# Supplementary Material

**Revealing HIV epidemic dynamics and contrasting responses in two WHO Eastern European countries: Insights from modeling and data triangulation**

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## **S1. The back-calculation model**

We describe in this section, in a general way, the back-calculation model [1] and how we used it to estimate the number of new HIV infections, the distribution of times from infection to HIV diagnosis, and the number of undiagnosed HIV infections [2]. Note that in our approach we estimated the distribution of time from infection to diagnosis for individuals who were newly infected in a specific year (and not for individuals who were diagnosed in a specific year), and throughout the text we used the term distribution of time from infection to diagnosis to refer to this distribution. Model inputs to produce these estimates are the number of newly diagnosed HIV cases, over time, stratified by clinical stage at HIV diagnosis (recent infection, AIDS, and neither AIDS nor recent infection). Estimates were produced independently for each subpopulation.

### **Assigning specific test-seeking behaviors to newly diagnosed individuals according to their clinical status at diagnosis**

We partitioned our quarterly data on newly diagnosed individuals according to the clinical status at diagnosis. We created two groups.

Group 1 consisted of individuals diagnosed with a recent infection. By definition, individuals belonging to group 1 were diagnosed very early in the course of the infection. Recent infection is reported by the diagnosing physician based on clinical symptoms of acute infection, a recent negative test, or a recent history of risk behaviors with a known HIV-positive partner.

Group 2 consisted of individuals diagnosed without any of the criteria defining a recent infection. Among them, some individuals were diagnosed with AIDS and others without AIDS. We assumed that individuals diagnosed with AIDS were not tested for HIV before being diagnosed with AIDS while individuals who were diagnosed without AIDS decided to be tested for other reasons than those of individuals belonging to group 1 (e.g. routine medical examination or onset of symptoms that occur towards the end of the incubation period). It is important to note that in group 2, among individuals diagnosed without AIDS, there are HIV-infected individuals who were diagnosed during the recent infection stage but not identified as such, because they did not experience and/or report symptoms of acute infection or did not report recent exposure or recent negative test. In our approach, we then consider three kind of clinical status at diagnosis: 1) recent infection; 2) AIDS; and 3) neither AIDS nor recent infection.

### **Specifying group-specific distributions of times from infection to diagnosis**

The next step consists in linking the observed number of newly diagnosed cases to the unobserved number of new HIV infections by specifying the distribution of times from infection to diagnosis for each of the two groups.

As for notation, denotes the observed number of individuals diagnosed in quarter (3-months period) *t* with clinical status of type D, and denotes the unobserved number of individuals newly infected in quarter *s* that are diagnosed with clinical status of type D, i.e. recent infection (P), AIDS (A), or neither AIDS nor recent infection (H).

The unobserved number of individuals newly infected in quarter *s* is:

(1)

We assume that are realizations of independent Poisson variables with mean .

*Group 1*

For individuals diagnosed with recent infection (group 1, G1), the duration from infection to diagnosis was assumed to be uniform from 0 to 6 months (i.e. the median length of the recent infection stage was assumed to be 3 months). Thus:

(2)

where is the mean number of new HIV infections in quarter *s* that are then diagnosed during recent infection, is the mean number of individuals diagnosed during recent infection in quarter *t* and is the probability that an infected individual is diagnosed during recent infection, *x* quarters after contracting HIV.

*Group 2*

For individuals diagnosed with AIDS and individuals diagnosed without AIDS or recent infection (group 2) we adopted the same approach as Becker *et al.* [3]. Basically, each (unobserved) newly HIV-infected individual belonging to group 2 was allocated, independently, a duration from infection to an AIDS diagnosis, in the absence of therapy, and a duration from infection to a diagnosis of HIV infection. Thus, a newly HIV-infected individual belonging to group 2 could either have AIDS when diagnosed, meaning that he/she was not tested for HIV before being diagnosed with AIDS, or be diagnosed without AIDS, meaning that he/she did not develop AIDS before being tested. Assuming that each individual in group 2, infected during a quarter *s*, is independently assigned a time from HIV infection to diagnosis, leads to:

(3)

(4)

where is the mean number of new HIV infections in quarter *s* that are then diagnosed with AIDS, or without AIDS or recent infection, is the mean number of individuals diagnosed without AIDS or recent infection in quarter *t*, is the mean number of individuals diagnosed with AIDS in quarter *t*, is the probability that an HIV-infected individual is diagnosed without AIDS or recent infection, *x* quarters after contracting HIV, without first developing AIDS, and is the probability that an infected individual is diagnosed with AIDS, *x* quarters after contracting HIV, and was not tested for HIV before developing AIDS.

The time from infection to AIDS diagnosis, , was assumed to follow a Weibull distribution with a median of 40 quarters (i.e. 10 years) [4] :

(5)

The distribution of the rate of pre-AIDS HIV testing was assumed to depend on two unknown parameters that represent uptake of routine testing ( and onset of symptoms that occur towards the end of the incubation period :

(6)

It is important to realize from equation (6) that we did not constraint to zero the probability of HIV testing within months after HIV infection for individuals supposedly diagnosed without AIDS or recent infection. In consequence, our approach accommodates the situation where some HIV-infected individuals diagnosed during the recent infection stage do not report symptoms of recent infection, recent exposure or recent negative test, and thus are classified as not having recent infection.

Assuming independence between the discrete random variables and , the probabilities in equations (3) and (4), were then specified by:

(7)

(8)

## **Estimating the number of new HIV infections and the distribution of times from infection to diagnosis**

The next step consisted in estimating the unknown parameters of the model (i.e. , {, ,). As we split the population into two mutually exclusive groups (group 1 and group 2), the mean numbers of new HIV infections were estimated separately for each of the two groups.

Under our assumptions, the were independent observations on Poisson variates, which gives the log-likelihood functions:

* for group 1: (9)
* for group 2: (10)

where is given by (2), is given by (3) and is given by (4).

For group 1, maximum likelihood estimates of were obtained by using the expectation-maximization-smoothing (EMS) algorithm [3]. For group 2, following Becker *et al.* [3], we derived estimates of the two unknown parameters of the distribution of the pre-AIDS HIV testing rate ( ,) and the mean numbers of new HIV infections that are then diagnosed with AIDS or that are then diagnosed without AIDS or recent infection () by using the Newton-Raphson method and the EMS algorithm (see ref. [3] for more details). Finally, by adding together the estimates of the mean number of new infections in each group, and , we obtained estimates of the mean numbers of new HIV infections ().

