed opioid use disorder in Canada
Relapse				
Monthly probability non-PWUD who previously used heroin resume heroin use among 26–60-year-olds	N/A	0.2 - 0.4	Zarkin, 2005[86]	1 million 18-60 y/o, representative of U.S.
Monthly probability non-PWUD who previously used heroin resume heroin use among 18–25-year-olds	N/A	10 - 20	Zarkin, 2005[86]	1 million 18-60 y/o, representative of U.S.

Abbreviations:

OD – Overdose
PWID – People who inject drugs
NSP – Needle and syringe programs
MMT – Methadone maintenance treatment
HCV – Hepatitis C Virus
OST – Opioid substitution therapy
PWUD – People who use drugs

Web Table 4: Calculated model parameters

Sub-topic	Value	Range	Model	Target Population
Heroin use				
Population of heroin dependent people	N/A	80,000 - 100,000	Chalmers, 2009[23]	Australian opioid-dependent people
Injection drug use				
Number of syringes per person per year	227.57	N/A	Barbosa, 2019[7]	Current and ex-PWID in Perry County, Kentucky and San Francisco
Annual no. of risky injections per injection drug user in methadone maintenance treatment	N/A	2.4 - 2.7	Zaric, 2000 (I)[84]	Adults ages 18-44 divided into nine compartments according to HIV infection status (uninfected, infected without AIDS, and AIDS) and risk group (injection drug users not in treatment, IDUs in treatment, and non-IDUs)
Annual no. of risky injections per injection drug user not in methadone maintenance treatment	N/A	40 - 45	Zaric, 2000 (I)[84]	Adults ages 18-44 divided into nine compartments according to HIV infection status (uninfected, infected without AIDS, and AIDS) and risk group (injection drug users not in treatment, IDUs in treatment, and non-IDUs)
Net reduction in risky injections associated with methadone maintenance treatment, %	94	N/A	Zaric, 2000 (I)[84]	Adults ages 18-44 divided into nine compartments according to HIV infection status (uninfected, infected without AIDS, and AIDS) and risk group (injection drug users not in treatment, IDUs in treatment, and non-IDUs)
MOUD treatment				
Duration on OST	24.93 months	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Number treated per year in France, 2001-2016	1,705 per year	923–3,148 per year	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Number treated per year in Hamburg	2005-2011: 60 per year 2011-2015: 72 per year	N/A	Fraser, 2018 (Europe)[33]	PWID across 11 sites in Europe
Naloxone				
Joint probability that distributed naloxone is used each year	0.136	0.004 - 0.631	Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses
Joint probability that naloxone is used	0.153	0.004 - 0.668	Coffin, 2013 (I)[27]	Russian cities
Joint probability that distributed naloxone is used each year (calculated)	0.17	N/A	Langham, 2018[50]	Adults at risk for heroin overdose in United Kingdom
Base Mortality				

Non-HIV, Non-HCV mortality (age 15-59, annual rate) - among IDU, in treatment	0.013	0.01 - 0.0311	Cipriano, 2012[26]	US urban center with a population of 2.5 million PWID and people who do not inject drugs
Opioid treatment				
New entrants to treatment	3500	N/A	Chalmers, 2009[23]	Australian opioid-dependent people
Numbers between treatment	41,100	N/A	Chalmers, 2009[23]	Australian opioid-dependent people
Treatment naïve	14,000	N/A	Chalmers, 2009[23]	Australian opioid-dependent people
Opioid use disorder transition				
Probability of transitioning to opioid use out of treatment for individuals receiving buprenorphine treatment	0.799	N/A	Jackson, 2015[44]	Simulated cohort of adult males aged 18–65 in the United States initiating pharmacotherapy for opioid dependence over a 6-month period
Probability of transitioning to opioid use out of treatment for individuals receiving extended-release naltrexone treatment	0.799	N/A	Jackson, 2015[44]	Simulated cohort of adult males aged 18–65 in the United States initiating pharmacotherapy for opioid dependence over a 6-month period
Probability of transitioning to opioid use out of treatment for individuals receiving methadone treatment	0.799	N/A	Jackson, 2015[44]	Simulated cohort of adult males aged 18–65 in the United States initiating pharmacotherapy for opioid dependence over a 6-month period
OD Mortality				
Proportion who survive overdose without medical assistance or lay naloxone	0.899	0.784 - 0.940	Coffin, 2013 (II)[28]	Hypothetical 21 y/o novice U.S. heroin user and more experienced users with scenario analyses

Abbreviations:

PWID: People who inject drugs
PWUD: People who use drugs
MMT: Methadone maintenance therapy
OD: Overdose
IDU: Injection drug use
NSP: Needle and syringe programs

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