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Modeling the impact of interventions during an outbreak of HIV infection among people who inject drugs in 2012-2013 in Athens, Greece.

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Abstract
Background
A large HIV outbreak in People Who Inject Drugs (PWID) occurred in Athens, Greece in 2011-2013. In response, opioid substitution treatment (OST) and needle and syringe programs (NSP) were scaled-up and a seek-test-treat program was implemented. We aim to assess the impact of these interventions.

Methods
A mathematical model of HIV transmission among PWID was calibrated to data available over time (2009-2013) on HIV prevalence, NSP/antiretroviral treatment (ART) coverage and high-risk injection. A combined interventions scenario, including decrease in high-risk injection through linkage to OST and modification of risk behaviours and access to NSP and ART, was compared to a counterfactual scenario (no improvement at the levels of these interventions), with HIV incidence being the main outcome.

Results
HIV incidence increased from <0.1 new cases/100 person-years in 2009 to 11.0 (95% CrI: 6.8,16.1) in 2012. Under both models, a subsequent decline was projected following early 2012, with incidence at the end of 2013 in the combined interventions scenario being lower by 77% compared to the counterfactual. The projected reduction in incidence under the intervention scenario was in agreement with empirical data. HIV prevalence would have escalated to 20.4% (95%CrI:16.9%,23.6%) in 2013 under the counterfactual scenario (vs. 16.8% (95%CrI:11.2%,23.0%) under the combined interventions scenario). In total, 31.4% of HIV cases (392) were averted over 2012-2013.

Conclusion
These results underline the importance of high-coverage harm reduction programs and of community-based interventions to rapidly reach PWID most in need.

Keywords: PWID; HIV; outbreak; harm reduction; modeling
1. Introduction

People who inject drugs (PWID) constitute a key affected population with high risk of HIV infection. The global prevalence of HIV among PWID is estimated to be 17.8% for the period 2008-2017, corresponding to 2.8 million PWID living with HIV (Degenhardt et al., 2017). The risk of HIV infection and transmission in this population remains high. Although the implementation of harm reduction programs and antiretroviral therapy (ART) following the early epidemics of HIV among PWID in 1980-90s have been successful in preventing HIV epidemics in Western Europe for many years, multiple HIV outbreaks have occurred recently in Europe (Athens, Bucharest, Dublin, Luxembourg, Scotland), Middle East, Canada and the US (Des Jarlais et al., 2020).

Greece was one of the first countries experiencing such an outbreak in 2011. HIV prevalence among PWID in Athens, Greece, escalated from 0.8% in 2010 (Paraskevis et al., 2013) to 16.5% in 2013 (Sypsa et al., 2017). During 2002-2010, less than 20 newly diagnosed cases per year were reported to the HIV surveillance system among PWID (Paraskevis et al., 2013), whereas 1,113 newly diagnosed cases were reported over 2011-2013 (National Public Health Organization, 2020). Economic recession and the low coverage of harm reduction programs have been proposed as the causes of this outbreak with people experiencing homelessness and migrants being the most affected populations among PWID (Hatzakis et al., 2015; Paraskevis et al., 2013; Sypsa et al., 2015; Sypsa et al., 2017). This was the largest HIV outbreak out of the outbreaks recorded since 2011 among PWID in 8 sites in Europe and North America (Des Jarlais et al., 2020).

In response to the outbreak, the coverage of needle and syringe programs (NSP) and opioid substitution treatment (OST) programs were scaled-up in Athens. In addition, a seek-test-treat program targeting PWID was implemented during 2012-2013 with the aim to rapidly identify as many PWID residing in Athens as possible, offer HIV testing and counselling, link patients to HIV care and OST and distribute syringes (ARISTOTLE program) (Hatzakis et al., 2015; Sypsa et al., 2015; Sypsa et al., 2017). The program included five recruitment rounds using Respondent-Driven Sampling (RDS), with PWID able to participate in multiple rounds. Through this design, ARISTOTLE reached a population
coverage of approximately 88% (3,320 PWID were enrolled) (Sypsa et al., 2017). During its implementation in 2012-2013, reductions in high risk injecting behaviours were documented as well as increases in awareness of HIV positivity and linkage to HIV care among participants (Sypsa et al., 2017). In addition, HIV incidence decreased by 78% over 2012-2013 (Sypsa et al., 2017).

While the immediate utility of such programs is obvious, the quantification of their impact is not straightforward. It is usually not possible to use randomisation to evaluate the impact of a public health intervention and, thus, to know how the epidemic would have evolved if interventions had not been launched or scaled-up. Mathematical modelling can provide insights by simulating the course of the epidemic under various scenarios, so allowing an estimation of the impact of the intervention while accounting for epidemic dynamics. To this end, numerous studies have used mathematical modelling to evaluate the impact of harm reduction programs, ART and changes in the prevalence of injecting risk behaviours on HIV transmission in various settings (Foss et al., 2007; Fraser et al., 2017; Mumtaz et al., 2018; Vickerman et al., 2006; Vickerman et al., 2014).