Using the group-specific estimates of the number of new HIV infections and the group-specific distributions of time from infection to diagnosis, we obtained the distribution of times from infection to diagnosis for individuals infected in quarter *s* as follows:

(11)

where is the estimated number of individuals infected in quarter *s* who are diagnosed *x* quarters after contracting HIV, and are respectively the estimated probability that an infected individual is diagnosed with AIDS, *x* quarters after contracting HIV, and was not tested for HIV before developing AIDS, and the estimated probability that an HIV-infected individual is diagnosed without AIDS or recent infection, *x* quarters after contracting HIV, without first developing AIDS.

It is important to note that, although the group-specific distributions are stationary, the distribution varies with time since and vary with time. Indeed, if individuals test for HIV more often, then more individuals are diagnosed in early stages of the HIV infection. Hence, the number of people diagnosed with recent infection (i.e. group 1) increases, while the number of people diagnosed without recent infection (i.e. group 2) decreases accordingly. As a result, the number of new infections among individuals belonging to group 1 () increases, the number of new infections among individuals belonging to group 2 () decreases, and the distribution of time from infection to diagnosis becomes shorter. Thus, our method allows for accounting some changes in test-seeking behaviors over calendar time.

## **Estimating the number of undiagnosed HIV-infected individuals**

Using equation (11), we obtained the cumulative probabilities of not being diagnosed *t* quarters after contracting HIV according to the time of infection (*s*): . We then combined these cumulative probabilities with the estimated number of newly HIV-infected individuals at each point in time to estimate those who were still undiagnosed in quarter *t*:

(12)

**S2. National surveillance data on newly diagnosed HIV cases**

In Latvia, HIV case reporting to the Center for Disease Prevention and Control, by both physicians and laboratories, is mandatory. All HIV positive tests are confirmed and reported by the National Microbiology Reference Laboratory of the Infectiology Center of Riga East University Hospital [5]. Data on newly diagnosed HIV cases were available from 1996 to 2016 and included diagnosis date, sex, age, exposure group, clinical stage at diagnosis (derived from ICD-10 code), and CD4 cell count at diagnosis.

In Estonia, it is also mandatory that all HIV cases be reported to the National Health Board, by both physicians and laboratories. Multiple registrations of the same case have occurred until 2009 and was estimated to have been between 6 and 34% of HIV diagnoses until then [6]. To address this issue, data reported to the National Health Board were recently linked, using unique national identification code, to two other data sources: the Estonian Health Insurance Fund database and the prisons health care database [7]. This allowed obtaining data on persons newly appearing with HIV in one of these three databases from 2000 to 2016 [7], including diagnosis date, sex, age, exposure group, clinical stage at diagnosis (derived from ICD-10 codes), and CD4 cell count at diagnosis.

Clinical stages at diagnosis were derived from ICD-10, as follow:

- Recent infection (group 1) – B23.0;

- Neither recent infection nor AIDS (group 2) – B23.1, Z21;

- AIDS (group 2) – B20-B24, excluding B23.0, B23.1, F02.4;

- Unknown – unspecified B23, R75.

**S3. Multiple imputation of missing data**

At the time of analysis, surveillance data on newly diagnosed HIV cases up to year 2016 were available in both countries. Multiple Imputation by Chained Equation (MICE package [8], R statistical language [9]) was used to impute missing values, for three variables in Latvia (clinical status at diagnosis, CD4 cell count at diagnosis, and HIV exposure group), and four variables in Estonia (clinical status at diagnosis, CD4 cell count at diagnosis, HIV exposure group, and county of residence) (see Tables S1 and S2). We used multinomial logit model for categorical variables with more than two levels (i.e., county of residence, exposure group, and clinical status at diagnosis), and predictive mean matching for continuous variables (i.e. CD4 count), which allows to tackle the issue of non-normal data [10]. The set of predictors used in both countries is listed in Tables S1 and S2.

We used a two-step procedure to perform the imputation to account for the fact that some variable had more missing values over certain period of time: HIV exposure group in Estonia before 2010 and CD4 count in Latvia before 2007 (see Tables S1 and S2). In Estonia, we first imputed missing data for the period 2010-2016 to generate five imputed databases; twenty iterations were used to produce each imputed dataset. Then, each of the five imputed databases was merged with the raw data for the period 2000-2009. Next, we imputed missing data over the 2000-2009 period and generated a total of 25 imputed databases, i.e. 5 new imputed databases for each merged database. In Latvia, we used the same two-step procedure, with a first imputation for the period 2007-2016 and a second one for the period 1996-2006. Imputed data on newly diagnosed HIV cases from 2000 to 2016 are shown on Figure S1.

## **S4. Precision of the estimates**

We assessed the precision of the estimates by using a bootstrap procedure. New datasets were simulated, from each of the 25 imputed databases, by generating new realizations of and from the Poisson distributions with respective mean and . Using this procedure, we generated a total of two thousand new datasets.

For each of the two thousand new datasets, the model was run and we obtained estimates for the annual numbers of new HIV infections () and the two parameters of the distribution of the pre-AIDS HIV testing rate ( ,), from which we derived the distribution of times from infection to diagnosis according to the year of infection and the number of undiagnosed HIV infections. From the two thousand estimated parameter sets, we calculated mean estimates and 95% confidence intervals (CI) using the percentiles method, for the annual numbers of new HIV infections and the distributions of times from infection to diagnosis according to the year of infection, over the period 2007-2016, and the numbers of undiagnosed HIV infections in 2016.

This step-by-step procedure was followed for each exposure group, thus we obtained specific and independent estimates for each exposure group.

## **S5. Estimating population sizes**

**Population sizes in Estonia**

To estimate population sizes in Estonia, in 2016, for the population aged 15-69 years, we used three data sources: Statistics Estonia [11], the European men-who-have-sex-with-men Internet Survey (EMIS) [12], a capture-recapture study on the prevalence of injecting drug use [13].

We obtained data on the national population size of people aged 15-69 years, by sex, for the year 2016, from Statistics Estonia [11].

The number of men who have sex with men (MSM) aged 15-64 years in Estonia in 2009 was estimated at 9195 from EMIS data [12], which gave a prevalence of 2.1% among men aged 15-64 years in 2009; MSM were defined as men having had at least one sexual contact with a man within the previous 12-24 months and no confidence interval was provided for the estimate [12]. To obtain an estimate of the number of MSM aged 15-69 years in 2016, we multiplied the 2009 prevalence by the population size of men aged 15-69 years in 2016 in Estonia.

In 2015, there was an estimated number of 9249 (95% CI: 8322-10367) people who injected drugs, according to a capture-recapture study [13]; PWID were defined as individuals who injected drugs at least once over 2010-2015 among men and women aged 15 and over. The sex distribution was 27% women and 73% men [13]. We assumed that the population sizes of male and female PWID in 2016 were similar to those obtained for the year 2015.

