HIV incidence and factors associated with HIV risk among people who inject drugs engaged with harm-reduction programmes in four provinces in South Africa: a retrospective cohort study

Adelina Artenie, Rachel Perry, Memory Mahaso, Thenjiwe Jankie, Anna L McNaughton, Jack Stone, Peter Vickerman, Andrew Scheibe**

Summary

Background HIV incidence among people who inject drugs in South Africa has never been estimated. We aimed to estimate HIV incidence and associations with risk and protective factors among people who inject drugs engaged with harm-reduction services.

Methods For this retrospective cohort study we used programmatic data collected from April 1, 2019, to March 30, 2022, by the Networking HIV and AIDS Community of South Africa, which offers harm-reduction services and HIV testing to people who inject drugs. During this 3-year period, services were delivered through drop-in centres and outreach in four South African provinces: Gauteng, KwaZulu-Natal, Western Cape, and Eastern Cape. Our cohort comprised people who inject drugs who did not self-report being HIV positive, were HIV negative at first testing, and had at least one follow-up test. Data were collected by outreach teams. We estimated HIV incidence, assuming seroconversions occurred at the midpoint between the last negative test and first positive test. We assessed associations between HIV seroconversion risk and several factors with Cox regression models, including sociodemographic characteristics, primary drugs used, uptake of interventions (ie, number of harm-reduction packs and opioid agonist treatment [OAT]), and HIV testing interval.

Findings Of 31 182 people who inject drugs accessing harm-reduction services, 20 955 (including 3409 self-reporting being HIV positive) were not tested for HIV. Of 10 227 people who tested at least once, 8152 were HIV negative at first test and of these, 2402 had at least two tests and formed the study cohort. Overall, 283 (11·8%) people who inject drugs acquired HIV over 2306·1 person-years. HIV incidence was higher in Gauteng (16·7 per 100 person-years; 95% CI 14·5–19·1) and KwaZulu-Natal (14·9 per 100 person-years; 11·3–19·3), than in the Eastern Cape (5·0 per 100 person-years; 2·3–9·6) and Western Cape (3·2 per 100 person-years; 1·9–4·9). In multivariable Cox models, HIV acquisition risk varied by race, primary drugs used, and interval between HIV tests. Additionally, people who injected drugs and received OAT in the past year had lower HIV risk (adjusted hazard ratio 0·48; 95% CI 0·22–1·03) than people who did not receive OAT, although the 95% CI was wide and crossed the null.

Interpretation Our study highlights a pressing need for scale-up of HIV prevention strategies, particularly opioid agonist treatment, for people who inject drugs in South Africa. Dedicated investments are needed to develop monitoring systems for HIV incidence, risk behaviours, and uptake of interventions to ensure effective and equitable programmes.

Funding Wellcome Trust, Canadian Institutes of Health Research, and Global Fund to Fight AIDS, Tuberculosis and Malaria.

Lancet HIV 2024; 11: e823–32

See **Comment** page e792

*Contributed equally

Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK (A Artenie PhD, R Perry BMBS, A L McNaughton PhD, J Stone PhD, Prof P Vickerman DPhil); **Networking HIV and AIDS Community of South Africa, Cape Town, South Africa** (M Mahaso MSc, T Jankie MPH); **Community Oriented Primary Care Research Unit, Department of Family Medicine, University of Pretoria, Pretoria, South Africa** (A Scheibe MD); **TB HIV Care, Cape Town, South Africa** (A Scheibe)

Correspondence to: Dr Adelina Artenie, Population Health Sciences, Bristol Medical School, University of Bristol, Bristol BS8 2BN, UK
adelina.artenie@bristol.ac.uk

Introduction

South Africa has the largest HIV epidemic in the world, with an estimated 160 000 new annual infections and 7·6 million people living with HIV.[1] Although people who inject drugs are one of the populations at highest risk of HIV acquisition globally, HIV incidence in South Africa has, to the best of our knowledge, never been estimated in this group. In a recent global systematic review of HIV incidence in people who inject drugs, only one estimate was available for the sub-Saharan African region (from Kenya, where the incidence was 2·6 per 100 person-years).[2] Another systematic review that synthesised HIV incidence from different population groups in sub-Saharan Africa from 2010 to 2019 identified 102 studies in South Africa.[3] However, most of these studies were done in cohorts of the general population, men who have sex with men, or female sex workers, and none among people who inject drugs.[3]

Cross-sectional studies in South Africa point to high levels of HIV risk among people who inject drugs.[4–7] In

Research in context

Evidence before this study

People who inject drugs are one of the populations at highest risk of HIV acquisition. Although South Africa has one of the largest HIV and AIDS epidemics in the world, HIV incidence among people who inject drugs in the country has never been estimated. In a global systematic review and meta-analysis of studies done between Jan 1, 2000, and Dec 12, 2022, that measured HIV incidence empirically in people who inject drugs, estimates ranged from 0·1 to 31·8 per 100 person-years, based on data from 27 countries. Only one estimate was found in the sub-Saharan region (in Kenya, with an incidence of 2·6 per 100 person-years). Another systematic review that synthesised directly measured HIV incidence estimates from different population groups in the sub-Saharan region identified 102 studies in South Africa in 2010–19. Most studies were done in general population cohorts, men who have sex with men, and female sex workers, and none among people who inject drugs. We searched PubMed on April 21, 2024, for studies on HIV incidence in people who inject drugs with the terms: ("Drug Users"[MeSH] OR "substance abuse, intravenous"[MeSH] OR "pwid*"[All Fields] OR "idu"[All Fields] OR "idus"[All Fields] OR "ivdu*"[All Fields] OR "inject drug*"[All Fields]) AND "HIV"[All Fields] AND "Africa"[All Fields] AND "incidence"[All Fields]. We restricted the search to papers published on Jan 1, 2022 onwards given the aforementioned global systematic review. We identified one study focused on estimating HIV incidence in key populations (ie, female sex workers, men who have sex with men, and people who inject drugs) in the sub-Saharan region. By use of mathematical modelling, HIV incidence was indirectly estimated to be 7·1 per 100 person-years in the eastern and southern Africa region among people who inject drugs. Data were considered insufficient to estimate HIV incidence at the country level.