In this paper, we develop and apply a mathematical model to data from the ARISTOTLE program and other available sources with the following aims: a) To estimate HIV incidence in the population of PWID in the years before and during the outbreak, and b) To assess the impact of the ARISTOTLE program and other interventions on reducing HIV incidence as soon as the outbreak was recognised. Given the large number of recent HIV outbreaks among PWID populations across Europe and North America (Des Jarlais et al., 2020), such an investigation may provide results that could be of use in other settings as well.

2. Methods

2.1. Model description and evaluated scenarios

We developed a deterministic compartmental model to simulate HIV transmission through injecting drug use among PWID (Figure 1). The modeled population is stratified according to infection state (Susceptible, Infected) and transmission risk (Low/High). Infected PWID
are further stratified by the initial acute high viraemia phase of infection and the subsequent chronic infection. Concerning transmission risk, based on ARISTOTLE data, injecting at least daily was the most important risk factor for HIV infection and was associated with a 10-fold hazard of HIV seroconversion (Sypsa et al., 2017). In a recent meta-analysis, higher levels of daily or more injecting were associated with higher prevalence of receptive needle–syringe sharing and HIV prevalence (Colledge et al., 2020). Thus, in the model, low- and high-risk PWID are defined based on the frequency of injecting drug use (high-risk: at least daily injecting drug use). Both susceptible and infected individuals are allowed to transition from high-risk to low-risk state at a rate κ to account for reductions in high-risk behaviours over time. Based on available data from ARISTOTLE, transitions from low- to high-risk occurred at much lower frequencies (5 times lower) and so were not included in the model.

New PWID enter the model through initiation of injecting as susceptible PWID at a rate h; a fraction of which (p) enter as high risk and the remainder (1−p) as low risk. PWID leave all states due to death (at a rate m) or cessation of injection (at a rate q). PWID can be infected with HIV at rates β_H or β_L if they are high or low-risk, respectively, whereupon they develop acute infection and then move to the next stage at a rate δ.

Interventions to reduce HIV transmission in Athens include the scale-up of OST and NSP, linkage of patients to ART as well as reductions in high-risk behaviours resulting from increased awareness of the outbreak or improved screening, diagnosis and counselling. To estimate the impact of interventions on the HIV outbreak during 2012-2013, we assessed two scenarios:

(i) A counterfactual scenario where the coverage of harm reduction programs and ART as well as the prevalence of high-risk behaviors were assumed to be stable at their early 2012 levels, i.e. before the scale-up of interventions, and

(ii) A combined intervention scenario where the scale-up of NSP and ART as well as reductions in risk behaviours due to the scale-up of OST and increased awareness (i.e. more rapid transition from high-risk to low-risk) were taken into account during 2012-2013.
Scale-up of ART: High-risk and low-risk infected individuals can be recruited onto ART at rates $g_H$ and $g_L$, respectively. The infectivity of HIV cases linked on ART is reduced by a factor $w$. For the relatively short period of our simulations, we assumed that once infected PWID start treatment, they remain in this state.

Scale-up of NSP: The protective effect of NSP was taken into account for those PWID who reported having received syringes through prevention activities during the last 30 days, by multiplying the infection rate by the factor $\Omega(t) = (1-nsp)+nsp*z$ ($nsp$: NSP coverage which may vary over time, $z$: the relative HIV injection transmission risk if on NSP compared to no NSP). The impact of NSP was taken into account in both scenarios assuming different NSP coverage.

Reduction in risk behaviours: Susceptible and infected individuals are allowed to transition from high-risk to low-risk state at a rate $\kappa$ to account for reductions in high-risk behaviours due to scale up of OST, increased testing and awareness.

In this model, the effect of OST was incorporated indirectly. OST programs lead to reductions in HIV transmission because, through them, the frequency of injection is reduced (Gowing et al., 2008). More than half of PWID entering OST during ARISTOTLE (55%) moved from the high-risk category to the low-risk category, while 31% and 14% remained in the low-risk and high-risk category respectively. Therefore, with the particular structure of the model, the benefit of OST is incorporated through the transition of PWID from high-risk to low-risk.

The model equations for the intervention and the counterfactual scenario are included in the Supplementary Material.

