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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Sacks-Davis R, van Santen DK, Boyd A, et al. Changes in incidence of hepatitis C virus reinfection and access to direct-acting antiviral therapies in people with HIV from six countries, 2010–19: an analysis of data from a consortium of prospective cohort studies. *Lancet HIV* 2024; published online Jan 12. https://doi.org/10.1016/S2352-3018(23)00267-9.

InCHEHC HCV reinfection supplementary material

Contents

1. Detailed methods

Primary HCV infection eligibility, case definition and follow-up

Primary HCV infection was measured for the purpose of calculating combined HCV incidence (defined as primary and reinfection incidence, including first and subsequent reinfections). Individuals with at least one HCV antibody negative test and a subsequent HCV test were included in the analysis of primary HCV infection. Primary HCV infection was defined as a positive antibody or RNA test result after the inclusion date. Estimated HCV primary infection date was the midpoint date between the last HCV antibody negative test date and the first HCV positive test. Individuals were considered be at risk for HCV infection from their first HCV antibody negative test until estimated infection date or the last HCV antibody negative test date. Follow up began at January 1, 2010, if previously antibody negative, or first negative antibody test after this date. Follow-up ended at the estimated primary HCV infection date or the last HCV antibody negative test during the study period. A subset of six cohorts from five countries were included in this analysis because they had HCV primary infection data (ACCESS, AQUITAINE, ATHENA, CoRIS, SAIDCC and SHCS).[1]

Subsequent HCV reinfection eligibility, case definition and follow-up

Multiple HCV reinfections per person were included in the analysis of combined HCV incidence (primary and reinfection incidence, including first and subsequent reinfections). Individuals who were reinfected once during the observation period were censored at the first reinfection event, but were eligible to re-enter the study if there was evidence of a subsequent treatment or spontaneous clearance event after the first reinfection, with at least one HCV RNA test after clearance enabling measurement of subsequent reinfection. Treatment clearance was sustained virological response (SVR), defined as a negative HCV RNA result at least 12 weeks after DAA or combined DAA and PEG-interferon treatment or 24 weeks after (PEG-) interferon treatment. Spontaneous clearance was defined as two consecutive undetectable HCV RNA tests, at least 28 days apart, following HCV infection in participants without a recorded HCV treatment.

We defined subsequent HCV reinfection as an RNA positive test following spontaneous clearance or SVR after the previous reinfection. We defined HCV RNA status (positive vs negative) based on a qualitative RNA or antigen test, or if there was no qualitative result available, an RNA quantitative test result. Quantitative RNA test results were classified as positive if the result was greater than or equal to the lower limit of detection, or 15 copies/mL if the lower limit of detection was unknown.

The estimated date of reinfection was the midpoint between the first HCV RNA positive test following spontaneous clearance or SVR, indicating reinfection, and the previous HCV RNA negative test.

Detailed methods: regression model for the change in slope of HCV reinfection incidence

We assessed whether the rate of change of HCV reinfection incidence (slope) differed by DAA access period using a Poisson regression model with a random intercept for each country. For this analysis, follow-up time was split at the calendar month level so that each record only spanned one DAA policy period, each of which was assumed to start on the first day of a calendar month. Time in months was included as a continuous variable and modelled as a linear spline with two knots at country-specific DAA access change-points. In this model, incidence was assumed to change by a fixed percentage each year, while allowing the slope to differ during each DAA period. The slope in each DAA period was common across countries but the calendar timing of the DAA periods varied between countries, depending on the country-specific timing of policy changes. Confidence intervals at the 95% level were calculated using an empirical bootstrap with 200 samples.

Detailed methods: regression equations for each model:

1. Average incidence per period model:

A Poisson regression model was used to estimate the average first HCV reinfection incidence in each DAA period for a given country. The model was implemented as a generalized linear model with a Poisson family and a *log* link. In the following regression equation, i represents a data record for a participant in country, j. The individual-level data are split by DAA period so that each record represents a period of time that is within a single participant and DAA-period. $I(Period = limited\ DAA\ access)_{i,j}$ is an indicator variable that specifies whether record i is in the limited DAA access period in country j. Similarly, $I(Period = broad\ DAA\ access)_{i,j}$ is an indicator variable that specifies whether record i is in the broad DAA access period in country j. The reference category is the pre-DAA period. $FollowUp_{i,j}$ represents the duration of follow-up for that data record and $Reinfection_{i,j}$ represents whether a first reinfection was observed in that follow-up period. β_0 represents the overall intercept, and e^{β_0} is the average HCV incidence in January 2010. $Country_j$ is the country-level random intercept, and $e^{\beta_0+\mu_j}$ is the average HCV incidence in January 2010 in country, j. β_1 and β_2 are the regression coefficients for the DAA period variables, e^{β_1} is the incidence rate ratio for the limited access period compared to the pre-DAA period, and e^{β_2} is the incidence rate ratio for the broad access period compared to the pre-DAA period. The term

