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Modeling the impact of changing drug markets and structural determinants on HCV and/or HIV transmission among people who inject drugs in the United States: A rural and urban comparison

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Abstract

Background: The impact of changing drug use patterns on hepatitis C virus (HCV) and HIV incidence among people who inject drugs (PWID) in the US is understudied.

Methods: An HCV and HIV transmission model was calibrated to urban and rural area data (San Diego, CA and Central/Northern Wisconsin). Fentanyl use among PWID was assumed to increase mortality and injecting-related risk of HIV and HCV based on San Diego data. We predicted

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Ethics approval

The authors declare that the work reported herein did not require ethics approval because it did not involve animal or human participation.

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HCV/HIV incidence with recent trends (in fentanyl use, transition from injecting to smoking drugs, opiate agonist treatment (OAT) and incarceration), and scenarios with no trend changes since 2020. We calculated the population attributable fraction of fentanyl on incidence, comparing to a no fentanyl counterfactual from 2015 to 2025.

Results: High and increasing self-reported fentanyl use among PWID was observed in Central/Northern Wisconsin (20 % in 2018 to 45 % in 2021) and San Diego (51 % in 2021 to 66 % in 2023). Between 2015–2025, modeling suggests fentanyl use contributed to 18 % (95 %CI 9–25) and 34 % (95 %CI 26–45) of new HCV infections among PWID in Central/Northern Wisconsin and San Diego, respectively. Fentanyl contributed to 10 % (95 %CI 1–26) of HIV infections in San Diego; no HIV was observed among Central/Northern Wisconsin PWID. Fentanyl-associated risk was mitigated by increased OAT, reduced incarceration (Wisconsin), and shifts from injecting to smoking drugs (San Diego).

Conclusions: Fentanyl use increased HCV and/or HIV in an urban and rural area, suggesting expanded access to harm reduction, alongside interventions to reduce blood-borne virus transmission risk among PWID who use fentanyl are urgently needed.

Keywords

Elimination; Smoking; Fentanyl; Opioids; Hepatitis C virus; HIV

Introduction

The United States has experienced a rapid expansion in the number of people who inject drugs (PWID) over the past decade, particularly in rural and suburban areas, with an estimated 3.7 million PWID in 2018 but with a need for newer estimates given high rates of overdose (~38,000 injection-related overdoses in 2020) (Bradley et al., 2023; Friedman & Shover, 2023; Hall et al., 2024). PWID are at high risk of HIV and hepatitis C virus (HCV) infection. HCV infection burden and incidence among PWID remains high in the United States, with 40 % of PWID chronically infected in 10 metropolitan statistical areas in the 2018 National HIV Behavioral Surveillance Program (Chapin-Bardales et al., 2024). HCV incidence has risen rapidly over the past two decades, especially among young adults (Price & Brandman, 2020). HIV outbreaks among PWID have been reported in areas such as Scott County, Indiana; Lawrence and Lowell, Massachusetts; West Virginia; and Seattle, Washington (Cranston et al., 2019; Hershow et al., 2022; Peters et al., 2016). Tackling the ongoing transmission of HCV and HIV among PWID is key to addressing the proposed White House Hepatitis C Elimination Initiative, and the Ending the HIV Epidemic initiative (Centers for Disease Control and Prevention (U.S.); Leslie, 2023).

Concurrently, the infiltration of fentanyl in the unregulated drug supply and precipitous rise of illicit fentanyl use in the last decade has resulted in a surge of overdose deaths in the United States (Casillas et al., 2024; Friedman & Shover, 2023) and has been ecologically linked to HIV outbreaks (Alpren et al., 2020). Additionally, a recent study among PWID in San Diego, California, found that self-reported fentanyl use (through any administration route) among PWID was independently associated with an increased risk of HCV seroconversion (aHR 1.57 95 % 1.03–2.40) (Friedman et al., 2024). Studies indicate

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fentanyl use is associated with increased injection frequency and receptive syringe sharing, which could explain some of this association; however the association remained when controlling for receptive syringe sharing (Friedman et al., 2024; Lambdin et al., 2019). An in vitro study indicates that fentanyl enhances HCV viral replication (Kong et al., 2021). It is additionally possible that fentanyl use has a destabilizing effect on the lives of PWID, and associated polysubstance use among PWID who use fentanyl may decrease health care and prevention engagement (Friedman & Shover, 2023; Lorvick et al., 2018). However, concurrently, several studies have reported shifts from injecting drugs to smoking drugs among urban cohorts of PWID in California (Eger et al., 2024; Kral et al., 2021). Overall, the potential interplay of these dynamics on HIV and HCV transmission is not well understood.

The COVID-19 pandemic may have changed the risk environment for PWID in both positive and negative ways. Limited access to harm reduction providers during the early pandemic may have been mitigated in part, or whole, by policy changes to expand access to opiate agonist treatment (OAT), such as allowing telehealth initiation and allowing take-home doses (Adams et al., 2023). As OAT medications such as buprenorphine and methadone are highly effective at preventing HIV and HCV transmission because persons on OAT stop injecting or reduce the frequency of injection (MacArthur et al., 2012; Platt et al., 2018), changes in access would likely impact infectious disease transmission dynamics. Decarceration initiatives during the COVID-19 pandemic (Wang et al., 2020) may have also led to lower incarceration rates among PWID, which could reduce HIV and HCV transmission as recent incarceration is associated with HCV and HIV incidence (Stone et al., 2018). Similarly, temporary housing initiatives such as Project Roomkey (Sloan et al., 2024) could potentially have reduced homelessness, and exposure associated with HCV and HIV incidence among PWID (Arum et al., 2021). Further, temporal, and spatial differences in drug markets, drug use practices, and structural determinants likely contribute to heterogeneity in HCV and HIV epidemics between locations, particularly between urban and rural areas. Incidence of reported acute HCV is higher in nonurban compared to urban US areas (Suryaprasad et al., 2014), with people from rural areas exhibiting lower HCV treatment uptake (Du et al., 2021) and experiencing longer driving times to OAT providers (Kleinman, 2020). Given the complex interplay of factors, it is unclear how these changing dynamics could have affected HCV and HIV incidence among PWID in rural and urban areas.

Simulation models are well suited to investigating how these complex and changing risk environments interact to fuel or dampen infectious disease transmission (Martin et al., 2013; Stone et al., 2022). To better understand the infectious disease implications of changing dynamics of drug use and exposures among PWID, we developed a dynamic model of HCV and HIV transmission among PWID calibrated to epidemiological data over time in one urban area (San Diego, CA) and one rural area (Central and Northern Wisconsin) in the United States. These settings were chosen to reflect different epidemic settings and because they had detailed epidemiological data to inform the model. We used this model to assess the contribution of increasing fentanyl use, shifts from injecting to smoking drugs, and changing harm reduction intervention access over time on HIV and HCV incidence among PWID.