We then obtained the number of heterosexual men and women in 2016, in Estonia, by respectively subtracting from the male population the estimated numbers of MSM and male PWID, and from the female population the estimated number of female PWID.

**Population sizes in Latvia**

To estimate population sizes in Latvia, in 2016, for the population aged 15-69 years, we used three data sources: the Central Statistical Bureau Latvia [14] the EMIS study [12], and a national report on drugs for the proportion of PWID [15].

We obtained data on the national population size of people aged 15-69 years, by sex, for the year 2016, from the Central Statistical Bureau Latvia [14].

The proportion of MSM among men was estimated at 1.65% in 2009 from EMIS data [12]; MSM were defined as men having had at least one sexual contact with a man within the previous 12-24 months and no confidence interval was provided for the estimate [12]. To obtain an estimate of the number of MSM aged 15-69 years in 2016, we multiplied the 2009 prevalence by the population size of men aged 15-69 years in 2016 in Latvia.

The prevalence rate of injecting drug use was estimated at 6.1 per 1000 (95% CI: 5.3-6.8) of the population aged 15-64 in 2016 (estimate derived using the treatment multiplier method where the proportion of PWID who received drug treatment services within the last year is taken from the drug users cohort study carried out in 5 cities in Latvia) [16]; in this study, PWID were defined as individuals who injected drugs in the last 12 months. The sex distribution was 28% women and 72% men. To obtain an estimate of the number of PWID aged 15-69 years in 2016, we multiplied the prevalence of injecting drug use estimated for the population aged 15-64 by the population size of people aged 15-69 years in 2016 in Latvia.

We then obtained the number of heterosexual men and women in 2016, in Latvia, by respectively subtracting from the male population the estimated numbers of MSM and male PWID, and from the female population the estimated number of female PWID.

Estimates of population sizes, at national level, by exposure group for Estonia and Latvia are given in Table S3. Note that to account for uncertainty in population sizes in our estimates of the rates of undiagnosed HIV prevalence and of HIV incidence (see section S6), we simulated two thousand values for the population sizes, when studies provided means and 95% confidence intervals.

## **S6. Estimating rates of undiagnosed HIV infections and of HIV incidence**

To estimate the rates of undiagnosed HIV infections, for each group, we divided the estimated number of undiagnosed HIV-infected individuals by the corresponding population size estimates. Since, two thousand estimates of the number of undiagnosed HIV-infected individuals and of the corresponding population sizes were generated, we obtained two thousand estimates of the rates of undiagnosed HIV infections, from which we derived mean and 95% confidence intervals using the percentile method.

To estimate the rates of HIV incidence, for each group, we divided the estimated number of new HIV infections by the corresponding estimated number of individuals at risk of HIV infection. The number of individuals at risk of HIV infection was estimated for each group by subtracting from the estimated size of the group the estimated number of individuals living with HIV. The number of individuals living with HIV for each exposure group was calculated using group-specific HIV prevalence, number or rate, previously published [17–20] (see Table S4). Specifically, we generated, for each group, two thousand values for the number of individuals living with HIV, using means and 95% confidence intervals provided in the previously published studies (Table S5). Each of these two thousand values were randomly matched with one of the two thousand generated value for the size of the group to obtain two thousand values of the number of individuals at risk of HIV infection for each group. Then, from the two thousand estimates of the number of new HIV infections and of the corresponding number of individuals at risk of HIV infection, we obtained two thousand estimates of the HIV incidence rates, from which we derived mean and 95% confidence intervals using the percentile method.

## **S7. Statistical tests for modelling estimates and source code**

Statistical comparisons were carried out using Mann-Whitney test for HIV incidence and undiagnosed rates, and using two-sided Kolmogorov-Smirnov test for the distribution of times between infection and diagnosis at the time of infection. Statistical analyses were performed using R3.6.0 [21]. The back-calculation model was written in C++ language using Xcode 9.4 and can be transmitted upon request to the authors.

## **S8. HIV surveillance and policies, harm reduction, opioid agonist treatment, HIV testing, and antiretroviral treatment in Estonia**

**HIV surveillance and policies**

First HIV case was identified in 1988 in Estonia [19]. By 1997, 70 people had been diagnosed with HIV and there was a major concern for a possible HIV outbreak among people who had started to inject drugs [23]. In 2001, 107 new HIV cases per 100,000 population were diagnosed [24] and the Ministry of Social Affairs declared that Estonia had a concentrated HIV epidemic among PWID [25].

Since 1987, the national HIV reference laboratory confirms all positive HIV test results. It has also been responsible for all HIV case reporting until late 2009. Under this previous HIV surveillance system, each positive result was associated to patient identifiable information, such as name and date of birth, except for cases diagnosed anonymously. Data on transmission mode was rarely available. Multiple registrations of new HIV cases have occurred, due to the inclusion of anonymous diagnoses or lack of unique identifiers in national statistics until the end of 2009. Since 2010, all new HIV cases are mandatorily electronically reported to the Estonian Health Board from both the laboratories as well as doctors newly diagnosing HIV using the patient’s national identity code [22]. In 1987-2017, the HIV reference laboratory had identified over 9000 HIV cases, yet the Health Board had uniquely identified only ca 2000 people in 2010-2017. To overcome this gap in data, a retrospective HIV cohort was established by combining data from the Health Board (period of 2010-2017), Estonian Health Insurance Fund (all HIV diagnosis related healthcare invoices outside prisons in 2000-2017), and HIV care records from prisons (period of 2008-2017) [26]. In that cohort, time of diagnosis was defined by the first appearance in the dataset. In this study, we used data from that retrospective HIV cohort on newly diagnosed HIV cases from 2000 to 2016 as inputs for the back-calculation model.

In 1992, Estonia initiated the National AIDS Prophylaxis Programme [27]. The first national HIV strategy was approved in 1997 for the period of 1997-2001 [20]. The three next strategies adopted were for periods 2002-2006 [22], 2006-2015 [25], and 2017–2025 [26]. Estonia applied for Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) funding in late 2002 [25], received, over 2003-2007, a Global Fund grant of 10.25 million USD, in addition to the state budget of 5.85 million USD allocated for 2002-2006 [22,27], and committed to funding HIV-related activities in the same amount as the Global Fund beyond 2007 [28].