Added value of this study

This is, to our knowledge, the first study in South Africa to estimate HIV incidence in people who inject drugs and to show that those receiving opioid agonist treatment have a lower HIV risk. We estimated overall HIV incidence to be 12·3 per 100 person-years (95% CI 10·9–13·8). Stratified by province, HIV incidence was higher in Gauteng and KwaZulu-Natal and lower in Eastern Cape and Western Cape. HIV risk varied according to several other factors, including race, primary drugs used, and HIV testing patterns. Although only a small portion of people who inject drugs received opioid agonist treatment, those who did had lower HIV seroconversion risk.

Implications of all the available evidence

HIV incidence and factors associated with HIV acquisition risk have been understudied among people who inject drugs in South Africa, even though they are one of the populations at highest risk of infection globally. Our study highlights a pressing need for scaling up HIV prevention strategies for people who inject drugs in South Africa, particularly opioid agonist treatment. Dedicated investments are also needed to develop monitoring systems for HIV incidence, risk behaviours, and the uptake of interventions among people who inject drugs in South Africa to guide strategies for intervention and to ensure effective and equitable HIV response programmes.

a multicity survey done in 2016–17 among 943 people who inject drugs accessing harm-reduction services, most participants reported being homeless (66%) and injecting drugs four or more times a day (69%), with 23% reporting that they had not used a new needle and syringe for their latest injection.[5] Although only 43% reported being sexually active in the past month, nearly half (48%) of those who were active did not use condoms during their most recent sexual activity.[5] Overall HIV prevalence was 21%,[5] higher than a similar survey done in 2013 (14%),[4] and varied substantially by city, reaching 38% in Pretoria. In a smaller-scale study in KwaZulu-Natal, published in 2023, participants indicated high levels of injecting practices in the past year, including sharing needles (42%) and other drug preparation materials (73%).[7]

Harm-reduction programmes are scarce in South Africa. With an estimated opioid agonist treatment (OAT) coverage of 1·2%, South Africa (along with the rest of the sub-Saharan African region) has one of the lowest OAT coverages globally.[8] Aside from small pilot projects introduced in some cities,[9] OAT is only available through private clinics, where treatment is expensive (~1500 ZAR per month [~£63] for a dose of 50 mg/day) and unaffordable for populations who face considerable socioeconomic disadvantages, such as people who inject drugs.[10] Among people who access harm-reduction services, coverage of needle and syringe programmes (estimated at 65 needles and syringes per person per year) is less than the WHO target of 200,[11] and few people who inject drugs have access to such services.

Understanding HIV incidence and the risk and protective factors associated with HIV acquisition is essential for guiding HIV prevention development and scale-up. Our aim was to use programmatic data from the Networking HIV and AIDS Community of South Africa (NACOSA) Global Fund People Who Use Drugs Programme to estimate HIV incidence and explore associations with risk and protective factors among people who inject drugs engaged with harm-reduction services in four provinces in South Africa.

Methods

Study design

In this retrospective cohort study, we analysed data from people who inject drugs visiting NACOSA-supported services from April 1, 2019, to March 30, 2022.

NACOSA includes more than 1000 community-based organisations focused on reducing the burden of HIV/AIDS in southern Africa. On April 1, 2019, NACOSA initiated a 3-year Global Fund People Who Use Drugs Programme, which was implemented by three civil society organisations: Anova Health Institute, TB HIV Care, and Tintswalo Home Based Care. Services operated in seven districts in South Africa, covering four provinces: Johannesburg, Sedibeng, and Ekurhuleni (Gauteng province); eThekwini and uMgungundlovu (KwaZulu-Natal); Cape Town (Western Cape); and Nelson Mandela Bay (Eastern Cape). Approximately half of the estimated 82 500 people who inject drugs in South Africa are based in these seven districts.[12] The programme offered harm-reduction education and counselling, sterile injecting equipment, condoms, HIV testing, verbal symptomatic screening for other communicable diseases (ie, tuberculosis and sexually transmitted infections), referrals for care, and (in Johannesburg, Cape Town, and eThekwini) OAT. Services were offered through fixed drop-in centres that operated 5 days per week (in Cape Town, eThewkini, and Nelson Mandela Bay) and community outreach in all districts once or twice a week with mobile vehicles that frequented spaces where people who inject drugs congregate (eg, streets, parks, and shelters). Outreach sites were mapped by outreach teams and hotspots were visited systematically to maximise coverage. Together, the drop-in centres and mobile outreach services represent all community-based harm-reduction organisations for people who inject drugs in these seven districts. The programme cycle ended on March 30, 2022, and a new cycle started afterwards.

Ethical approval for this study was granted through the University of Pretoria Research Ethics Committee (533/2023).

Participants

We formed a retrospective cohort comprising people who inject drugs visiting NACOSA-supported services who had an initial HIV-negative test and one or more subsequent HIV tests during the first cycle (ie, until March 30, 2023) of the programme. The outcome was time-to-HIV seroconversion. We excluded people who had 45 days or less between their first and last HIV tests because follow-up was too short to detect HIV seroconversion, if it occured.[13] We also excluded people who tested HIV negative after a previous positive test because we could not guarantee the accuracy of these data. Finally, we excluded people who had different demographic information recorded at follow-up visits (ie, either different date of birth and gender or date of birth and district) because we could not accurately determine whether the demographic differences were reporting errors or if the same identifier had been erroneously assigned to different people.

At initial engagement, each person who reported active injection drug use and had injection marks was assigned a unique identifier, which was used at subsequent visits to link their data over time. The identifier was composed of personal information (ie, name and date of birth), and thus it was unique to each person and easy to remember. All participants who engaged with the NACOSA-supported programmes signed an informed consent for the collection and use of their data by a third party, conditional on maintaining their privacy. This study was exempt from seeking additional informed consent from participants by the University of Pretoria Research Ethics Committee, as the data were de-identified and anonymised before being shared for analysis.

Procedures

Data were collected each time people who inject drugs were in contact with one of the NACOSA-supported organisations, regardless of the services received, and were collected by the outreach team. Data on sociodemographic characteristics, risk behaviours, and services provided (including distribution of harm reduction packages containing 15 needles and syringes, cookers, filters, sterilised water, alcohol swabs, lubricants, and condoms; HIV testing; and OAT) were recorded on paper forms. Data collection forms were checked daily and transferred to a central electronic database, except data on risk practices, which were not transferred and therefore available for this analysis.