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Methods

Model

We adapted a previously published dynamic, deterministic HIV and HCV transmission model among PWID to newly account for fentanyl use and homelessness, and to simplify the incarceration dynamics to align with available data (Stone et al., 2023). The population modeled is an open population of PWID, who continually enter through initiation of injecting drug use. The model is stratified by gender (man/woman), OAT status (off/on), homelessness status (no/yes), incarceration status (never or not recently incarcerated/recently incarcerated in the past 3 or 6 months), and fentanyl use regardless of administration route (no/yes). The model tracks HIV infection stages (susceptible, acute, latent, pre-AIDS, AIDS) with HIV infection stages stratified by antiretroviral treatment (ART) status (on/off, with individuals able to cycle between states). The model additionally tracks HCV infection stage based on antibody (Ab) and HCV RNA results and treatment history: susceptible never infected (Ab−), susceptible spontaneous clearance (Ab+/RNA−), chronically infected (Ab+/RNA+), and previously treated and cured (Ab+/RNA−). PWID exit the model due to mortality (drug related or non-drug related) or permanent cessation of injection drug use (to either non-injection drug use or no drug use). People who use drugs by both injection and non-injection remain in the model as PWID. Entries are assumed to balance cessation and non-infectious mortality exits in the absence of fentanyl and OAT, such that the population is stable without HIV, HCV, fentanyl, and OAT. We assume PWID enter as susceptible to HIV and HCV, off OAT, never or not recently incarcerated, and not using fentanyl. Based on the increasing presence of fentanyl in the drug supply, PWID experience a time-varying transition rate from non-use to use of fentanyl (0 prior to 2015 and then piecewise constant to fit fentanyl use prevalences at two timepoints in each setting), whereby we assume they remain in the fentanyl use stage until cessation. Our fentanyl use compartment represents use of fentanyl via any administration route, although all PWID in our model currently inject drugs of some kind. Fentanyl use among PWID is associated with increased drug-related mortality (when not on OAT (Park et al., 2018; Pearce et al., 2020)) and also increased injecting transmission (based on HCV seroconversion data from San Diego (Friedman et al., 2024)). PWID can cycle in and out of periods receiving OAT. We incorporate a time-varying injecting cessation rate in San Diego based on observations of recent shifts from injecting to smoking drugs among PWID (Eger et al., 2024).

The model simulates injecting-related HIV and HCV transmission among PWID, and heterosexual transmission of HIV among PWID. The model therefore neglects HIV transmission from non-PWID sexual partners based on the low general population prevalence(Agency & Epidemiology and Immunization Services Branch, 2016). Based on global systematic reviews, being recently incarcerated and experiencing homelessness are associated with elevated risk of HIV and HCV acquisition (Arum et al., 2021; Stone et al., 2018). Based on reviews, being on OAT is associated with reduced HIV and HCV injecting transmission risk (MacArthur et al., 2012; Platt et al., 2018), reduced overdose (but with elevated risks in the first 4 weeks of initiation and cessation (Sordo et al., 2017)), increased rates of ART uptake and reduced ART loss to follow-up (Low et al., 2016). Based on data from PWID in San Diego (Friedman et al., 2024), fentanyl use (via any administration

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route) is associated with increased HIV and HCV incidence, which we model through an increase in injecting transmission risk (which increases both HCV and HIV injecting related transmission). We assume fentanyl use is additionally associated with increased risk of drug-related mortality among PWID not on OAT (Park et al., 2018; Pearce et al., 2020). Based on evidence from Canada that the protective effect of OAT on mortality increased as fentanyl use became widespread (with mortality rates increasing for those off OAT but stable for those on OAT) (Pearce et al., 2020), we assume those on OAT have the same drug-related mortality rates regardless of fentanyl use status. We do not explicitly model syringe service programs (SSP), and instead implicitly include their impact in our calibrated injecting transmission rate due to a lack of unbiased estimates of SSP coverage and no evidence of changes in coverage over time in these two areas.

HIV transmission is dependent on HIV stage (with elevated transmission from the acute, pre-AIDS, and AIDS stages compared to latent), with being on ART associated with reduced sexual and injecting related HIV transmission (Fraser et al., 2016; Quinn et al., 2000). ART use is also associated with reduced HIV disease progression and mortality (Nosyk et al., 2015). Heterosexual HIV transmission is simulated between male and female PWID (based on unpublished data that >85 % of sexual partners also inject drugs among PWID in San Diego), with the assumption that heterosexual transmission is negligible from other groups given the low HIV prevalence in the general population. HCV transmission is based on the prevalence of infection (with those who are RNA+ contributing to transmission), and intervention coverage. Individuals who are exposed to HCV can spontaneously clear their infection (with lower rates of clearance among people with HIV, and higher rates among women compared to men) or can progress to chronic infection. Individuals who are chronically infected can be treated and, if successfully cured, move to the previously treated and cured compartment where they are at risk of reinfection.

Parameterization and calibration

We parameterized and calibrated the model to data from two areas: San Diego, California, and rural Central/Northern Wisconsin. The model simulated HCV and HIV in San Diego, and only HCV in Central/Northern Wisconsin due to a lack of HIV among PWID. By using data from 2020 to 2023 (in San Diego) and 2018 & 2021 (in Central/Northern Wisconsin) we examined recent trends in the COVID-19 era to inform the model calibration. Most model parameters were location-specific, with the exception of intervention effect parameters for OAT and ART as well as risks associated with homelessness and incarceration (derived from meta-analysis where possible) and natural history parameters (shared model parameters shown in Supplementary Table S1). The San Diego simulation was seeded for HIV and HCV in 1990, whereas in Central/Northern Wisconsin, HCV was seeded in 2009 based on no heroin overdoses reported in rural Wisconsin counties in 2003 (Meiman et al., 2015), and an average duration of injecting of 9 years in the 2018 UG3 survey (indicating a 2009 initiation year; unpublished data). In both areas, we assume HCV and HIV treatment was available from 2015 to 2002 onwards, respectively.

The model was calibrated with local epidemiological data for HCV (and HIV in San Diego), as well as to local temporal trends in exposures such as fentanyl use (increasing in

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both areas), recent incarceration (decreasing in Central/Northern Wisconsin, stable in San Diego), recent homelessness (high and stable), and recent OAT (increasing). Specifically, we calibrated to (Table 1 for San Diego and Table 2 for Central and Northern Wisconsin): HCV seroprevalence (multiple data points for Wisconsin), relative HCV seroprevalence risk ratio among women compared to men, chronic HCV prevalence among Ab+ PWID by gender (multiple data points for Wisconsin), % using fentanyl (over time), % homeless (over time), % recently on OAT (over time), % recently incarcerated (over time). Additionally, for San Diego, the model was calibrated to: HCV incidence, HIV seroprevalence, HCV antibody prevalence among HIV-infected PWID, and % of HIV-infected PWID on ART; these were not stratified by gender due to a lack of power. We calibrated the model using an approximate Bayesian computation sequential Monte Carlo scheme (ABC SMC(Sisson et al., 2007)) which incorporates both uncertainty in the underlying parameters as well as the calibration data (see details in Supplementary Materials “Model Calibration”). This produced 1000 model fits to the data which were used for the projections; no further sampling was performed.

San Diego, California

Specific model parameters for San Diego are shown in Table 1. Data from PWID in San Diego were primarily obtained from the La Frontera cohort, an ongoing longitudinal cohort study among 612 PWID recruited using street outreach from mobile vans (initial recruitment was from October 2020 to October 2021, most recent follow-up for this analysis in 2023) as previously described (Strathdee et al., 2021). Eligible participants were PWID aged ≥18 years who had injected drugs in the past month and were living in San Diego County, CA, or Tijuana, Mexico, at screening. Half of the San Diego participants were intentionally recruited to reflect those who had crossed the border to use drugs in Tijuana in the previous two years (‘cross border drug use’). As the focus of our modeling is on HCV and HIV transmission within San Diego County, our statistical analyses were limited to 204 participants residing in San Diego County. Following informed consent procedure where written consent was obtained through forms available in English and Spanish, participants completed interviewer-administered structured surveys and HIV/HCV serological testing at baseline and during 6-month follow-ups. HCV RNA testing was performed on those testing HCV Ab+. La Frontera was approved by Institutional Review Boards at the University of California San Diego and Universidad Xochicalco in Tijuana.