The National Institute for Health Development (NIHD), created in 2003, was the primary recipient of GFATM grant. It has been in charge of conducting the bio-behavioral HIV surveillance among key population and coordinating HIV prevention interventions (e.g. needle-syringe exchange programs, opioid agonist treatment). Regular bio-behavioral HIV survey studies started in 2003 for the youth, in 2004 for MSM, in 2005 for PWID, and in 2006 for sex workers, and provided information on risk behaviors and uptake of prevention and care services. Since 2004, a few HIV-related questions are routinely added to the Health Behavior among Estonian Adult Population study. This information together with data reported by the HIV Treatment Concilium were used in this study to describe, over 2000-2016, the coverage of harm reduction, HIV testing, and antiretroviral therapy (see below).

**Harm reduction: needle and syringe exchange programs and opioid agonist treatment**

Free needles-syringes are available at harm reduction sites (or historically syringe exchange points (SEP)) to all who ask for them. First SEP was opened in 1997 and the first state-funded SEP was opened in 2001 [25]. Since 2003, harm reduction has been coordinated and financed by NIHD on a national level and provided by NGOs. By the end of 2004, there were a total of 21 SEPs [25]. By end 2016, there were 38 sites providing free needles-syringes [29]. Harm reduction sites annually report the numbers of distributed needles-syringes to the NIHD since 2003. In this paper, we report these numbers, which do not include the number of needles-syringes that people buy themselves.

Opioid agonist treatment (OAT)with methadone was officially introduced in 2001, but has been scaled up since 2003 [32]. OAT is coordinated and financed by NIHD, it is provided only by psychiatrists in special centres and is free of charge for patients. In 2017, eight OAT centers operated [29]. The centers providing methadone treatment annually report the number of methadone users to NIHD since 2004. The number of people on OAT reported in this paper refers to the number of patients on OAT in the national program. Buprenorphine is prescribed since 2003, it is not state-funded, and its provision is not included in the number of people on OAT. Additionally, OAT provided in prisons and when self-funded are not included in the reported number of people on OAT in this paper. Until 2020, NIHD did not collect unique identifier based data on patients on OAT and thus the number may be overestimated. In 2016, a study collected unique identifier based information from OAT centers in Estonia and found that 840 unique people received OAT in total which differs from the 1248 reported by NIHD [33].

**HIV testing**

HIV testing began in 1987 [22,34]. Estonia has national HIV testing guidelines since 2012 [35]. Only healthcare workers can test for HIV. Testing costs are covered by the national health insurance and since 2016, state funds also HIV tests done in all healthcare settings for people who do not have the insurance [34]. Besides that, anonymous and free of charge HIV testing is available since 1988 at voluntary counseling and testing centers [36]. These centers also provide community-based anonymous and free HIV testing since late 1990’s (mostly in gay clubs, harm reduction sites, social housing, public events). Rapid HIV tests have been available in Estonia since 2009 [36].

In this study, we obtained data on HIV testing rates among the general population from the Health Behavior among Estonian Adult Population study [37–40]. The questionnaire-based study is conducted bi-annually since 1990 using a random sample from the Estonian population aged between 16 to 64 years. HIV-testing-related questions were only included for the studies conducted in 2006, 2008, 2010, and 2014, and the wording of these questions slightly changed over time. Of the 5000 people the questionnaire is sent each time by post, crude response rate was 57% in 2006, 60% in 2008, 61% in 2010, 51% in 2014. The denominator is the number of respondents to that question, and the results are not weighted.

Data on HIV testing coverage among PWID were obtained from cross-sectional structural interview studies conducted routinely since 2005, using respondent driven sampling, in three cities with the highest incidence of newly diagnosed HIV cases in Estonia (2007, 2009, 2013 in Tallinn; 2007, 2012, 2016 in Kohtla-Järve; 2010, 2014 in Narva) [19,20,41–44]. Sample size has been 350 PWID in each town, apart from years 2012 in Kohtla-Järve (n=600), and years 2009 and 2013 in Tallinn (n=307 and n=328 respectively). According to the ELISA HIV test results, 48-66% of study participants were HIV infected throughout the years. HIV testing coverage was determined using the number of people who had never tested for HIV, or had tested and were negative, or had tested and were positive for the first time within the last 12 months of the study (denominator), and the number of people from them who had tested for HIV in the last 12 months (nominator).

Data on having tested for HIV in the last 12 months among men who identified themselves as gay or bisexual were derived from online surveys since 2004 [18,45–49]. Call for participations have been distributed on gay dating and other websites. The number of people completing the survey was used as a denominator. Sample sizes were n=312 in 2004, n=232 in 2005, n=361 in 2007, n=594 in 2010 (part of EMIS 2010) and n=265 both in 2013 and 2016. In the former years (2004-2007), HIV-test result was not asked, and between 2010-2016, of participants who had tested for HIV, 3-4% self-reported to have been HIV-infected. Therefore, HIV prevalence has only a small confounding effect on HIV testing proportions.

**Antiretroviral therapy**

Highly active antiretroviral therapy became available in Estonia in 1997 and since then antiretroviral treatment (ART) is free of charge to all people living with HIV (PLHIV) [50]. It is prescribed by infectious disease doctors, who provide HIV care in Estonia. The Estonian Society for Infectious Diseases has always followed the most recent international HIV clinical guidelines (mainly WHO, CDC, EACS), including when to initiate ART. ART has been recommended to all whose CD4<350 until 2011, under CD4<500 between 2011-2015 and regardless of CD4 count since late 2015. The drugs have been procured by the Ministry of Social Affairs based on the needs estimated by the HIV Treatment Concilium.

In this study, data on ART coverage come from three sources: the annual national HIV Treatment Concilium reports (Ministry of Social Affairs, unpublished), the retrospective national HIV cohort from linking electronic HIV records with the national death registry [26], and the beforementioned PWID studies using respondent-driven-sampling method [19,20,41–44].

To derive data on national ART coverage, we used the number of people on ART estimated by the HIV Treatment Concilium as a numerator. The methodology is not described in the Concilium reports. For the denominator, we used the number of people who were alive or died that year according to the retrospective HIV cohort study [26]. The cohort does not capture emigration and might include people who had HIV marked mistakenly on their healthcare invoice (<14% had not been linked to HIV care and infectious disease doctors affirm they use ICD-10 codes correctly for HIV), which could overestimate the number of people diagnosed with HIV. Furthermore, the cohort is representative of people diagnosed with HIV for the period of 2008-2016 when prisons databases became electronic. For the period of 2000-2007, the cohort underestimated the number of people diagnosed with HIV and overestimated the coverage with ART.

To determine ART coverage among PWID, from the PWID studies, the number of people self-reporting to be HIV infected were used as a denominator and the number of PWID self-reporting to be currently on ART as a numerator; except for 2007. In 2007, having been on ART within the last 6 months was asked about.

