Potential impact of implementing and scaling up harm reduction and antiretroviral therapy on HIV prevalence and mortality and overdose deaths among people who inject drugs in two Russian cities: a modelling study

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Summary

Background Most new HIV infections among people who inject drugs (PWID) in eastern Europe and central Asia occur in Russia, where PWID have a high risk of overdose. In Russia, use of opioid agonist therapy (OAT) is prohibited, and coverage of needle and syringe programmes (NSPs) and antiretroviral therapy (ART) is poor. We aimed to assess the effects that scaling up harm reduction (ie, use of OAT and coverage of NSPs) and use of ART might have on HIV incidence and the frequency of fatal overdoses among PWID in two cities in the Ural Federal District and Siberian Federal District, where the prevalence of HIV is high or increasing in PWID.

Methods In this modelling study, we developed a dynamic deterministic model that simulated transmission of HIV through injection drug use and sex among PWID. We calibrated this model to HIV prevalence data among PWID in two Russian cities: Omsk (which has high but increasing prevalence of HIV among PWID) and Ekaterinburg (which has very high but stable prevalence of HIV). The source data were from research studies supported by the Global Fund to Fight AIDS, Tuberculosis, and Malaria and US Centers for Disease Control and Prevention and surveillance studies from WHO and regional AIDS centres. We modelled the effects of no intervention scale-up (no use of harm reduction measures and 30% of HIV-positive PWID receiving ART) versus combinations of scaling up of OAT, receipt of high coverage of NSPs, and use of ART on the incidence of HIV infections, mortality from HIV, and the frequency of fatal overdoses from 2018 to 2028.

Findings Without intervention, HIV prevalence among PWID in Omsk could increase from 30% in 2018 to 36% (2·5–97·5 percentile interval 22–52) in 2028 and remain high in Ekaterinburg, estimated at 60% (57–67) in 2028. Scaling up OAT to 50% coverage for a duration of 2 years could prevent 35% of HIV infections and 19% of deaths associated with HIV in Omsk and 20% (11–29) of HIV infections and 10% (4–14) of deaths associated with HIV in Ekaterinburg. Further, this scaling up could prevent 33% of overdose deaths over the next 10 years. Scaling up of NSPs and OAT to 50% coverage and tripling recruitment to ART (reaching about 65% of HIV-positive PWID) could prevent 58% (46–69) of HIV infections and 45% (36–54) of deaths associated with HIV in Omsk and 38% (26–50) of HIV infections and 32% (23–41) of deaths associated with HIV in Ekaterinburg by 2028.

Interpretation Legalisation of OAT and increased use of ART and NSPs for PWID are urgently needed to prevent HIV and fatal overdose among PWID in Russia.

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Introduction

Despite a global decrease in the incidence of HIV, the epidemic in eastern Europe and central Asia continues to spread, with Russia contributing the greatest number of new HIV infections (80% in 2015).[1] HIV/AIDS is a leading cause of premature death in Russia, causing a reduced life expectancy.[2] HIV prevalence is high (30% [range 18–43]) among people who inject drugs (PWID) in Russia,[3] where there is also a high incidence of fatal overdoses (2·3 per 100 person-years).[4] The prevalence of HIV is increasing in the Ural Federal District and Siberian Federal District, which have high numbers of new HIV diagnoses (>100 people per 100 000 population), nearly half of which are among PWID.[5]

There are effective options for HIV treatment and methods of harm reduction to improve health and prevent transmission of HIV, but access to these interventions among PWID in Russia is low. Since withdrawal by the Global Fund to Fight AIDS, Tuberculosis, and Malaria from HIV prevention programmes in Russia in 2010, the number of needle and syringe exchange programmes (NSPs) reduced from 80 programmes to ten to 20, despite their effectiveness at preventing HIV incidence by more

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For the **Institute for Health Metrics and Evaluation data on Russia** see: http://www.healthdata.org/russia

Research in context

Evidence before this study

Eastern Europe and central Asia are two of the few regions in the world where the HIV epidemic continues to spread, with a substantial increase in infections in the Ural and Siberian federal districts of Russia. In Russia, injecting drug use is the predominant mode of HIV transmission, and the frequency of overdose among people who inject drugs (PWID) is high. Despite this, Russian laws prohibit opioid agonist therapy (OAT), and coverage of antiretroviral therapy (ART) for HIV and needle and syringe programmes (NSPs) among PWID is poor. We searched PubMed for studies published in English before or on April 2, 2018, with the search terms ("modeling" or "modelling") AND "HIV" AND ("harm reduction" OR "syringe exchange" OR "needle syringe program" OR "opioid substitution therapy" OR "medically assisted treatment") AND ("treatment" OR "antiretroviral therapy"). We identified five studies that included dynamic epidemic models of HIV among PWID in eastern Europe and central Asia (three studies in Ukraine, one in Russia, and one multicountry analysis of other former Soviet republics). The study from Russia assessed the coverage of harm reduction measures (OAT and NSPs) and ART needed to halve HIV incidence and prevalence in Saint Petersburg. However, no modelling analyses have been done in other areas of Russia, such as the Siberian and Ural federal districts. Further, previous modelling studies from eastern Europe and central Asia did not consider the dual outcomes of HIV and fatal overdose.

Added value of this study

To our knowledge, this is the first study to model the dual benefit of OAT in reducing the incidence of HIV and frequency of fatal opioid overdose among PWID in Russia, where OAT is prohibited. Additionally, we believe that this study is the only modelling analysis in Russia to study populations of PWID with HIV outside of Saint Petersburg, instead focusing on areas with the highest incidence of reported cases of HIV. We show that without further intervention, the prevalence of HIV will increase to 36% of PWID in Omsk, Russia, by 2028, and prevalence will remain high in Ekaterinburg, Russia (about 60%). Legal changes to allow OAT would decrease both HIV incidence and fatal overdose among PWID and would increase ART coverage through increased recruitment and retention to these regimens. Scaling up of harm reduction services (OAT and NSPs to 50% coverage) and tripling recruitment to ART could prevent more than half of HIV infections in Omsk, a third of HIV infections in Ekaterinburg, and a third of fatal opioid overdoses in both settings over the next 10 years.