HIV seroprevalence, HCV antibody (Ab) prevalence, and HCV RNA prevalence among those who were HCV Ab+ were determined at baseline among La Frontera participants who resided in San Diego County, stratified by gender. HCV and HIV seroprevalence and computer-assisted interviewer-administered surveys were assessed every 6 months thereafter. Longitudinal trends in self-reported injecting behaviors (% injected drugs past 6 months, % used fentanyl among those who reported injecting past 6 months), harm reduction access (% used OAT in past 6 months, % used SSP in past 6 months), and social determinants of health (% homeless past 6 months, % time spent in jail or prison in past 6 months) were assessed among participants who had at least one follow-up visit (as of 4/24) and reported residing in San Diego at all study visits. Descriptive statistics using frequencies and proportions for binary variables and means and standard deviations, as well

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as medians and interquartile ranges for continuous variables, were used to describe the study participants at baseline as well as each follow-up visit. To evaluate the impact of time (i.e., study visit) on selected outcomes, we used Poisson regression models with robust variance estimation via Generalized Estimating Equations (GEE), which is appropriate for estimating relative risks for binary outcomes that represent counts or rates (Zou, 2004). An unstructured correlation structure was specified to account for within-subject correlations induced by the repeated measurements. In each model, study visit (visit 1 to visit 6) was used as the primary predictor (categorical variable with visit 1 as the reference category) and cross-border drug use status at the time of recruitment (yes vs. no) was used as a covariate to control for potential differences due to targeted recruitment of PWID residing in San Diego based on cross-border drug use. Furthermore, we estimated Relative Risks for each follow-up visit (vs. baseline) along with the corresponding 95 % confidence intervals (CIs) and Chi-square significance tests.

Central and Northern Wisconsin

Specific model parameters for rural Central and Northern Wisconsin (Central/Northern Wisconsin) are shown in Table 2. Data from PWID in Central/Northern Wisconsin were obtained from the Wisconsin site of the Rural Opioid Initiative Research Consortium (Jenkins et al., 2022), a community-based study which recruited PWID via respondent driven sampling (RDS) in two waves: 1) a cross-sectional survey among 991 PWID from January 2018-July 2019 (UG3 phase) and 2) the baseline visit from a longitudinal cohort of 326 PWID recruited from November 2020-December 2022 (UH3 phase). Eligible participants were those who reported injection of any drug in the past 30 days, were aged ≥15 years and were residents of one of six participating counties in Central and Northern Wisconsin. Participants completed computer-assisted interviews and underwent rapid HIV and HCV testing, with specimens testing HCV Ab+ tested for HCV RNA. Descriptive statistics using frequencies and proportions for binary variables and means and standard deviations as well as medians and interquartile ranges for continuous variables were used to describe the study participants. Due to challenges observed with the RDS recruitment strategy (Jenkins et al., 2022), we did not account for use of RDS recruitment weights or clustering of individuals that result from the network-based recruitment strategy.

For each wave of data collection, we calculated: HCV antibody prevalence stratified by gender, HCV RNA prevalence among those who were HCV Ab+ stratified by gender, and self-reported measures of % used fentanyl in the past month among those who reported past month injecting, % recently used OAT, % homeless past 3 months, % spent time in jail or prison past 3 months. We compared trends in exposures between the UG3 survey (2018/19) to the baseline of UH3 phase (2020–2022).

Scenario analyses

With our calibrated model fits, we assess HIV and HCV incidence over time among PWID from 2015 to 2030. To assess the impact of recent changes in drug use behaviors and exposures since the COVID-19 pandemic on HIV and HCV incidence, we simulate:

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- **Status quo observed scenario in San Diego and Central/Northern Wisconsin:** Historical changes observed in each area, assuming stable initiation rates of fentanyl from 2021 onwards (which leads to an increase in fentanyl use over time in both areas)
- **Counterfactual with no changes in exposures since 2020 in San Diego and Central/Northern Wisconsin:** We assume no change in proportions of PWID using fentanyl, on OAT, or recently incarcerated and no cessation rate changes (i.e., shifts from injecting to smoking drugs) from 2020 onwards.
- **Counterfactual with no increase in fentanyl use among PWID since 2020 in San Diego and Central/Northern Wisconsin:** No new transitions into fentanyl use in both areas from 2020 onwards (those using fentanyl remain in the fentanyl use category), leading to stable levels of fentanyl use.
- **Counterfactual with no increased injection cessation in San Diego since 2020 (as a result of shift from injecting to only smoking drugs):** No change in injecting cessation rate in San Diego from 2020 onwards.

Model outcomes

We assess HIV and HCV incidence from 2015 to 2025 in each area. To assess the population attributable fraction (PAF) of fentanyl use on HCV and HIV incidence, we compare the status quo scenario to a counterfactual with no fentanyl penetration into the drug supply from 2015 to 2025 (10-year fentanyl PAF). We compare the cumulative number of new HCV and HIV infections between 2015 and 2025 for each scenario and present the relative % increase in new infections between our no fentanyl and status quo scenarios.

Sensitivity analyses

To assess the sensitivity of our assumptions on projected incidence rates in 2030, we simulate scenarios with a) no impact of fentanyl use on drug-related mortality, b) triple the initiation rate into fentanyl use from 2024 onwards, c) sustained cessation rate among PWID in San Diego from 2020 onwards (0.14/year), and d) increase in cessation rate among PWID in Central/Northern Wisconsin to that observed in San Diego (0.14/year) from 2024 onwards.

Results

Epidemiological changes among PWID in San Diego and Central/Northern Wisconsin during COVID-19

In Central/Northern Wisconsin (Table 2), Self-reported use of fentanyl (through any administration route) among PWID increased, from 20 % in 2018 to 45 % in 2021. Recent OAT receipt was low (15 % in 2018), increasing to 29 % in 2021. Homelessness was high (63 % in 2018) and unchanged over time. Recent incarceration was high in 2018 (56 %) and decreased significantly in 2021 to 33 %.

In San Diego (Table 1), PWID at baseline in 2020/2021 reported a high prevalence of any fentanyl use (51 %), low coverage of recent OAT (15 %), high burden of recent

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homelessness (68 %), and low prevalence of recent incarceration (14 %). After 2 years of follow-up, there was a significant increase in fentanyl use (to 66 %), a significant increase in recent OAT use (to 22 %), and no change in homelessness or recent incarceration (Supplementary Information and Table 1). As previously reported, there was also a substantial shift from injecting to smoking drugs over time in San Diego (Eger et al., 2024), such that at 2 years after baseline (when 100 % of participants injected drugs according to study eligibility criteria), only 76 % of participants were still injecting drugs and 24 % reported smoking drugs but not injecting; this is higher than our estimated 10 % injecting drug cessation at 2 years (Table 1).

Baseline status quo projections

Both models calibrated well to the epidemiological data trends, with increasing fentanyl use in both areas, increases in recent OAT, decreases in incarceration (in WI only), and stable but high homelessness (Figs. 1,2). In Central/Northern Wisconsin, the model projects an increasing HCV incidence rate (from a mean 5.7 per 100 person-years [/100py] in 2015 to 15.4/100py in 2030) without additional scale-up of interventions, mainly due to the recently introduced HCV epidemic in these areas (estimated in 2009) and in part due to the expected continued increase in fentanyl use over time (Fig. 3). However, a decrease in the susceptible population results in a flattening of new HCV infections over time from 2020 onwards (from 77 new infections per 1000 PWID in 2020 to 80 new infections per 1000 PWID in 2030).

In San Diego, despite having an older HCV epidemic (estimated introduction in the 1990s), the model predicts an increasing HCV incidence rate over time, from a mean 3.2 per 100 person-years [/100py] in 2015 to 22.5/100py in 2030 (Fig. 3). However, due to the substantial decrease in PWID population size in San Diego (due to the shift to smoking) and decreasing susceptible population, the annual number of new HCV infections is expected to stabilize between 2025 and 2030. Model projections of HIV incidence rates and annual new infections were low but increasing from an incidence rate of 0.6/100py in 2015 to 1.1/100py in 2030 (Fig. 3). The smaller relative increase in HIV incidence compared to HCV was due to the estimated high contribution of sexual risk to HIV transmission (due to the low HCV prevalence among HIV+ individuals, supported by a high burden of sexually transmitted infections among PWID in SD [not shown]).

