

Additional file 1. Supplementary methods and results

Reactive markers of HIV, hepatitis B, hepatitis C and syphilis among people who use drugs in Sofia, Bulgaria: a cross-sectional bio-behavioural survey

This document contains the causal diagram underlying covariate selection, the analyses of the rarer markers, the sensitivity and robustness analyses, and the model performance assessment.

S1. Causal structure and covariate selection

Covariates for the multivariable models were selected from the directed acyclic graph in Figure S1 rather than by stepwise or significance-driven screening, following current guidance on causal diagrams in observational epidemiology [1–3]. Minimal sufficient adjustment sets were derived with the `dagitty` package.

Edges were oriented by temporal order wherever the exposure is a lifetime measure. Because the injecting variable records whether a participant has *ever* injected, opioid agonist treatment can only be initiated after injecting has begun, and the graph carries `Injecting` → `OAT`. With the edge oriented this way, opioid agonist treatment is not part of any adjustment set.

On the assumed structure the minimal sufficient adjustment sets are:

- **Housing instability** → **reactivity**: {sex, education}, or equivalently {age, injecting, sex}
- **Injecting** → **reactivity**: {age, housing, sex}, or equivalently {age, education, sex}

The main models in the article include age, sex, education, housing and injecting. This set contains a sufficient adjustment set for each of the two exposures and no mediator, so the coefficient of each exposure is an adjusted association under the assumed structure; the coefficients of the other covariates are not interpreted as effects. Estimates from the minimal sets are given in Table S5.

Needle sharing and opioid agonist treatment lie on causal paths running from structural disadvantage to reactivity. They are mediators, not confounders, and conditioning on them would remove part of the association a harm reduction programme would seek to act upon. Both were excluded from all models.

The diagram is used to choose a defensible covariate set and to identify what must not be conditioned upon. It does not license a causal reading of the estimates, because the cross-sectional design cannot establish the temporal ordering of housing instability, injecting and seroconversion.

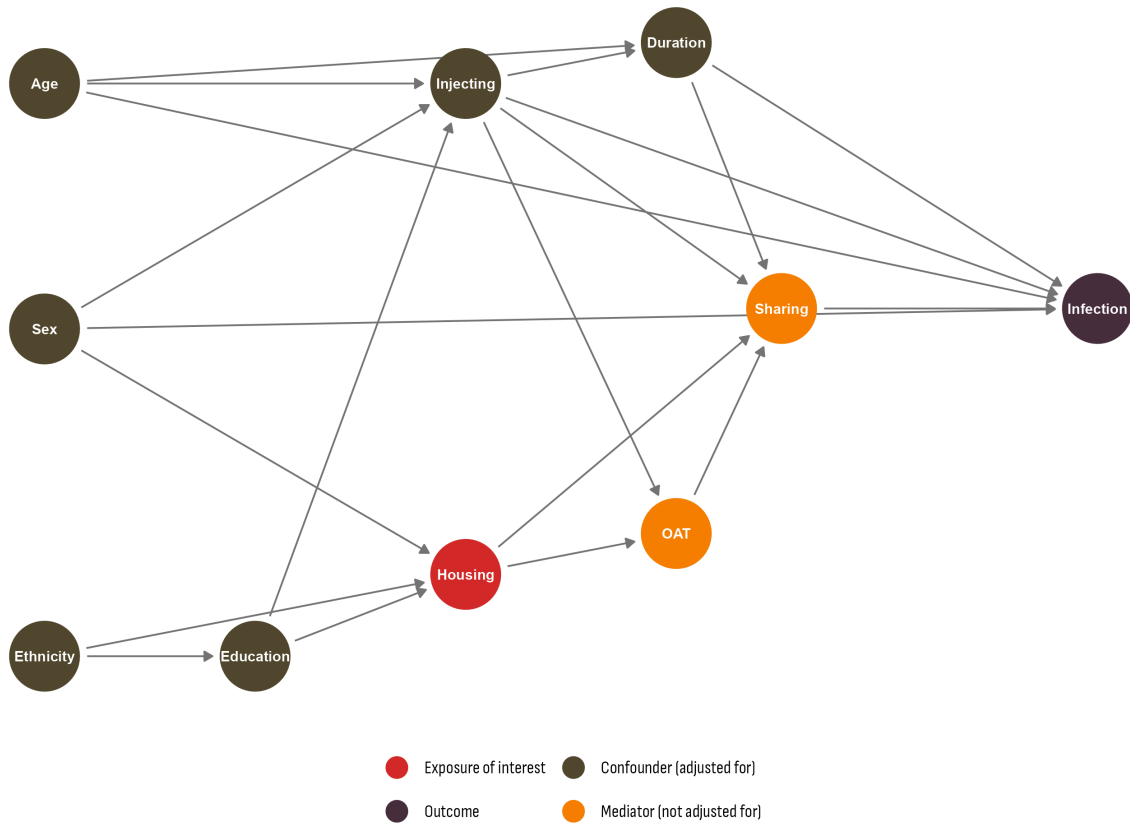


Figure S1: Assumed causal structure used to select the adjustment sets. Needle sharing and opioid agonist treatment lie on the path from housing instability to reactivity and are treated as mediators. Because the injecting variable is a lifetime measure, opioid agonist treatment is placed downstream of injecting.