Implications of all the available evidence

Current Russian drug policy is driving the dual epidemics of HIV infection and opioid overdose among PWID, which has implications for the general population both nationally and regionally. Legalisation of OAT and expansion of NSPs and ART coverage among PWID are crucial to address the increase in morbidity and mortality associated with use of injection drugs. Failure to adopt evidence-based drug policies will be measured in Russian lives lost to HIV and overdose.

than 50% in high-income settings.[6–8] Although pharmacies sell syringes cheaply, they are prohibited from offering HIV testing[9] and some PWID report police harassment and arrest outside the pharmacies.[10] Furthermore, opioid agonist therapy (OAT), such as the use of methadone or buprenorphine, remains illegal in Russia, despite evidence from meta-analyses[11,12] documenting its effectiveness in reducing the risk of HIV transmission by 54% and preventing overdose. Similar effects are observed for hepatitis C virus: combination use of NSPs and OAT reduces its incidence by 74%.[13]

Naltrexone, an opioid antagonist, is legal in both oral and injectable forms, but its efficacy against HIV transmission is unclear, and cost remains a barrier to more widespread use of this drug.[14] Antiretroviral therapy (ART) is free for people living with HIV, but coverage remains low (36% in 2017)[5] and is probably low among PWID (estimated <1% among HIV-positive PWID in 2010).[15] Although ART is approved for PWID, considerable heterogeneity in institutional policy and clinical practice has been documented; in 2004, denial by policy makers and providers to supply active PWID has been shown in Saint Petersburg.[16] Russian clinical guidelines[17] from 2017 recommend initiation of ART immediately after HIV diagnosis, but stipulate the possibility of delaying initiation in patients with severe drug addiction, without specifying how severity would be evaluated, which could prevent ART scale-up among PWID.

A 2018 Commission[18] by *The Lancet* on advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals discusses the potential effects of HIV service integration on the incidence of HIV and other outcomes across different global settings. Because of the low availability of HIV services among PWID in Russia, we aimed to use epidemic modelling to project the effects of introducing HIV services on reducing the incidence of HIV and the frequency of fatal overdose in two of the most affected areas of Russia. Only three analyses[19–21] have modelled HIV epidemics in Russia; these analyses focused on Saint Petersburg, a city that is socioeconomically distinct from other urban centres. We also aimed to investigate the effects of policy changes to facilitate the expansion of harm reduction (specifically, NSPs and OAT), ART, or both on HIV incidence, mortality associated with HIV, and the frequency of fatal overdose among PWID in two urban centres in the Siberian Federal District and the Ural Federal District.

Methods

Model design

We modelled two major cities with differing epidemic profiles among PWID: Omsk in the Siberian Federal District, which has an increasing prevalence of HIV, and Ekaterinburg in the Ural Federal District, which has a high but stable prevalence of HIV. In Omsk (which has 15 000–25 000 PWID), HIV prevalence among PWID increased from 9% in 2009, to 17% in 2011, and to 19% by 2014, and showed an increase in new HIV diagnoses (appendix p 11).[22–24] In Ekaterinburg, HIV prevalence among PWID increased from 34% in 2001 to stabilise at 59–65% from 2007 to 2014.[23,25] The number of PWID in Ekaterinburg is unknown but is thought to be around 20 000–40 000 people. Heroin is the one of the most commonly used injectable drugs in both settings, although use of bath salts has been increasing in Ekaterinburg since 2014.

We modelled the intervention scenarios by use of data on the coverage levels of OAT, NSPs, and ART use in other global settings (OAT or high coverage NSP use in >50% of PWID in western Europe,[6,26] and ART use in >60% of PWID with HIV, as reported by survey data[6] in Estonia) and WHO targets (OAT use in >40% of PWID and PWID receiving 200 syringes per year from an NSP).[27] We calibrated our model to these HIV prevalence data (with the first data from 2001), which were sourced from research studies supported by the Global Fund and the US Centers for Disease Control and Prevention and surveillance studies from WHO and regional AIDS centres. We could therefore project HIV prevalence among PWID until 2028 and estimate the proportion of new HIV infections, deaths associated with HIV, and fatal overdoses that could be prevented in 2018–28, comparing each scenario with the base-case (ie, no change in any of the interventions). Results are presented as medians with 2·5–97·5 percentile intervals.

There were several modelled scenarios. The first base-case scenario assumed no harm reduction or scale-up of recruitment to ART from 2018 data (ie, 26% of HIV-positive PWID receiving ART in 2014). The second scenario was of ART expansion for PWID, which assumed that the recruitment to ART tripled from 2018 data and reached about 65% coverage among HIV-positive PWID by 2028. The third scenario was scale-up of OAT for a short duration (3 months) among PWID to reach 50% coverage in 3 years, which assumed legal changes to enable scale-up in 2018. Because OAT duration varies by setting, we used a very short duration (appendix p 6) to represent settings with a focus on detoxification. OAT was also assumed to increase recruitment to ART and reduce attrition from ART regimens.[28] The fourth scenario was scale-up of a long duration (2 years) of OAT among PWID in 2018 to reach 50% coverage in 3 years. This scenario was based on data on OAT retention from low-income and middle-income countries (appendix p 6). The fifth scenario was scale-up of high-coverage NSPs from 2018 among PWID to reach 50% coverage among PWID within 3 years, assuming a long duration (2 years) of NSPs. This scenario assumed scale-up of NSPs in 2018 to 50% coverage among PWID within 3 years. The sixth scenario was scale-up of a single NSPs and OAT intervention among PWID from 2018 for a long duration (2 years) to 50% coverage within 3 years. The final scenario was scale-up of a single OAT and NSPs intervention from 2018 to reach 50% coverage within 3 years, assuming long duration on the intervention (2 years), combined with tripled recruitment rates to ART from 2018 data within both the community and intervention.