2.2. Model parameters

We assume that HIV prevalence was negligible before 2009 (Nikolopoulos et al., 2008) and we modelled the outbreak starting from 2009. Model parameters were either obtained from the literature or were specific to the Athens epidemic (Table 1). For the latter, they
were mainly derived from ARISTOTLE data on 3,320 PWID. As ARISTOTLE was implemented in five successive recruitment rounds during a period of 16 months, for the counterfactual scenario we used estimates from the first round (August-October 2012) and assumed that they apply throughout the period 2009-2013. For the combined interventions scenario, we used round-specific estimates that reflect the evolving trends in HIV prevalence, risk behaviors, NSP and ART coverage over time.

**PWID-related parameters**

The inflow of PWID ($h$) was set to a value that ensured a stable population over the modeled period (2009-2013). A fraction of these new injectors were classified as high-risk susceptible PWID and the remainder as low-risk. This was based on the proportion ($p$) of those reporting injecting drug use at least daily among “new” injectors participating in ARISTOTLE (i.e. persons with ≤2 years injecting drug use). In the combined interventions scenario, the proportion $p$ of high-risk injectors entering the population was set to be equal to the proportions observed in each ARISTOTLE round (from 44.6% up to round A to 20.2% in round E), whereas for the counterfactual scenario, the high-risk proportion among “new” injectors from the first round (44.6%) was used throughout 2009-2013 (Table 2).

Subsequently, PWID in the various compartments of the model could transition from high-risk to low-risk (i.e. injecting at least daily to less frequently). The corresponding transition rate $\kappa$ was estimated in order to fit the high-risk proportions among all injectors observed in ARISTOTLE survey rounds (Table 2). During ARISTOTLE, the proportion of high risk PWID decreased from 45.2% in round A to 18.8% in round E (reduction by 58.4%). In the combined interventions scenario, we estimated an overall transition rate $\kappa$ for the whole period by fitting the model to the round-specific high-risk proportions whereas, for the counterfactual scenario, the transition rate $\kappa$ was obtained by fitting the model to the high-risk proportion from the first round (45.2%) and was used throughout 2009-2013.

The mortality rate per year ($m$) was obtained from a systematic review and meta-analysis published in 2013 (Mathers et al., 2013), i.e. the crude mortality rate of 2.31% per years for Western Europe that takes into account deaths due to drug overdose and AIDS as the primary causes of death. HIV-related death was not explicitly included because of the short
timescale being modeled (4 years). Data on injecting cessation (1/average duration of injecting drug use) were obtained from ARISTOTLE data (Hatzakis et al., 2015).

**Infection rate**

For the high-risk state, the infection rate is multiplied by a factor $u$ (i.e. $\beta_H = u \beta_L$), where $u$ was obtained from the hazard ratio of HIV seroconversion for PWID injecting at least daily compared to those injecting less frequently (10-fold risk) (Table 1) (Sypsa et al., 2017). The infection rate was calibrated to fit the available HIV prevalence data from PWID accessing drug treatment services during the period 2009-2011 (Paraskevis et al., 2013) and from the ARISTOTLE program for the period 2012-2013 for the combined interventions scenario, or only from the first round for the counterfactual scenario (Table 2 & Supplementary Table 1) (Sypsa et al., 2017). HIV prevalence estimates obtained from ARISTOTLE were weighted to account for the sampling procedure that was used (Respondent-Driven Sampling) (Volz and Heckathorn, 2008). Additionally, those in the initial phase of high viraemia have heightened transmission (cofactor $r$ equal to 26) compared to the infection rate of those in the latent phase of HIV (Hollingsworth et al., 2008).

**NSP**

The protective effect of NSP depends on two parameters: NSP coverage over time and the relative HIV injection transmission risk if on NSP compared to no NSP if receiving syringes ($z$). The latter was set equal to 0.66 (Table 1) (Aspinall et al., 2014). Concerning NSP coverage in Athens over time, until 2011 when the outbreak was recognized, this was very low (seven syringes per PWID per year) (Malliori et al., 2013). Initiatives to scale-up NSP were put in place from December 2011. In order to incorporate the boost in needle distribution, a linear regression analysis was performed to simulate the gradual increase in NSP coverage from December 2011 (assumed to be 5%) up to the first round of ARISTOTLE in August-October 2012 (15% of participants reported adequate syringe coverage in the last 30 days in that round) (Table 2). For NSP coverage in the subsequent period (October 2012-end of 2013), the estimate of the first round was used for the counterfactual scenario (15%) and round-specific estimates were used for the combined
interventions scenario (15%, 20%, 29%, 14% and 20% in rounds A, B, C, D, and E, respectively). The fluctuations in NSP coverage reflect shortages in these periods.

