CONCISE COMMUNICATION

Reducing HIV infection in people who inject drugs is impossible without targeting recently-infected subjects

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Objective: Although our understanding of viral transmission among people who inject drugs (PWID) has improved, we still know little about when and how many times each injector transmits HIV throughout the duration of infection. We describe HIV dynamics in PWID to evaluate which preventive strategies can be efficient.

Design: Due to the notably scarce interventions, HIV-1 spread explosively in Russia and Ukraine in 1990s. By studying this epidemic between 1995 and 2005, we characterized naturally occurring transmission dynamics of HIV among PWID.

Method: We combined publicly available HIV *pol* and *env* sequences with prevalence estimates from Russia and Ukraine under an evolutionary epidemiology framework to characterize HIV transmissibility between PWID. We then constructed compartmental models to simulate HIV spread among PWID.

Results: In the absence of interventions, each injector transmits on average to 10 others. Half of the transmissions take place within 1 month after primary infection, suggesting that the epidemic will expand even after blocking all the post–first month transmissions. Primary prevention can realistically target the first month of infection, and we show that it is very efficient to control the spread of HIV-1 in PWID. Treating acutely infected on top of primary prevention is notably effective.

Conclusion: As a large proportion of transmissions among PWID occur within 1 month after infection, reducing and delaying transmissions through scale-up of harm reduction programmes should always form the backbone of HIV control strategies in PWID. Growing PWID populations in the developing world, where primary prevention is scarce, constitutes a public health time bomb. Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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Introduction

HIV in people who inject drugs (PWID) has, to date, posed a secondary burden worldwide after sexual transmission, with the striking exceptions of eastern European and central Asian countries [1]. Much work has been done to study how HIV spreads in PWID, and now we have interventions that proved to be effective to slow down the HIV epidemic in this group [2]. Still, research to date has not measured forward transmission (i.e. number of transmissions that can be attributed to an infected person), and our knowledge is limited to the force of infection (i.e. the probability of PWID getting infected over time) [3].

With almost 1 million HIV-infected individuals and a PWID population of around 2 million people [1], Russia and Ukraine provide a unique opportunity for studying HIV transmission dynamics in this group. The epidemic in these countries has been accompanied by very limited harm reduction services [4], making it a large-scale 'natural experiment' of HIV spread among PWID. By studying the epidemiological dynamics of the largest HIV epidemic among PWID, we might understand epidemics emerging in countries of the Middle East and northern Africa [5,6], southeastern Asia [7], Europe [8,9], and the USA [10]. Critically, although harm reduction approaches among PWID since the 1980s have had significant effects in the developed world [11], it remains unclear whether these preventive strategies should be prioritized over newer approaches such as treatment as prevention (TasP) [12] in resource-limited settings.

Here, we combined the evolutionary epidemiology approach with simple mathematical modelling to describe transmission dynamics of the HIV epidemic among PWID in Ukraine and Russia that started in the mid-1990s and assess factors mitigating HIV epidemics in PWID.

Methods

Nucleotide sequences
We compiled three HIV-1 sequence alignment datasets with sequences available from the Los Alamos HIV sequence database (http//:hiv.lanl.gov) (Supplementary Table 2, http://links.lww.com/QAD/A996): a *reference dataset A* of 2199 *pol* sequences; *dataset B* with 418 *pol* sequences from Russia and Ukraine sampled in 1997–2013; *dataset C* with 92 *env* sequences from Russia and Ukraine sampled in 1993–2011. All sequence alignments were performed using MEGA 6.0 software [13] and then manually edited. We built Bayesian Skyline Plots with BEAST 1.8.1 [14,15].

Estimates of epidemiological parameters
To obtain estimations of some of the epidemiological parameters, we used our previously described methods

[16]. We estimated the number of secondary infections per primary infection in a completely susceptible population as

$$R_0 = \frac{j+q}{jq}\left[\frac{1}{t}\ln\frac{N_e(t)}{N_e(0)}\right] + 1$$

where $N_e(t)$ is the effective population size at time t, $N(0)$ is the effective population size at the baseline of the exponential growth phase, j is the rate of progression from the recent to long-term infection (1/0.5 a year, 2.0), and q is the overall mortality rate of HIV-infected individuals (in the absence of prevention assumed to average 1/10 years, 0.1).

We assume that $R_{0,a}$ is the mean number of secondary infections per transmitter (per injector) for our epidemiological settings:

$$R_0 = uR_{0,a},$$

where u is the proportion of PWID in the HIV-infected population.

