



Research Paper

A new outbreak of HIV infection among people who inject drugs during the COVID-19 pandemic in Greece



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ABSTRACT

Background: Multiple HIV outbreaks have been recorded among people who inject drugs (PWID) since 2010. During an intervention for PWID in 2019–2021 in Thessaloniki, Greece, an increasing number of HIV cases was documented. Here, we provide an analysis of this new outbreak.

Methods: ALEXANDROS was a community-based program and participation included interviewing, rapid HIV/HCV tests, counselling and linkage to care. PWID were recruited through Respondent-Driven Sampling (RDS) in five sampling rounds. Crude and RDS-weighted HIV prevalence estimates were obtained. HIV incidence was estimated from data on 380 initially seronegative PWID with at least two tests. Multivariable Cox proportional hazards model was used to assess risk factors for HIV seroconversion.

Results: In total, 1,101 PWID were recruited. At first participation, 53.7% were current PWID, 20.1% homeless, 20.3% on opioid substitution treatment and 4.8% had received syringes in the past 12 months. HIV prevalence (95% CI) was 7.0% (5.6–8.7%) and an increasing trend was observed over 2019–2021 ($p = 0.002$). Two-thirds of the cases (67.5%) were new diagnoses. HIV incidence was 7.0 new infections/100 person-years (95% CI: 4.8–10.2). Homelessness in the past 12 months (HR: 2.68; 95% CI: 1.24–5.81) and receptive syringe sharing (HR: 3.86; 95% CI: 1.75–8.51) were independently associated with increased risk of seroconversion. By the end of the program, 67.3% of the newly diagnosed cases initiated antiretroviral treatment.

Conclusions: A new HIV outbreak among PWID was documented in Greece during the COVID-19 pandemic with homelessness and syringe sharing being associated with increased risk of HIV acquisition. Peer-driven programs targeting the population of high-risk underserved PWID can be used to early identify emerging outbreaks and to improve linkage to HIV care.

Introduction

People who inject drugs (PWID) constitute a key population with disproportionate burden of HIV (Degenhardt et al., 2017). After the early HIV epidemics during the 1980s through the 1990s in Western Europe and North America, combined prevention and care interventions - such as needle and syringe (NSP) and opioid agonist treatment

(OAT) programs, HIV testing and linkage to antiretroviral treatment (ART) - were introduced and scaled-up (Des Jarlais, Kerr, Carrieri, Feelymyer, & Arasteh, 2016). This approach allowed to control the epidemics among PWID in the 2000s in several locations including New York City, Vancouver and France (Des Jarlais et al., 2016). However, outbreaks may continue to occur in this population. HIV risk associated with drug injecting is affected by behavioural, social, structural and political-

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economic factors (Friedman, Rossi, & Braine, 2009; Nikolopoulos et al., 2015; Rhodes, Singer, Bourgois, Friedman, & Strathdee, 2005). High coverage as well as continuity of HIV prevention interventions for PWID is vital. Disruptions in service delivery due to economic crisis, complacency towards maintaining low HIV incidence in this population (Des Jarlais et al., 2020) or other health threats, such as pandemics, may have a detrimental effect on what has been achieved so far in many countries. The fragility of the situation was demonstrated by a series of multiple HIV outbreaks occurring in Western Europe, Israel and North America after 2010 (Arendt et al., 2019; Des Jarlais et al., 2020; Hanke et al., 2020; McAuley et al., 2019; Sypsa et al., 2017). The largest of these recent epidemics occurred in Athens, Greece, where HIV prevalence in this population increased from less than 1% in 2010 to 16.5% in 2013 (National Public Health Organisation, 2020; Sypsa et al., 2017). Community economic problems, homelessness, and changes in drug injection patterns were among the factors that were common to many of these outbreaks. Additional epidemics were recorded during 2016–2019 in multiple locations in US (Lyss, Buchacz, McClung, Asher, & Oster, 2020).