See Online for appendix

We developed a dynamic, deterministic model of transmission of HIV by injection drug use and sex among PWID (appendix pp 12–13). Briefly, we stratified the model by HIV disease stage, stage of ART, and access to harm reduction (ie, receiving OAT and NSPs or not). On the basis of multivariable log-binomial regression analyses of survey data from each site to identify factors associated with prevalent HIV (appendix pp 7–8), we also stratified the model by sex and risk (low or high, defined by history of incarceration) and assumed proportional mixing. PWID can be recruited onto ART, which reduces mortality associated with HIV and risk of HIV transmission (appendix p 6). Individuals can also drop out of ART at a rate that differs by their intervention status.

The harm reduction scenarios evaluated scale-up of high-coverage NSPs only (defined as receiving one or more sterile syringes per injection), OAT only, or a combined programme to deliver both NSPs and OAT. Each harm reduction intervention is assumed to reduce an individual's risk of infection by and transmission of HIV through injection drug use. We incorporated the synergistic effects of OAT on ART recruitment and retention and prevention of fatal opioid overdose but assumed an increased risk of overdose in the first 4 weeks of starting or stopping OAT (appendix p 9).

Model parameterisation and calibration

Apart from intervention effects, the parameters of the model (table 1, appendix p 9) were mostly defined with setting-specific data, primarily behavioural and sociodemographic data from cross-sectional surveys[22] from Omsk in 2009 and Ekaterinburg in 2007 and unpublished data in 2014 from Ekaterinburg (appendix pp 7–8).

Self-reported data (unpublished) from Ekaterinburg revealed that 26% of HIV-positive PWID were receiving ART in 2014. We assumed that ART scale-up began in 2006 (appendix p 1) to reach 26% among HIV-positive PWID by 2014. No ART data were available in Omsk, so we assumed the same coverage as in Ekaterinburg. Since laws prohibit OAT, we assumed no OAT in the base-case. Data were unavailable on coverage of NSPs, but a systematic review[7] from 2017 estimated use of one to three syringes by each PWID per year provided by NSPs

	Mean (95% CI) of generated distribution	Sampling distribution and parameters
ART		
Relative sex-related transmissibility while receiving ART versus in latent phase (ωsex)	0·07 (0·02–0·21)	Lognormal (mean –2·66, SD 0·58)
Relative injection-related transmissibility while receiving ART versus in latent phase (ωinj)	0·50 (0·26–0·74)	Uniform (minimum 0·25, maximum 0·75)
Cofactor reduction in mortality associated with HIV if initiating ART in latent or pre-AIDS stage (ν)	0·27 (0·20–0·33)	Uniform (minimum 0·2, maximum 0·33)
Cofactor reduction in mortality associated with HIV if initiating ART in AIDS stage (ρ)	0·51 (0·39–0·62)	Uniform (minimum 0·38, maximum 0·63)
Needle and syringe programmes		
Relative risk of HIV through injection transmission if on needle and syringe programmes only versus if not on these programmes (RR_{NSP})	0·42 (0·21–0·81)	Lognormal (mean –0·42, SD 0·22)
OAT		
Relative risk of HIV through injection transmission if receiving OAT only versus not receiving OAT (RR_{OAT})	0·46 (0·31–0·68)	Lognormal (mean –0·78, SD 0·19)
Relative risk of ART discontinuation if receiving OAT versus not receiving OAT (ψ_{OAT})	0·77 (0·63–0·95)	Lognormal (mean –0·26, SD 0·11)
Relative increase in recruitment to ART if receiving OAT versus not receiving OAT (χ_{OAT})	1·69 (1·32–2·14)	Lognormal (mean 0·52, SD 0·12)
Relative risk of fatal opioid overdose if receiving OAT versus not receiving OAT (Ψ_{OAT})	0·21 (0·12–0·35)	Lognormal (mean –1·57, SD 0·26)
Relative risk of death within the first 4 weeks of starting OAT versus when receiving OAT ($RR_{odonOAT}$)	1·97 (0·93–4·00)	Lognormal (mean 0·68, SD 0·37)
Relative risk of death within the first 4 weeks of stopping OAT versus not receiving OAT ($RR_{odoffOAT}$)	2·38 (1·53–3·75)	Lognormal (mean 0·87, SD 0·23)
Needle and syringe programme and OAT		
Relative HIV injection transmission risk if receiving OAT and on a needle and syringe programme versus neither (RR_{BOTH})	Product of RR_{NSP} and RR_{OAT}	..
Relative risk of ART discontinuation, ART recruitment, fatal opioid overdose, and risks of death on entry or exit if on a needle and syringe programme and receiving OAT versus neither (ψ_{BOTH}, χ_{BOTH}, Ψ_{BOTH}, $RR_{odonOAT}$, $RR_{odoffOAT}$)	Equal to OAT alone	..

For references, see appendix p 9. ART=antiretroviral therapy. OAT=opioid agonist therapy.

Table 1: **Efficacy assumptions of the interventions for model and sampling distributions**