Impact of changes since COVID-19

In Central/Northern Wisconsin, without an increase in fentanyl use since 2020, HCV incidence would have been 12 % lower (mean 12.4/100py compared to 14.1/100py in 2025). However, this increased risk associated with fentanyl use was offset by an increase in OAT access and reduction in incarceration, such that HCV incidence in 2025 in a scenario with no changes since 2020 is similar to the baseline status quo (Fig. 4).

In San Diego, the shift from injecting drugs to smoking drugs (of any kind) is predicted to have had a profound impact on new HCV infections due to a predicted reduction in PWID population size (by ~20 % between 2021 and 2024) and therefore fewer PWID at risk of acquiring HCV. In a scenario without a shift from injecting to smoking drugs (and therefore constant injecting cessation rates), HCV incidence rates would have been similar but there

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would have been a mean relative 17.5 % more annual HCV infections in 2025 (Fig. 5). Without an increase in fentanyl use, HCV incidence would have been lower (a relative 9.5 % lower in 2025 compared to status quo). However, overall, without changes observed since 2020, the model predicts there would have been similar but slightly lower incidence rates and a higher number of new infections. Trends were similar for HIV. Overall, the model indicates that some of the additional risk of fentanyl was mitigated by increased OAT use, but most of the mitigation impact was driven by shifts from injection to smoking drugs.

10-Year fentanyl population attributable fraction (PAF)

Our modeling indicates that since fentanyl penetration into the drug supply from 2015 to 2025, the 10-year PAF of fentanyl on new HCV infections in Central/Northern Wisconsin (Fig. 6) is estimated to be 18 % (95 %CI 9–25 %). In San Diego, which has higher prevalence of fentanyl use, the fentanyl PAF was 34 % (26–45 %) for new HCV infections. The PAF for HIV was lower in San Diego compared to HCV (HIV PAF 10 % [95 %CI 1–26 %]) because the model calibration indicated that most HIV transmission was sexually acquired over this period, with injecting risk playing a lesser role.

Sensitivity analyses

In San Diego, projections of annual new HCV infections in 2030 were sensitive to assumptions regarding future cessation rates, such that new HCV infections were 23 % lower in 2030 compared to the status quo prediction in 2030 if recent cessation rates (0.14/yr) observed in San Diego continued from 2020 onwards. This is due to a declining PWID population, despite minimal (<10 % relative) differences in incidence rates (/100py) between scenarios. A scenario of tripled transition rates to fentanyl from 2024 onwards led to marginally higher incidence rates but 18 % lower new HCV infections in San Diego due to a dwindling susceptible population. San Diego predictions were not sensitive (<10 % relative difference compared to status quo) to a sensitivity analysis with no impact of fentanyl on drug-related mortality. In Central/Northern Wisconsin, model projections of HCV incidence rates and annual new infections in 2030 were not sensitive to any of our sensitivity analyses, deviating <10 % relative difference from status quo predictions (supplementary information).

Discussion

Our modeling predicted that fentanyl use may have contributed to 18 % and 34 % of new HCV infections among PWID over 2015–2025 in Central/Northern Wisconsin and San Diego, respectively. Increasing HCV and HIV transmission risk associated with fentanyl use among PWID was partially mitigated by a shift from injecting to smoking drugs (in San Diego), modest increases in OAT (in both areas), and reductions in incarceration (in Central/Northern Wisconsin). These findings have important implications for the prevention and treatment of HCV and HIV infection among PWID in these and possibly other areas.

Some researchers as well as governmental and non-governmental organizations support the promotion of safer smoking supplies as a harm reduction strategy to reduce infectious disease transmission (SAMHSA, 2023) and skin and soft tissue infections (Megerian et al.,

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2024), although no federal funding can currently be used to purchase smoking supplies. Further, some PWID believe they can better control their dose, thereby reducing their risk of overdose (Tapper et al., 2023). Although a recent study showed that people who injected fentanyl had a higher rate of nonfatal overdose than those who smoked it (Megerian et al., 2024), smoking fentanyl has become the primary documented route of drug administration among fatal overdoses across the United States (Tanz et al., 2024). Providing smoking supplies at SSPs may also engage more PWUD, including those who use drugs via non-injection routes, and improve access to services and care for this population.

The risk of HCV transmission among people who smoke drugs is generally considered low (Hermanstyne et al., 2012), but is not well characterized in the fentanyl era (Friedman et al., 2024). It is possible that sharing smoking paraphernalia (e.g., pipes) could transmit HCV, although results on this topic have been mixed. The distribution of smoking pipes at harm reduction organizations has shown promise in reducing the risk of infectious disease transmission from pipe sharing and has also been associated with a decrease in injection frequency among PWID (Dunham et al., 2024; Fitzpatrick et al., 2022). Additionally, the consideration of decriminalizing safer smoking supplies, such as pipes, may potentially facilitate a transition from injecting to smoking and potentially contribute to reducing the transmission of HCV (Dunham et al., 2024).

The rising HCV incidence and high burden of chronic infection observed in both areas highlights the need for enhanced efforts to increase HCV testing and treatment among PWID, combined with evidence-based harm reduction. The availability of point-of-care HCV RNA testing is an important opportunity to increase diagnoses of PWID, but these tests are only FDA-approved for adults aged 22 and older, which excludes many PWID who lack health insurance (Cepheid, 2024; Lewis et al., 2020). Expanded access to evidence-based harm reduction such as OAT and SSPs is urgently needed as these interventions reduce the risk of HCV and HIV infection, particularly if used in combination (MacArthur et al., 2012; Platt et al., 2018). Additionally, the burden of homelessness in both settings was very high (>60 %), and unchanged over time. Housing initiatives could aid elimination efforts as homelessness is associated with HIV and HCV incidence among PWID (Arum et al., 2021), and future modeling work examining the potential impact of housing policies on infectious disease transmission is warranted.

Despite many similarities, there were important differences between the settings examined with policy implications. Most notably, there was no observed HIV among PWID in Central/Northern Wisconsin. Although encouraging, there are several rural areas where HCV outbreaks/epidemics preceded HIV epidemics among PWID (Hudson et al., 2023; Ramachandran et al., 2018), and so vigilance and harm reduction expansion is needed (Gonsalves & Crawford, 2018). Additionally, in San Diego, the relatively low HCV/HIV coinfection prevalence indicates high sexual HIV risk among PWID (Vickerman et al., 2013), pointing towards a need for interventions to address both sexual and injecting risks among PWID.

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Strengths and limitations

Our study is the first model to examine the implications of fentanyl use and injection methods on HCV and HIV epidemics among PWID. A strength of our study is the use of rich data over time from local epidemiological studies among PWID to characterize drug use and exposure trends in one rural and one urban US area. However, like all modeling studies, our analysis is limited by uncertainties in key parameters. First, there is uncertainty in future behaviors, such as fentanyl use and injecting to smoking transitions, so we explore several possible scenarios in our analysis. It is unclear whether recent shifts from injecting to smoking, as has been observed in San Diego, are permanent or temporary, and whether current smokers will transition back to injecting. Although transition back from smoking to injecting has not yet been observed in San Diego, ongoing follow-up will help elucidate these dynamics. Nevertheless, our study provides insight into the substantial potential impact of these changes on future infectious disease transmission.

Second, many of our parameters are based on self-reported data, including fentanyl use. As such, misclassification of fentanyl use could have occurred, and may have changed over time, as individuals may be unaware of fentanyl presence in their drugs (Bailey et al., 2022; Canadian Centre on Substance Use & Addiction, 2024). This could have led us to under-estimate the potential impact of fentanyl use on HCV incidence, but future trends are difficult to predict. However, we note the association between fentanyl use and HCV incidence observed in San Diego was also based on self-report data, so there is consistency in exposure reporting between the studies. Regardless, a better understanding of the mechanisms by which fentanyl use increases HIV and HCV transmission is warranted to inform effective interventions, and our study could underestimate the impact of fentanyl if true use is higher.