Point-of-care HIV fingerstick rapid antibody testing was offered to people who inject drugs and self-reported being HIV-negative or were unaware of their HIV status. HIV testing followed national health guidelines with the use of a serial algorithm.[14] Briefly, a first rapid antibody test was done as a screen; if non-reactive, an HIV-negative result was given. If reactive, the HIV test was repeated with a different rapid HIV test to substantiate the result (appendix p 2). Following national recommendations,[14] HIV-negative people who inject drugs were offered retesting if they had not been tested within the previous 6 weeks. Testing was done by trained staff and offered to eligible people who inject drugs on each engagement through drop-in centres and mobile outreach. Results were available within 20–40 min, and people newly diagnosed with HIV were started on antiretroviral therapy (ART) or referred for treatment.

See Online for appendix

Covariates examined in relation to HIV seroconversion risk included the specific organisation implementing the programme (ie, ANOVA Health Institute, TB HIV Care, or Tintswalo Home Based Care), sociodemographic characteristics, primary drugs used, and uptake of interventions through the programme. Sociodemographic factors included age (categorised as <24 years, 25–29 years, 30–34 years, 35–39 years, and ≥40 years, as in a previous study on HIV incidence in sub-Saharan Africa[15]); gender (options were male, female, transgender female, or transgender male), race (Black, Coloured,

White, Indian, or Asian), province and housing status (house, homeless, and hostel, shelter, or other unstable housing). Age was categorised because younger people who inject drugs typically have a higher HIV risk than older people who inject drugs,[2] but we did not expect the association between age and HIV risk to be linear. Coloured is a South African term referring to people who have mixed ancestries. Primary drugs used included heroin (and whoonga or nyaope), methamphetamine, cocaine or other. Whoonga and nyaope are street-based mixtures commonly injected among people who inject drugs in South Africa that include heroin (herein referred to as heroin). We created a three-level drug variable: heroin only, heroin and stimulants, and only stimulants or other drugs. The categories of only stimulants or other drugs were combined because they represented a small proportion of all observations and we found no difference in HIV risk among people who inject drugs when separating them. Uptake of interventions through the programme was defined as the number of harm reduction packages received at each engagement and recent OAT. The number of harm reduction packages received was categorised as 0, 1–2, 3–4, and 5 or more. People who reported injecting more frequently were typically given more harm-reduction packages. Recent OAT was defined as having received OAT through one of the NACOSA-supported programmes in the past year. Previous studies that used routine programmatic data to estimate HIV incidence have suggested that people with shorter intervals between consecutive HIV tests have higher HIV risk.[2,16,17] Thus, we also included a variable reflecting HIV testing interval (categorised as ≤3 months, >3 to ≤6 months, >6 to ≤12 months, and >12 months).

Statistical analysis

The planned sample size was based on the anticipated reach of the NACOSA-supported programmes. At the start of the programme in 2019, it aimed to include 70% of the estimated 11589 people who inject drugs in the districts included. However, the programme reached many more people than anticipated as the 2019 estimated population of people who inject drugs turned out to be an underestimate.

We used descriptive statistics to compare all people who inject drugs engaged with the programme according to whether they were not tested for HIV; were tested and were HIV positive at first test; were HIV negative at first test and had no follow-up test; or were HIV negative at first test and had at least one follow-up test. The latter group (ie, HIV negative at first test with subsequent retest) formed the study sample. Reasons for not being tested or retested if eligible were not recorded. Some people who inject drugs might have had fewer opportunities for testing due to engaging with the programme later than others, so we also compared the proportion in each group who had 1 year or less that had elapsed since their first engagement and study end.

For all participants, follow-up started at the first HIV test. For people who seroconverted, the date of seroconversion was estimated as the midpoint between their last negative test and first positive test. People who remained HIV negative throughout were censored at their last test. The HIV incidence rate was estimated with the person-time method and 95% CIs based on the Poisson distribution. We fitted Kaplan–Meier curves showing the cumulative incidence of HIV seroconversion by province. To estimate hazard ratios and corresponding 95% CIs of associations between covariates and risk of HIV seroconversion, we fitted time-varying univariable and multivariable Cox regression models. Aside for gender, race, implementing organisation, and province, covariates were updated at each visit to reflect the most recent information recorded and we lagged them one visit relative to outcome. Because of correlation between race and implementing organisation with province, we included only race and implementing organisation in the multivariable models. We fitted two multivariable models, one including only age, gender, race, and implementing organisation (ie, intrinsic or external variables that cannot be confounded by the other variables considered), and a second including all other variables. This approach was taken to avoid erroneously controlling for potential mediators or colliders.[18] As missing data were infrequent, we imputed the median values for missing continuous variables and modal values for missing categorical variables.

As we could not determine the date of HIV seroconversion with precision, we did two sensitivity analyses for the overall and province-specific HIV incidence rates, each time varying the estimated date of seroconversion, as previously done for a similar study design.[16] First, as some people who inject drugs could be motivated to have an HIV test soon after exposure to risk behaviours, we used 1 month before a positive HIV test as the seroconversion date. Second, we used 2 weeks after last negative test in case individuals had already been exposed to HIV at that time but had tested too early. Additionally, we did two sensitivity analyses for the multivariable Cox models. First, we replaced race and implementing organisation by province. Second, we categorised age into quartiles. All analyses were done in R v4.2.2.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From April 1, 2019, to March 30, 2022, 31182 people who inject drugs visited NACOSA-supported programmes, of whom 10227 (32·8%) were tested for HIV at least once (figure 1). Among those tested, 2075 (20·3%) were HIV positive at first test. Of the remaining 8152 who tested

HIV negative, 2402 had at least one valid follow-up test and formed the study cohort. 81 (3·3%) of otherwise eligible participants were excluded due to inconsistent data between follow-up visits, either an HIV-negative test result after a positive one or different demographic information.

Compared with people who inject drugs who were never tested or people who inject drugs who tested HIV negative and had no follow-up test, our cohort was more likely to be from the Western Cape than Gauteng, to indicate being of Coloured race rather than Black, to have received OAT in the past year, and to have had their first contact with the programme more than a year before the end of the study (appendix pp 3–4). Relative to people who inject drugs and who were never tested, our cohort was also more likely to have received more harm reduction packages. We found no differences by age, gender, housing, and drug use, although drug use data were not collected for people who inject drugs who were not tested.