	Omsk	Ekaterinburg
HIV prevalence among PWID in 2001	..	34% (23·7–44·6)[25]
HIV prevalence among PWID in 2007, by sex	..	Male: 60·6% (53·6–67·7); female: 70·5% (62·0–79·1); from survey data[22]
HIV prevalence among PWID in 2009, by sex	Male: 8·5% (5·1–11·9); female: 9·0% (2·9–15·0); from survey data[22]	..
HIV prevalence among PWID in 2009, by incarceration status	Ever incarcerated: 12·7% (7·1–18·2); never incarcerated: 5·8% (2·6–9·0); from survey data[22]	..
HIV prevalence among PWID in 2011	16·7% (12·9–20·8)[23]	58·5% (53·4–63·8)[23]
HIV prevalence among PWID in 2014, by sex	..	Male: 58·2% (52·0–64·4); female: 77·9% (70·9–85·0); from unpublished survey data
HIV prevalence among ever incarcerated PWID in 2014, by incarceration status	..	Ever incarcerated: 70·3% (64·4–76·2); never incarcerated: 56·6% (48·4–64·9); from unpublished survey data
HIV prevalence among PWID in 2014	19·4%; from survey data[24]	..
Antiretroviral therapy coverage among HIV-positive PWID in 2014	26% (20–31); assumed similar coverage to Ekaterinburg	26% (20–31); from unpublished data
Proportion of PWID with a history of incarceration	40·9% (35·7–46·0) in 2009; from survey data[22]	37·7% (32·2–43·2) in 2007; from survey data[22]
Proportion of incident infections attributed to sexual transmission among PWID	8–28% in 2009; estimated from HIV and hepatitis co-infection survey data and published modelling (appendix p 5)	7–27% in 2007; estimated from HIV and hepatitis co-infection survey data and published modelling (appendix p 5)

Data are HIV prevalence (95% CI) by year, unless otherwise indicated. 95% CIs are the computed Wald confidence limits from survey data. Distribution for the likelihood calculations were beta for all data except the proportion of incident infections attributed to sexual transmission among people who inject drugs, in which the distribution was uniform. PWID=people who inject drugs.

Table 2: **Model calibration data for people who inject drugs in Omsk and Ekaterinburg, Russia**

in Russia. No NSPs are available in Omsk. An NSP is available in Ekaterinburg but, in 2014, only 28% of PWID reported accessing an NSP in the past year and the number of syringes obtained were unavailable. Because the likely proportion receiving high-coverage NSPs is lower than these estimates, we assume that coverage of NSPs was not high in either setting.

We used Latin hypercube sampling (MATLAB version 2016a) to generate 500 parameter sets from uncertainty distributions, except for specific parameters

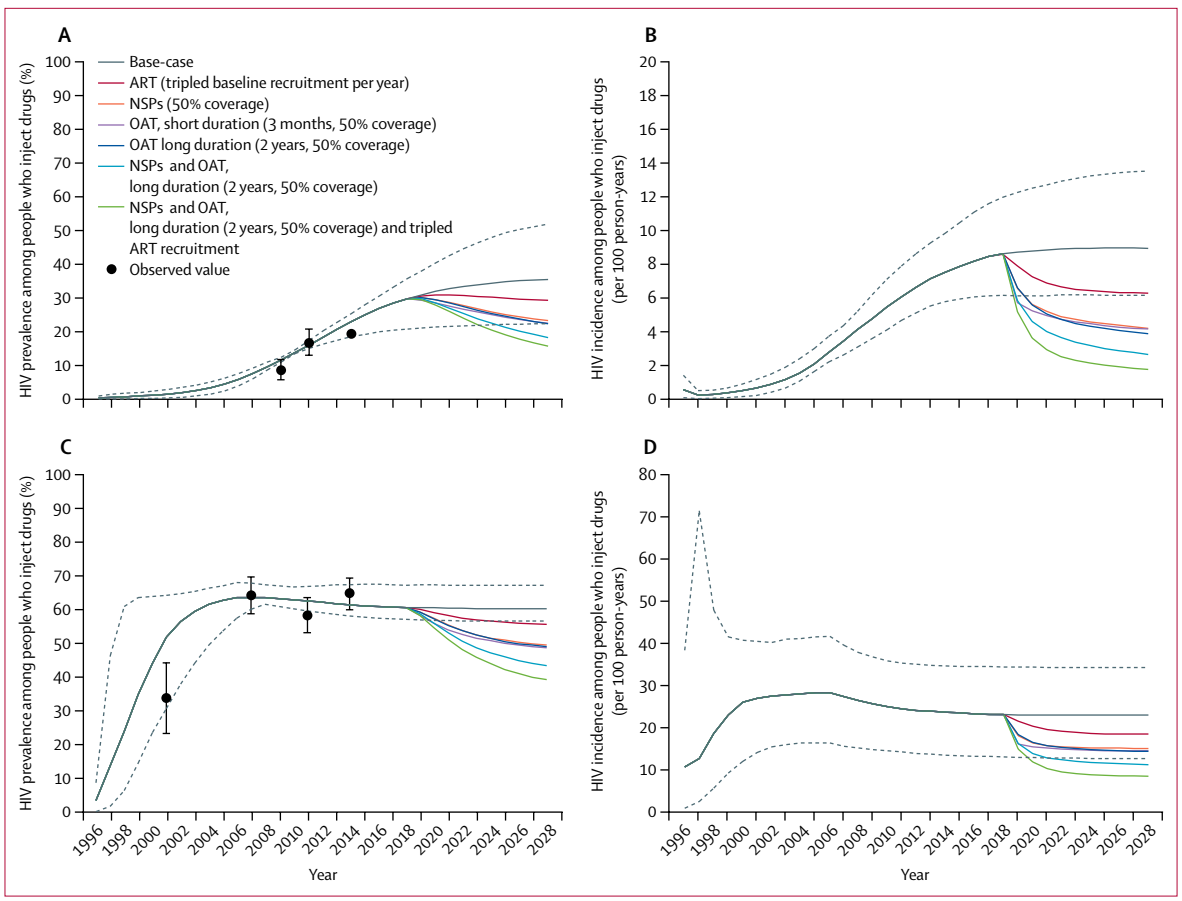

Figure 1: **Model projections of HIV prevalence and incidence among people who inject drugs with different intervention scenarios**
Data are projected (A) prevalence and (B) incidence in Omsk, Russia; and (C) prevalence and (D) incidence in Ekaterinburg, Russia. Solid lines represent median model projections; dashed lines represent the 2·5–97·5 percentile intervals of the base-case. ART=antiretroviral therapy. NSPs=needle and syringe programmes. OAT=opioid agonist therapy.