In the beginning of the COVID-19 pandemic, researchers supported that the recent Coronavirus Disease (COVID-19) pandemic may have a negative effect on HIV risk as it is a health crisis affecting societies and economies and could have an impact on essential services for PWID (Vasylyeva, Smyrnov, Strathdee, & Friedman, 2020). According to a survey in 13 sites with recent HIV outbreaks among PWID in Europe, North America and Israel, OAT, NSP and treatment for HIV and hepatitis C continued during the pandemic, but with important reductions and operational changes (Wiessing et al., 2023). Similar findings have been reported for PWID elsewhere. For example, higher levels of mental health issues, syringe reuse, and alcohol consumption as well as greater reductions in syringe service programs and buprenorphine utilization were recorded in New York City (Aponte-Melendez et al., 2021). Higher levels of mental health issues and drug use – with consistent access to harm reduction services though – were reported in rural Illinois in US (Bolinski et al., 2022). There were reductions in HIV testing and NSP in Scotland (Trayner et al., 2022) as well as negative impacts on health, behaviours and access to essential harm reduction, testing and treatment service in England, Wales and Northern Ireland (Croxford et al., 2021). Reductions in access to OAT have been reported in Maryland, US (Genberg et al., 2021). In Asia, group methamphetamine use and unsafe sex were recorded during the lockdown in Vietnam (Nguyen et al., 2022) and there were decreases in HIV-related service utilization in India (McFall et al., 2022).

During 2019–2021, and in the midst of the COVID-19 pandemic, a community-based intervention offering testing and linkage to care for HCV and HIV infections to PWID was implemented in Thessaloniki, the second largest city in Greece (ALEXANDROS program). Before this intervention, HIV testing data from PWID accessing drug treatment programs in Thessaloniki indicated low HIV prevalence in 2017 and 2018 (1.1% and 0.7%, respectively) (National Documentation & Information Centre on Drugs & Drug Addiction, 2019; National Documentation & Information Centre on Drugs & Drug Addiction 2020). In 2019, there were approximately 1900 OAT clients and the waiting time to be admitted in the program was 3 months (National Documentation & Information Centre on Drugs & Drug Addiction, 2020). There are no estimates of OAT coverage specifically for Thessaloniki but coverage was overall high in Greece in 2017 (>60%) (EMCDDA, 2019). However, NSP coverage was low in the recent past years in this area with one syringe per PWID in 2016 (National Documentation and Information Center on Drugs and Drug Addiction, personal communication). During the intervention implemented in 2019–2021 in Thessaloniki, an increasing number of HIV cases was documented. The aim of this analysis is to describe this new HIV outbreak among PWID (prevalence, incidence, risk factors for HIV seroconversion) that was documented through this intervention during the COVID-19 pandemic.

Methods

Design of ALEXANDROS program

ALEXANDROS program was a peer-driven community-based program designed to increase testing and linkage to care for HIV and HCV infections in the population of high-risk PWID. It involved reaching out to PWID through peer-driven chain referral, engaging them in HIV testing and linking them to care with the help of navigators. In total, five consecutive recruitment rounds were employed with a short break in-between; PWID could participate in multiple rounds, but only once in each round.

The program was implemented during September 2019–July 2021 at a fixed location in the center of Thessaloniki, in an area easily accessible to PWID. The personnel included a doctor or nurse, two psychologists and a peer-navigator. Before the initiation of the program, formative research was conducted. This involved interviews with a small number of PWID as well as discussions with key informants in order to collect information on the target population to ensure appropriate implementation of the program.

Respondent-Driven Sampling (RDS), a type of peer-driven chain-referral sampling, was used to reach the target population (Heckathorn, 1997). Recruitment began with a number of initial recruits ("seeds"). Individuals received coupons and were asked to draw from their existing injection networks to identify up to five potential recruits and give them referral coupons. A dual incentive system was used in which participants received incentives for participating in the program (primary incentives) as well as for recruiting others (secondary incentives).

Participation included the following steps (Supplementary Figure 1): 1) Persons arriving at the site with a valid coupon were screened for eligibility before participation; 2) Eligible persons were asked to provide written informed consent; 3) Participants were interviewed by the personnel using a structured questionnaire; 4) Rapid HCV and HIV testing was performed followed by counselling as well as blood sample collection for those testing positive for additional laboratory testing; 5) Participants were invited to return to the study site in the following days to collect their test results and patients were linked to care.

Eligibility criteria

Respondents were eligible to participate if they were aged 18 years or older, they reported injecting drugs without a prescription in the past, lived in Thessaloniki metropolitan area, had not previously participated in the current RDS round, and presented a valid RDS coupon.