Third, due to a lack of data on the impact of fentanyl use on HCV transmission in rural Wisconsin, we used an effect estimate derived from the San Diego cohort. Due to the observed associations between fentanyl use and increased injecting frequency, it appears plausible that the positive association between fentanyl and HCV is generalizable. However, the strength of this association may vary across different areas. Therefore, our study could potentially overestimate or underestimate the contribution of fentanyl to HCV in Central/Northern Wisconsin. Additional studies in other areas examining the relationship between fentanyl use and HCV incidence are needed to ascertain whether San Diego findings are generalizable.

Fourth, although we include the competing risk of mortality and impact of the increasing use of fentanyl on mortality over time in our estimates of HIV and HCV transmission, our analysis was not specifically focused on mortality (all-cause and overdose-related). This would require data on mortality rates among PWID over time in San Diego and Wisconsin as well as more detailed modeling to characterize overdose and other mortality dynamics more accurately.

Fifth, our model focuses on two areas, San Diego and rural Central/Northern Wisconsin, and our modeling may not be generalizable to other areas. However, fentanyl has become increasingly prevalent in the drug supply nationally and so we believe these are not

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necessarily isolated trends (Ciccarone, 2021). A shift from injecting to smoking among PWID has been also reported in San Francisco (Kral et al., 2021), but more studies are required to determine whether this is being observed in other US PWID populations, whether there has been any impact on injecting drug use initiation, and any resulting implications on infectious disease transmission.

Sixth, as our study is observational, we cannot attribute any observed changes directly to the COVID-19 pandemic. It is plausible that policy changes made during the pandemic which relaxed restrictions around OAT prescribing (such as take-home doses) could have contributed to the observed increases in OAT uptake among PWID. Similarly, it is plausible that at least some of the observed reductions in incarceration among PWID (in Central/Northern Wisconsin) were influenced by prison release efforts during COVID-19 in that state (personal communication, R Westergaard). However, other factors could play a role. Importantly, the PWID cohort in San Diego started in 2020, and so are insufficient to assess before and after trends. Indeed, many of the observed trends (such as increased fentanyl use) predated COVID-19 (Ciccarone, 2021), and so while it is possible that the pandemic may have led to changes in the drug supply and injecting practices, these could have occurred independently. Further, it is possible that some of the observations among the longitudinal PWID cohort in San Diego are due to cohort effects. Future work examining the potential causal impact of policy changes such as these on health among PWID is warranted to inform better policies in the future.

Seventh, our study modeled injecting-related fentanyl use risk among PWID, and therefore could potentially underestimate the total impact of fentanyl use among injecting and non-injecting PWID. For example, if fentanyl use is associated with increased sexual risk, then the contribution of fentanyl to new HIV infections among PWID and former PWID would be larger. Further studies would be needed to assess whether there are any relationships between fentanyl use and sexual risk.

Conclusions

Our modeling indicates that increasing fentanyl use is driving HCV and/or HIV transmission among PWID in both an urban and rural setting. The investigation of tailored interventions to reduce blood-borne virus transmission risk among PWID who use fentanyl is urgently needed. Increasing access to OAT and removing barriers to accessing safer smoking supplies could serve to reduce blood-borne virus transmission among this population. Finally, reductions in HIV and HCV could be facilitated through expanded access to point-of-care HCV and HIV testing and treatment alongside evidence-based harm reduction such as OAT and SSP.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of competing interest

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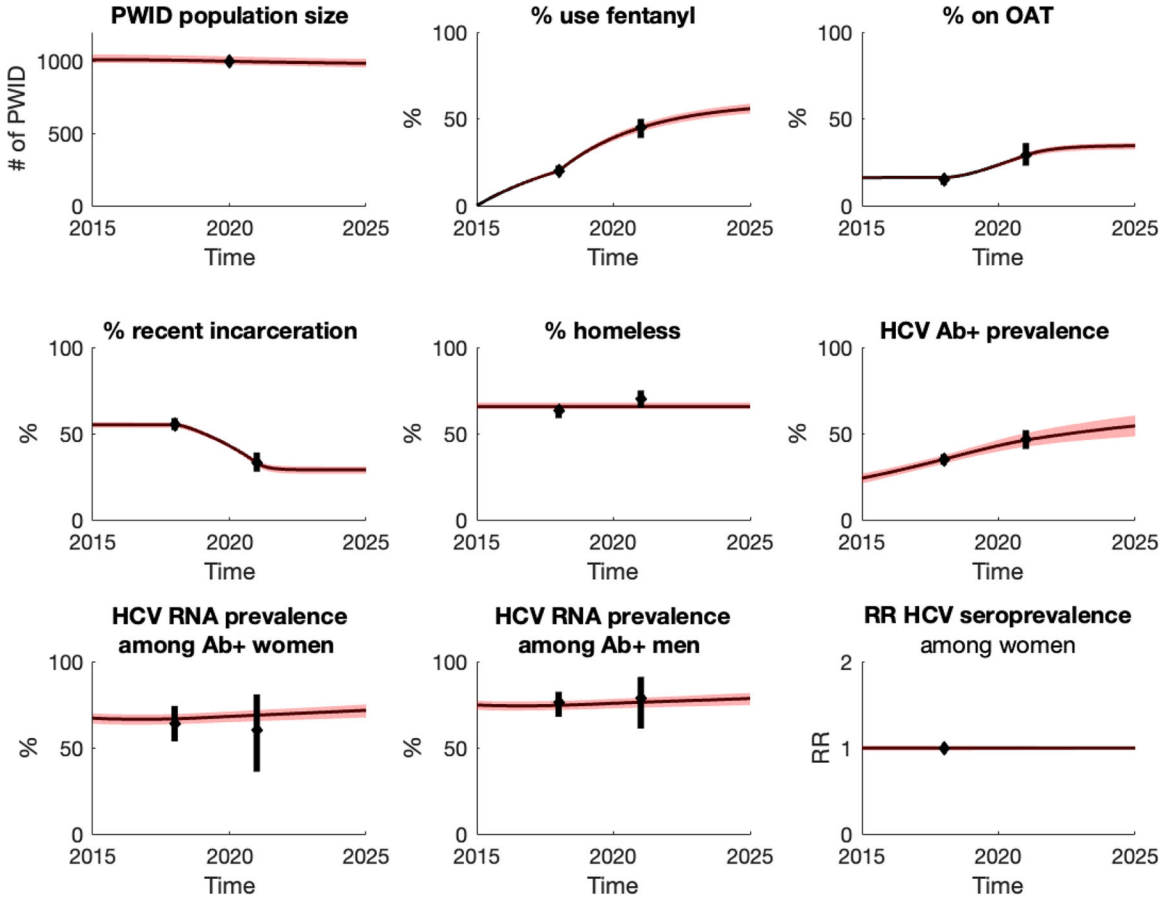


Fig. 1. Model calibration to data for Central/Northern Wisconsin.

Black line denotes median model fit, red shading represents the 2.5–97.5 % projections. Diamonds represent the calibration data points. PWID: people who inject drugs. HCV: hepatitis C virus. RNA: Ribonucleic acid. Ab: Antibody. OAT: Opiate agonist therapy. The PWID population is standardized to 1000 individuals in 2020 due to a lack of data.