that were used to calibrate the model (table 2). For each setting, the model was calibrated to HIV prevalence among PWID at several times (2009, 2011, and 2014 for Omsk and 2001, 2007, 2011, and 2014 for Ekaterinburg), stratified by sex and incarceration status where available (2009 for Omsk and 2007 and 2014 for Ekaterinburg). We also calibrated to ART use among HIV-positive PWID in 2014, the proportion of PWID who were at high risk for HIV (ever incarcerated in 2009 for Omsk and 2007 for Ekaterinburg), and the proportion of incident HIV infections associated with sexual risk among PWID in 2009 for Omsk and 2007 for Ekaterinburg (appendix p 5). For each parameter set, we varied the following parameters to fit to these data: number of PWID in 1996, seed HIV prevalence among PWID in each group in 1996, rates of transmission of HIV (ie, the rate of effective contacts between susceptible and infectious individuals, multiplied by the probability of infection in this context) from sex and injection drug use in the latent stage, number of PWID recruited to ART from 2006, and the transition rate from low risk to high risk (never to ever incarcerated). The model was calibrated with a global optimisation solver (fmincon with multistart in MATLAB) by minimising the sum log-likelihood of the calibration points.

Sensitivity analyses

We did sensitivity analyses to test the effects of assumptions, such as eligibility for harm reduction, preferential mixing by injecting risk group, ART coverage in 2018, and the rate of cessation of injection drug use on results for the combined NSPs and OAT with ART scale-up scenario. First, some PWID might not access harm reduction or would not benefit from OAT. For example, heroin is widely used by PWID in Russia (99% of PWID in Omsk [2009] and Ekaterinburg [2007] reported injecting with heroin in the past 30 days) but, in 2014, 49% of PWID in Ekaterinburg reported exclusively injecting bath salts. We therefore did a sensitivity analysis in which 49% of PWID never accessed OAT. Second, we modelled 50% preferential (like with like) mixing by injecting risk (versus fully proportional). Third, we modelled no ART use before 2018 in Omsk versus our base-case assumption of use by 26% of PWID in 2014. Fourth, we examined

reduced cessation of injection drug use in Omsk (to 0 in 2009) because of uncertainty of trends in the number of PWID (appendix p 6). Fifth, we examined a worst-case sensitivity analysis by use of the lower bounds of the intervention effects for OAT, NSPs, and ART on HIV transmission and overdose. Finally, because of uncertainty in overdose parameters, we assessed the effects of use of the lower bound OAT overdose effect combined with varied overdose rates (0·5% or 3·5% per year *vs* 2% in the base-case scenario).