S2. Missing data

Missing data were minimal for all model covariates: education was unrecorded for 11 participants (2.3%), homelessness in the past year for 3 (0.6%), and all other model variables were complete. Models were fitted on complete cases and the analytic denominator is stated for every model in the main text.

Injecting duration and needle sharing were asked only of participants reporting a history of injecting. These are structural skips, not missing data, and are denominated on the 304 participants who had ever injected. Access to sterile equipment was asked of all participants and was answered by 408. Table S1 distinguishes the two situations. The consequences of the complete-case restriction were tested by multiple imputation (Section S6).

Table S1: Missing data and skip-logic denominators. Variables asked only of participants reporting a history of injecting are structural skips, not missing data.

Variable	n miss- ing	% miss- ing	Note
HIV (anti-HIV) reactive	0	0	
HCV (anti-HCV) reactive	0	0	
HBV (HBsAg) reactive	0	0	
Syphilis (anti-TP) reactive	0	0	
Age (years)	0	0	
Sex	0	0	
Educational attainment	11	2.3	
Ethnicity	0	0	
No stable housing	0	0	

Variable	n	miss- ing	% miss- ing	Note
Homeless >1 month, past 12 months	3		0.6	
Ever injected drugs	0		0	
Frequency of drug use	5		1	
Ever treated for substance use	15		3.1	
Ever received OAT	0		0	
Condom at last intercourse	108		22.5	
Sexual intercourse, past 12 months	9		1.9	
Duration of injecting	176		36.7	asked only if ever injected (structural skip)
Shared needle or syringe	181		37.7	asked only if ever injected (structural skip)
Can obtain sterile equipment when needed	72		15	asked of all participants

S3. Co-occurrence of reactive markers

Because the four markers were measured in the same individuals, co-occurrence was assessed against the frequency expected under independence given the two marginal prevalences, rather than by simple tabulation. This distinguishes co-reactivity that merely reflects two common markers in one population from genuine clustering within individuals.

Only the HIV–HCV pairing departed appreciably from independence (53 observed against 38.8 expected; OR 4.38, 95% CI 2.00–10.95, $p < 0.001$), which is what a shared parenteral route predicts [4, 5]. HBsAg with HCV, treponemal antibody with HCV, and the remaining pairings were all indistinguishable from chance at this sample size (Figure S2; Table 4 of the main article).

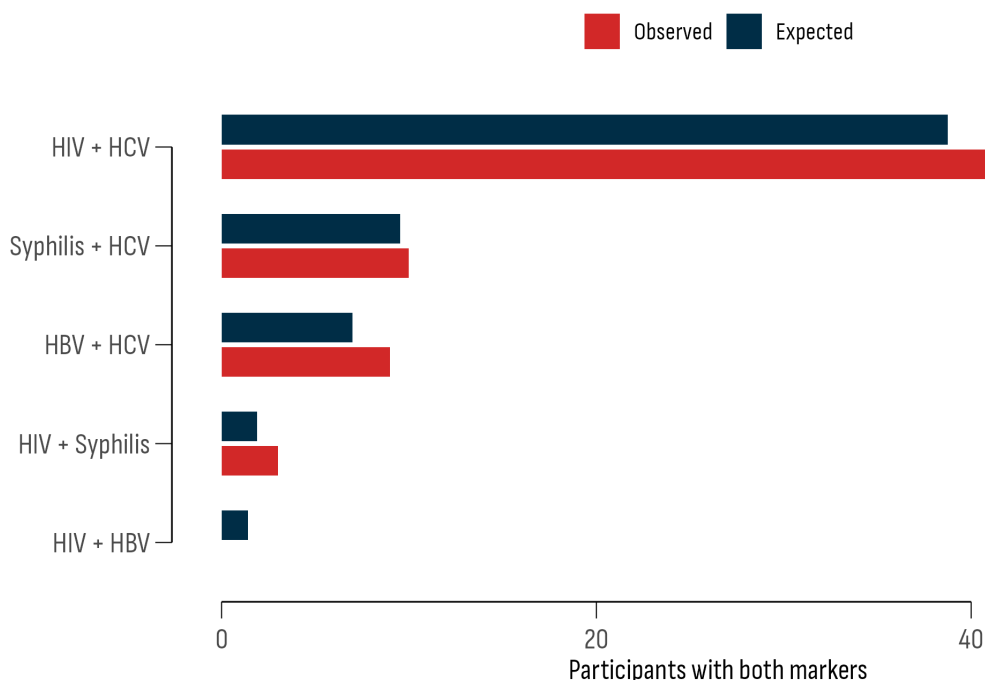


Figure S2: Observed co-occurrence of reactive markers against the count expected if the two markers were independent, given their marginal prevalences.