$offset[\log(FollowUp_{i,j})]$ is the offset, which is constrained at 1 and facilitates prediction of incidence using a Poisson regression model.

$$\log(Reinfection_{i,j}) = \beta_0 + Country_j + \beta_1 \times I(Period = limited\ DAA\ access)_{i,j} + \beta_2 \times I(Period = broad\ DAA\ access)_{i,j} + offset[\log(FollowUp_{i,j})]$$

This model is equivalent to a piecewise exponential survival model, where the time scale is divided into intervals, in this case DAA access periods, and the hazard function is assumed to be constant within each interval. As described by Austin, a piecewise exponential model can be fit using a generalized linear model with a Poisson family and log link using an offset, which has the advantage that a random effect can be used to account for clustering:

Austin, P.C. (2017). A Tutorial on Multilevel Survival Analysis: Methods, Models and Applications. International Statistical Review. 85 (2): 185-203. doi:10.1111/insr.12214

2. Change in slope model:

A change in slope model was used to estimate the change in slope in first HCV reinfection incidence associated with changes in DAA period. In the following regression equation, *i* represents a data record for a participant in country, *j*. The data are split by calendar month so that each record represents a period of time that is within a single participant and calendar month. Each calendar month is nested in a single DAA-period by definition because the start of each DAA-period, within a country, was defined as the first day of the calendar month in which they occurred. Time in years was modelled as a linear spline with two knots at country-specific DAA access change-points. This was achieved using three time variables to model the time in each of the three DAA access periods. For records occurring in the pre-DAA period, $Time1_{i,j}$ was the time in years since January 2010 at the end of follow-up for record *i* in country *j*. To ensure that the incidence rate at the start of the limited DAA access period was equal to the incidence rate at the end of the pre-DAA access period, for records occurring during limited or broad DAA access, $Time1_{i,j}$ was the time in years since January 2010 at the start of the limited DAA access period. For records occurring during the limited DAA access period, $Time2_{i,j}$ was the time in years since the start of the limited access period at the end of follow-up for record *i* in country *j*. For records occurring in the pre-DAA access period, $Time2_{i,j}$ was 0. For records occurring in the broad DAA access period, $Time2_{i,j}$ was the time in

years from the start of the limited DAA access period to the start of the broad DAA access period. $Time3_{i,j}$ was the time in years since the start of the broad access period at the end of follow-up for record *i* in country *j*. If the end of follow-up for record *i* in country *j* is prior to the beginning of broad access in country *j*, then $Time3_{i,j}$ was equal to 0. $FollowUp_{i,j}$ represents the duration of follow-up for that data record and $Reinfection_{i,j}$ represents whether a first reinfection was observed in that follow-up period. β_0 represents the overall intercept, and e^{β_0} is the overall average HCV incidence in January 2010 across all countries. $Country_j$ is the country-level random intercept, and $e^{\beta_0 + Country_j}$ is the average HCV incidence in January 2010 in country, j. β_1 represents the slope in the pre-DAA period, β_2 represents the slope in the limited DAA-access period, and β_3 represents the slope in the broad DAA -access period. The term $offset[\log(FollowUp_{i,j})]$ is the offset, which is constrained at 1 and facilitates prediction of incidence using a Poisson regression model.

$$\log(Reinfection_{i,j}) = \beta_0 + Country_j + \beta_1 \times Time1_{i,j} + \beta_2 \times Time2_{i,j} + \beta_3 \times Time3_{i,j} + offset[\log(FollowUp_{i,j})]$$

Effectively, this model is fitting a linear spline for time with knots at the boundaries between DAA periods. The knot placement varies between countries because the timing of changes to DAA access vary between countries. The changes in slope in the limited and broad DAA periods compared to the pre-DAA period were calculated by taking the difference between β_1 and β_2 and β_3, respectively.

3. <u>Interrupted time series model (Sensitivity Analysis 1):</u>

In addition to the two models included in the primary analysis, we also considered an interrupted time series model as a sensitivity analysis. In the following regression equation, *i* represents a data record for a participant in country, *j*. Similar to the data set up for the change in slope model, the data are split by calendar month so that each record represents a period of time that is within a single participant and calendar month. Each calendar month is nested in a single DAA-period by definition because start of each DAA-periods within a country were defined as the first day of the calendar month in which they occurred. Similar to the average incidence per period model, $I(Period = limited\ DAA\ access)_{i,j}$ is an indicator variable that specifies whether record *i* is in the limited DAA access period in country *j* and $I(Period = broad\ DAA\ access)_{i,j}$ is an indicator variable that specifies whether record *i* is in the broad DAA access period in country *j*. Similar to the change in slope model, $Time1_{i,j}$ was the time in years since January 2010 at the end of follow-up for record *i* in