Regarding MSM, we could not determine ART coverage as the studies reporting on ART coverage among MSM, over the period of interest, included very few HIV-infected MSM (<10) [18,45–49].

## **S9. HIV surveillance and policies, harm reduction, opioid agonist treatment, HIV testing, and antiretroviral treatment in Latvia**

**HIV surveillance and policies**

The first HIV case was identified in 1987 in Latvia. By 1997 the number of annual newly registered cases was low and transmitted mainly via homosexual contacts. But starting from the end of 20th century a rapid increase in cases among PWID was observed and reached its peak in 2001 when 807 new cases were registered [51] (i.e. 34.5 per 100,000 population [52]).

HIV case registry was established in 1994 [52]. Within three working days the newly diagnosed case has to be reported by the doctor, who referred the patient to the HIV test, via a paper-based form to the HIV case registry [53]. Data on tests performed and test results gained is also reported by the laboratories providing HIV testing and the HIV reference laboratory (only one laboratory placed in Riga). Thus, if the doctor who referred the patient to HIV test has not sent the reporting form, he/she is identified from the data provided by laboratories and contacted by staff of the Centre for Disease Prevention and Control of Latvia (CDPC) who manage the HIV case registry. Separate reporting form is also sent when patient is diagnosed with AIDS and when patient has died. To avoid existence of died cases in the registry, it is linked annually with the Database of Causes of Death of Inhabitants of Latvia. In this study, we used data on newly diagnosed HIV cases from the HIV case registry as inputs for the back-calculation model.

The first national strategy for elimination of the spread of HIV in Latvia was adopted in 1999 for the period 1999-2003 [54]. The two next strategies adopted were for periods 2003-2007 [55] and 2009-2013 [56]. For the years 2014-2017, there was no national strategy. The most recent strategy is developed for the period 2018-2020 [57]. Latvia, unlike Estonia, never received funding from Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM).

The data that we report in this study regarding the coverage of harm reduction, HIV testing and, ART were obtained from national surveillance system (see below).

**Harm reduction: needle and syringe exchange programs and opioid agonist treatment**

The first HIV Prevention Point (HPP) was introduced in Latvia in 1997 and till 2017 the network has developed by reaching 20 operating HPPs in 16 municipalities all around the country. Parallel to the stationary services, several points provide services of mobile units and are carrying out the outreach work (on streets among PWID, in gay clubs, in festivals during the summer time etc.). The spectrum of services provided free of charge by the HPP network include syringe and needle exchange, condom distribution, rapid testing (HIV, HBV, HCV, syphilis), informative materials (brochures, posters etc.), information and counseling (health, social and psychological issues), support groups, food packages, etc. Initially, the HPP network provided services specifically to PWID, but currently the services are also provided to few female sex workers and few MSM, as well as the general population [58].

HPP network reports data on the number of needles, syringes, and number of performed HIV tests and counseling since 1997. In 2012, with the support of United Nations Office for Drugs and Crime (UNODC), an electronic data reporting system for HPP network was established. Thus, the raw individualized data are available starting from the mentioned year. Before 2012, each HPP reported paper-based aggregated data to the main HIV prevention governmental body [59]. In this study, we give the number of needles-syringes distributed as reported by HPP network; note, however, that for the years 2000-2009 and 2011, only the number of syringes was available.

OAT with methadone was introduced in 1996 in Latvia and with buprenorphine (not covered by state budget) in 2005. Thanks to the UNODC funding the methadone program has been significantly scaled up since 2008 and available not only in the capital city Riga (as it was till 2008) but also in other regions. The OAT centers are placed both in treatment settings and outside them (as low threshold services) [60]. Data on the number of OAT clients (both methadone and buprenorphine) is centrally annually collected by CDPC [61] since 1997. In this study, we report on this data for the number of OAT clients.

**HIV testing**

HIV testing in Latvia is available since 1987 when the first case of infection was registered [51]. Latvia still has no national HIV testing guidelines. Only healthcare workers can provide HIV tests. Testing is free of charge for all inhabitants of Latvia. Only the co-payments to the doctor for the pre- and post-test counseling should be paid. In HPP network the rapid testing can be received anonymously and totally free of charge. People can get tested anonymously and with no counseling in private laboratories by paying the costs of the service by themselves. No self-testing was available in Latvia by 2017 [61,62].

As for testing, two indicators were available: the number of persons tested each year and the number of tests provided each year (adding up all tests whether a person is tested many times a year or not). Both indicators are reported by laboratories and HPP network independently and are available from 2012 to 2016. From 2000 to 2011, HPP network was only reporting the number of tests provided annually. We therefore derived the number of persons tested in HPP network from 2000 to 2011 by, first, estimating the mean number of annual tests per person tested in HHP network from 2012 to 2016, and second, dividing the number of tests provided each year from 2000 to 2011 in HPP network by the mean number of tests per person tested obtained in the first step. We report in this paper information on the number of persons tested in laboratories as well as in HPP network from 2000 to 2016. The data are given for the general population as well as for PWID in a sex-stratified manner. To obtain HIV testing coverage, we divided the numbers of persons tested by the population size.

Regarding MSM, there is no data on HIV testing from national surveillance system. Here, we report the proportion of MSM tested within the last 12 months in 2010 estimated in the EMIS study [63].

**Antiretroviral therapy**

Highly active antiretroviral therapy became available in Latvia since 1997 [64] and since then ART is free of charge to all PLHIV. It is prescribed by infectious disease doctors, who provide HIV care in the country. Latvia has not followed the international HIV clinical guidelines regarding the threshold of CD4 for asymptomatic patients. Till 2015 the threshold was still as low as 200 cells/mm3 [65]. It was increased to 350 cells in 2016 [66] and to 500 cells in 2017 [67]. Also, till 2009 the treatment was highly individualized (i.e. the different combinations of medications were as high as 67) thus increasing the costs of the treatment and limiting the amount of people who can receive it. Due to the influence of international stakeholders (UNODC and WHO), after 2009, the treatment guidelines were updated and the treatment schemes became standardized, close to those recommended by the WHO. Till 2009 there were also problems in the ART drug procurement process, which resulted in therapy discontinuation. Drugs were only distributed by the central HIV clinic in Riga (the capital city). At the end of 2009, legislation amendments have been made introducing the inclusion of HIV medicines in the list of reimbursable drugs. Thus each patient could receive the medicine in any pharmacy shop close to the place of living [68]. However, even though since 2010 [69] HIV care and treatment are provided also outside the capital city Riga, still by the end of 2017 it remains highly centralized and ensured by the central HIV clinic in Riga [70], probably due to the lack of information among PLHIV about HIV care and treatment outside Riga, due to the fact that CD4 cell count can be checked and treatment initiated only by council of HIV infectious disease doctors in Riga or because of the PLHIV concerns about confidentiality issues outside Riga in smaller cities.