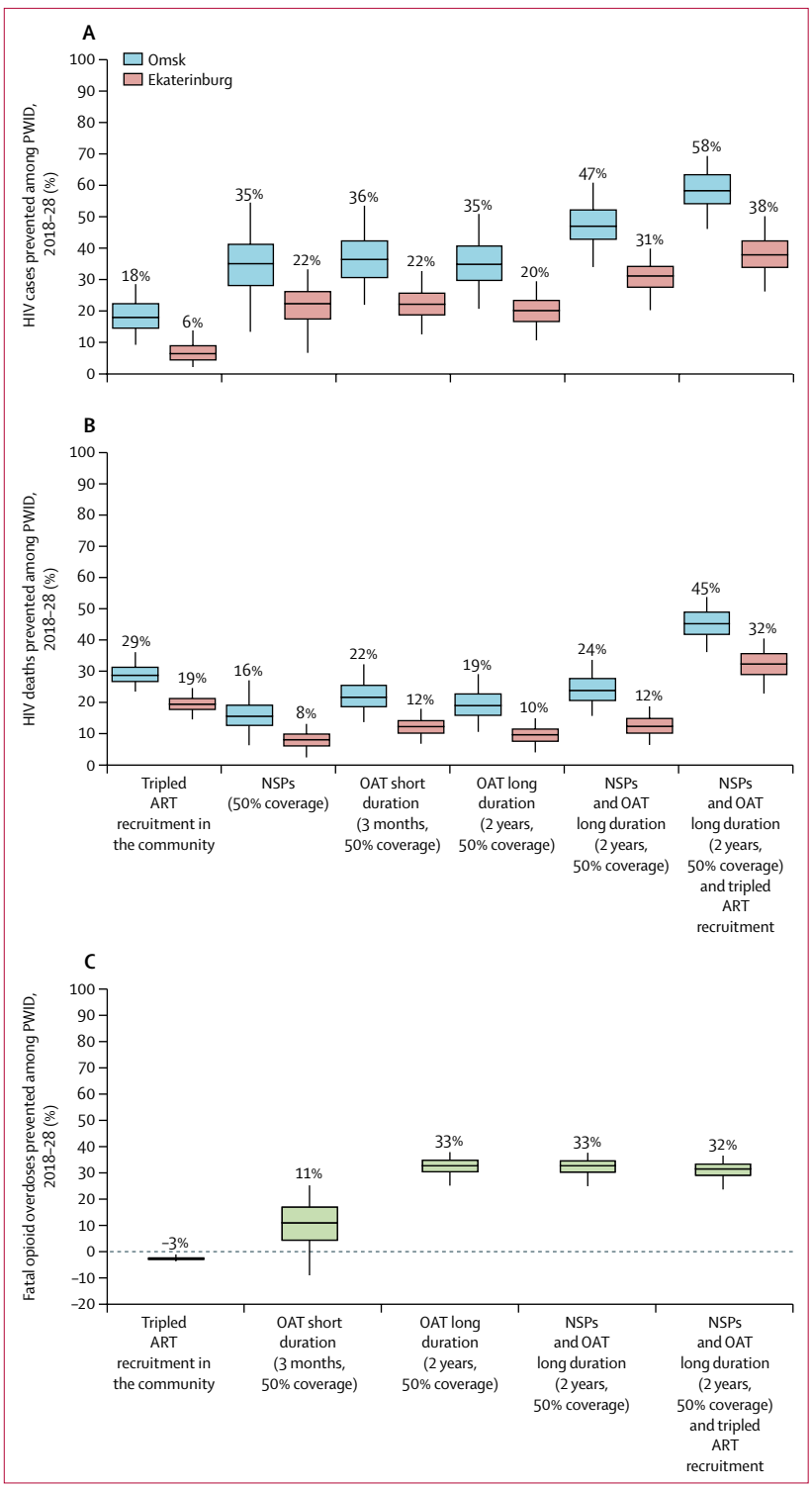

Figure 2: **Projected (A) prevalence of HIV in 2028 and (B) deaths associated with HIV prevented in Omsk and Ekaterinburg from 2018 to 2028; and (C) fatal overdoses prevented in Omsk from 2018 to 2028**
Data for (C) in Ekaterinburg were similar. Data are the median (middle line) projections, the IQRs (boxes), and 2·5–97·5 percentile intervals (whiskers). Median estimates are reported above the boxplots. ART=antiretroviral therapy. NSPs=needle and syringe programmes. OAT=opioid agonist therapy.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Model projections for HIV prevalence and incidence among PWID without intervention show that the model fits the data well (appendix pp 14–18). On the basis of the calibrated coverage of ART in 2014 (26%), the model projects 30% ART coverage by 2018, remaining stable thereafter (appendix p 18).

Without additional interventions, the median HIV prevalence among PWID in Omsk is predicted to increase from 30% (2·5–97·5 percentile interval 20–36) in 2018 to 36% (22–52) in 2028, with a projected incidence of nine new infections per 100 person-years (6–14) in 2028 (figure 1). In Ekaterinburg, HIV prevalence (60% , 2·5–97·5 percentile interval 57–67) and incidence (23 new infections per 100 person-years, 13–34) among PWID is predicted to remain high in 2028 (figure 1).

Removal of structural barriers regarding harm reduction and expanding ART could have substantial effects. Tripling recruitment to ART from 2018 (resulting in ART coverage of about 60% by 2028) could prevent a median of 18% (2·5–97·5 percentile interval 9–29) of new HIV infections in Omsk and 6% (2–14) of new HIV infections in Ekaterinburg by 2028 (figures 1 and 2). Expanding NSPs to 50% of PWID could prevent 35% (2·5–97·5 percentile interval 13–54) of new HIV infections in Omsk and 22% (7–33) of new HIV infections in Ekaterinburg by 2028. Similarly, scaling up OAT to 50% coverage among PWID for a long duration could prevent 35% (2·5–97·5 percentile interval 21–51) of new HIV infections in Omsk and 20% (11–29) of new HIV infections in Ekaterinburg by 2028. The benefits of OAT on recruitment to and retention on ART regimens would lead to an increase in ART coverage (from 30% to about 40% by 2028). Similar effects on HIV incidence to the longer duration of OAT use were predicted if OAT

duration was shorter (3 months) and provide the same overall coverage. Scaling up a combined OAT and NSPs programme to 50% coverage among PWID could prevent 47% (2·5–97·5 percentile interval 34–61) of new HIV infections in Omsk and 31% (20–40) of new HIV infections in Ekaterinburg by 2028. An integrated HIV prevention and care package that incorporated harm reduction (OAT and NSPs at 50% coverage and tripled recruitment to ART) could prevent 58% (2·5–97·5 percentile interval 46–69) of new HIV infections in Omsk and 38% (26–50) of new HIV infections in Ekaterinburg by 2028, which would result in ART coverage of 65% of PWID by 2028, a predicted result that is roughly 10% higher than if ART is scaled up alone.

These interventions are also predicted to affect mortality associated with HIV and overdose (figure 2). In Omsk, tripling ART recruitment could prevent 29% (2·5–97·5 percentile interval 23 to 36) of deaths associated with HIV by 2028, which would probably be accompanied by small increases in overdose mortality (3% increase over 10 years) due to increased survival and competing risk of death from overdose. Scaling up long-duration OAT to 50% coverage in Omsk could reduce median mortality from HIV to 19% (2·5–97·5 percentile interval 11 to 29), which was a similar result to that achieved with a short duration of OAT, and could reduce the frequency of overdose. The effect of OAT on mortality from overdose varied by OAT duration; a 3 month OAT duration (but equal coverage) would prevent fewer deaths relative to longer duration OAT and could potentially increase mortality due to excess mortality within the first 4 weeks of initiation and discontinuation of OAT. Specifically, a 3 month OAT duration prevents 11% (2·5–97·5 percentile interval –9 to 26) of fatal overdoses, whereas OAT with an average duration of about 2 years could prevent 33% (25 to 38) of deaths from overdose in Omsk by 2028. As with HIV incidence, an integrated harm reduction plus ART expansion strategy would have the greatest effects, preventing 45% (2·5–97·5 percentile interval 36 to 54) of deaths associated with HIV and 32% (24 to 37) of deaths from overdose in Omsk by 2028. Roughly half the benefit on mortality associated with HIV was observed in Ekaterinburg compared with Omsk because of different epidemic characteristics but a similar effect from overdose (figure 2).