*Antiretroviral therapy*

For the combined interventions scenario, the recruitment rate onto ART ($g_L$) was calibrated to fit the proportion of low-risk HIV-infected PWID on ART in different rounds, as assessed by self-reported data (low-risk PWID: increase from 9.0% in round A to 32.0% in round E, Table 2) (Sypsa et al., 2017). We also assumed that low-risk individuals initiated ART at a higher rate compared to high-risk, i.e. that $g_L = \nu g_H$ where $\nu = 1.69$ (we used the relative increase in ART recruitment if on OST compared to no OST) (Low et al., 2016). This was based on the observation that on the first visit of HIV-infected ARISTOTLE participants, 9.0% and 13.4% of low and high risk, respectively, reported being currently in ART. For the counterfactual scenario, we assumed that ART coverage among low-risk PWID remained at 9.0% throughout (i.e. based on the first round) with high-risk PWID having the same difference in ART recruitment.

The reduction in HIV infectivity due to linkage to ART is denoted by a factor $w$. Due to the substantial uncertainty in this parameter, we sampled values from a uniform distribution between 0.25 and 0.75 (Cepeda et al., 2018).

**2.3. Model analyses**

HIV prevalence, the proportion of PWID that are high-risk and coverage of ART among HIV-infected PWID (Table 2) were sampled using triangular distributions, whilst the proportion of new injectors that are high-risk and of PWID with adequate syringe coverage in the last 30 days were sampled using uniform distributions to give 1,000 model parameter sets. For each parameter set, the infection rate $\beta_L$, the transition rate from high- to low-risk $\kappa$ and the treatment rate $g_L$ were varied to fit the model to the observed data for HIV prevalence for the years 2009-2013, and the proportion of PWID that are high-risk and ART coverage for 2012-2013, respectively. This was done using the Matlab function `lsqnonlin` that minimises the sum of the squared error between the data points and the best-
fit curve (Matlab version R2015b); 1,000 full model fits along with their 2.5, 50 and 97.5 percentiles were obtained.

We evaluated the fit of the model by assessing graphically whether the model under the combined interventions scenario captures adequately the trends in HIV prevalence, the proportion of high-risk PWID and proportion of HIV-infected PWID on ART over time. In addition, to validate the model, we compared the projected HIV incidence rates obtained from the intervention model with empirical incidence estimates. The latter were derived from data on HIV seroconversions recorded in a cohort of seronegative ARISTOTLE participants (Sypsa et al., 2017). The model was not calibrated to incidence data.

We obtained the model-based estimates of HIV prevalence and HIV incidence rate over time (number of new infections/100 person-years (PY)) under the counterfactual and the combined interventions scenarios. The corresponding cumulative number of new HIV cases through 2009-2012 was obtained and the number of HIV infections averted, as a result of the interventions implemented during 2012-2013, was calculated. Ninety-five percent credible intervals (95% CrI) were produced using the 2.5–97.5 percentile range in the projections across the 1000 model fits.

A univariate sensitivity analysis was undertaken in order to examine the possible impact of various parameters on the estimates (Supplementary Material).

2.4. Ethical Issues

ARISTOTLE program received ethical approval by the Institutional Review Boards of the Medical School of the National and Kapodistrian University of Athens (protocol number: 1748) and the Hellenic Scientific Society for the Study of AIDS, STDs and Emerging Diseases.

3. Results
3.1. HIV prevalence, HIV incidence and cumulative number of new infections under the counterfactual and the combined interventions scenario

Under the combined interventions scenario, the model captured adequately the trends in HIV prevalence over 2009-2013 (Figure 2a). Under the counterfactual scenario, it is predicted that HIV prevalence would escalate to 20.4% (95% CrI: 16.9%, 23.6%) by the end of 2013, i.e. almost 22% higher compared to the corresponding estimate obtained under the combined interventions scenario (16.8% (95% CrI: 11.2%, 23.0%)).

The model was also used to estimate the trends in HIV incidence and the cumulative number of HIV infections during the outbreak. The incidence rate is estimated to increase from 0.073 new infections/100 PY (95% CrI: 0.072, 0.073) in 2009 to 11.0/100 PY (95% CrI: 6.8, 16.1) in January 2012, i.e. approximately a 150-fold increase in three years (Figure 3). The subsequent scale-up of interventions and decline in risk behaviours observed during 2012-2013 resulted in an 89% decrease in incidence at the end of 2013 (1.23 new cases per 100 PY (95% CrI: 0.84, 1.90)) as compared to the peak observed in early 2012 (Figure 3). Based on the counterfactual model, HIV incidence would have still decreased after 2012 to 5.40 new infections/100 PY (95% CrI: 4.39, 6.57) by the end of 2013 (Figure 3). It is noteworthy that the estimated HIV incidence under the combined interventions model agreed with the observed data, even though the model was not calibrated to HIV incidence data (Figure 3).