Interview-Questionnaire

Computer assisted personal interviewing was used for the interview. The questionnaire included an eligibility screener as well as a core questionnaire with sections on injecting network size, demographics, injecting and non-injecting drug use history, sexual behavior, alcohol use, alcohol and drug treatment, HCV and HIV testing, HCV and HIV treatment history, imprisonments, and access to harm reduction services. The questionnaire had been used previously in the population of PWID in Athens, Greece (Hatzakis et al., 2015; Sypsa et al., 2017).

HIV testing

All participants underwent rapid test (antibody) for HIV-1/2 (bioLytical). A blood sample was collected on the same day for those with a positive rapid HIV test for additional testing using a qualitative enzyme immunoassay (Genscreen Ultra HIV Ag-Ab-Biorad) and confirmation by Geenius HIV 1/2 Confirmatory Assay (Biorad).

Confirmed HIV positive cases were reported to the national HIV/AIDS surveillance system of the National Public Health Organization. We defined as newly diagnosed cases those not previously reported to the surveillance system.

Counselling and linkage to HIV care

HIV counselling was provided to participants following the rapid test as well as when they returned to receive their confirmatory test result. The personnel arranged appointments with the infectious diseases units for newly diagnosed patients as well as for all those who were not linked to HIV care. The personnel accompanied the patients to their first visit to the clinic to facilitate linkage to HIV care.

Statistical methods

HIV prevalence

We estimated HIV prevalence for the period 2019–2021 as well as by calendar year in the sample of all unique participants. For those with multiple participations, the last available test result was used. To assess linear trend in HIV prevalence over the three calendar years, we used the Cochran-Armitage nonparametric test.

In addition, we obtained estimates of HIV prevalence by recruitment round (crude and RDS-II weighted) (Volz & Heckathorn, 2008). Weighting takes into account the differential network sizes of the participants (people with smaller injection network size are weighted more) as well as differential recruitment in order to obtain population estimates of key variables (Heckathorn, 2002). For the 95% confidence intervals (95% CIs) of the RDS-II weighted estimates, we used bootstrap with 1000 replications. We have assessed recruitment homophily, i.e. whether HIV-positive PWID tended to recruit other HIV-positive peers. A value of 1 indicates that there is little evidence of recruitment homophily. We have used graphical diagnostics (bottleneck and convergence plots) to assess whether the samples in each round were sufficiently large to overcome the potential biases that are introduced during seed selection (seed dependence) (Gile, Johnston, & Salganik, 2015). RDS-II HIV prevalence estimates, homophily and diagnostic plots (convergence and bottleneck plots) were obtained using RDS Analyst version 0.71 (Handcock, Fellows & Gile, 2019).

We have included a large number of seeds in each RDS round as a considerable portion of them was unproductive (they did not recruit any participants) and overall peer-driven chain-referral was complicated by social distancing measures due to COVID-19 pandemic. To explore whether this had an impact on HIV prevalence estimates per round, we have conducted sensitivity analysis by excluding unproductive seeds.

HIV incidence

To estimate HIV incidence, we analysed 380 initially seronegative participants with at least two HIV tests performed during the program. PWID with a negative HIV test followed by a positive test were defined as HIV-1 seroconverters. The seroconversion time for these subjects was estimated by the midpoint of the interval between the last negative and the first positive test date. For participants who remained HIV negative, person-time at risk was calculated as the interval between the first and the last available HIV test. The incidence rate was calculated as the total number of HIV seroconversions divided by the total person-years at risk (per 100 person-years [PYs]).

Predictors of HIV seroconversion

The Cox proportional hazards regression model was used to identify predictors of HIV seroconversion. Variables included in the multivariable model were age and sex, as well those selected using Collett's algorithm (Collett, 2015). Using this algorithm, we first identified variables

significant at the 0.20 level by fitting univariate models, we then fitted them in a multivariate model to eliminate non-significant variables and then considered variables that were not significant in the first step. To assess the proportionality of the hazards, we used log-log plots of the survival against time for each category of the identified risk factors for HIV seroconversion as well as tests based on the Schoenfeld residuals (Grambsch & Therneau, 1994).