In this study, data on the total annual number of persons receiving ART come from the National Health Service, which is the main governmental body who administrates the state budgetary funds prescribed for health care. Data on the number of PWID who are receiving ART are poor and reported by the central HIV clinic in Riga for couple of years. To estimate annual ART coverage, the numbers of persons receiving ART were divided by the number of HIV-diagnosed individuals still alive at the end of the year. National ART coverage was available for PWID and overall. Regarding MSM, we could not determine ART coverage as there is no national data for MSM and the studies reporting on ART coverage among MSM included very few HIV-infected MSM (<30) [63,71].

## **S10. Statistical tests to compare service coverage between Estonia and Latvia**

We performed statistical tests to compare HIV testing and ART coverage in Latvia versus Estonia. These data include both sample-based estimated proportions (i.e. in Estonia, HIV testing coverage among PWID and the general population, ART coverage among PWID) and proportions of the whole population (i.e. in Estonia, ART coverage among all people diagnosed with HIV, and in Latvia, HIV testing, and ART coverage for each group). No statistical test was required for comparisons of proportions of the whole population (i.e. for ART coverage among all people diagnosed with HIV in Estonia versus Latvia). Regarding statistical comparisons between sample-based estimated proportion and proportion of the whole population, we performed one sample Z-tests (i.e. for HIV testing coverage among PWID and general population, and for ART coverage among PWID).

## **S11. Comparison of our estimates with previous studies**

We found two studies that provided point estimates for HIV incidence or number of undiagnosed infections for Estonia (none for Latvia), one cohort study that described patients’ characteristics in Estonia, and two studies that used mathematical models to understand HIV transmission among persons who inject drugs (PWID) in Estonia. In Estonia, in 2013, an estimated 1425 (464-2386) persons were living with undiagnosed HIV infection [6], which compares with 990 (735-1398) for 2016 in our study (Table S7). A cohort study showed that the proportion of individuals reporting sexual HIV transmission was higher among people entered in care over 2009-2013 compared to those entered in care until 2008 [72], which is consistent with our finding that most new and undiagnosed infections affected individuals reporting heterosexual transmission in 2016 (Tables S6 and S7). A modeling study suggested that NSP and ART helped to reduce HIV transmission among PWID in Tallinn over 2005-2011 [73], which is consistent with our finding showing a decrease in HIV incidence among PWID in Estonia (Figure 1C). However, our estimates for the national incidence and incidence among PWID in Estonia were much lower than those found in a study, where they were estimated at 0.06%, corresponding to 642 new infections, and 1.48% respectively in 2013 [74], which compares with respectively 0.02%, 171 and 0.45% in 2016 in our study (Table S6).

## **S12. Ethic statement**

In Estonia, data collection on HIV cases was approved by Tallinn Medical Research Ethics Committee and Estonian Data Protection Agency, and in Latvia by the Cabinet of Ministers of the Republic of Latvia. Consent waivers were obtained for the study in both countries. A strict attention to confidentiality is present at every stage of data collection, analysis and storage. All other data used in this manuscript were obtained from publicly available databases and publications.

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**Table S1: Percentage of missing values, according to the period, type of variable, and imputation method used for each imputed variable in Estonia**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Percentage missing over 2000-2009** | **Percentage missing over 2010-2016** | **Type of variable** | **Imputation method** |
| **Clinical stage at diagnosis** (recent infection, AIDS, neither AIDS nor recent infection) | 5% | 21% | Categorical | Multinomial logit model |
| **HIV exposure group at diagnosis** (heterosexual, MSM, PWID) | 98% | 54% | Categorical | Multinomial logit model |
| **County of residence at diagnosis\*** (Ida-Viru county, Harju county, other) | 28% | 13% | Categorical | Multinomial logit model |
| **Nationality\*** (Estonian, Russian, other) | 56% | 40% | Categorical | Multinomial logit model |
| **CD4 count at diagnosis\*** | 100% | 72% | Continuous | Predictive mean matching |

MSM: men who have sex with men, PWID: persons who inject drugs.

The set of predictors used for each of these variables are all the other imputed variables plus: date (year and quarter) of HIV diagnosis, sex, age, and whether the patient has been linked to care; \*The variable County of residence at diagnosis, Nationality and CD4 count at diagnosis were imputed but they were not used in the back-calculation model.

**Table S2: Percentage of missing values, according to the period, type of variable, and imputation method used for each imputed variable in Latvia**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Percentage missing over 1996-2006** | **Percentage missing over 2007-2016** | **Type of variable** | **Imputation method** |
| **Clinical stage at diagnosis** (recent infection, AIDS, neither AIDS nor recent infection) | 12% | 7% | Categorical | Multinomial logit model |
| **HIV exposure group at diagnosis** (heterosexual, MSM, PWID) | 14% | 25% | Categorical | Multinomial logit model |
| **CD4 count at diagnosis\*** | 53% | 43% | Continuous | Predictive mean matching |

MSM: men who have sex with men, PWID: persons who inject drugs.

The set of predictors used for each of these variables are all the other imputed variables plus: date (year and quarter) of HIV diagnosis, whether the person was diagnosed in prison, whether transmission occurred through sexual contact with his/her main partner (Yes/No), with his/her spouse (Y/N), with a bisexual partner (Y/N), or with a person who inject drugs (Y/N), country where the persons has been infected, whether he/she is a permanent Latvian inhabitant, whether he/she is a foreigner, county where he/she is living at diagnosis; \*the variable CD4 count at diagnosis was imputed but it was not used in the back-calculation model.

**Table S3: Estimated population sizes (and 95% confidence intervals) for individuals aged 15-69 years, in Estonia and Latvia, in 2016, by sex and HIV exposure group**

|  |  |  |
| --- | --- | --- |
|  | Estonia | Latvia |
| MSM | 9419 | 10,819 |
| Heterosexual women‡ | 469,291 (469,056–469,481) | 711,226  (710,969–711,547) |
| Heterosexual men‡ | 436,009 (435,193–436,668) | 638,847  (638,185–639,672) |
| PWID (all) | 9238\* (8336–10,356) | 8360  (7215–9280) |
| PWID women | 2494 (2251–2796) | 2341  (2020–2598) |
| PWID men | 6744 (6085–7560) | 6019  (5195–6681) |
| Total men | 452,172 | 655,685 |
| Total women | 471,231 | 713,567 |
| Total | 923,403 | 1,369,252 |

MSM: men who have sex with men; PWID: persons who inject drugs; \*to be able to account for uncertainty in population sizes in our study we simulated values for the population sizes using means and 95% confidence intervals reported in the published studies (see section S5). Therefore the mean estimate and confidence interval (CI) reported in our study may slightly differ from the values reported in the literature (i.e. 9238 (8336-10,356) in our study versus 9249 (95% CI: 8322-10,367) PWID in Estonia in [13]); **‡**the number of heterosexual men and women were obtained by respectively subtracting from the male population the estimated numbers of MSM and male PWID, and from the female population the estimated number of female PWID.