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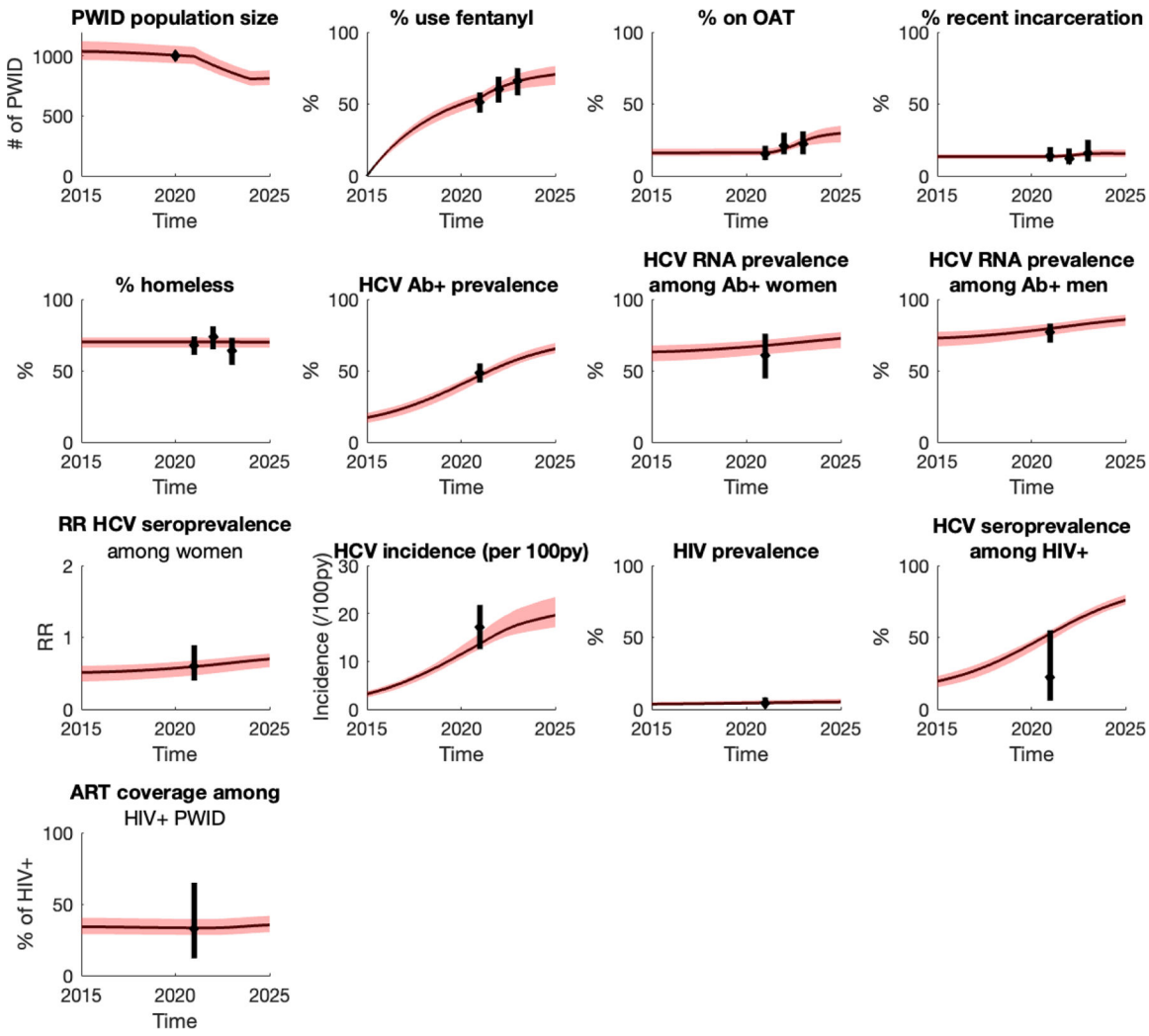


Fig. 2. Model calibration to data for San Diego.

Black line denotes median model fit, red shading represents the 2.5–97.5 % projections. Diamonds represent the calibration data points. PWID: people who inject drugs. HCV: hepatitis C virus. RNA: Ribonucleic acid. Ab: Antibody. HIV: Human immunodeficiency virus. ART: HIV antiretroviral treatment. OAT: Opiate agonist therapy. The PWID population is standardized to 1000 individuals in 2020 due to a lack of robust population size data.

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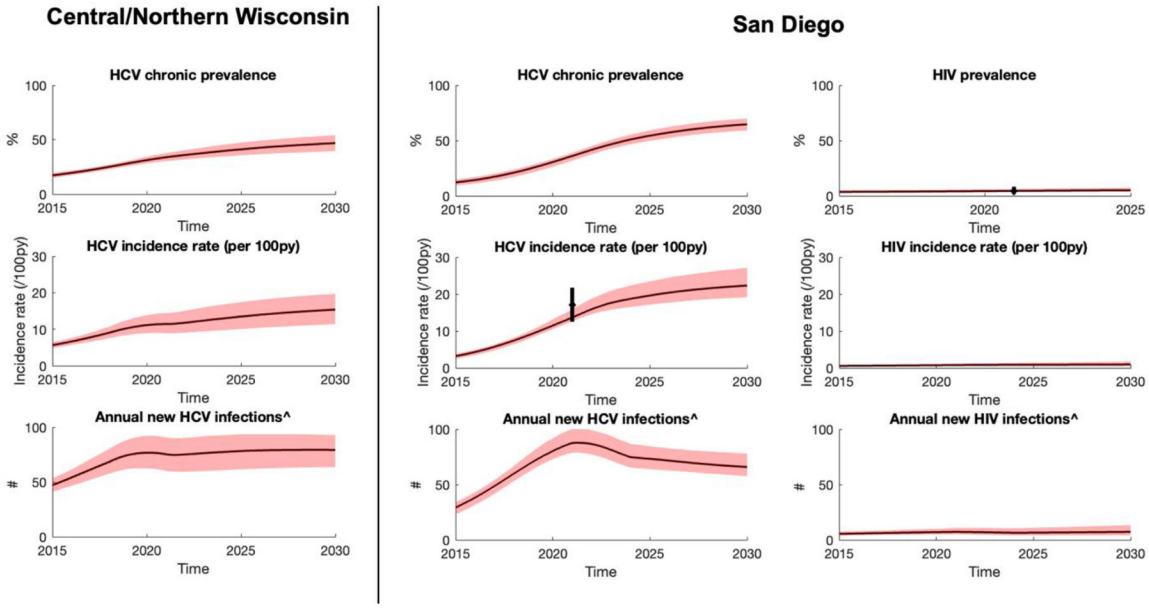


Fig. 3. Status quo model projections of HCV (Central/Northern Wisconsin and San Diego) and HIV (San Diego only) from 2015 to 2030.

Black line denotes median model fit, red shading represents the 2.5–97.5 % projections. Diamonds represent the calibration data. ^Annual new infections calculated among a standardized PWID population size of 1000 in 2020 given no or uncertain PWID population sizes in each area. Annual new infections are calculated each year, with the PWID population remaining stable over time in Central/Northern Wisconsin but declining in San Diego (from a scaled population of 1000 PWID in 2020 to 810 in 2024, see Fig 2). HCV: hepatitis C virus. HIV: Human immunodeficiency virus.