Ethical issues

The study protocol and informed consent form were approved by the Bioethics Committee of the Medical School of the National and Kapodistrian University of Athens (protocol number/date: 115/15 April 2019) and of the Hellenic Scientific Society for the Study of AIDS, STDs, and Emerging Diseases. Persons who were eligible to participate based on the eligibility screening process were asked to provide written informed consent. The informed consent form included information about the program, explained that confidentiality would be protected, and that participants were free to withdraw their consent at any point of the process. The questionnaire and the blood sample were linked through the RDS coupon number. Participants were asked to provide their full names as this would facilitate assessing repeat participation in the same round, identifying HIV seroconversions and changes in behaviors during the program and linking patients to care. There was provision to record the initials of name/surname along with complete birthdate, in case a participant did not wish to disclose his/her name (although all participants provided their names). The name of the participant was not recorded in the questionnaire database or on the blood collection tube. The correspondence between the names and coupon numbers was recorded in a separate file that could only be accessed by authorized members of the research team.

Results

Number of participants, sociodemographic characteristics and injecting drug use

Five recruitment rounds took place from September 2019 through July 2021. During the program, 1757 interviews and HIV tests were performed. In total, 1101 unique PWID were recruited and 35.4% of them participated in multiple rounds ($N = 390$). At first participation, their mean (SD) age was 40.1 (8.5), 87.0% were men, 82.7% of Greek origin and 20.1% reported having been homeless in the past 12 months (Table 1). Concerning injecting drug use in the past 12 months, 28.7% injected daily and 16.9% reported receptive syringe sharing. More than half (53.7%) were active PWID (injecting in the past 30 days).

Access to prevention services

At first participation to the program, 20.3% of PWID were currently on OAT. Only a small proportion (4.8%) reported having received free syringes in the past 12 months (among PWID with history of injection in that period). Approximately half of the participants ($N = 610$, 56.7%) reported having ever been tested for HIV. Based on a subset of participants with known date of the last HIV test performed, only 24.6% of the participants were tested in the past 12 months.

Population coverage of the program

According to official estimates, there were 1200 high risk drug users in Thessaloniki in 2016, i.e. with injecting drug use or long duration/regular use of opioids, cocaine and/or amphetamines (National Documentation and Information center on Drugs and Drug Addiction, personal communication). In our sample, there were 833 participants with injecting drug use in the past 12 months, which corresponds to a population coverage of approximately 69.4%.

Table 1

Sociodemographic characteristics, injecting drug use behavior and access to prevention services of 1101 people who inject drugs recruited to ALEXANDROS program in Thessaloniki, 2019–2021 (as assessed at their first visit to the program).

Socio-demographic and network characteristics	
Age (years), mean (SD)	40.1 (8.5)
Sex, n (%)	
Male	958 (87.0)
Female	142 (12.9)
Other	1 (0.1)
Country of origin, n (%)	
Greece	910 (82.7)
Other	191 (17.3)
Highest level of education completed, n (%)	
High school or higher	314 (28.8)
Middle/secondary school or below	777 (71.2)
Experiencing homelessness ^a , n (%)	
No	877 (79.9)
Yes	221 (20.1)
Currently with health insurance coverage, n (%)	
Yes	183 (16.8)
No	907 (83.2)
History of imprisonment, n (%)	
No	737 (67.2)
Yes	360 (32.8)
Size of participant's network, median (25th, 75th)	15 (10, 20)
Injecting drug use	
Main substance of use (past 12 months from last use), n (%)	
Cocaine/Speedball	139 (12.7)
Heroin	928 (84.7)
Other	28 (2.6)
Injecting drug use in the past 30 days, n (%)	
No	508 (46.3)
Yes	590 (53.7)
Frequency of injecting drug use ^a , n (%)	
At least once daily	314 (28.7)
At least once weekly	236 (21.6)
Less than once weekly	544 (49.7)
Receptive syringe sharing ^a , n (%)	
No	907 (83.1)
Yes	185 (16.9)
Injecting with a used syringe picked-up from the street ^a , n (%)	
No	1026 (93.6)
Yes	70 (6.4)
Access to prevention services	
Currently on OAT, n (%)	
Yes	222 (20.3)
No	874 (79.7)
Received free syringes ^{a, b} , n (%)	
Yes	40 (4.8)
No	797 (95.2)
Ever tested for HIV, n (%)	
Yes	610 (56.7)
No	466 (43.3)