Under the intervention scenario, the cumulative number of new HIV cases occurring during 2009-2013 was 1,696 (95% CrI: 1,139, 2,392) as compared to 2,169 (95% CrI: 1,493, 2,940) under the counterfactual scenario (Figure 2b). During 2012-2013, i.e. the period of scale-up of interventions and change of behaviours, the cumulative number of new HIV cases estimated under the intervention scenario was 792 (95% CrI: 510, 1,130) and 1,154 (95% CrI: 897, 1,369) in the counterfactual scenario. Overall, it is estimated that 31.4% of HIV cases were averted in 2 years.

3.2. Sensitivity Analysis
In the sensitivity analysis, assuming a more pronounced impact of NSP on reducing transmission (relative reduction in infection rate if received syringes \( z \) equal to 0.42 vs. 0.66 assumed in the main analysis) would result in slightly higher proportion of averted cases (34.7% in 2 years) as compared to the main analysis (Supplementary Figure 1). Increasing the sampling range of the factor \( w \) related to reduction in the infection rate if on ART, by 0.20 (between 0.25-0.95 vs. 0.25-0.75) resulted in an estimate similar to that in the main analysis (Supplementary Figure 1).

Finally, variations in the duration of injecting drug use have a minimal impact; under shorter (9 years) or longer (15 years) injecting duration (vs. 12 years in the main analysis), the benefit in HIV cases would reach 32.2% and 30.0%, respectively (as compared to 31.4% in the main analysis) (Supplementary Figure 1).

4. Discussion

The HIV outbreak of Athens was the first of a series of epidemics occurring since 2010 in the population of PWID in Europe and the US (Des Jarlais et al., 2020). Previously, the course of this outbreak has been analysed based on HIV surveillance data as well as data on HIV seroconversions collected from ARISTOTLE participants during 2012-2013 and molecular epidemiology methods applied on HIV sequences (Paraskevis et al., 2015; Sypsa et al., 2017). Here, we used mathematical modeling to reconstruct the course of the outbreak. We identified a 150-fold increase in HIV incidence from 2009 to 2012, with a peak at 11.0 new infections/100 PY. Following this peak, a steep decline of 89% occurred within two years. The model predicted that, in the absence of scale-up in HIV screening, linkage to ART and harm reduction programs as well as changes in high-risk injecting practices, HIV incidence and HIV prevalence would have reached 5.40 new infections/100 PYs and 20.4%, respectively, by the end of 2013 (vs. 1.23/100 PYs and 16.8% under the combined interventions scenario). Overall, it is estimated that the implemented interventions averted approximately one third of new HIV infections during 2012-2013.
In an earlier paper, we had argued that the steep decline in incidence during 2012-2013, as documented by seroconversion data, and the fact that the outbreak was contained at a relatively moderate HIV prevalence suggest that the reduction of transmission could not be attributed to saturation effects only (Sypsa et al., 2017). This analysis agrees with that assertion, with our modelling suggesting that the outbreak had the potential to reach a higher prevalence and a 4-fold higher incidence rate at the end of 2013, as shown by the counterfactual scenario, with apparent implications concerning the cumulative number of infections in the population of PWID. Based on the counterfactual scenario, HIV incidence would have still decreased after 2012. This decline could be partly attributed to the scale-up of NSP in late 2011 - the first measure implemented in response to outbreak - which was incorporated in both scenarios (with different coverage after mid-2012). It should be noted that, following 2013, the number of newly diagnosed HIV cases among PWID reported to the HIV surveillance system has not returned to the pre-outbreak levels; in 2018-2020, there were 81-120 diagnosed cases per year among PWID in Greece compared to 10-20 cases before the outbreak (National Public Health Organization, 2020). In addition, based on an analysis of repeatedly tested PWID recruited in ARISTOTLE in 2012-2013 as well as in a similar program implemented in 2018-2020 in Athens (ARISTOTLE HCV-HIV), HIV transmission did not decline further after 2013 (Roussos et al., 2022). Our combined interventions scenario included the reduction in injection frequency during the Athens outbreak. According to an analysis of the ARISTOTLE data, this change was observed at a similar rate among HIV-infected PWID (independently of whether they were aware or not of their serostatus) and uninfected participants (Pavlopoulou et al., 2020). Data from earlier HIV epidemics among PWID have shown that they are willing to modify their HIV risk behaviours (Des Jarlais et al., 1996). In Athens, PWID may have become gradually aware of the outbreak and been informed about HIV and transmission routes either through their contact with harm reduction programs and interventions (such as ARISTOTLE) or from their injection network. During ARISTOTLE, an estimated 88% of the target population was reached and received HIV testing/counselling (Sypsa et al., 2017). The reduction in injection frequency can also be attributed to the increasing coverage of OST. Based on ARISTOTLE data, high-risk PWID who subsequently entered OST reduced their injection frequency at a much higher
proportion (55%) than those who did not enter OST (28%). Linkage to ART was an additional factor that was considered in the interventions scenario, although its coverage did not reach high levels within the first two years of the outbreak. The large number of identified cases in a small period of time as well as structural and personal barriers resulted in a slow increase of ART coverage. Finally, NSP was an additional intervention implemented during that period. However, although there was an increase in NSP coverage compared to the pre-outbreak levels, it did not reach the recommended levels (World Health Organization, 2012) and PWID were not consistently covered during 2011-2013. It should be noted that repeat ARISTOTLE participants reported higher rates of adequate syringe coverage, linkage to HIV care, and OST, as well as awareness of their serostatus compared with first-time participants (Sypsa et al., 2017).