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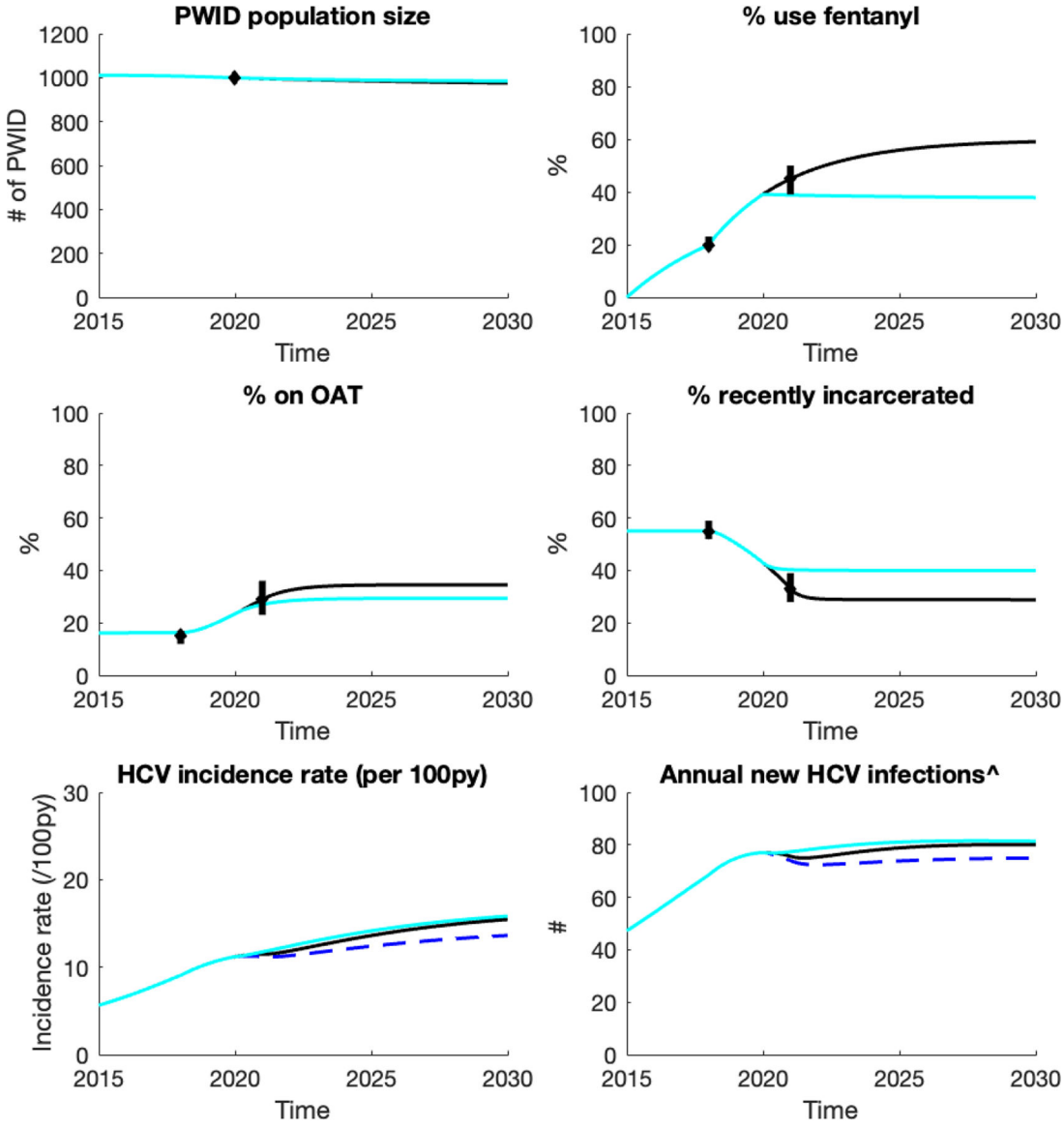


Fig. 4. Scenario projections from 2015 to 2030 for Central/Northern Wisconsin for the COVID counterfactuals scenarios.

Mean projection for the base case scenario (black line), no changes since 2020 counterfactual (aqua line) where fentanyl, OAT, and incarceration are stable from 2020 onwards, and no increase in fentanyl use since 2020 counterfactual (blue dashed line). Diamonds and whiskers represent the calibration data for the base case scenario. ^Annual new infections calculated among a standardized PWID population size of 1000 in 2020 given no or uncertain PWID population sizes in each area. Annual new infections are calculated each year, with the PWID population remaining stable over time in Central/ Northern Wisconsin).

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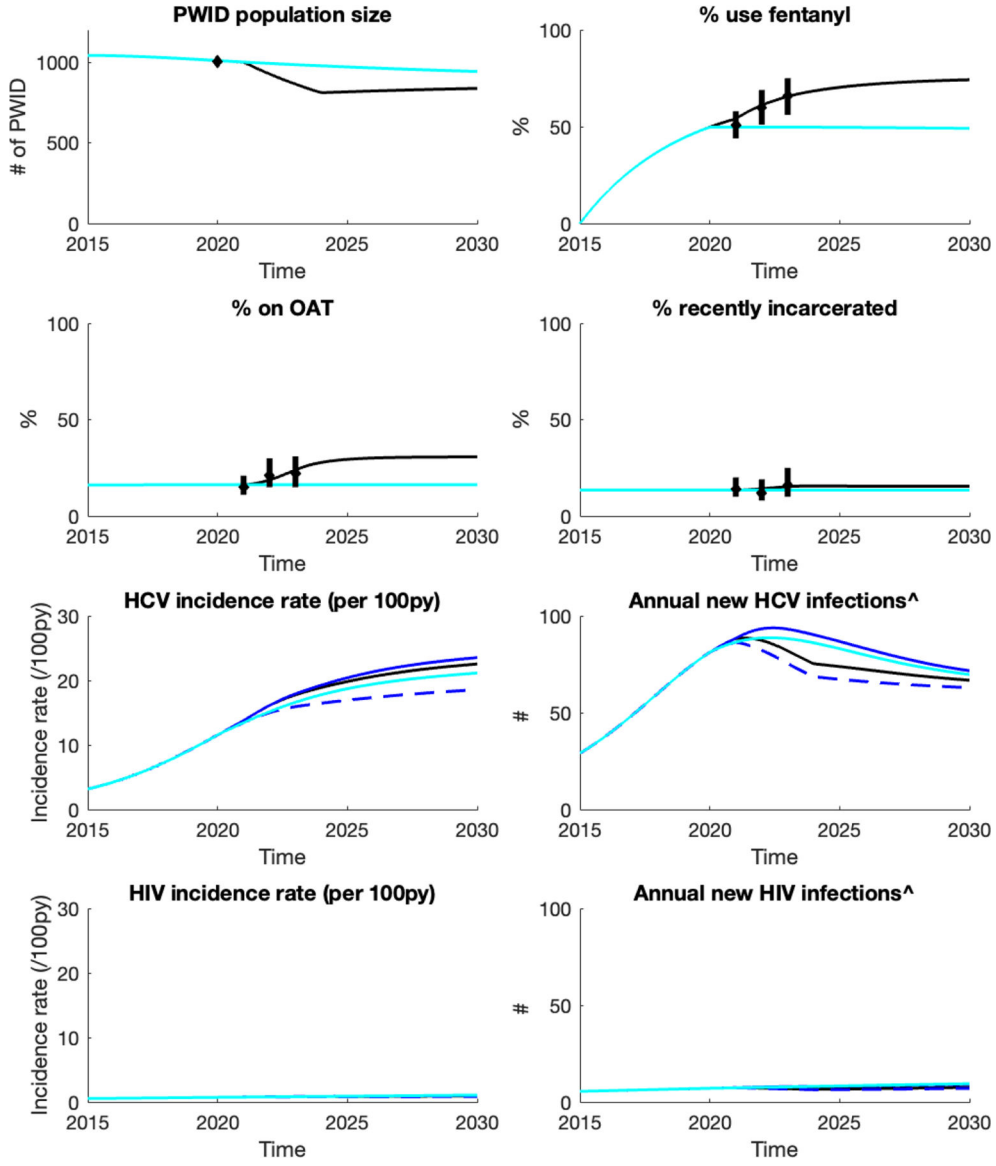


Fig. 5. Scenario projections from 2015 to 2030 for San Diego for the COVID counterfactuals scenarios.

Mean projection for the base case scenario (black line), no changes since 2020 counterfactual (aqua line) where fentanyl, OAT, and incarceration are stable from 2020 onwards, no increase in fentanyl use since 2020 counterfactual (blue dashed line), no change in cessation (blue solid line). ^Annual new infections calculated among a standardized PWID population size of 1000 in 2020 given no or uncertain PWID population sizes in each area. Annual new infections are calculated each year, with the PWID population declining in San Diego (from a scaled population of 1000 PWID in 2020 to 810 in 2024, see Fig 2).