^a in the past 12 months

^b among those who reported having injected in the past 12 months

HIV prevalence

Of 1101 participants, 77 (7.0%) were found to be HIV positive at any participation during the program (95% CI: 5.6–8.7%) (Table 2). Two-thirds (52/77, 67.5%) were newly diagnosed cases as they had not been previously reported to the national HIV/AIDS surveillance system. HIV prevalence increased from 3.8% (95% CI: 2.3–6.1%) in 2019 to 8.7% (95% CI: 6.3–11.5%) in 2021 (test for trend: $p = 0.002$) (Supplementary Figure 2).

HIV prevalence was also estimated by RDS round (Table 2). Crude prevalence (95% CI) increased from 3.9% (2.6–5.7%) in round A to 9.3% (5.0–15.4%) in round E (test for trend: $p < 0.001$). RDS-weighted HIV prevalence (95% CI) per round increased from 2.0% (0.0–4.6%) to

13.4% (0.9–25.9%). Recruitment homophily per round ranged between 0.99 and 1.03. As a result, there is no indication that PWID respondents preferred to recruit from their own group (as defined by HIV status), rather than at random. The convergence plots of HIV prevalence showed that this variable converged on the population estimate in all five rounds (with somewhat later convergence in the round E) (Supplementary Fig. 3). The bottleneck plots for HIV prevalence per round in the first 3 rounds appeared to converge on the point estimate, suggesting low homophily, and are suggestive of sample homophily in round E and, at a lesser extent, in round D (Supplementary Fig. 3). When unproductive seeds were excluded in the sensitivity analysis, crude prevalence increased from 4.0% in round A to 7.6% in round E and RDS-weighted from 2.1% to 13.6%, respectively (Supplementary Table 1).

HIV incidence

There were 380 PWID who tested negative for HIV at their first visit and had at least two HIV tests available. This cohort was followed up for a total of 386.6 person-years and 27 seroconversions were recorded yielding to an HIV incidence rate of 7.0 new infections/100 PYs (95% CI: 4.8–10.2).

Risk factors for HIV seroconversion

Table 3 presents the results of the analysis on the predictors of HIV seroconversion (a more detailed analysis is provided in Supplementary Table 2). The two factors independently associated with increased risk of HIV seroconversion were homelessness in the past 12 months [Hazard Ratio (Yes vs. No): 2.68; 95% CI: 1.24–5.81] and receptive syringe sharing [Hazard Ratio (Yes vs. No): 3.86; 95% CI: 1.75–8.51].

Linkage to HIV care of newly diagnosed cases

By the end of the program, 67.3% of the newly diagnosed cases (35 out of 52) initiated ART. For the remaining 17 cases, an appointment had been scheduled for 11 of them whereas six declined linkage to HIV care.

Concerning the 25 participants who were known HIV cases before their enrolment to ALEXANDROS, 21 had already initiated ART at a median (25th, 75th) of 3.5 (0.9–6.1) years before their first participation to the program. One patient was linked to ART during ALEXANDROS whereas the remaining three HIV cases did not initiate treatment until the end of the program.

Discussion

This study documents an HIV prevalence of 7.0% among PWID in Thessaloniki in 2019–2021 and a significant increasing trend over that period. Two-thirds of the diagnosed cases were reported for the first time to the national HIV surveillance system and more than half of the newly diagnosed cases were confirmed new infections (seroconverted during the program). HIV incidence was 7.0 new infections/100 PYs with PWID experiencing homelessness as well as those sharing syringes being at higher risk of seroconversion. With the help of the program personnel who arranged appointments with the infectious diseases units and accompanied the patients to their first visit to the clinic, two-thirds of the newly diagnosed cases initiated ART by the end of the program.

There are no data on HIV incidence in this population before the study period and information on HIV prevalence is available only for persons entering drug treatment programs. The increase in HIV prevalence in the recent years was considerable as from the stable levels of 1.1% and 0.7% in drug treatment entrants in 2017 and 2018, respectively (National Documentation & Information Centre on Drugs & Drug Addiction, 2019; National Documentation & Information Centre on Drugs & Drug Addiction 2020), it reached 3.8% in 2019 and 8.7% in 2021 in community-recruited participants of ALEXANDROS.