Most participants were from Gauteng (58·1%), and fewer from the Western Cape (20·1%), KwaZulu-Natal (15·6%), and Eastern Cape (6·2%). 1112 (46·3%) participants were aged 29 years or younger. Most were Black, homeless, and reported heroin only as their primary drug (table 1). No participants were Asian. Only 133 (5·5%) of 2402 received OAT in the previous year and most received harm reduction packages (table 1). Sociodemographic characteristics differed by province. Compared with people who inject drugs in Gauteng and KwaZulu-Natal, there were more people in Western Cape and Eastern Cape who were older, were women, and

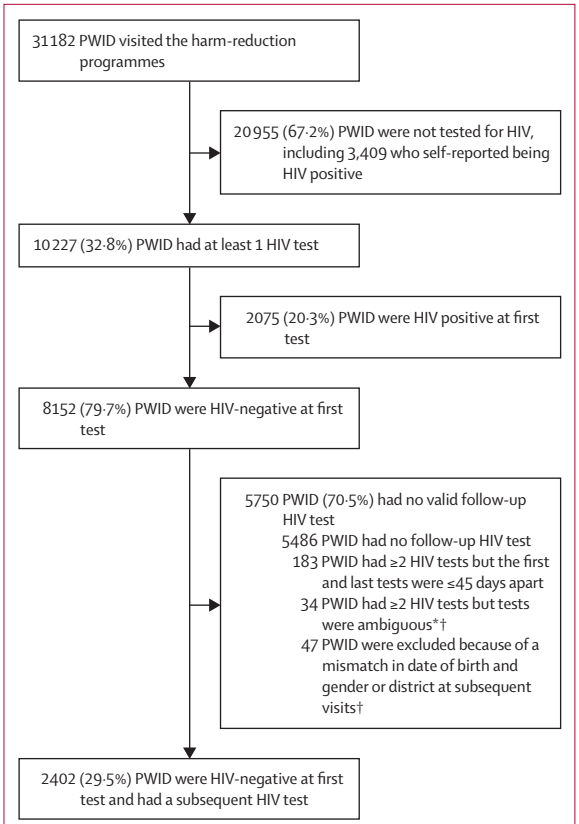

Figure 1: **Flowchart showing the selection of study participants**
PWID=people who inject drugs. *Ambiguous tests were defined as an HIV-negative test result after a previous positive test result. †A total of 81 (3·3%) of otherwise eligible HIV-negative people who inject drugs were excluded because of errors potentially linked to data collection.

	Overall, n=2402	Gauteng, n=1395	KwaZulu-Natal, n=374	Western Cape, n=484	Eastern Cape, n=149
Implementing organisation					
ANOVA Health Institute	1191 (49·6%)	1191 (85·4%)	0	0	0
TB HIV Care	1007 (41·9%)	0	374 (100·0%)	484 (100·0%)	149 (100·0%)
Tintswalo Home Based Care	204 (8·5%)	204 (14·6%)	0	0	0
Age, years					
≤24	330 (13·7%)	196 (14·1%)	87 (23·3%)	32 (6·6%)	15 (10·1%)
≥25 to 29	782 (32·6%)	533 (38·2%)	140 (37·4%)	77 (15·9%)	32 (21·5%)
≥30 to 34	687 (28·6%)	422 (30·3%)	85 (22·7%)	146 (30·2%)	34 (22·8%)
≥35 to 39	368 (15·3%)	165 (11·8%)	45 (12·0%)	129 (26·7%)	29 (19·5%)
≥40	235 (9·8%)	79 (5·7%)	17 (4·5%)	100 (20·7%)	39 (26·2%)
Gender					
Male	2172 (90·4%)	1323 (94·8%)	355 (94·9%)	391 (80·8%)	103 (69·1%)
Female	228 (9·5%)	71 (5·1%)	19 (5·1%)	92 (19·0%)	46 (30·9%)
Transgender*	2 (0·1%)	1 (0·1%)	0	1 (0·2%)	0
Race†‡					
Black	1739 (72·4%)	1333 (95·6%)	321 (85·8%)	48 (9·9%)	37 (24·8%)
Coloured	448 (18·7%)	29 (2·1%)	13 (3·5%)	381 (78·7%)	25 (16·8%)
Indian	29 (1·2%)	7 (0·5%)	21 (5·6%)	1 (0·2%)	0
White	186 (7·7%)	26 (1·9%)	19 (5·1%)	54 (11·2%)	87 (58·4%)
Current housing§					
House	731 (30·4%)	517 (37·1%)	10 (2·7%)	139 (28·7%)	65 (43·6%)
Homeless	1469 (61·2%)	693 (49·7%)	363 (97·1%)	334 (69·0%)	79 (53·0%)
Shelter, hostel, or other unstable housing	202 (8·4%)	185 (13·3%)	1 (0·3%)	11 (2·3%)	5 (3·4%)
OAT in the previous year					
Yes	133 (5·5%)	41 (2·9%)	22 (5·9%)	70 (14·5%)	0
No	2269 (94·5%)	1354 (97·1%)	352 (94·1%)	414 (85·5%)	149 (100·0%)
Number of harm-reduction packs received¶					
0	414 (17·2%)	32 (2·3%)	216 (57·8%)	155 (32·0%)	11 (7·4%)
1–2	965 (40·2%)	524 (37·6%)	151 (40·4%)	212 (43·8%)	78 (52·4%)
3–4	522 (21·7%)	404 (29·0%)	6 (1·6%)	90 (18·6%)	22 (14·8%)
≥5	501 (20·9%)	435 (31·2%)	1 (0·3%)	27 (5·6%)	38 (25·5%)
Primary drugs used					
Only heroin	1773 (73·8%)	1228 (88·0%)	308 (82·4%)	185 (38·2%)	52 (34·9%)
Heroin and stimulants	492 (20·5%)	141 (10·1%)	56 (15·0%)	258 (53·3%)	37 (24·8%)
Only stimulants or other drugs	137 (5·7%)	26 (1·9%)	10 (2·7%)	41 (8·5%)	60 (40·3%)

OAT=opioid agonist treatment. *Because so few transgender people are included, we do not present these data separately. †No participants were Asian. ‡112 (4·7%) participants had missing race data. §130 (5·4%) participants had missing housing data. ¶Each harm-reduction pack contains 15 needles and syringes, cookers, filters, sterilised water, alcohol swabs, lubricants, and condoms.

Table 1: **Baseline characteristics of people who inject drugs included in this cohort, overall and by province**

were not Black (table 1). Additionally, more people in Western Cape reported receiving OAT recently than in KwaZulu-Natal, Gauteng, and Eastern Cape (table 1). Baseline characteristics stratified by race are shown in the appendix (p 5).