**Table S4: Data used to estimate national HIV prevalence in Estonia and Latvia by sex and HIV exposure group**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Estonia** | | **Latvia** | | |
|  | **Estimates** | **References** | **Estimates** | **References** |
| **MSM** | 3.1%\* | [18] | 4.0% | [17] |
| **Male PWID** | 57.9%‡ | [19,20] | 25.5% | [17] |
| **Female PWID** | 60.6%‡ | [19,20] | 25.5% | [17] |
| **Men** | 4500 (3900–5100)† | [75] | 3300 (2900–3700)† | [75] |
| **Women** | 2500 (2200–2700)† | [75] | 1500 (1300–1600)† | [75] |

MSM: men who have sex with men. PWID: persons who inject drugs; \*Self-reported HIV prevalence rate (i.e. diagnosed HIV prevalence only). Thus, for MSM in Estonia, we added the undiagnosed HIV prevalence estimated in this study to obtain an estimate of the HIV prevalence; ‡average HIV prevalence estimated from two RDS studies conducted in 2014 [19] and 2016 [20]; †To obtain HIV prevalence among heterosexual women and men, we subtracted from the HIV prevalence among men the estimated HIV prevalence among MSM and male PWID, and from the HIV prevalence among women the estimated HIV prevalence among female PWID.

**Table S5: Estimated national HIV prevalence in Estonia and Latvia by sex and HIV exposure group for individuals aged 15-69 years**

|  |  |  |
| --- | --- | --- |
|  | **Estonia** | **Latvia** |
| **MSM** | 371  (137 – 611) | 429  (166 – 694) |
| **Heterosexual women** | 982  (867 – 1063) | 906  (831 – 966) |
| **Heterosexual men** | 239  (207 – 271) | 1341  (1178 – 1499) |
| **Male PWID** | 3904  (3353 – 4553) | 1535  (1231 – 1841) |
| **Female PWID** | 1514  (1251 – 1800) | 598  (487 – 714) |

MSM: men who have sex with men. PWID: persons who inject drugs.

**Table S6. Estimated number and rates of new HIV infections (and 95% confidence intervals) for Estonia and Latvia in 2007 and 2016, by sex and HIV exposure group**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Estonia** | | | | **Latvia** | | | |
| **Number of new HIV infections** | | | **Incidence rate per 100,000 inhabitants aged 15-69** | **Number of new HIV infections** | | | **Incidence rate per 100,000 inhabitants aged 15-69** |
| **2007** | **2016** | **% change between 2007 and 2016** | **2016** | **2007** | **2016** | **% change between 2007 and 2016** | **2016** |
| **Global¶** | 440  (362-525) | 171  (100-278) | -61%  (-30%;-78%) | 19  (11-30) | 275  (240-309) | 471  (370-600) | +72%  (+29%;+131%) | 35  (27-44) |
| **Female** | 132  (103-184) | 55  (20-111) | -58%  (-7%;-85%) | 12  (4-24) | 100  (77-121) | 191  (131-278) | +94%  (+23%;+233%) | 27  (18-39) |
| **Male** | 308  (242-372) | 115  (58-209) | -62%  (-24%;-81%) | 26  (13-47) | 174  (148-201) | 280  (202-377) | +62%  (+11%;+132%) | 43  (31-58) |
| **PWID** | 212  (170-248) | 17  (3-43) | -92%  (-79%;-98%) | 448  (84-1224) | 101  (80-124) | 173  (117-239) | +73%  (+9%;+152%) | 2786  (1853-3950) |
| **Female PWID** | 27  (15-42) | 11  (1-38) | -52%  (-96%;+74%) | 1228  (96-4157) | 23  (14-36) | 49  (19-92) | +121%  (-24%;+321%) | 2844  (1091-5370) |
| **Male PWID** | 185  (146-217) | 5  (0-13) | -97%  (-100%;-93%) | 183  (0-501) | 78  (59-98) | 123  (81-174) | +62%  (-4%;+145%) | 2764  (1798-4003) |
| **Sexual transmission** | 229  (169-304) | 154  (85-262) | -30%  (-64%;+39%) | 17  (9-29) | 173  (145-201) | 298  (215-412) | +74%  (+19%;+161%) | 22  (16-30) |
| **Heterosexual**  **women** | 106  (80-153) | 44  (13-97) | -58%  (-87%;+2%) | 9  (3-21) | 77  (57-95) | 142  (92-221) | +90%  (+12%;+272%) | 20  (13-31) |
| **Heterosexual**  **men** | 117  (69-166) | 85  (38-171) | -18%  (-68%;+118%) | 20  (9-39) | 76  (61-96) | 95  (46-168) | +28%  (-42%;+144%) | 15  (7-26) |
| **MSM** | 6  (2-12) | 25  (3-66) | +418%  (-67%;+1800%) | 276  (32-734) | 20  (13-28) | 61  (25-106) | +218%  (+20%;+506%) | 588  (241-1024) |

¶excluding vertical transmission; MSM: men who have sex with men; PWID: person who inject drugs. Note that large confidence intervals for recent estimates (Figure 1) translates into large CIs for the variation in incidence between 2007 and 2016.