Table 2

Human immunodeficiency virus (HIV) prevalence in people who inject drugs participating in ALEXANDROS by recruitment round (crude and respondent-driven sampling-weighted estimates with 95% confidence intervals).

	Round A (N = 663) Sep2019–Jul2020	Round B (N = 352) Jul2020–Oct2020	Round C (N = 302) Oct2020–Mar2021	Round D (N = 300) Mar2021–Jun2021	Round E (N = 140) Jun2021–Jul2021	Total (N = 1101 unique participants)
Number of HIV-positive	26	20	23	25	13	77
Newly diagnosed, n (%)	15 (57.7%)	14 (70.0%)	14 (60.9%)	20 (80.0%)	12 (92.3%)	52 (67.5%)
HIV prevalence,% (95% CI)						
Crude	3.9 (2.6–5.7)	5.7 (3.5–8.6)	7.6 (4.9–11.2)	8.3 (5.5–12.1)	9.3 (5.0–15.4)	7.0 (5.6–8.7)
RDS-II weighted	2.0 (0.0 ^a –4.6)	3.6 (0.5–6.7)	6.0 (1.5–10.5)	7.2 (0.6–13.7)	13.4 (0.9–25.9)	–

^a Negative lower limit was changed to 0.0.

Table 3

Predictors of HIV seroconversion in people who inject drugs in Thessaloniki, Greece from a Cox proportional hazards model (N = 380 initially seronegative participants with at least two available HIV tests).

Variable	Crude Hazard Ratio (95%CI)	p	Adjusted Hazard Ratio (95% CI)	p
Age (per year)	0.98 (0.94–1.03)	0.488	0.99 (0.94–1.04)	0.721
Sex				
Female	1			
Male	0.77 (0.27–2.23)	0.631	0.60 (0.21–1.77)	0.356
Country of origin				
Greece	1			
Other	1.21 (0.46–3.18)	0.707		
Experiencing homelessness ^a				
No	1			
Yes	3.21 (1.51–6.84)	0.002	2.68 (1.24–5.81)	0.012
Main substance of use ^a				
Heroin	1			
Cocaine	1.00 (0.35–2.91)	0.993		
Injecting drug use in the past 30 days				
No	1			
Yes	2.75 (1.04–7.26)	0.041		
Frequency of injecting drug use ^a				
Once per day or less				
More than once per day	3.13 (1.41–6.97)	0.005		
Receptive syringe sharing ^{a,b}				
No	1		1	
Yes	4.50 (2.11–9.62)	<0.001	3.86 (1.75–8.51)	0.001
Use drugs divided with a syringe that someone else had already injected with ^a				
No	1			
Yes	4.57 (2.14–9.77)	<0.001		

^a past 12 months.

^b including using used syringes collected from the street.

The observed seroconversions and the increasing trend in HIV prevalence recorded during the program indicate the emergence of a new HIV outbreak in the population of PWID in Thessaloniki during 2019–2021. HIV incidence was similar to that identified in the Athens outbreak at the end of 2012 (7.8 new cases/100 person-years) (Sypsa et al., 2017) when a similar program was initiated as a response to the epidemic. In Athens, HIV prevalence reached 16.5%, incidence had peaked at around 11 new cases/100 persons years in early 2012 and has stabilized to 1.94 new cases/100 person-years in 2014–2020 (Flountzi et al., 2022; Roussos et al., 2022; Sypsa et al., 2017). It is unclear whether the outbreak in Thessaloniki has already reached its peak during the period studied here. Even if transmission has been mitigated, a large fraction of the PWID population has been exposed to HIV. Comparing the overall HIV prevalence of 7.0% to estimates from Western Europe, only 7 out of 23 countries had similar or higher HIV prevalence among PWID (Larney et al., 2020).

The increased risk in PWID experiencing homelessness, identified in our analysis, is a finding consistently reported in most recent HIV outbreaks. Current homelessness was independently associated with the risk of HIV infection in the Athens outbreak (Sypsa et al., 2015, 2017) and a distinct concentration of new HIV infections among PWID experiencing homelessness has been reported in almost all settings with outbreaks in Europe, Israel and North America since 2011 (Des Jarlais et al., 2020; Golden et al., 2019; Lyss et al., 2020). According to

a meta-analysis of studies published between 2000 and 2017, recent homelessness or unstable housing was associated with an increased risk of acquiring HIV in PWID (Arum et al., 2021). The plethora of these data underlines the need for housing and combined HIV prevention measures focusing on homeless people.