The 2402 people included in the study sample contributed 6328 HIV tests and their median follow-up was 0·80 years (IQR 0·40–1·40). Median time between consecutive tests was 0·44 years (0·25–0·77). Overall, 283 (11·8%) people who inject drugs acquired HIV during 2306·1 person-years, yielding an HIV incidence of 12·3 per 100 person-years (95% CI 10·9–13·8). Stratified by province, HIV incidence was 16·7 per 100 person-years (14·5–19·1) in Gauteng and 14·9 (11·3–19·3) in KwaZulu-Natal, compared with 5·0 (2·3–9·6) in Eastern Cape and 3·2 (1·9–4·9) in Western Cape. The Kaplan–Meier plot illustrates a similar pattern in cumulative HIV incidence for the four provinces (figure 2).

In univariable models, compared with people who inject drugs based in Gauteng, there was no evidence of a difference in HIV risk for people who inject drugs in KwaZulu-Natal, but risk was lower among people who inject drugs in the Eastern Cape and Western Cape (table 2). People recruited through TB HIV Care had a lower HIV risk than did those recruited through the ANOVA Health Institute (table 2). Compared with people aged 24 years or younger, there was no evidence of a difference in HIV risk among people aged 25–29 years or 30–34 years, but risk was lower among those aged 35–39 and 40 years and older (table 2). HIV risk was lower among women than men and among people of all other race groups compared with Black people (although the difference was not significant for Indian people; table 2). Risk of HIV seroconversion gradually increased with an increase in the number of harm reduction packages received and decreased with increasing length of time between HIV tests (table 2). Relative to people who did not receive OAT recently, people who did had a lower HIV risk (table 2). We found no evidence of a difference in HIV risk by housing status and primary drug used.

There was a correlation between race and implementing organisation with province, with χ^2 p values less than 0·0001. Missing data were infrequent (≤5% for any one variable). In multivariable model 1, which included implementing organisation, age, gender, and race, the association with race persisted, whereas the others did not; the association with gender was no longer evident when adjusting for race. In multivariable model 2, which included all variables considered, associations between HIV testing interval and recent OAT with HIV risk persisted, although the 95% CI for recent OAT were wide and crossed the null. The association with primary drugs used was now indicating greater risk for people who inject heroin and stimulants compared with those using heroin only; this change occurred after adjusting for race.

In a sensitivity analysis in which we varied the date of HIV seroconversion, HIV incidence rates remained similar (appendix p 6). In sensitivity analyses in which the multivariable Cox regression models included province instead of implementing organisation and race, and in which we used an alternative age categorisation, associations remained largely similar (appendix pp 7–10).

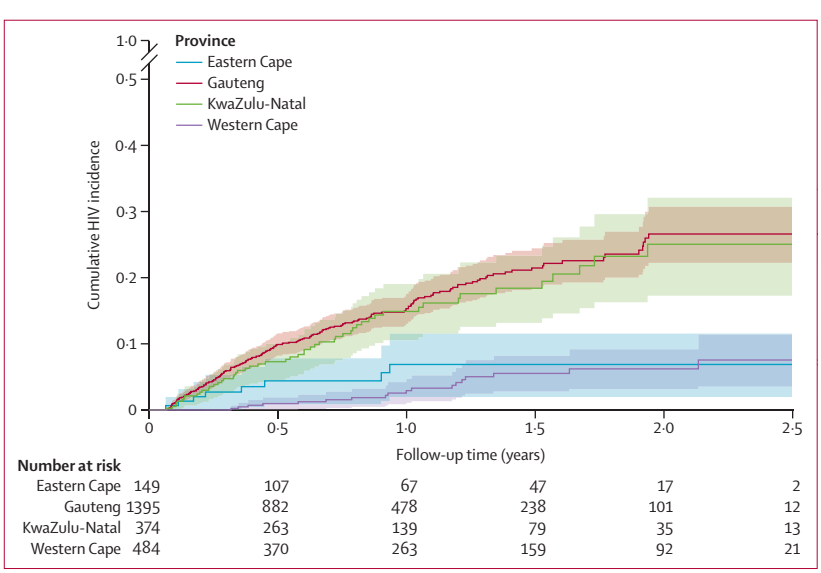

Figure 2: **Kaplan–Meier plot of the cumulative hazard of HIV seroconversion by province**

Discussion

We found very high HIV incidence among people who inject drugs engaging with harm-reduction programmes and who received repeat HIV testing in two provinces in South Africa: 16·7 per 100 person-years in Gauteng and 14·9 per 100 person-years in KwaZulu-Natal. Incidence was lower than in these provinces but still high in the other two provinces: Eastern Cape (5·0 per 100 person-years) and Western Cape (3·2 per 100 person-years). We also found that people receiving OAT in the past year had a considerably lower HIV risk than those who did not receive OAT, although the 95% CI for this association was wide and crossed the null. HIV risk varied according to several other factors, including race, primary drugs used, and HIV testing patterns.

Our estimated HIV incidence is considerably higher than the pooled HIV incidence estimate (3·2 per 100 person-years) for low-income and middle-income countries reported in a recent global systematic review.[2] Yet, such high incidence is not unprecedented, with studies done in settings with little access to harm-reduction programmes, with Ukraine (31·8 per 100 person-years), India (21·3 per 100 person-years), and Russia (18·7 per 100 person-years) reporting similarly high levels.[2] In South Africa, studies done in other vulnerable populations have also found high HIV incidence, including among men who have sex with men (12·5 per 100 person-years)[19] and female sex workers