We also did sensitivity analyses with differing assumptions regarding preferential mixing by risk (50% preferential *vs* fully proportional), access to or

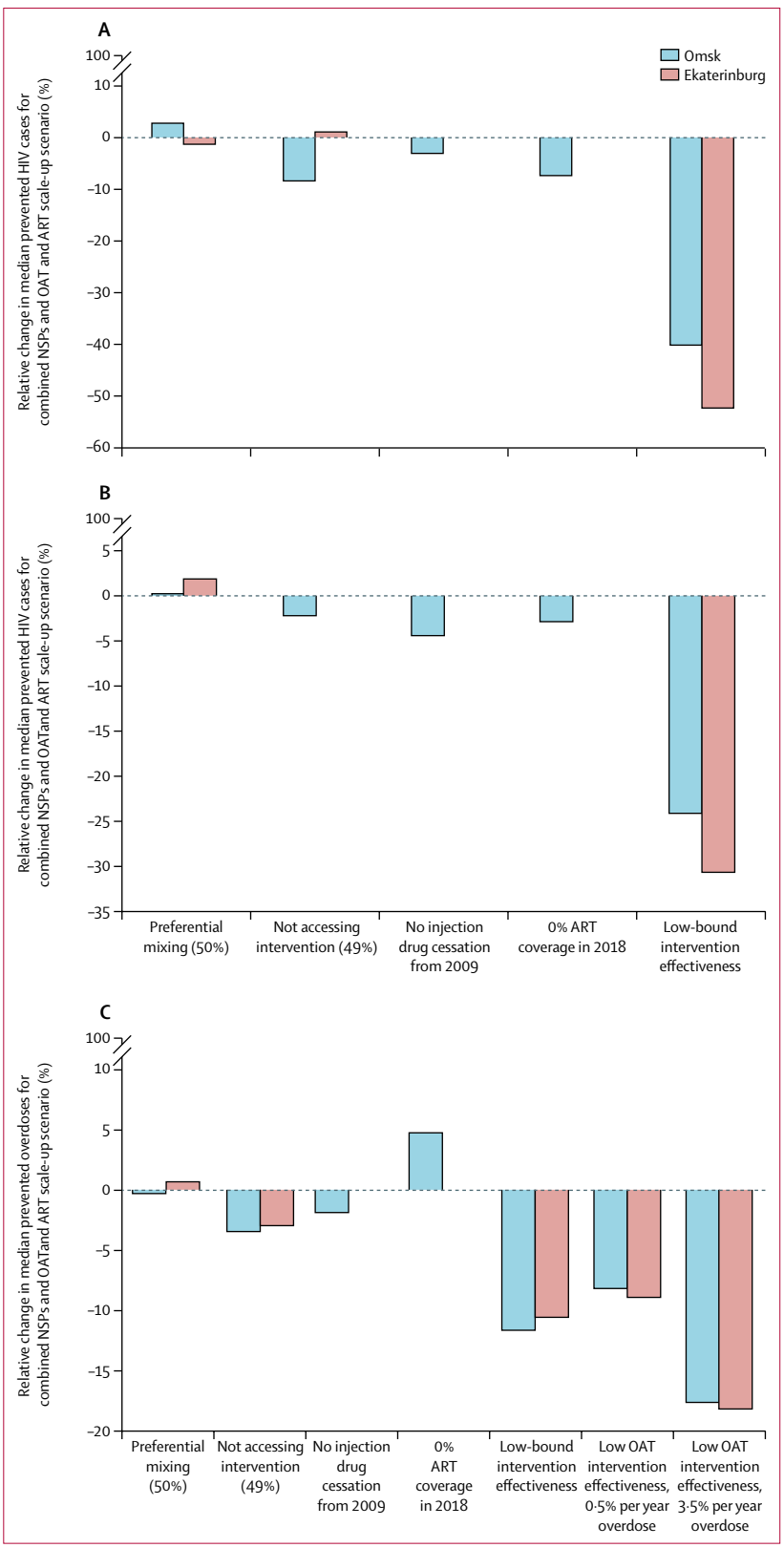

***Figure 3*: Relative median change in effects in 2028 after adjustment in sensitivity analyses**

Data are proportion of (A) HIV cases, (B) deaths from HIV, and (C) fatal overdoses predicted to be avoided in Omsk and Ekaterinburg with the combined NSPs, OAT, and ART scale-up scenario with different model assumptions. ART=antiretroviral therapy. NSPs=needle and syringe programmes. OAT=opioid agonist therapy.

eligibility for harm reduction (49% never accessing harm reduction *vs* all), ART coverage in Omsk (0% in 2014 *vs* 26%), and cessation of injection drug use in Omsk (reduced to 0 from 2009 *vs* constant). Predictions for prevented HIV infections, deaths from HIV, and fatal overdoses were not sensitive (<10% relative difference) to these variations (figure 3). However, the model was sensitive to intervention effect assumptions; use of lower bound estimates for OAT, NSPs, and ART effects resulted in half the number of HIV infections prevented relative to baseline. Estimates were less sensitive to overdose uncertainty; use of the lower bound estimates of OAT effects on overdose predicted that, in Omsk, a median 8% fewer overdoses would be prevented, assuming an annual overdose rate of 0·5%, and 18% fewer overdoses would be prevented, assuming an annual overdose rate of 3·5%.

Discussion

Without urgent intervention, modelling indicates that the burden of HIV among PWID in Russia will worsen, escalating in settings like Omsk and remaining endemically high in settings such as Ekaterinburg. Substantial effects on HIV incidence and mortality related to HIV and overdoses among PWID could be achieved through policy and programme changes that allow OAT, provide funding for expansion of NSPs, and increase ART coverage for PWID. About half of new infections and deaths associated with HIV could be prevented if harm reduction is increased to 50% coverage and recruitment to ART is tripled in settings with worsening epidemics, such as Omsk. Further, about a third of new infections, deaths from HIV, and overdoses could be prevented in settings with high prevalence, such as Ekaterinburg. However, failure to scale-up harm reduction and solely scaling up ART coverage would prevent fewer cases of HIV and fatal overdose than this combination intervention.

In settings with a high burden of HIV and overdose among PWID, like Russia, harm reduction should be a cornerstone of prevention interventions. We project that high coverage OAT (of either prolonged duration or high-throughput short duration) could prevent HIV transmission and enhance ART benefits. However, only OAT that is given for a prolonged duration is likely to substantially reduce overdose deaths, consistent with a chronic disease model of care as recommended by WHO.[27] Conversely, short-duration OAT could increase the number of fatal overdoses because OAT is associated with temporary increases in overdose at initiation and discontinuation.