S4. Full characteristics by serostatus

Table S2 and Table S3 give the complete comparison of demographic, socioeconomic, drug use and behavioural characteristics by HIV and HCV serostatus respectively, including the substance use variables.

The substance use comparisons are unadjusted. They largely separate a long-standing, predominantly injecting opioid-using group (methadone, heroin, clonazepam) from a younger, largely non-injecting group using cannabis and synthetic cannabinoids. Because injecting is so strongly associated with both markers, we read these differences as markers of which drug scene a participant belongs to rather than as independent correlates of reactivity. Individual substances were not modelled, and the inverse association of cannabis with reactivity should not be read as a finding about cannabis.

Table S2: Characteristics of participants by HIV serostatus.

Characteristic	N	HIV non-reactive	HIV reactive	p-value
Age (years)	480	40.00 (32.00, 44.00)	40.00 (34.00, 43.00)	>0.9
Age group	480			0.001
<20		5 (1.2%)	0 (0%)	
20–29		85 (20%)	3 (4.9%)	
30–39		106 (25%)	26 (43%)	
40–49		191 (46%)	31 (51%)	
50+		32 (7.6%)	1 (1.6%)	
Sex	480			0.3
Female		92 (22%)	10 (16%)	
Male		327 (78%)	51 (84%)	
Educational attainment	469			0.14
None		31 (7.6%)	4 (6.8%)	
Primary		56 (14%)	15 (25%)	
Lower secondary		133 (32%)	21 (36%)	
Upper secondary		172 (42%)	18 (31%)	
Higher		18 (4.4%)	1 (1.7%)	
Unknown		9	2	
Ethnicity	480			0.5
Bulgarian		289 (69%)	44 (72%)	
Roma		91 (22%)	15 (25%)	
Turkish		11 (2.6%)	1 (1.6%)	
Other		28 (6.7%)	1 (1.6%)	
No stable housing	480	67 (16%)	17 (28%)	0.023
Homeless >1 month, past 12 months	477	121 (29%)	21 (34%)	0.4
Unknown		3	0	
Ever injected drugs	480	252 (60%)	52 (85%)	<0.001
Duration of injecting	304			0.2
<1 year		16 (6.3%)	0 (0%)	
1–5 years		17 (6.7%)	3 (5.8%)	
>5 years		219 (87%)	49 (94%)	
Unknown		167	9	
Frequency of drug use	475			>0.9
Less than weekly		24 (5.8%)	4 (6.6%)	

Characteristic	N	HIV non-reactive	HIV reactive	p-value
Weekly		68 (16%)	9 (15%)	
Daily or more		322 (78%)	48 (79%)	
Unknown		5	0	
Shared needle or syringe	299	24 (9.7%)	14 (27%)	<0.001
Unknown		172	9	
Can obtain sterile equipment when needed	408	326 (93%)	59 (100%)	0.059
Unknown		70	2	
Ever treated for substance use	465	234 (58%)	43 (70%)	0.062
Unknown		15	0	
Ever received OAT	480	192 (46%)	36 (59%)	0.054
Sexual intercourse, past 12 months	471	336 (82%)	37 (62%)	<0.001
Unknown		8	1	
Condom at last intercourse	372	103 (31%)	21 (58%)	<0.001
Unknown		83	25	
Heroin	480	108 (26%)	15 (25%)	0.8
Methadone	480	212 (51%)	45 (74%)	<0.001
Cocaine	480	48 (11%)	5 (8.2%)	0.4
Methamphetamine	480	138 (33%)	16 (26%)	0.3
Cannabis	480	96 (23%)	3 (4.9%)	0.001
Synthetic cannabinoids	480	94 (22%)	8 (13%)	0.10
Clonazepam	480	92 (22%)	18 (30%)	0.2

Table S3: Characteristics of participants by HCV serostatus.