	Observations, n	Follow-up, person-years	Incident cases, n	HIV incidence rate, per 100 person-years (95% CI)	HR (95% CI)	Model 1,* aHR (95% CI)	Model 2,† aHR (95% CI)
Overall	3926	2306·1	283	12·3 (10·9–13·8)	..	..	..
Province							
Gauteng	2322	1215·1	203	16·7 (14·5–19·1)	1 (ref)	..	..
KwaZulu-Natal	526	361·7	54	14·9 (11·3–19·3)	0·90 (0·67–1·21)	..	..
Eastern Cape	233	158·7	8	5·0 (2·3–9·6)	0·31 (0·15–0·64)	..	..
Western Cape	845	570·5	18	3·2 (1·9–4·9)	0·20 (0·12–0·32)	..	..
Implementing organisation							
ANOVA Health Institute	1866	985·9	173	17·5 (15·1–20·3)	1 (ref)	1 (ref)	NS
TB HIV Care	1604	1092·5	80	7·3 (5·8–9·1)	0·44 (0·33–0·57)	0·75 (0·54–1·02)	NS
Tintswalo Home Based Care	456	227·7	30	13·2 (9·1–18·6)	0·80 (0·54–1·19)	0·85 (0·57–1·26)	NS
Age (years)							
≤24	483	256·0	43	16·8 (12·3–22·4)	1 (ref)	1 (ref)	NS
≥25 and ≤29	1255	699·9	106	15·2 (12·5–18·2)	0·98 (0·68–1·39)	0·97 (0·68–1·38)	NS
≥30 and ≤34	1162	674·1	88	13·1 (10·5–16·0)	0·91 (0·63–1·31)	1·02 (0·71–1·48)	NS
≥35 and ≤39	624	411·5	27	6·6 (4·4–9·4)	0·47 (0·29–0·76)	0·63 (0·38–1·02)	NS
≥40	402	264·9	19	7·2 (4·4–11·0)	0·53 (0·31–0·91)	0·86 (0·49–1·52)	NS
Gender							
Male	3526	2063·9	265	12·8 (11·4–14·5)	1 (ref)	1 (ref)	NS
Female	397	240·4	18	7·5 (4·6–11·6)	0·59 (0·37–0·96)	0·79 (0·48–1·29)	NS
Transgender‡	3	1·9	0	NA	NA	NA	NS
Race§							
Black	2781	1541·4	250	16·2 (14·3–18·3)	1 (ref)	1 (ref)	NS
Coloured	807	528	20	3·8 (2·4–5·7)	0·24 (0·16–0·38)	0·33 (0·20–0·54)	NS
Indian	43	31·1	1	3·2 (0·2–15·9)	0·21 (0·03–1·48)	0·24 (0·03–1·74)	NS
White	295	205·6	12	5·8 (3·2–9·9)	0·38 (0·21–0·68)	0·50 (0·25–0·98)	NS
Current housing status							
House	1167	630·3	85	13·5 (10·8–16·6)	1 (ref)	..	1 (ref)
Homeless	2377	1476·8	171	11·6 (9·9–13·4)	0·88 (0·67–1·14)	..	1·04 (0·79–1·37)
Shelter, hostel, or other unstable housing	382	199	27	13·6 (9·1–19·5)	1·02 (0·66–1·57)	..	0·91 (0·57–1·45)
Number of harm-reduction packs received currently							
0	596	385·9	40	10·4 (7·5–14·0)	1 (ref)	..	1 (ref)
1–2	1518	908·4	99	10·9 (8·9–13·2)	1·13 (0·78–1·64)	..	0·76 (0·50–1·15)
3–4	932	529·7	71	13·4 (10·6–16·8)	1·45 (0·98–2·13)	..	0·83 (0·51–1·33)
≥5	880	482·1	73	15·1 (12·0–18·9)	1·73 (1·17–2·56)	..	0·84 (0·52–1·38)
Primary drugs used							
Only heroin	2822	1638·1	217	13·2 (11·6–15·1)	1 (ref)	..	1 (ref)
Heroin and stimulants	873	525·8	56	10·7 (8·1–13·7)	0·84 (0·62–1·13)	..	1·37 (1·00–1·88)
Only stimulants or other	231	142·2	10	7·0 (3·6–12·5)	0·55 (0·29–1·05)	..	0·92 (0·47–1·77)
Time between HIV tests, months							
≤3	890	166·1	47	28·3 (21·0–37·3)	1 (ref)	..	1 (ref)
>3 and ≤6	1211	432·6	73	16·9 (13·3–21·1)	0·54 (0·37–0·78)	..	0·57 (0·39–0·82)
>6 and ≤12	1189	816·3	103	12·6 (10·4–15·2)	0·40 (0·29–0·55)	..	0·42 (0·29–0·60)
>12	636	891·2	60	6·7 (5·2–8·6)	0·22 (0·16–0·32)	..	0·25 (0·16–0·38)
OAT in the previous year							
No	3642	2159·6	277	12·8 (11·4–14·4)	1 (ref)	..	1 (ref)
Yes	284	146·5	6	4·1 (1·7–8·5)	0·39 (0·19–0·82)	..	0·48 (0·22–1·03)

Gender, race, implementing organisation, and province were time-fixed variables. All other variables were updated at each visit. aHR=adjusted hazard ratio. HR=hazard ratio. NA=not available. NS=not shown. OAT=opioid agonist treatment. *Model 1 includes the implementing organisation, age, race, and gender; province is not included because it is correlated with race and implementing organisation (χ^2 p<0·0001) and the remaining variables were not included because they are unlikely to act as confounding factors for either the implementing organisation, age, race, or gender. †Model 2 includes all variables listed in the table except for province, but the estimates for implementing organisation, age, race, and gender are not shown as the corresponding effect sizes should be interpreted based on model 1 only. ‡HIV incidence could not be estimated given the low number of person-years at risk. §No participants were Asian.

Table 2: **HIV incidence and univariable and multivariable associations between sociodemographic characteristics, uptake of interventions, and HIV testing patterns with HIV acquisition risk among 2402 people who inject drugs in South Africa**

(5–13 per 100 person-years).[20,21] Nearly half of participants in our study were younger than 30 years and two-thirds were homeless or unstably housed, and previous systematic reviews have shown an increased HIV risk for these groups.[2,22] Although data on risk behaviours were not available, multiple other cross-sectional studies done among people who inject drugs in South Africa indicate high levels of injection drug use and sharing of injection equipment.[4–7] Taken together, in a setting with a large, generalised HIV epidemic, very low access to OAT and needles or syringes, and low (~20%) ART coverage in people who inject drugs,[23] high HIV transmission among people who inject drugs seems probable. Sexual transmission could also be an important driver of HIV risk among people who inject drugs, given its prominent role in South Africa's HIV epidemic and evidence of sexual risk behaviours in this population.[4–6]

It is also possible that HIV incidence is overestimated in our study if people who inject drugs who received HIV retesting were at higher risk than were those who never tested or did not retest. However, compared with people excluded because they had no test or follow-up, included participants had characteristics that were similar or associated with lower HIV risk, except for receiving more harm reduction packages, which could indicate higher risk. Among participants included in the study, the observed differences in HIV risk for people with varying intervals between tests suggest that the estimated incidence is sensitive to participants' testing patterns. Nevertheless, HIV incidence was elevated (6·7 per 100 person-years) even among those with longer testing intervals.