**Table S7. Estimated number and rates of HIV undiagnosed infections (and 95% confidence intervals) in Latvia and Estonia in 2016, overall, and by sex and exposure group.**

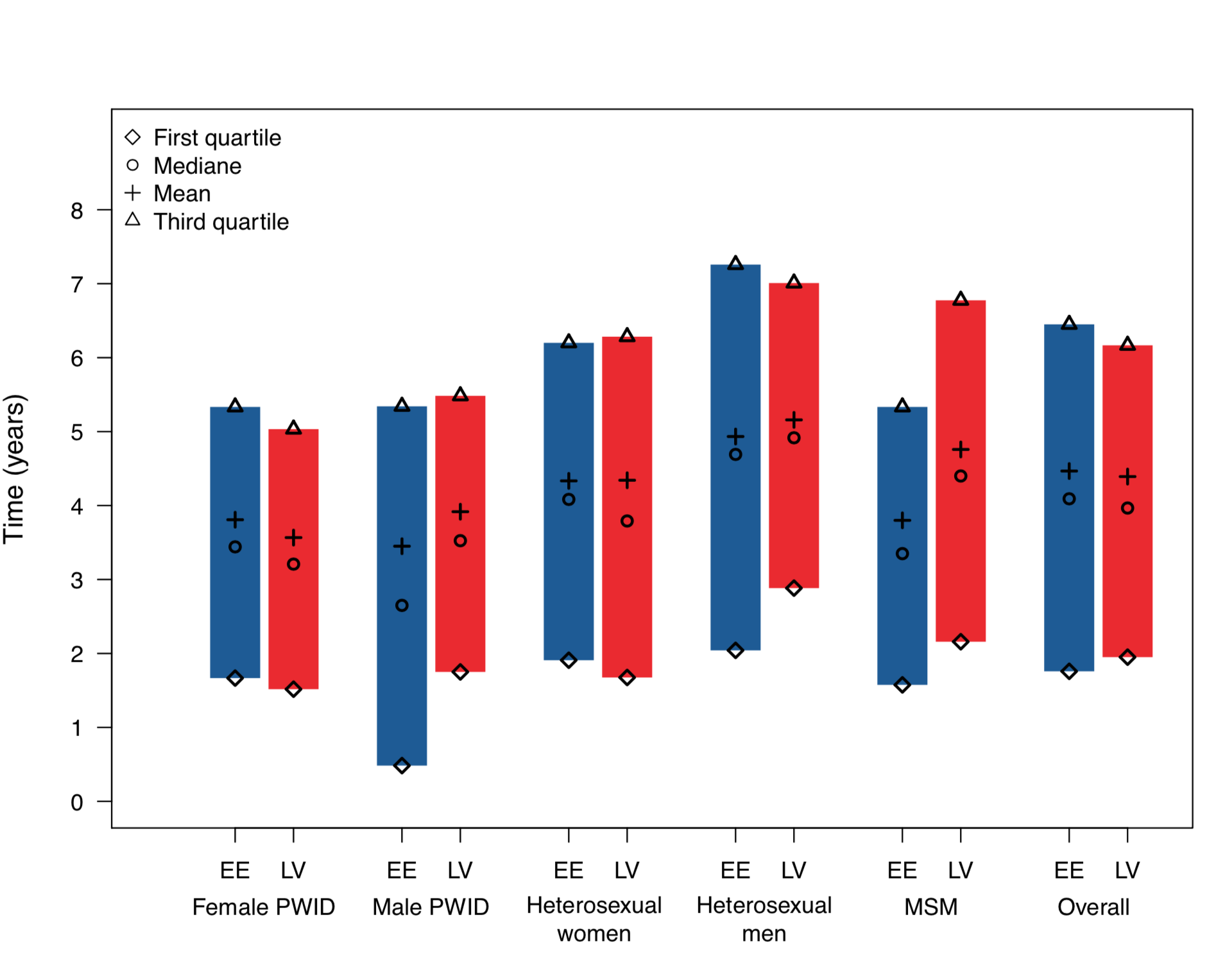
|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **Latvia** | | | **Estonia** | | |
|  | **Undiagnosed infections** | **Population size**  **aged 15-69\*** | **Rate per 100,000** | **Undiagnosed infections** | **Population size**  **aged 15-69\*** | **Rate per 100,000** |
| **Global¶** | 1855  (1532-2329) | 1,369,252 | 135  (112-170) | 990  (735-1398) | 923,403 | 107  (80-151) |
| **Women** | 643  (472-981) | 713,567 | 90  (66-137) | 354  (247-531) | 471,231 | 75  (52-113) |
| **Men** | 1212  (964-1543) | 655,685 | 185  (147-235) | 636  (443-1035) | 452,172 | 141  (98-229) |
| **PWID** | 631  (479-840) | 8360  (7215-9280) | 7583  (5607-10389) | 156  (100-232) | 9235  (8336-10345) | 1697  (1073-2560) |
| **Female PWID** | 158  (81-277) | 2341  (2020-2598) | 6740  (3383-12031) | 50  (20-117) | 2493  (2241-2793) | 2013  (788-4661) |
| **Male PWID** | 474  (351-636) | 6019  (5195-6681) | 7910  (5674-10764) | 107  (66-144) | 6742  (6059-7552) | 1580  (941-2182) |
| **Sexual transmission** | 1224  (952-1654) | 1,360,892  (1,359,972-1,362,037) | 90  (70-122) | 834  (590-1250) | 914,168  (913,058-915,103) | 91  (65-137) |
| **Heterosexual women** | 486  (349-805) | 711,226  (710,969-711,547) | 75  (50-117) | 304  (207-474) | 468,737  (468,438-468,990) | 65  (44-101) |
| **Heterosexual men** | 482  (318-746) | 638,847  (638,185-639,672) | 68  (49-113) | 453  (284-830) | 436,011  (435,201-436,694) | 104  (65-190) |
| **MSM** | 258  (159-401) | 10,819 | 2377  (1463-3703) | 78  (23-179) | 9419 | 820  (240-1892) |

¶excluding vertical transmission; MSM: men who have sex with men; PWID: persons who inject drugs. \* see section S5 in the supplementary information for explanations on how populations were estimated

**Figure S1. Mean annual number of new HIV diagnoses and proportions of people with a recent infection and AIDS from all annual diagnoses over 2000-2016, by exposure group, in Estonia (A, C, E) and in Latvia (B, D, F).** MSM: men who have sex with men. PWID: persons who inject drugs.

**../_figureS1.pdf**

**Figure S2. Estimated distributions of time from infection to HIV diagnosis in Estonia (in blue) and in Latvia (in red), overall and by exposure group, in years**. Box plots filled with blue display estimates for Estonia for individuals infected with HIV over 2012-2016, box plots filled with red display estimates for Latvia for individuals infected with HIV over 2012-2016. EE: Estonia; LV: Latvia; MSM: men who have sex with men; PWID: persons who inject drugs.

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**Figure S3.** **Estimated distributions of time from infection to HIV diagnosis, in years, in Estonia (A) and in Latvia (B), overall and by exposure group.** Box plots filled with blue (respectively red) display estimates for Estonia (respectively Latvia) for individuals infected with HIV over 2012-2016, and box plots with blue hatched lines (respectively red blue hatched lines) display estimates for Estonia (respectively Latvia) for individuals infected with HIV over 2005-2011. MSM: men who have sex with men; PWID: persons who inject drugs.