Modeling has been used to assess the effect of interventions on HIV transmission among PWID in various settings. In most cases, a substantial impact was predicted, though not in such a short time as in Athens. In PWID populations in Eastern Europe and Central Asia, it was found that achievable coverage of combined interventions (NSP, OST and ART) could lead to 30%-50% decline in HIV incidence over a period of 10 years (Vickerman et al., 2014). In Bangladesh, NSP was estimated to account for a 90% reduction in HIV incidence over a period of 8 years (Foss et al., 2007). In a modeling study examining the impact of interventions on HIV infection among PWID around the world, it was found that high coverage of NSP, OST and ART (around 50% annual recruitment), would result in a median reduction in HIV incidence of 29% (10th-90th percentile: 17–50%) in 5 years (Degenhardt et al., 2010). Modeling has been applied to the 2014 HIV epidemic in Scott County in the US where it was estimated that reactive implementation of NSP programs would result in a 61% decrease in the cumulative number of cases over a 5-year period as compared to the scenario without NSP (Goedel et al., 2019). The effectiveness of HIV prevention activities for PWID in USA was demonstrated by another modeling study estimating that 50% coverage of OST and NSP could avert up to 22,000 and 35,000 infections, respectively (Bernard et al., 2017). Based on modeling applied to data on PWID in Russia, scaling-up OST and NSP by 50% for 2 years and increasing linkage to ART (reaching approximately 65% of HIV positive PWID) could prevent 58% and 38% of HIV deaths over 10 years in Omsk and Ekaterinbourg, respectively (Cepeda et al., 2018).
Our model made use of available HIV prevalence estimates over time in the PWID population to reconstruct the course of the outbreak over 2009-2013. An advantage of this analysis is that there was a wealth of data collected during the course of the outbreak through successive recruitment rounds of the ARISTOTLE program from a large sample of PWID. This allowed us to obtain important model parameters at multiple time points during the ongoing outbreak in Athens - e.g. the proportion of high-risk PWID, NSP coverage and ART coverage - and, thus, we were able to capture the changes taking place over that period. An additional strength of the analysis is that, although the model was not calibrated to HIV incidence data, it captured its trends satisfactorily with the projected reduction in incidence under the intervention scenario being in close agreement with empirical data.

We assessed the impact of the interventions rolled out during the HIV outbreak in Athens using mathematical modelling rather than experimental designs. Although randomised controlled trials (RCT) are considered to provide the best evidence on cause and effect, there are several limitations that make their applicability in assessing the impact of complex public health interventions questionable (Centre for Epidemiology and Evidence, 2019). First, adherence to the protocol of an RCT in community-based interventions may not be realistic. In addition, randomisation would not be ethically acceptable as this would mean withholding services that are known to improve health outcomes from the control group during an ongoing HIV outbreak (e.g. testing and linkage to HIV care). Finally, the implementation of interventions in a group of PWID in Athens would most probably result in contamination of the comparison population, i.e. the assumption that one group is exposed to the effects of the intervention, whereas another is not, would be violated. There are alternative experimental designs for the evaluation of public health interventions such as cluster RCT or the stepped-wedge design. However, a cluster RCT would still pose ethical considerations. The stepped-wedge design is a modified cluster RCT where the intervention is implemented sequentially in clusters, so it is proposed when withholding the intervention is not considered equitable. However, in the case of an ongoing epidemic, delays in offering services in groups of PWID would not be ethically accepted. In addition, both designs could not overcome the risk of contamination as the clusters would have to be selected from the same site (i.e. Athens) and there would be contact between the
intervention clusters and the control clusters. Apart from these limitations, these designs generally require a large budget and more control over the program setting (Centre for Epidemiology and Evidence, 2019). Mathematical modelling allowed us to assess the impact of interventions implemented during a public health emergency when controlled trials were ethically and logistically impossible. In addition, it allowed us to reconstruct the course of the epidemic over time and to obtain useful quantities (e.g. peak incidence) that could not be estimated otherwise.