We estimate the generation time T (the expected time from initial HIV infection to transmission to other individuals) as

$$T = uR_{0,a}\frac{1+(1-u)R_{0,a}}{N(t)/(N_e(t)\times T)},$$

where $N_e(t) \times T$ is estimated from the Bayesian Skyline Plot reconstructed from the HIV sequences (*env* gene).

Compartmental modelling
We used a compartmental Susceptible − Recently Infected − Chronically Infected (Susceptibles − individuals who are not infected, but are at risk of infection; Recently Infected − individuals who acquired infection within the last 6 months; and Chronically Infected − individuals who acquired infection longer than 6 months ago) model to describe dynamics of HIV epidemic among PWID in Russia and Ukraine (Supplementary Fig. 1, http://links.lww.com/QAD/A996). We further advanced this model to include the compartment of treated individuals and take into account the uncertainty of our estimates.

More details on the methods can be found in Supplementary text. A description of the model parameters is provided in Supplementary Table 1, http://links.lww.com/QAD/A996.

Results

Phylodynamics and epidemiologic parameters estimates
The Bayesian Skyline Plots of the HIV population in Ukraine and Russia (Fig. 1) estimated from the *pol* and
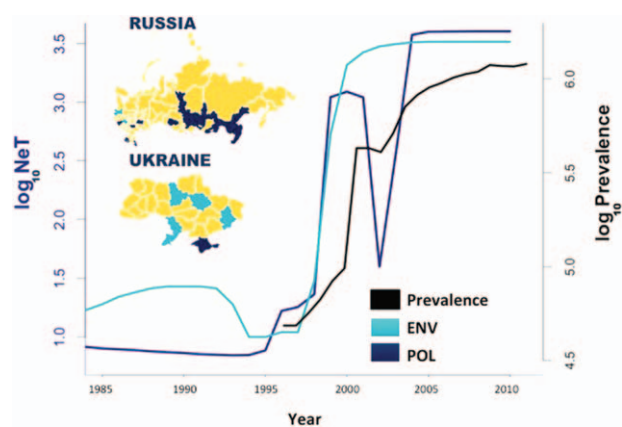
Fig. 1. Bayesian Skyline Plot estimated from pol (dark blue line) and env (cyan line). Maps show representation of sequences by geographical regions within the countries. The UNAIDS estimates of HIV prevalent cases are shown by the black line (prevalence).

env alignments closely followed the epidemiological estimates of HIV prevalent cases: the epidemic grew rapidly between 1995 and 2000, and slower growth continued until 2005. Using the skyline plot and the estimated number of prevalent cases, we calculated $R_{0,a}$ to be 6−15 for corresponding values of the duration of infectivity (p) 5−15 years (Supplementary Fig. 2A, http://links.lww.com/QAD/A996). A plausible duration of infectivity for untreated HIV-infected PWID is unlikely to be more than 8−10 years [17], suggesting that the epidemic in Russia and Ukraine had an $R_{0,a}$ of 8−10. We calculated T using different values of the proportion of transmitters, u, approximated by the proportion of PWID among the HIV infected population. T was estimated to be 25 days when $R_{0,a}$ is around 10 and $u = 70\%$ (Supplementary Fig. 2B, http://links.lww.com/QAD/A996); T would exceed 3 months if u was less than 30%.

Modelling the establishment of HIV epidemics in people who inject drugs

In the natural epidemic model without treatment or prevention, HIV prevalence among PWID was predicted to reach 86% [credibility interval (CI) 81−88%] after 20 years (Supplementary Fig. 3, http://links.lww.com/QAD/A996). The proportion of transmissions attributed to recently infected individuals rapidly decreased over the first years of the epidemic and stabilized at around 20% after 7 years (Supplementary Fig. 4, http://links.lww.com/QAD/A996).

In absence of prevention, but with treatment, the model showed that HIV prevalence would still reach 83% (CI 73−87%) after 20 years if 50% of long-term infected individuals receive treatment on average 4 years after becoming infected (Fig. 2a). If treatment was provided to a small proportion (25%) of recently infected individuals,

after 20 years we did not observe a dramatic reduction in prevalence (72%, CI 62−80%) (Fig. 2b). We next investigated the scenario where R_0 was reduced from the very beginning of an outbreak by scaling up harm reduction interventions and changing risky behaviours. By reducing $R_{0,a}$ by 60% (studies show that harm reduction programmes can help to reduce risky practices by 60% [18,19] and incidence in PWID by 80% [20]) to $R_{0,a} = 4$, we were able to prevent the epidemic from establishing, provided that treatment was offered to at least 25% of recently infected PWID (Fig. 2d). There was no intervention scenario to prevent the epidemic from being established when treatment was not provided to recently infected individuals (Fig. 2c). For the scenarios with the well established epidemic (30% baseline HIV prevalence) (Fig. 2e−h), the best case scenario was also to treat at least a small proportion of recently infected individuals while scaling up prevention.