Receptive syringe sharing is a primary driver of HIV transmission among PWID and was identified as a risk factor in our analysis as well. Based on participants' self-reports, syringe coverage in Thessaloniki was far from sufficient as only 4.8% of those injecting in the past 12 months had received syringes in that period. The official data support this finding; 93% of distributed syringes in 2019 were provided in Athens (National Documentation and Information Centre on Drugs and Drug Addiction 2021) and there was a reduction in NSP coverage in the country in 2020 as a result of the suspension of these programs due to the COVID-19 pandemic (National Documentation & Information Centre on Drugs & Drug Addiction, 2022). In addition, HIV testing was low with only one fourth of the participants reporting a test in the past 12 months. These inadequacies in preventions services are notable given the recent experience of a large HIV outbreak among PWID in Athens. It should be mentioned that, following the dissemination of the initial findings to key stakeholders, the Organization Against Drugs increased the distribution of clean syringes in Thessaloniki from 0 in 2019 to 12,300, 54,400 and 67,900 in 2020, 2021 and 2022, respectively (personal communication).

The risk of an HIV outbreak among PWID in this area was high due to the low levels of prevention services in the preceding years. It could be argued that this outbreak might have been triggered or exacerbated by the COVID-19 pandemic. Greece applied stringent measures during the pandemic. A nationwide lockdown restricting all nonessential movement throughout the country was enforced during March–early May 2020 followed by a second nationwide lockdown - with curfew during night hours - during November 2020–March 2021. In that second lockdown, Thessaloniki was the most affected area in Greece with a sharp rise in the number of COVID-19 cases and hospitals overwhelmed with patients. Based on reports from EU countries and elsewhere as well as from sites with recent HIV outbreaks among PWID, the COVID-19 pandemic posed substantial barriers to accessing prevention services whereas access to drugs was not severely affected (Aponte-Melendez et al., 2021; EMCDDA, 2020; United Nations 2021; Wiessing et al., 2023). There are two reports about a surge of HIV cases among PWID during COVID-19; one in Tijuana, Mexico (Skaathun et al., 2022) and another in Philadelphia where, following an outbreak in 2018, HIV diagnoses were on the rise again in 2022 (Philadelphia Department of Public Health AIDS Activities Coordinating Office, 2022). In Kanawha County (West Virginia, US), an increase in the number of new HIV diagnoses among PWID had been already recorded in 2019 as a result of suspension of syringe services programs; challenges in HIV prevention and treatment were exacerbated by the COVID-19 pandemic and more cases were recorded in 2020–2021 (Hershow et al., 2022). A phylogenetic analyses of HIV sequences in British Columbia, Canada, revealed increased transmission rates among PWID as compared to men who have sex with men in a limited number of clusters and rapid growth or PWID-dominated clusters in 2022 as well (Miller et al., 2022). As suggested by these authors, the exponential nature of viral transmission underlines the need for early and rapid response.

Innovative approaches are needed to early identify emerging outbreaks and to improve continuum of care outcomes that are known to be considerably lower for PWID than for people living with HIV overall (ECDC, 2021). ALEXANDROS is an example of such an approach. First, it was a community-based program implemented through multiple waves of peer-to-peer recruitment. This allowed to reach and offer HIV testing to underserved PWID (people actively injecting, experiencing homelessness, not linked to OAT) - i.e. those at higher risk of infection - and to achieve a high population coverage. This has been shown as well in a similar program in Athens in 2012 (Sypsa et al., 2017). Second, the program allowed the early identification of the epidemic. The outbreak in Thessaloniki might have gone unnoticed for long if ALEXANDROS had not been implemented. HIV surveillance relies on testing, which was inadequate in that setting/period. However, even if testing was adequate, there would inevitably be PWID not linked to any services with no or limited access to frequent testing and prevention services. This underserved high-risk population is captured by peer-driven RDS community-based interventions. In addition, as the population size of PWID in Thessaloniki is relatively small, the number of diagnosed cases would not be as easily noticed as in other areas (e.g. the population of PWID in Athens in 2011 was approximately 7 times higher). Third, the personnel arranged appointments with the infectious diseases units and accompanied patients to their first visit to the clinic. This was particularly important during the pandemic, where infectious diseases units were overwhelmed by the increasing number of COVID-19 patients. Fourth, as PWID could participate multiple times, it was possible to identify patients who were not successfully linked in a previous round and to try engaging them to care. By the end of the program, two-thirds of the newly diagnosed cases initiated ART, despite the burden of the health-care system in that period. Fifth, the fact that PWID could be tested for HIV in multiple rounds allowed early identification of new infections. Overall, the program contributed in closing the gap in diagnosis and linkage to antiretroviral treatment as well as in achieving early diagnosis.