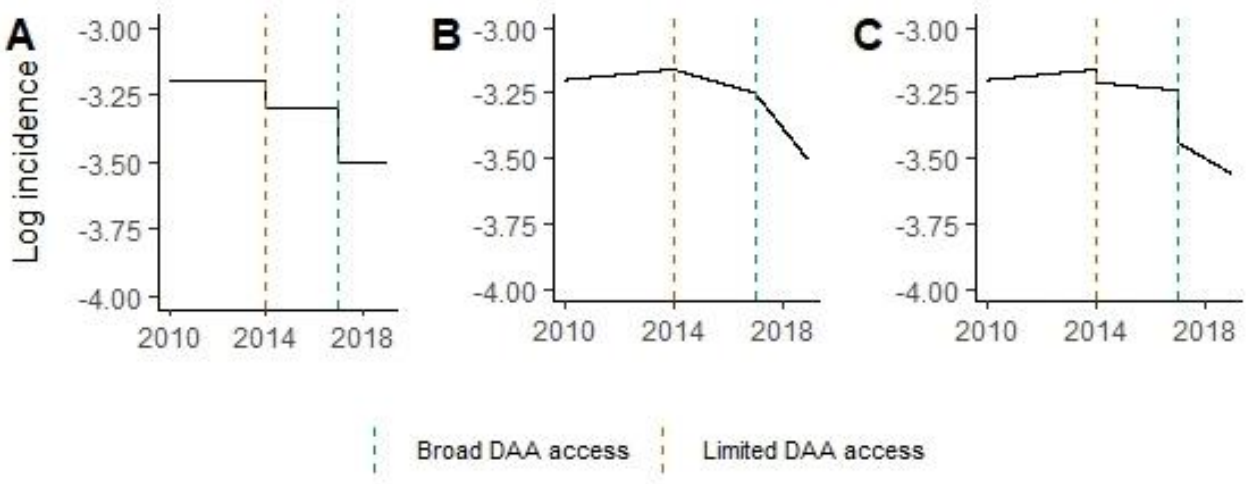
country j for records occurring in the pre-DAA period and the time in years since January 2010 at the start of the limited DAA access period for records occurring during limited or broad DAA access. For records occurring during the limited DAA access period, $Time2_{i,j}$ was the time in years since the start of the limited access period at the end of follow-up for record *i* in country *j*. For records occurring in the pre-DAA access period, $Time2_{i,j}$ was 0. For records occurring in the broad DAA access period, $Time2_{i,j}$ was the time in years from the start of the limited DAA access period to the start of the broad DAA access period. $Time3_{i,j}$ was the time in years since the start of the broad access period at the end of follow-up for record *i* in country *j*. If the end of follow-up for record *i* in country *j* is prior to the beginning of broad access in country *j*, then $Time3_{i,j}$ was equal to 0.

$FollowUp_{i,j}$ represents the duration of follow-up for that data record and $Reinfection_{i,j}$ represents whether a first reinfection was observed in that follow-up period. β_0 represents the overall intercept, and e^{β_0} is the average HCV incidence in January 2010. $Country_j$ is the country-level random intercept, and $e^{\beta_0 + Country_j}$ is the average HCV incidence in January 2010 in country, j. β_1 and β_2 are the regression coefficients for the DAA period variables, e^{β_1} is the incidence rate ratio for immediate change in incidence at the start of the limited access period compared to the end of the pre-DAA period, and e^{β_2} is the incidence rate ratio for the immediate change in incidence at the start of the broad access period compared to the end of the limited access period. β_3 is the slope in the pre-DAA period, β_4 is the slope in the limited DAA-access period, and β_5 is the slope in the broad DAA -access period. The term $offset[\log(FollowUp_{i,j})]$ is the offset, which is constrained at 1 and facilitates prediction of incidence using a Poisson regression model.

$$\log(Reinfection_{i,j}) = \beta_0 + Country_j + \beta_1 \times I(Period = limited\ DAA\ access)_{i,j} + \beta_2 \times I(Period = broad\ DAA\ access)_{i,j} + \beta_3 \times Time1_{i,j} + \beta_4 \times Time2_{i,j} + \beta_5 \times Time3_{i,j} + offset[\log(FollowUp_{i,j})]$$

This model differs from the change in slope model in that at each boundary there is a change in both level and slope. Whereas in the change in slope model, the slopes join at the knots; in this model, there can be a step between slopes.