We note some other limitations. First, an absence of data on risk behaviours, such as syringe sharing and unprotected sex, limits a better understanding of the underlying mechanisms driving HIV risk and the differences in incidence between provinces. Second, although the association between OAT and HIV acquisition risk was adjusted for several potentially confounding factors, variables unaccounted for (eg, severity of opioid use disorder) could partly explain the observed effect. Third, the absence of data on sterile needles or syringes (measured in this study through the number of harm reduction packages received) and OAT obtained outside of NACOSA-supported programmes could lead to misclassification in the exposure to these interventions and potentially bias associations with HIV risk. However, external access to these interventions is expected to be very low. Fourth, the use of routine programmatic data in research typically carries a greater risk of data inaccuracies, which could have introduced biases into our findings. 81 otherwise eligible people who inject drugs were excluded due to inconsistencies in basic demographic information or HIV test results, which could have been the result of data collection errors (eg, incorrect assignment of participant identifier). However, overall, the proportion of people who inject drugs excluded for this reason was small (3·3%). Fifth, although people who inject drugs had to engage with harm-reduction programmes to be included in this study, which could limit the generalisability of our findings, the use of mobile vans to reach individuals where they live and use drugs mitigated this issue and helped engage a broader, more representative segment of the population than a fixed drop-in centre alone.

South Africa has substantial geographical, racial, and gender variation in the HIV epidemic, with high HIV incidence and prevalence clustering in Gauteng, KwaZulu-Natal, and Eastern Cape, Black people, and women.[24,25] These geographical and racial differences were largely apparent in our study. Differences have been attributed to structural and historical factors, primarily racist policies during the Apartheid period, which have led to disparities in socioeconomic status, access to health-care services, and HIV prevention and treatment interventions.[26–28] One exception to the trends previously reported in the general population was the lower HIV incidence among people who inject drugs in the Eastern Cape.[24,25] This difference could be because the province's high overall HIV levels are largely driven by very high prevalence among women,[29] yet our sample of people who inject drugs predominantly included men. It is also possible that we are underestimating HIV incidence among people who inject drugs in this region because data were only available for Nelson Mandela Bay, which has lower HIV levels than other districts in the province.[30]

Although women who inject drugs had a lower HIV risk than men in our study, this difference was no longer evident when adjusting for race or province. This result is because women were more likely to be from areas associated with or of races associated with lower HIV risk. These findings are in line with two cross-sectional surveys done among people who inject drugs in South Africa, which found no significant difference in HIV prevalence between women and men.[4,5] It is unclear why the higher HIV acquisition risk reported for women compared with men in the general population was not reflected in our study. If injection-related behaviours are the main drivers of HIV risk among people who inject drugs, then these might obscure any gender differences in sexual risks. It is also possible that the most vulnerable women who inject drugs might be under-represented in studies of people who inject drugs. A qualitative study among women who inject drugs in Durban (KwaZulu-Natal, South Africa) highlighted the profound stigma, criminalisation, and violence that they face, which hinders their ability to engage with harm-reduction programmes.[31]

Despite being on the WHO Essential Medicines List, neither methadone nor buprenorphine are included in South Africa's Essential Medicines List. OAT is only available through the private sector or small pilot projects, therefore few people who inject drugs have

access to it. In our study, the effect size for the association between recent OAT and HIV risk was large (aHR 0·48; 95% CI 0·22–1·03), aligning with evidence from previous studies in other countries.[32] However, given the few people receiving OAT, the 95% CI was wide and crossed the null. Nevertheless, our finding is important as it shows the potential of scaling up this intervention to reduce HIV transmission among people who inject drugs in South Africa. The finding that people who inject both heroin and stimulants have a higher HIV risk than those injecting heroin alone highlights a need for a comprehensive HIV response, including a package of interventions, such as needles or syringe programmes, condoms, pre-exposure prophylaxis, and ART, in line with WHO recommendations.[33]

In conclusion, our study suggests that there is an important need for strengthening HIV prevention among people who inject drugs in South Africa. Going forward, it is essential to invest in developing monitoring systems to collect regular, high-quality data on HIV incidence, risk behaviours, and access to interventions to tailor strategies to those most in need. Otherwise, there is a risk that people who inject drugs will be excluded from national efforts to end HIV and AIDS.

Contributors

AA, RP, MM, TJ, PV, and AS conceptualised the study. AA and RP (with guidance from AA) did the analyses and wrote a first draft of the manuscript. MM and TJ provided access to the data. All authors contributed to data interpretation, writing of the manuscript, and approved the final version. AA, RP, MM, and TJ accessed and verified the data reported in the study. AA, RP, MM, TJ, ALM, PV, and AS had full access to all the data in the study; JS joined the study after the data agreement was signed with NACOSA and had access to aggregated data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

PV received investigator-sponsored research funding from Gilead Sciences for research not related to this study. All other authors declare no competing interests.

Data sharing

A de-identified dataset can be made available on request to researchers who provide a methodologically sound proposal upon approval by AA, MM, TJ, PV, and AS and subject to ethical approval. Proposals should be directed to adelina.artenie@bristol.ac.uk, andrew.scheibe@gmail.com, and memory@nacosa.org.za

Acknowledgments

This work was supported by the Wellcome Trust (WT 226619/Z/22/Z). AA also acknowledges support from the Canadian Institutes of Health Research. PV acknowledges support from the UK National Institute for Health Research's Health Protection Research Unit for Evaluation of Interventions and Behavioural Science at the University of Bristol (NIHR200877), in partnership with the UK Health Security Agency. The Networking HIV and AIDS Community of South Africa programme for people who inject drugs was funded through the Global Fund. We thank Lorraine Moses for her support in collating information on HIV testing algorithms used by NACOSA-supported programmes in each of the four provinces.