The sustainability of similar programs with multiple RDS rounds may not be easily maintained. However, the findings of this intervention as well as of a similar program implemented in an earlier epidemic among PWID in Athens suggest that they constitute an effective way to reach the population most in need and respond to an outbreak (Chan & Flanigan, 2017; Flountzi et al., 2022; Sypsa et al., 2017). Furthermore, the recent HIV outbreaks, even in areas with well-established high-coverage harm reduction programs, suggest that there is a population of PWID not accessing services at high risk of transmission/infection (Des Jarlais et al., 2020; Sypsa, 2019).

Our analysis has some limitations. HIV incidence was estimated using data from a subsample of seronegative PWID participating at least twice to the program. It is possible that high-risk PWID or those aware of possible exposure to HIV were more likely to return to the program and, thus, incidence might be overestimated. In addition, injection behaviors and access to prevention services were based on self-reports. Another point to consider is that the population coverage of the program is an approximation as the numerator (people with injecting drug use in the past 12 months) and the denominator (size of high-risk drug-using population) are not directly comparable. In addition, the denominator was based on the official estimate of high-risk drug-using population from an earlier year (2016). The actual coverage is anticipated to be higher as the population size of active PWID in Greece declined considerably between 2016 and 2020 (National Documentation & Information Centre on Drugs & Drug Addiction 2022; National Documentation & Information Centre on Drugs & Drug Addiction 2018). In addition, we had no information on the uncertainty of the population size estimate for Thessaloniki. As a result, we were not able to estimate the uncertainty of the population coverage of the intervention. Despite this important limitation, we included this information as an indication of the reach of the program. Finally, despite the fact that HIV prevalence in 2021 was twice as high as in 2019, the high HIV incidence and the large proportion of newly diagnosed cases, we cannot document whether the outbreak was actually triggered by the pandemic. Phylogenetic analysis of viral sequences would allow to further investigate this outbreak.

All the available evidence since 2011 indicate that we have entered a new era where HIV outbreaks among PWID re-emerge in high-income countries. The COVID-19 pandemic may have intensified this phenomenon through disruptions in service delivery. Interventions that address the specific risk factors (homelessness, syringe sharing) are needed along with peer-driven seek-test-treat programs implemented on a routine basis and addressing the population of active injectors who are not necessarily linked to harm reduction services.

Declaration of Competing Interest

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VS has received grants from Gilead and AbbVie. She has served as a lecturer for Gilead and AbbVie.

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SR, DParaskeva, CT, DC, EP and ET have nothing to declare

CRediT authorship contribution statement

Vana Sypsa: Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization, Funding acquisition, Data curation. **Sotirios Roussos:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Formal analysis, Data curation. **Efrossini**

Tsirogianni: Writing – review & editing, Project administration, Methodology, Data curation. **Dimitra Paraskeva:** Writing – review & editing, Data curation. **Theofilos Chrysanthidis:** Writing – review & editing, Data curation. **Dimitrios Chatzidimitriou:** Writing – review & editing, Data curation. **Evaggelia Papadimitriou:** Writing – review & editing, Data curation. **Dimitrios Paraskevis:** Writing – review & editing, Methodology, Formal analysis. **Ioannis Goulis:** Writing – review & editing, Project administration, Methodology, Data curation. **George Kalamitsis:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition. **Angelos Hatzakis:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Ethics approval

The authors declare that they have obtained ethics approval from an appropriately constituted ethics committee/institutional review board where the research entailed animal or human participation.

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