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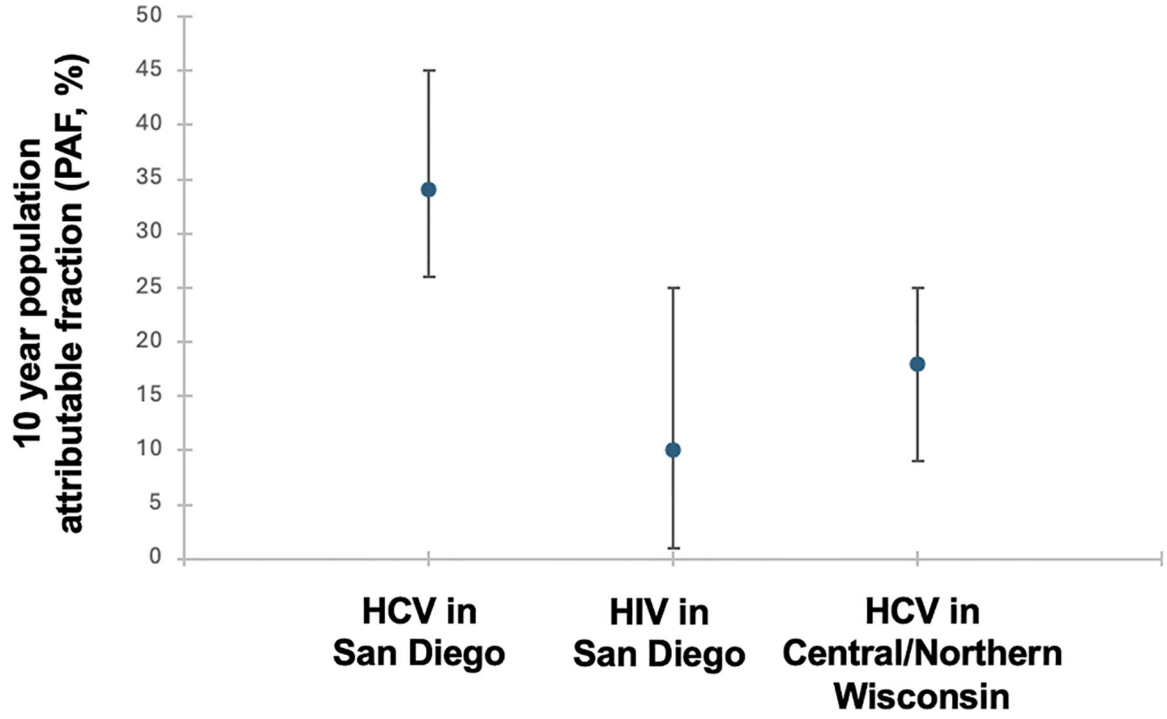


Fig. 6. 10-year population attributable fraction (PAF) of fentanyl use on HCV and HIV incidence (2015–2025) in San Diego and Central/Northern Wisconsin.

HCV: hepatitis C virus. HIV: human immunodeficiency virus.

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Table 1

San Diego specific key model parameters or calibration data.

Parameter	Value (95 %CI)	Reference
Proportion PWID who are women *(%)	27 %	La Frontera baseline
HCV seroprevalence	2021: 49 % (42–55 %)	La Frontera baseline
Relative HCV seroprevalence among women compared to men	2021: 0.60 (0.40–0.89)	La Frontera baseline
HCV RNA+ among Ab+ men	2021: 77 % (70–83 %)	La Frontera baseline
HCV RNA+ among Ab+ women	2021: 61 % (46–74 %)	La Frontera baseline
HCV incidence (per 100 py)	2021: 17.1 (12.5–21.8)	La Frontera
HIV seroprevalence	2021: 4.4 % (2.3–8.2 %)	La Frontera baseline
HCV antibody among people with HIV	2021: 22 % (6–55 %)	La Frontera baseline
% of people with HIV on ART	2021: 12 % (4–30 %)	La Frontera baseline
% PWID who self-report fentanyl use (through any administration route)	2021: 51 % (44–58 %) 2022: 60 % (51–69 %) 2023: 66 % (56–75 %)	La Frontera longitudinal data. Assume increasing trend based on statistical analysis, with fentanyl introduction in 2015 (Supplementary information)
% PWID with recent incarceration (jail or prison)	2021: 14 % (10–20 %) 2022: 12 % (8–19 %) 2023: 16 % (10–25 %)	La Frontera longitudinal data. Assume stable trend based on statistical analysis (Supplementary information)
% PWID experiencing recent homelessness	2021: 68 % (61–74 %) 2022: 74 % (65–81 %) 2023: 64 % (54–73 %)	La Frontera longitudinal data. Assume stable trend based on statistical analysis (Supplementary information)
% PWID with recent OAT	2021: 15 % (11–21 %) 2022: 21 % (15–30 %) 2023: 22 % (15–31 %)	La Frontera longitudinal data. Assume stable prior to 2021 and increasing trend based on statistical analysis (Supplementary information)
Injecting cessation rate *(per year)	Prior to 2021: 0.05 (0.04–0.07) 2021–2023: 0.14 2024-onwards: assume same as prior to 2021 for baseline scenario	La Frontera Prior to 2021: 1/average duration of injection (±25 %). 2021–2023: % who report not recently injecting over time (100 % in at baseline, 76 % after 2 years, converted to an annual rate)2024-onwards: assumption

* Denotes data used for parameterization, otherwise the data were used for calibration.

PWID: people who inject drugs. HCV: hepatitis C virus. RNA: Ribonucleic acid. Ab: Antibody. HIV: Human immunodeficiency virus. ART: HIV antiretroviral treatment. OAT: Opiate agonist therapy.

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Table 2

Central/Northern Wisconsin specific key model parameters.

Parameter	Value (95 % CI)	Reference
Proportion PWID who are women *(%)	40 %	UG3 and UH3 baseline
HCV seroprevalence	2018: 35 % (32–38 %) 2021: 47 % (41–52 %)	UG3 UH3 baseline
Relative HCV prevalence among women compared to men	1.0	UG3/UH3 No sig difference by gender
HCV RNA+ among Ab+ men	2018: 76 % (68–82 %) 2021: 79 % (62–89 %)	UG3 UH3 baseline
HCV RNA+ among Ab+ women	2018: 64 % (54–74 %) 2021: 60 % (39–78 %)	UG3 UH3 baseline
HIV seroprevalence	0 %	UG3/UH3
% PWID who self-report fentanyl use (through any administration route)	2018: 20 % (18–23 %) 2021: 45 % (39–50 %)	UG3 & UH3 baseline. Assume increasing trend based on non-overlapping confidence intervals, with fentanyl introduction in 2015.
% PWID with recent incarceration (jail or prison)	2018: 56 % (52–59 %) 2021: 33 % (28–39 %)	UG3 & UH3 baseline. Assume stable prior to 2018 and decreasing trend thereafter based on non-overlapping confidence intervals.
% PWID experiencing recent homelessness	2018: 63 % (59–66 %) 2021: 70 % (65–75 %)	UG3 & UH3 baseline. Assume stable trend based on overlapping confidence intervals.
% PWID with recent OAT	2018: 15 % (12–17 %) 2021: 29 % (23–36 %)	UG3 & UH3 baseline. Assume stable prior to 2018 and increasing trend thereafter based on non-overlapping confidence intervals.
Injecting cessation rate *(per year)	0.06 (0.04–0.1)	1/ average duration of injection from NHBS (Centers for Disease Control and Prevention 2018) ± 50 %

*Denotes data used for parameterization, otherwise the data were used for calibration.

PWID: people who inject drugs. HCV: hepatitis C virus. RNA: Ribonucleic acid. Ab: Antibody. HIV: Human immunodeficiency virus. ART: HIV antiretroviral treatment. OAT: Opiate agonist therapy. Data were obtained from a community-based study which recruited PWID in two waves: 1) a cross-sectional survey from January 2018-July 2019 (UG3 phase) and 2) the baseline visit from a longitudinal cohort recruited from November 2020-December 2022 (UH3 phase).