Characteristic	N	HCV non-reactive	HCV reactive	p-value
Age (years)	480	33.00 (26.00, 40.00)	42.00 (38.00, 45.00)	<0.001
Age group	480			<0.001
<20		5 (2.9%)	0 (0%)	
20–29		66 (38%)	22 (7.2%)	
30–39		54 (31%)	78 (26%)	
40–49		40 (23%)	182 (60%)	
50+		10 (5.7%)	23 (7.5%)	
Sex	480			0.003
Female		50 (29%)	52 (17%)	
Male		125 (71%)	253 (83%)	
Educational attainment	469			0.002
None		14 (8.3%)	21 (7.0%)	
Primary		36 (21%)	35 (12%)	
Lower secondary		63 (38%)	91 (30%)	

Characteristic	N	HCV non-reactive	HCV reactive	p-value
Upper secondary		50 (30%)	140 (47%)	
Higher		5 (3.0%)	14 (4.7%)	
Unknown		7	4	
Ethnicity	480			<0.001
Bulgarian		101 (58%)	232 (76%)	
Roma		47 (27%)	59 (19%)	
Turkish		8 (4.6%)	4 (1.3%)	
Other		19 (11%)	10 (3.3%)	
No stable housing	480	43 (25%)	41 (13%)	0.002
Homeless >1 month, past 12 months	477	67 (39%)	75 (25%)	0.001
Unknown		2	1	
Ever injected drugs	480	33 (19%)	271 (89%)	<0.001
Duration of injecting	304			0.007
<1 year		6 (18%)	10 (3.7%)	
1–5 years		2 (6.1%)	18 (6.6%)	
>5 years		25 (76%)	243 (90%)	
Unknown		142	34	
Frequency of drug use	475			0.031
Less than weekly		10 (5.8%)	18 (5.9%)	
Weekly		38 (22%)	39 (13%)	
Daily or more		124 (72%)	246 (81%)	
Unknown		3	2	
Shared needle or syringe	299	1 (3.0%)	37 (14%)	0.10
Unknown		142	39	
Can obtain sterile equipment when needed	408	104 (87%)	281 (98%)	<0.001
Unknown		55	17	
Ever treated for substance use	465	44 (27%)	233 (78%)	<0.001
Unknown		10	5	
Ever received OAT	480	36 (21%)	192 (63%)	<0.001
Sexual intercourse, past 12 months	471	146 (85%)	227 (76%)	0.013
Unknown		4	5	
Condom at last intercourse	372	45 (31%)	79 (35%)	0.4
Unknown		29	79	
Heroin	480	35 (20%)	88 (29%)	0.032
Methadone	480	42 (24%)	215 (70%)	<0.001
Cocaine	480	6 (3.4%)	47 (15%)	<0.001
Methamphetamine	480	56 (32%)	98 (32%)	>0.9
Cannabis	480	53 (30%)	46 (15%)	<0.001

Characteristic	N	HCV non-reactive	HCV reactive	p-value
Synthetic cannabinoids	480	65 (37%)	37 (12%)	<0.001
Clonazepam	480	21 (12%)	89 (29%)	<0.001

S5. Hepatitis B surface antigen and treponemal antibody

With eleven HBsAg-reactive and fifteen treponemal-antibody-reactive participants, ordinary maximum likelihood is unreliable and these outcomes were modelled with Firth's penalised likelihood, with age, sex, housing and injecting as covariates (Table S4). Education was omitted because of sparse cells.

No variable was associated with HBsAg carriage, and all confidence intervals were wide enough to be uninformative. For treponemal antibody the only association was with sex, and in the opposite direction to the parenteral markers: men had lower odds of reactivity than women (OR 0.29, 95% CI 0.11–0.77, $p = 0.013$), while injecting was unrelated (OR 1.25, 0.41–3.81). This is consistent with the only dedicated meta-analysis of sexually transmitted infection among people who inject drugs, in which active syphilis was substantially more prevalent among women [6].

Table S4: Firth penalised logistic regression for HBsAg and treponemal antibody reactivity.

Outcome	Variable	OR (95% CI)	p
HBsAg	Age, per 10 years	1.50 (0.74–3.08)	0.264
HBsAg	Male sex	6.11 (0.44–83.87)	0.176
HBsAg	No stable housing	0.24 (0.02–3.47)	0.297
HBsAg	Ever injected drugs	0.74 (0.20–2.74)	0.654
Treponemal Ab	Age, per 10 years	0.71 (0.38–1.31)	0.271
Treponemal Ab	Male sex	0.29 (0.11–0.77)	0.013
Treponemal Ab	No stable housing	1.11 (0.34–3.68)	0.864
Treponemal Ab	Ever injected drugs	1.25 (0.41–3.81)	0.688

S6. Alternative specifications, interaction and sensitivity analyses

Alternative model specifications

Table S5 reports the DAG-implied minimal adjustment sets for housing instability and for injecting alongside the specification used in the main text. The housing–HIV association is stable across specifications (adjusted prevalence ratio 1.77–1.97). The housing–HCV association strengthens somewhat in the DAG-implied specification (0.76, 95% CI 0.61–0.95) but is shown below to reflect confounding by injecting history. The injecting estimates are almost identical to those of the main model (HIV 4.22 vs 4.29; HCV 4.18 vs 4.13).