Discussion

We analysed the uncontrolled and extensive HIV epidemic in Russia and Ukraine that began in the mid-1990s with an evolutionary epidemiology approach. We estimated that at the time, each injector transmitted to at least five individuals within the first month after getting infected. We thus showed that in the absence of prevention, HIV transmissions in PWID occur rapidly after primary infection.

Can we realistically target the first month of the infection? With primary prevention, such as syringe exchange programmes (SEPs) and safe practice training, we intervene from the very first day of infections. As the infectivity drops after the first month as a result of lower viral load and established immune responses, if we were to increase generation time, we would reduce the probability of infection per contact; we would then have more time to intervene with treatment.

Indeed, we show that TasP has a place in controlling an outbreak only when we introduce large-scale primary prevention and appeared to be more effective when we targeted recently infected individuals. Other studies show the importance of recently infected individuals in sexually driven HIV epidemics [21−23], but no consensus was reached on whether aiming HIV prevention efforts specifically at the recently infected group would be game-changing [24,25]. While such evidence for PWID is largely missing, we show that prevention of early transmissions provides major gains when we reduce transmissibility by reducing risky injecting practices.

Our findings provide insights on the dynamics of recently emerging HIV outbreaks such as those in Athens [8], Romania [9], or Indiana [26]. Crucially, HIV epidemics in
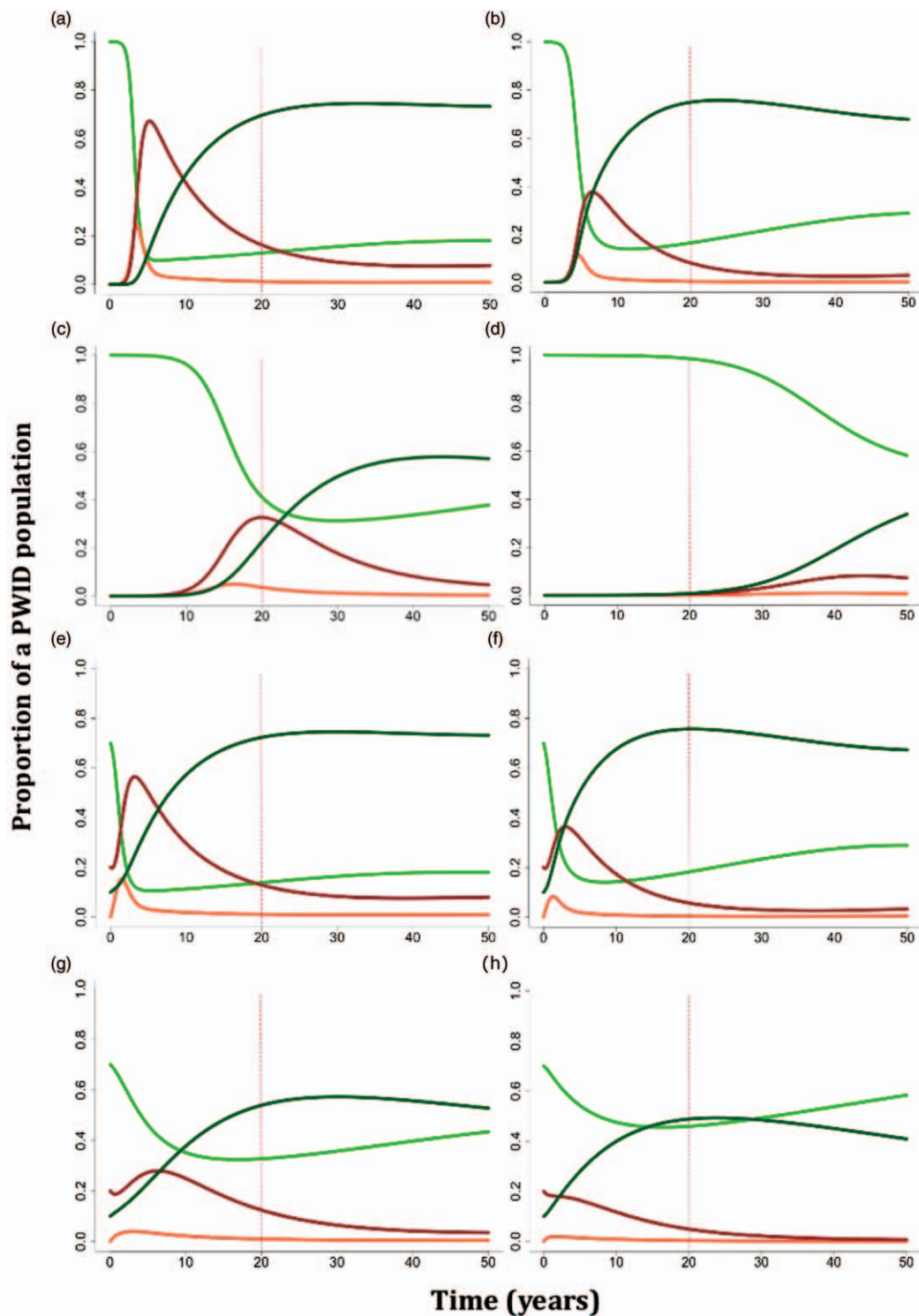
Fig. 2. Results of the compartmental model representing HIV spread under different treatment scenarios. (a)–(d) HIV spread during an outbreak. (a) and (b) Scenarios when 0 and 25% of recently infected individuals, respectively, and 50% of long-term infected individuals (for both a and b) are provided with treatment, while no other preventive services are suggested. (c) and (d) Scenarios when, in addition to providing treatment, other harm reduction interventions are introduced, so that $R_{0,a}$ is reduced to 4. (e)–(h) HIV spread in a well established epidemic. (e) and (f) Scenarios when 0 and 25% of recently infected individuals, respectively, and 50% of long-term infected individuals (for both e and f) are provided with treatment, while no other preventive services are suggested. (g) and (h) Scenarios when, in addition to providing treatment, other harm reduction interventions are introduced, so that $R_{0,a}$ is reduced to 4.