4.1. Limitations

A limitation of the model is that the HIV prevalence estimates that were used to fit the model were available from PWID entering drug treatment programs for the years 2009-2011 and from ARISTOTLE data for 2012-2013. This may possibly result in underestimated prevalence for 2009-2011 although it should be noted that HIV infected individuals were prioritised to enter OST. Another limitation for ARISTOTLE data is that the frequency of injection, as well as both the NSP and ART coverage, were based on self-reported data. The former could be affected by social desirability bias, with participants under-reporting high-risk behaviors.

4.2. Conclusions

The HIV outbreak in Athens is the largest recent outbreak among PWID out of the outbreaks recorded in 8 sites in Europe and North America since 2011 (Des Jarlais et al., 2020). Our modeling suggests that changes in injection behaviors resulting from increased OST coverage and HIV testing/counselling through a high-coverage community-based program had a substantial impact in reducing further transmission. A unique interventional component of that program was the use of multiple respondent-driven sampling rounds to implement the seek-test-treat model of care. However, there is no time for complacency. Preliminary data from sites in Europe and North America with recent HIV outbreaks among PWID suggest that the COVID-19 pandemic has severely impacted essential HIV prevention services (Wiessing et al., 2020). The risk of new or resurgent HIV epidemics is imminent. The example of the HIV outbreak in Athens underlines the importance of high-coverage harm reduction programs and of implementing community-based interventions.
to rapidly reach those most in need (active PWID, people experiencing homelessness, not linked to other services) and offer testing/counselling and linkage to care.
Data Availability Statement

The code is available at github+++
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**Table 1.** Model parameters and prior ranges before fitting for the counterfactual and the combined interventions scenario

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<th>Model parameter</th>
<th>Counterfactual Scenario</th>
<th>Combined interventions scenario</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of cessation of injection in years ($q$) (=1/mean duration)</td>
<td>1/12</td>
<td></td>
<td>(Hatzakis et al., 2015)</td>
</tr>
<tr>
<td>Mortality rate per year ($m$)</td>
<td>2.31%</td>
<td></td>
<td>(Mathers et al., 2013)</td>
</tr>
<tr>
<td>Factor increase in injection related HIV transmission risk if high-risk ($u$)</td>
<td>10</td>
<td></td>
<td>(Sypsa et al., 2017)</td>
</tr>
<tr>
<td>Entry rate of new PWID per year ($h$)</td>
<td>0.09</td>
<td></td>
<td>Set to ensure stable population</td>
</tr>
<tr>
<td>PWID population size in Athens (95% CI) in 2011 ($N$)</td>
<td>8056</td>
<td></td>
<td>Based on the official population size estimate of high risk opioid users(^\text{1}) in Athens (Greek Documentation and Monitoring Centre for Drugs, 2012)</td>
</tr>
<tr>
<td>Percentage of new injectors ($\leq$2 years injecting drug use) defined as high-risk (injecting drug use at least daily) ($p$)</td>
<td>44.6% (0.29.7% – 0.61%) triangular ($a$=28.9%, $b$=44.6%, $c$=61.5%)</td>
<td>Table 2</td>
<td>ARISTOTLE data (unpublished)</td>
</tr>
<tr>
<td>Injection related infection rate per month amongst low risk injectors (95% CrI) ($\beta_{L}$)</td>
<td>0.0045 (0.004-0.0049)</td>
<td></td>
<td>Varied to fit to ARISTOTLE estimates across rounds (Table 2) (Sypsa et al., 2017)</td>
</tr>
<tr>
<td>Cofactor increase in HIV transmission for those in the acute phase ($r$)</td>
<td>26</td>
<td></td>
<td>(Hollingsworth et al., 2008)</td>
</tr>
<tr>
<td>Duration of initial acute phase of high viraemia in years ($I/\delta$)</td>
<td>1/3</td>
<td></td>
<td>(Hollingsworth et al., 2008)</td>
</tr>
<tr>
<td>Parameter</td>
<td>Estimate</td>
<td>CI</td>
<td>Source</td>
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<td>--------------------------------------------------------------------------</td>
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<tr>
<td>Relative HIV injection transmission risk if on NSP compared to no NSP (z)</td>
<td>0.66</td>
<td></td>
<td>(Aspinall et al., 2014)</td>
</tr>
<tr>
<td>Percentage of participants receiving adequate syringe (95% CrI) (nsp)</td>
<td></td>
<td></td>
<td>(Sypsa et al., 2017)</td>
</tr>
<tr>
<td>Factor-decrease in infection rate if on ART (w)</td>
<td>0.50</td>
<td>(0.26–0.74)</td>
<td>(Cepeda et al., 2018)</td>
</tr>
<tr>
<td>Transition rate from high to low risk per year (95% CrI) (κ)</td>
<td>0.005</td>
<td>(0.021–0.083)</td>
<td>Varied to fit to ARISTOTLE estimates</td>
</tr>
<tr>
<td>Recruitment rate onto ART per month in low-risk PWID (95% CrI) (gL)</td>
<td>0.005</td>
<td>(0.003–0.009)</td>
<td>Varied to fit to ARISTOTLE estimates</td>
</tr>
<tr>
<td>Factor increase in ART recruitment for low-risk PWID compared to high-risk (v)</td>
<td>1.69</td>
<td></td>
<td>(Low et al., 2016)</td>
</tr>
<tr>
<td>Proportion on ART (self-reported) for low risk participants (95% CI)</td>
<td></td>
<td></td>
<td>ARISTOTLE data (unpublished)</td>
</tr>
</tbody>
</table>