Table S5: Alternative model specifications: DAG-implied minimal adjustment sets for housing instability and for injecting.

Outcome	Specification	Variable	aPR (95% CI)	p
HIV	DAG-implied, housing	Male sex	1.44 (0.76–2.72)	0.266
HIV	DAG-implied, housing	Lower secondary education	0.73 (0.42–1.28)	0.271
HIV	DAG-implied, housing	Upper secondary or higher	0.52 (0.29–0.95)	0.033
HIV	DAG-implied, housing	No stable housing	1.77 (1.07–2.94)	0.027
HIV	DAG-implied, injecting	Age, per 10 years	0.81 (0.61–1.07)	0.136
HIV	DAG-implied, injecting	Male sex	1.27 (0.67–2.40)	0.468
HIV	DAG-implied, injecting	No stable housing	1.97 (1.18–3.29)	0.009
HIV	DAG-implied, injecting	Ever injected drugs	4.22 (1.93–9.23)	<0.001
HCV	DAG-implied, housing	Male sex	1.25 (1.03–1.51)	0.025

Outcome	Specification	Variable	aPR (95% CI)	p
HCV	DAG-implied, housing	Lower secondary education	1.09 (0.88–1.36)	0.435
HCV	DAG-implied, housing	Upper secondary or higher	1.34 (1.10–1.63)	0.003
HCV	DAG-implied, housing	No stable housing	0.76 (0.61–0.95)	0.018
HCV	DAG-implied, injecting	Age, per 10 years	1.10 (1.02–1.20)	0.018
HCV	DAG-implied, injecting	Male sex	1.10 (0.94–1.27)	0.227
HCV	DAG-implied, injecting	No stable housing	0.88 (0.77–1.02)	0.087
HCV	DAG-implied, injecting	Ever injected drugs	4.18 (3.05–5.74)	<0.001

Additive interaction

Departure from additivity for injecting and unstable housing on HIV reactivity was estimated on the risk scale from a modified Poisson model containing ever injecting, unstable housing, their product, age and sex, with confidence intervals from 2000 case-resampling bootstrap replicates. These measures are defined on the risk scale. Computing them from a logistic model, whose exponentiated coefficients are odds ratios, materially overstates the departure from additivity when the outcome is not rare, as here [7].

Relative to participants who neither injected nor lacked stable housing, the prevalence ratio was 3.94 for injecting alone, 1.68 for unstable housing alone and 8.03 for both. The relative excess risk due to interaction was 3.41 (95% CI –1.01 to 13.94), the attributable proportion 0.42 (–0.16 to 0.74) and the synergy index 1.94 (0.79 to 7.55). All three intervals include the null and we report no evidence of departure from additivity. With 14 HIV-reactive participants in the doubly exposed stratum, the analysis has little power to distinguish synergy from additivity.

Table S6: Additive interaction between ever injecting and unstable housing on HIV reactivity, estimated on the risk scale. Prevalence ratios (PR) are relative to participants who had never injected and were stably housed. ^a The bootstrap lower limit is unstable because few participants who had never injected were HIV reactive.

Measure	Estimate (95% CI)
PR, ever injected and stably housed	3.94 (1.73 to 16.91)
PR, never injected and unstably housed ^a	1.68 (<0.01 to 7.32)
PR, ever injected and unstably housed	8.03 (3.38 to 31.73)
Relative excess risk due to interaction	3.41 (–1.01 to 13.94)
Attributable proportion	0.42 (–0.16 to 0.74)
Synergy index	1.94 (0.79 to 7.55)

E-values

E-values express the minimum association an unmeasured confounder would need with both exposure and outcome, conditional on the measured covariates, to reduce an observed association to the null [8]. They are reported as a descriptive property of the observed associations, not as evidence of causation, a distinction whose conflation has attracted justified criticism [9].

The injecting associations are not readily explained away: a confounder would have to be associated with both injecting and reactivity by a risk ratio above 7.7 to account for either. The housing–HIV association is more fragile, and a moderately strong unmeasured confounder could account for it (Table S7). Where the confidence interval already includes the null, the E-value for the confidence limit is 1 by definition.

Table S7: E-values for the principal adjusted associations. An E-value is the minimum association, on the risk-ratio scale, that an unmeasured confounder would need with both exposure and outcome to reduce the observed association to the null.