To our knowledge, this is the first study to explore the dual benefits of combination HIV prevention on both HIV incidence and fatal overdose in Russia, which has one of the most rapidly worsening HIV epidemics worldwide. We focused on two areas that have attracted international concern because of their high numbers of HIV diagnoses. It is unclear whether our findings will be generalisable; other settings, such as Irkutsk and Saint Petersburg, have stably high prevalence of HIV among PWID, similar to Ekaterinburg, but there is evidence of worsening epidemics in western Siberia, including the Altai Krai region, similar to Omsk.[29] Additionally, our work supports previous modelling that has highlighted the benefits of harm reduction and ART among PWID in Saint Petersburg and in other global settings.[19] In contrast to modelling[18] that has indicated a substantial value in integration of existing HIV services with non-communicable diseases and sexually transmitted infection services in settings such as South Africa and India, our work highlights the need for developing these basic services in Russia, ideally in an integrated manner.

Our study has several limitations. First, there was parameter uncertainty, which we incorporated by sampling parameters from distributions and presenting the associated uncertainty into our future projections. For example, because of low use of interventions among PWID in Russia, we used published intervention effect estimates from global meta-analyses to incorporate uncertainty. Our sensitivity analyses indicated a substantial effect of all examined interventions, even when using lower bound estimates. One key area of uncertainty surrounds the effects of NSPs, given that syringes can be obtained from pharmacies.[10] The proportion of PWID receiving full coverage (one sterile syringe per injection) from pharmacies is unknown, so some proportion of PWID might not receive additional benefit from increased provision of NSPs. Conversely, pharmacy provision could enhance the effects of NSPs by providing another source for PWID to reach full coverage. Importantly, pharmacies do not provide many ancillary services that are recommended for NSPs by WHO, such as HIV testing, harm reduction education, and counselling. Further research on access to pharmacies, use of syringes, and preferences of NSPs among PWID is needed. Additionally, we lacked site-specific overdose mortality data, and available data were of low quality and outdated. More robust data are required on mortality from overdoses and the effect of interventions in Russia. Further, historical and future trends in the main drugs injected are not known. In Ekaterinburg, we observed a shift from opioids to stimulants (such as bath salts), which might limit the relevance of OAT. We examined the effect of this change in drug use with sensitivity analyses, and we found that the main results were robust to these variations. However, if opioid injecting becomes increasingly rare, then high coverage of OAT could be unrealistic.

Second, our analysis considered only NSPs, OAT, and ART, and neglected other interventions to prevent HIV and overdose. We note that, although OAT is illegal, naltrexone (an opioid antagonist treatment) is available in oral and injectable forms. A 2018 study[30] in the USA found that extended-release naltrexone improves viral suppression in prisoners, but there is inadequate evidence of its effectiveness at preventing HIV, so we did not consider it in

the current study. Additionally, high costs present a crucial barrier to scale-up: implants cost approximately 20 000 rubles (US$300), whereas the net average wage is $620 per month. WHO recommends pre-exposure prophylaxis for people at substantial risk of HIV, including PWID.[31] However, given the low coverage of ART among HIV-positive individuals in Russia and uncertainty of the cost-effectiveness of pre-exposure prophylaxis for PWID,[32] we prioritised ART scale-up. Finally, although naloxone is effective at preventing fatal overdose and is cost-effective in Russia,[33] this drug was not assessed because we chose interventions that prevent HIV.

Third, we focused solely on HIV transmission and overdose and did not evaluate additional benefits of harm reduction. For example, OAT and NSPs reduce acquisition of hepatitis C virus, which could yield substantial benefits because about 72% of PWID in Russia have a history of infection.[13] Additionally, OAT reduces drug-related criminal behaviour and could reduce incarceration and prison-associated infections.[34] We did not examine any behaviour change resulting from HIV diagnosis. If diagnosis results in reduced HIV risk behaviour, programmes targeting HIV testing could have a greater effect than we estimated. Further, we found higher prevalence of HIV among people with a history of incarceration, as in other settings.[34] The potential role of medications for opioid use disorder in increasing adherence to ART among incarcerated populations and reducing the increased risk of overdose associated with recent prison release is increasingly being examined, benefits that we did not incorporate into our models.[30] Although incarceration might disrupt HIV prevention, it could be an important point of contact for PWID, because scaled up HIV services in prison could provide a substantial benefit to the community.[34]

Finally, we did not address cost or cost-effectiveness. Given the paucity of HIV prevention services for PWID, the economic implications of the scenarios examined are uncertain; however, we previously estimated that scaling up OAT and NSPs to half of the 1·88 million PWID in Russia could cost $333–521 million annually.[18] Additionally, ART for PWID is cost-effective in Russia,[20] OAT is hypothetically cost-effective in Russia,[35] and NSPs are cost-effective in Ukraine and Belarus.[36,37]

In conclusion, there is a high prevalence of HIV among PWID in Russia, yet harm reduction and HIV services for PWID reach few in need. Legalisation of OAT and support for expansion of NSPs and ART is urgently required for PWID in Russia, which we have found could reduce the incidence of HIV and fatal overdoses among PWID in two Russian settings, among other potential benefits on infectious disease and incarceration.

Contributors

JAC, CB, and NKM devised the analysis. JAC and NKM wrote the first draft of the manuscript. JAC did all modelling analyses in consultation with NKM, PV, and AB. KE, AL, MS, and VO provided site-specific data and interpreted findings with input from LB, MH, and CB. All authors critically reviewed and provided extensive feedback on all drafts of the manuscript.

Declaration of interests

MH reports personal fees from MSD, AbbVie, Gilead, and JanSsen, outside the submitted work. CB served as co-chair of the International AIDS Society–*Lancet* Commission on advancing global health and strengthening the HIV response in the era of the Sustainable Development Goals, for which the basis of this modelling work was first done, and was Immediate Past President of the International AIDS Society. NKM reports unrestricted research grants from Gilead and MSD that are unrelated to this work and honoraria from Gilead and AbbVie. All other authors declare no competing interests.

Data sharing

The code for the modelling is available from the first author on request.

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