1 People with injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamines
**Table 2.** HIV prevalence, risk behaviours and access to prevention and HIV treatment over the five recruitment rounds of ARISTOTLE program in Athens, Greece (2012-2013)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>HIV prevalence</td>
<td>14.2 (10.3-18.0)</td>
<td>16.1 (12.0-20.1)</td>
<td>16.2 (11.9-20.4)</td>
<td>13.5 (9.5-17.5)</td>
<td>12.0 (8.6-15.5)</td>
</tr>
<tr>
<td>Proportion injecting at least daily (95% CI)</td>
<td>45.2 (39.4-51.0)</td>
<td>20.3 (16.2-24.3)</td>
<td>21.3 (16.7-25.9)</td>
<td>18.9 (14.7-23.0)</td>
<td>18.8 (15.2-22.4)</td>
</tr>
<tr>
<td>Proportion of “new” injectors injecting at least daily (95% CI)</td>
<td>44.6 (28.9-61.5)</td>
<td>25.9 (14.3-42.1)</td>
<td>27.5 (12.2-50.9)</td>
<td>16.2 (9.6-26.1)</td>
<td>20.2 (10.9-34.4)</td>
</tr>
<tr>
<td>Proportion with adequate syringe coverage in past month (95% CI)</td>
<td>15.0 (11.1-19.9)</td>
<td>20.1 (15.8-25.2)</td>
<td>28.8 (23.3-35.0)</td>
<td>13.8 (10.8-17.3)</td>
<td>20.4 (16.8-24.5)</td>
</tr>
<tr>
<td>Proportion on ART (self-reported) for low risk participants with HIV (95% CI)</td>
<td>9.0 (4.0-18.0)</td>
<td>21.2 (15.0-29.0)</td>
<td>33.0 (25.0-41.0)</td>
<td>38.0 (29.0-46.0)</td>
<td>32.0 (25.0-41.0)</td>
</tr>
</tbody>
</table>

1. RDS-II estimates. The corresponding unweighted estimates are provided in Supplementary Table 2
2. “New” injectors: persons with ≤2 years injecting drug use
3. Adequate syringe coverage in the past month was defined as receiving as many or more syringes in a month as they needed for their frequency of injection
Figure 1. Model schematic for the counterfactual and the combined interventions scenario.

In both models, new PWID are introduced into the model as Susceptible high-risk or Susceptible low-risk at a rate $hp$ and $h(1-p)$ respectively, then move to the Acute phase as high-risk or low-risk at a rate $\beta_H$, $\beta_L$ respectively and proceed to the latent phase (at $\delta$ rate per unit time). PWID leave all states due to cessation of injection (at $q$ rate per unit time) or death (with mortality $m$ per unit of time). In both scenarios, high-risk PWID transition to low-risk at a rate $\kappa$ and low risk or high risk HIV cases receiving ART enter the “Under treatment” state at a rate $g_L$ and $g_H$ respectively.
Figure 2. Model estimates over time under the counterfactual scenario (black line) and the combined interventions scenario (red line) for (a) HIV prevalence, and (b) Cumulative number of HIV cases in the population of PWID in Athens, Greece. The coloured area denotes the 95% CrI for the two scenarios (grey for the counterfactual scenario and red for the combined intervention scenario). The circles depict: (a) HIV prevalence among PWID based on data from two different sources: PWID accessing treatment services for 2009-2011 (hollow circles) and data from ARISTOTLE program (filled circles) (Sypsa et al., 2017) (the vertical lines indicate the corresponding 95% confidence intervals), (b) Cumulative number of new HIV diagnoses among PWID from surveillance data (National Public Health Organization, 2020).
**Figure 3.** HIV incidence estimates among PWID over time under the counterfactual scenario (black line) and the combined interventions scenario (red line). The coloured area denotes the 95% CrI for the two scenarios (grey for the counterfactual scenario and red for the combined intervention scenario). The circles depict HIV incidence estimates among PWID in Athens based on observed seroconversion data from ARISTOTLE program (Sypsa et al., 2017).