Out-come	Association	aPR (95% CI)	E-value, point estimate	E-value, CI limit
HIV	Ever injected drugs	4.29 (2.01–9.16)	8.05	3.43

Out- come	Association	aPR (95% CI)	E-value, point estimate	E-value, CI limit
HIV	No stable housing	1.88 (1.14–3.11)	3.17	1.54
HIV	Male sex	1.32 (0.71–2.45)	1.96	1.00
HIV	Age, per 10 years	0.85 (0.64–1.13)	1.62	1.00
HCV	Ever injected drugs	4.13 (2.99–5.70)	7.73	5.43
HCV	Age, per 10 years	1.10 (1.01–1.20)	1.43	1.12
HCV	Male sex	1.08 (0.94–1.26)	1.39	1.00
HCV	No stable housing	0.88 (0.77–1.02)	1.52	1.00

Sensitivity analyses

Four sensitivity analyses were conducted. Two of them qualify the main findings materially.

Alternative housing exposure. Substituting homelessness of more than a month in the past 12 months for current absence of stable accommodation attenuated the HIV association to the null (aPR 1.25, 95% CI 0.77–2.02, $p = 0.375$). The housing–HIV association therefore attaches to *current* housing instability, not to any experience of homelessness during the preceding year, and the main text describes it in those terms.

Restriction to participants who had ever injected. Restricting to the 304 participants who had ever injected removed the inverse HCV–housing association entirely (aPR 1.02, 95% CI 0.92–1.13, $p = 0.758$) while leaving the HIV association intact (aPR 1.90, 1.08–3.32, $p = 0.025$). This confirms that the apparently protective association between housing instability and HCV in the full sample is confounding by injecting status: housed participants are older, longer-injecting and near-uniformly anti-HCV reactive.

Log-binomial regression. Log-binomial models failed to converge for either outcome. This is expected with common outcomes and several covariates, and is the reason modified Poisson was chosen as the primary approach [10, 11].

Multiple imputation of education. Twenty imputations by chained equations, pooled by Rubin’s rules over robust variances, produced estimates indistinguishable from the complete-case analysis (HIV: housing 1.84 vs 1.88, injecting 4.56 vs 4.29; HCV: age 1.10 vs 1.10, injecting 4.17 vs 4.13). The complete-case restriction is not consequential.

Table S8: Sensitivity analyses. Past-year homelessness: homelessness of more than a month in the past 12 months in place of current unstable housing. Ever injected only: restricted to participants who had ever injected. Log-binomial: log-binomial regression. Imputed education: multiple imputation of missing education (20 imputations).

Analysis	Out- come	Variable	aPR (95% CI)	p
Past-year homelessness	HIV	Age, per 10 years	0.82 (0.62–1.10)	0.185
Past-year homelessness	HIV	Male sex	1.30 (0.70–2.43)	0.409
Past-year homelessness	HIV	Lower secondary education	0.68 (0.39–1.17)	0.162
Past-year homelessness	HIV	Upper secondary or higher	0.42 (0.23–0.75)	0.003
Past-year homelessness	HIV	Homeless >1 month	1.25 (0.77–2.02)	0.375
Past-year homelessness	HIV	Ever injected drugs	4.26 (1.96–9.27)	<0.001
Past-year homelessness	HCV	Age, per 10 years	1.10 (1.01–1.20)	0.023
Past-year homelessness	HCV	Male sex	1.08 (0.93–1.25)	0.312
Past-year homelessness	HCV	Lower secondary education	1.01 (0.86–1.18)	0.948
Past-year homelessness	HCV	Upper secondary or higher	1.03 (0.89–1.19)	0.700