PWID have been recently emerging in resource-limited countries in the Middle East and north Africa (particularly Afghanistan, Egypt, and Morocco) [5], as well as in some southeast Asian countries (e.g. Indonesia and Philippines) [7,27]. PWID populations in these locations were historically small, but their growth created the potential for new HIV outbreaks. Our study suggests that, if primary prevention is not introduced in countries with increasing prevalence of drug use, the epidemics in this group will expand rapidly when started and remain uncontrolled until sufficient primary prevention is put in place. Given that intravenous drug use is increasing faster than preventive responses in the developing world, it is a matter of time that these public health time bombs will explode again.

Changes in drug-taking behaviour might also influence transmission dynamics and introduce new pools of susceptible individuals within PWID populations. In our results, the drop of N_eT around 2002 might be partly attributed to the shift in the Russian−Ukrainian drug scene towards stimulant drugs (associated with risky injecting behaviours [28]). Thus, settings with changing drug scenes, including changes in drug of choice or demographic changes, should also be addressed with basic prevention scale–up.

Our modelling suggested that increasing SEP coverage and reducing risky injecting practices in addition to treatment provision to half of the infected PWID will yield an additional 15% decrease in HIV prevalence after 20 years. Another modelling study that was informed by data from Ukraine showed that a 40% reduction in HIV prevalence within 10 years period should be expected if at least 60% of the unmet needs of harm reduction services (including SEPs and opioid substitution treatment) and treatment were covered [29], but this study did not model differences in transmissibility among recently and chronically infected. Our modelling suggested that such a steep decrease in HIV prevalence can be obtained only if we additionally provide at least 25% of recently infected individuals with treatment.

Apart from epidemiological reasons, early treatment initiation provides clear benefits for the patients themselves [30,31]. Thus, a combination of the expansion of existing harm reduction interventions and the development of new approaches to identify and treat recently infected people should be applied to settings with PWID-driven HIV epidemics [32]. Unfortunately, reaching those recently infected is extremely challenging, especially in settings in which preventive responses have been limited due to the sociopolitical context in which the outbreak arises. In the 1990s, social stigmatization of PWID in Russia and Ukraine was reflected in govern-mental and healthcare sectors, which limited the implementation of harm reduction services [4,33]. Other developing countries experiencing HIV outbreaks among PWID face similar problems; for example, despite decriminalization of drug use, police harassment of PWID in Indonesia undermines the success of SEPs [34]. Political support to reduce stigmatization of PWID could significantly increase access to health services and mitigate HIV spread in this vulnerable group.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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