References

1 UNAIDS. Country factsheets: South Africa. 2023. https://www.unaids.org/en/regionscountries/countries/southafrica (accessed Feb 15, 2024).
2 Artenie A, Stone J, Fraser H, et al. Incidence of HIV and hepatitis C virus among people who inject drugs, and associations with age and sex or gender: a global systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2023; **8:** 533–52.
3 Joshi K, Lessler J, Olawore O, et al. Declining HIV incidence in sub-Saharan Africa: a systematic review and meta-analysis of empiric data. *J Int AIDS Soc* 2021; **24:** e25818.
4 Scheibe A, Makapela D, Brown B, et al. HIV prevalence and risk among people who inject drugs in five South African cities. *Int J Drug Policy* 2016; **30:** 107–15.
5 Scheibe A, Young K, Moses L, et al. Understanding hepatitis B, hepatitis C and HIV among people who inject drugs in South Africa: findings from a three-city cross-sectional survey. *Harm Reduct J* 2019; **16:** 28.
6 Scheibe A, Young K, Versfeld A, et al. Hepatitis B, hepatitis C and HIV prevalence and related sexual and substance use risk practices among key populations who access HIV prevention, treatment and related services in South Africa: findings from a seven-city cross-sectional survey (2017). *BMC Infect Dis* 2020; **20:** 655.
7 Zanoni BC, Milford C, Sithole K, et al. High risk injection drug use and uptake of HIV prevention and treatment services among people who inject drugs in KwaZulu-Natal, South Africa. *PLoS One* 2023; **18:** e0281030.
8 Colledge-Frisby S, Ottaviano S, Webb P, et al. Global coverage of interventions to prevent and manage drug-related harms among people who inject drugs: a systematic review. *Lancet Glob Health* 2023; **11:** e673–83.
9 Marks M, Scheibe A, Shelly S. High retention in an opioid agonist therapy project in Durban, South Africa: the role of best practice and social cohesion. *Harm Reduct J* 2020; **17:** 25.
10 Scheibe A, Shelly S, Lambert A, et al. Using a programmatic mapping approach to plan for HIV prevention and harm reduction interventions for people who inject drugs in three South African cities. *Harm Reduct J* 2017; **14:** 35.
11 Harm Reduction International. Harm reduction: financing landscape analysis in South Africa. 2022. https://hri.global/wp-content/uploads/2023/04/SOUTH-AFRICA-DESIGN_FINAL.pdf (accessed April 5, 2024).
12 Scheibe A, Shelly S, Stowe M. Insights into the value of the market for cocaine, heroin and methamphetamine in South Africa. *J Illicit Econ Dev* 2024; **5:** 1–17.
13 Pebody R. What is the window period for HIV testing. 2021. https://www.aidsmap.com/about-hiv/what-window-period-hiv-testing (accessed Oct 5, 2023).
14 South African Department of Health. National HIV testing services. 2016. https://sahivsoc.org/Files/HTS%20Policy%20 28%20July%20final%20copy.pdf (accessed Dec 5, 2023).
15 Risher KA, Cori A, Reniers G, et al. Age patterns of HIV incidence in eastern and southern Africa: a modelling analysis of observational population-based cohort studies. *Lancet HIV* 2021; **8:** e429–39.
16 Jones HS, Hensen B, Musemburi S, et al. Temporal trends in, and risk factors for, HIV seroconversion among female sex workers accessing Zimbabwe's national sex worker programme, 2009–19: a retrospective cohort analysis of routinely collected HIV testing data. *Lancet HIV* 2023; **10:** e442–52.
17 McNaughton AL, Stone J, Oo KT, et al. Trends in HIV incidence following scale-up of harm reduction interventions among people who inject drugs in Kachin, Myanmar, 2008–2020: analysis of a retrospective cohort dataset. *Lancet Reg Health West Pac* 2023; **34:** 100718.
18 Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology* 2009; **20:** 488–95.
19 Lane T, Osmand T, Marr A, Struthers H, McIntyre JA, Shade SB. Brief Report: high HIV incidence in a South African community of men who have sex with men: results from the Mpumalanga Men's Study, 2012–2015. *J Acquir Immune Defic Syndr* 2016; **73:** 609–11.
20 Kassanjee R, Welte A, Otwombe K, et al. HIV incidence estimation among female sex workers in South Africa: a multiple methods analysis of cross-sectional survey data. *Lancet HIV* 2022; **9:** e781–90.

21 Naicker N, Kharsany ABM, Werner L, et al. Risk factors for HIV acquisition in high risk women in a generalised epidemic setting. *AIDS Behav* 2015; **19:** 1305–16.

22 Arum C, Fraser H, Artenie AA, et al. Homelessness, unstable housing, and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. *Lancet Public Health* 2021; **6:** e309–23.

23 Hajarizadeh B, Kairouz A, Ottaviano S, et al. Global, regional, and country-level coverage of testing and treatment for HIV and hepatitis C infection among people who inject drugs: a systematic review. *Lancet Glob Health* 2023; **11:** e1885–98.

24 Human Sciences Research Council. Summary sheet: the sixth South African national HIV prevalence, incidence, behaviour and communication survey. 2022. https://sahivsoc.org/Files/SABSSMVI-SUMMARY-SHEET-2023.pdf (accessed Aug 27, 2024).

25 Johnson LF, Dorrington RE. Modelling the impact of HIV in South Africa's provinces: 2023 update. 2023. https://www.spotlightnsp.co.za/wp-content/uploads/2023/05/ProvincialModel2023.pdf (accessed Sept 8, 2024).

26 Johnson LF, Dorrington RE, Moolla H. HIV epidemic drivers in South Africa: a model-based evaluation of factors accounting for inter-provincial differences in HIV prevalence and incidence trends. *South Afr J HIV Med* 2017; **18:** 695.

27 Kim H, Tanser F, Tomita A, Vandormael A, Cuadros DF. Beyond HIV prevalence: identifying people living with HIV within underserved areas in South Africa. *BMJ Glob Health* 2021; **6:** e004089.

28 Bell GJ, Ncayiyana J, Sholomon A, Goel V, Zuma K, Emch M. Race, place, and HIV: the legacies of apartheid and racist policy in South Africa. *Soc Sci Med* 2022; **296:** 114755.

29 Ugwu CLJ, Ncayiyana JR. Spatial disparities of HIV prevalence in South Africa. Do sociodemographic, behavioral, and biological factors explain this spatial variability? *Front Public Health* 2022; **10:** 994277.

30 Human Sciences Research Council. Survey reveals uneven progress in Eastern Cape's fight against HIV. 2024. https://hsrc.ac.za/wp-content/uploads/2024/08/15-08-2024-Press-Release-SABSSM-VI_EC-Provincial-findings_Final-002.pdf (accessed Aug 28, 2024).

31 Harm Reduction International. Barriers to harrm-reduction among women who use drugs: Experiences from Ethekweni (Durban), South Africa. 2020. https://www.hri.global/files/2020/06/10/Barriers_to_Harm_Reduction_for_Women_2.pdf (accessed Aug 27, 2024).

32 MacArthur GJ, Minozzi S, Martin N, et al. Opiate substitution treatment and HIV transmission in people who inject drugs: systematic review and meta-analysis. *BMJ* 2012; **345:** e5945.

33 WHO. People who inject drugs. https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/populations/people-who-inject-drugs (accessed Aug 29, 2024).