Analysis	Out- come	Variable	aPR (95% CI)	p
Past-year homelessness	HCV	Homeless >1 month	0.91 (0.81–1.02)	0.092
Past-year homelessness	HCV	Ever injected drugs	4.07 (2.95–5.61)	<0.001
Ever injected only	HIV	Age, per 10 years	0.73 (0.52–1.03)	0.077
Ever injected only	HIV	Male sex	1.34 (0.68–2.67)	0.400
Ever injected only	HIV	Lower secondary educa- tion	0.69 (0.37–1.27)	0.236
Ever injected only	HIV	Upper secondary or higher	0.52 (0.28–0.98)	0.042
Ever injected only	HIV	No stable housing	1.90 (1.08–3.32)	0.025
Ever injected only	HCV	Age, per 10 years	1.05 (0.99–1.12)	0.093
Ever injected only	HCV	Male sex	1.08 (0.95–1.22)	0.246
Ever injected only	HCV	Lower secondary educa- tion	1.04 (0.92–1.18)	0.542
Ever injected only	HCV	Upper secondary or higher	1.04 (0.93–1.17)	0.500
Ever injected only	HCV	No stable housing	1.02 (0.92–1.13)	0.758
Log-binomial	HIV	Did not converge	–	–
Log-binomial	HCV	Did not converge	–	–
Imputed education	HIV	Age, per 10 years	0.84 (0.64–1.11)	0.231
Imputed education	HIV	Male sex	1.35 (0.73–2.51)	0.343
Imputed education	HIV	Lower secondary educa- tion	0.67 (0.39–1.16)	0.152
Imputed education	HIV	Upper secondary or higher	0.43 (0.24–0.76)	0.004
Imputed education	HIV	No stable housing	1.84 (1.12–3.02)	0.016
Imputed education	HIV	Ever injected drugs	4.56 (2.15–9.69)	<0.001
Imputed education	HCV	Age, per 10 years	1.10 (1.01–1.20)	0.022
Imputed education	HCV	Male sex	1.10 (0.94–1.27)	0.229
Imputed education	HCV	Lower secondary educa- tion	1.01 (0.86–1.18)	0.920
Imputed education	HCV	Upper secondary or higher	1.04 (0.89–1.20)	0.646
Imputed education	HCV	No stable housing	0.89 (0.77–1.02)	0.095
Imputed education	HCV	Ever injected drugs	4.17 (3.03–5.72)	<0.001

S7. Model discrimination and calibration

Discrimination and calibration were computed from the logistic versions of the main models and are reported to describe how much of the variation in reactivity the measured variables account for. Neither model is proposed as a screening instrument, and neither should be used as one.

The multivariable HCV model discriminated well, with an area under the receiver operating characteristic curve of 0.877 (95% CI 0.841–0.914), a Brier score of 0.114 and no evidence of miscalibration across deciles of predicted risk (Hosmer-

Lemeshow $\chi^2 = 6.74$, $df = 8$, $p = 0.565$). Observed and predicted risks track closely across the full range (Figure S3). The HIV model discriminated considerably less well: 0.714 (0.645–0.784), Brier 0.102, Hosmer-Lemeshow $p = 0.411$.

Injecting history, age, sex, education and housing account for most of the variation in HCV reactivity, as expected of a marker acquired almost entirely parenterally and approaching saturation with cumulative exposure. The same variables account for much less of the variation in HIV reactivity, implying that HIV in this population is structured by determinants this survey did not measure, such as injecting network position, incarceration history, and the specific circumstances in which sharing occurs [12, 13].

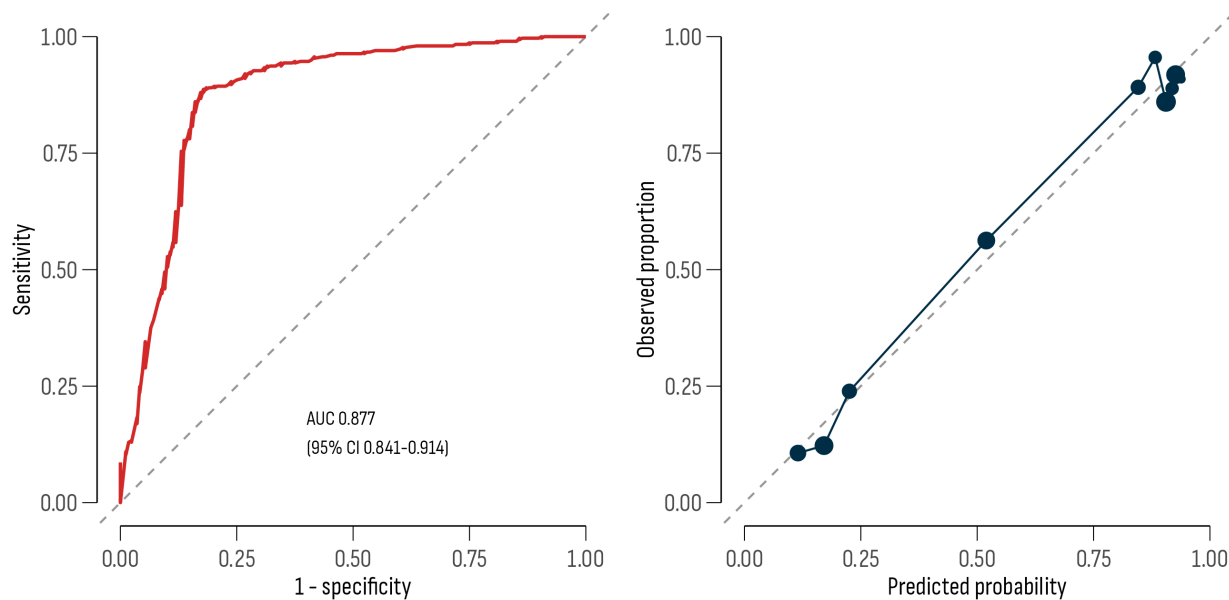


Figure S3: Discrimination (left) and calibration (right) of the multivariable HCV model. Calibration points are deciles of predicted risk, sized by the number of participants; the dashed line is perfect calibration.

S8. Software

All estimation was performed with the following software (Table S9). Robust variance, Firth penalised likelihood, ROC analysis and summary tables were computed through `kkstatfun` 0.2.7 and its dependencies, including `sandwich`, `pROC` and `gtsummary`, whose individual versions were not recorded at run time. Every derived variable was reconciled against the counts in the source data before analysis.

Table S9: Software used for the analysis.

Component	Version
R	R version 4.5.3 (2026-03-11 ucrt)
Platform	x86_64-w64-mingw32/x64
kkstatfun	0.2.7
tidyverse	2.0.0
dagitty	0.3.4
mice	3.19.0
Analysis run	19 July 2026

References

Bibliography

1. Digitale JC, Martin JN, Glymour MM. Tutorial on directed acyclic graphs. *Journal of clinical epidemiology*. 2022;142:264–7. <https://doi.org/10.1016/j.jclinepi.2021.08.001>.

2. Etminan M, Collins GS, Mansournia MA. Using causal diagrams to improve the design and interpretation of medical research. *Chest*. 2020;158:S21–8. <https://doi.org/10.1016/j.chest.2020.03.011>.
3. Yusuf E, Martinuka O, Rosendaal FR. Potential biases in observational infectious disease studies: examples using directed acyclic graphs. *Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*. 2026;32:1603–10. <https://doi.org/10.1016/j.cmi.2026.05.027>.
4. Rockstroh JK, Spengler U. HIV and hepatitis C virus co-infection. *The Lancet Infectious diseases*. 2004;4:437–44. [https://doi.org/10.1016/S1473-3099\(04\)01059-X](https://doi.org/10.1016/S1473-3099(04)01059-X).
5. Chapin-Bardales J, Asher A, Broz D, Teshale E, Mixson-Hayden T, Poe A, et al. Hepatitis C virus infection and co-infection with HIV among persons who inject drugs in 10 U.S. cities-National HIV Behavioral Surveillance, 2018. *The International journal on drug policy*. 2025;144:104387. <https://doi.org/10.1016/j.drugpo.2024.104387>.
6. Price O, Webb P, Grebely J, Peacock A, Medland N, Read P, et al. Sexually transmitted infection prevalence and testing coverage among people who inject drugs: A systematic review. *Drug and alcohol dependence*. 2025;273:112732. <https://doi.org/10.1016/j.drugalcdep.2025.112732>.
7. Mutsert R de, Jager KJ, Zoccali C, Dekker FW. The effect of joint exposures: examining the presence of interaction. *Kidney international*. 2009;75:677–81. <https://doi.org/10.1038/ki.2008.645>.
8. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Annals of internal medicine*. 2017;167:268–74. <https://doi.org/10.7326/M16-2607>.
9. Ioannidis JPA, Tan YJ, Blum MR. Limitations and misinterpretations of E-values for sensitivity analyses of observational studies. *Annals of internal medicine*. 2019;170:108–11. <https://doi.org/10.7326/M18-2159>.
10. Talbot D, Mésidor M, Chiu Y, Simard M, Sirois C. An alternative perspective on the robust Poisson method for estimating risk or prevalence ratios. *Epidemiology (Cambridge, Mass)*. 2023;34:1–7. <https://doi.org/10.1097/EDE.0000000000001544>.
11. Sawada K, Hagiwara Y, Matsuyama Y. Choosing between modified Poisson and log-binomial regression: evidence for the superiority of modified Poisson regression under heterogeneous risk ratios. *American journal of epidemiology*. 2025;kwaf232. <https://doi.org/10.1093/aje/kwaf232>.
12. Stone J, Fraser H, Lim AG, Walker JG, Ward Z, MacGregor L, et al. Incarceration history and risk of HIV and hepatitis C virus acquisition among people who inject drugs: a systematic review and meta-analysis. *The Lancet Infectious diseases*. 2018;18:1397–409. [https://doi.org/10.1016/S1473-3099\(18\)30469-9](https://doi.org/10.1016/S1473-3099(18)30469-9).
13. Roussos S, Paraskevis D, Psychogiou M, Kostaki EG, Flountzi E, Angelopoulos T, et al. Ongoing HIV transmission following a large outbreak among people who inject drugs in Athens, Greece (2014-20). *Addiction (Abingdon, England)*. 2022;117:1670–82. <https://doi.org/10.1111/add.15812>.