The following figure illustrates the characteristics of the average incidence per period model, the change in slope model and the interrupted time series model side-by-side, in order to clarify how they differ. Plots are on a log scale. Please note that this figure is purely stylistic and does not match the fitted model parameters based on the study data.



A: Average incidence per period model, B: change in slope model, C: interrupted time series model

4. Change in slope model with random slopes per country for each DAA period

We also attempted to fit a change in slope model with random slopes for each country to estimate the change in slope in first HCV reinfection incidence associated with changes in DAA period, while allowing the slope and change in slope to vary between country in each DAA period. In the following regression equation, i represents a data record for a participant in country, j. The data are split by calendar month so that each record represents a period of time that is within a single participant and calendar month. Each calendar month is nested in a single DAA-period by definition because the start of each DAA-period, within a country, was defined as the first day of the calendar month in which they occurred. $Time1_{i,j}$, $Time2_{i,j}$, $Time3_{i,j}$, $FollowUp_{i,j}$ and $Reinfection_{i,j}$ were defined in the same way as in the change in slope model described above. β_0 represents the overall intercept, and e^{β_0} is the average HCV incidence in January 2010. $Country_{0j}$ is the country-level random intercept, and $e^{\beta_0+Country_{0j}}$ is the average HCV incidence in January 2010 in country, j. β_1 is the average slope in the pre-DAA period across countries, $Country_{1j}$ is the random component of the slope which allows the pre-DAA slope to differ by country. Similarly, β_2 and β_3 represent the average slopes in the limited and broad DAA -access periods, respectively. $Country_{2j}$ and $Country_{3j}$ represent the

random components of the slopes in the limited and broad DAA access periods, respectively. Similar to the other models, the term $offset[\log(FollowUp_{i,j})]$ is the offset, which is constrained at 1 and facilitates prediction of incidence using a Poisson regression model.

$$\log(Reinfection_{i,j}) = \beta_0 + Country_{0j} + (\beta_1 + Country_{1j}) \times Time1_{i,j} + (\beta_2 + Country_{2j}) \times Time2_{i,j} + (\beta_3 + Country_{3j}) \times Time3_{i,j} + offset[\log(FollowUp_{i,j})]$$

Effectively, this model is fitting a separate linear spline for time with knots at the boundaries between DAA periods for each country. The knot placement varies between countries because the timing of changes to DAA access vary between countries. This model differs from the change in slope model described above because it does not assume a common slope between countries in any of the DAA periods. However, when we tried to fit this model, that led to an estimate of zero variance for the random slopes in the pre-DAA and limited DAA access periods (data not shown), indicating no support in the data for this more complex model.

5. Change in slope model with a random slope per country for the broad DAA access period (Sensitivity Analysis 2)

Finally, we fitted a change in slope model with only one random slope in the broad DAA access period. The model was defined similarly to the previous model, but without random slope components for the pre-DAA or limited DAA access periods:

$$\log(Reinfection_{i,j}) = \beta_0 + Country_{0j} + \beta_1 \times Time1_{i,j} + \beta_2 \times Time2_{i,j} + (\beta_3 + Country_{3j}) \times Time3_{i,j} + offset[\log(FollowUp_{i,j})]$$

Effectively, this model is fitting a linear spline for time with knots at the boundaries between DAA periods for each country. The knot placement varies between countries because the timing of changes to DAA access vary between countries. This model differs from the random slope model described above because it assumes a common slope between countries in the first two periods (pre-DAA and limited DAA access) and only allows the slope to vary between countries in the broad DAA access period.

References

1. van Santen DK, Sacks-Davis R, van der Valk M, et al. Effect of direct acting antivirals on HCV incidence among people living with HIV. CROI. Boston; 2021.
2. Braun DL, Hampel B, Ledergerber B, et al. A treatment as prevention trial to eliminate hepatitis C among men who have sex with men living with HIV in the Swiss HIV Cohort Study. *Clin Infect Dis* 2020.

2. Supplementary Tables and Figures

***Table S1**: Study design and characteristics of countries and cohort studies included in this analysis*

Country	Limited DAA availability	Limited DAA availability definition	Broad DAA availability	Cohort	Study design and coverage of PHIV in care in the respective country	Start cohort	Primary HCV incidence data available
Australia	NA	NA	March 2016	ACCESS	Nationwide linked database from primary care, community clinics, hospitals, and pathology laboratories covers 59% PHIV in care in Australia	2009	✓
Canada	June 2014	Moderate to severe fibrosis (varied by Province)	March 2017	Canadian coinfection cohort	Multi-site prospective observational (18 clinical/community-based sites). Covers 15% of PHIV with HCV antibodies in Canada.	2003	
France	January 2014	Severe fibrosis, and patients with comorbidities, including HIV coinfection	August 2017	AQUITAINE	Multi-site prospective hospital-based cohort (13 sites through South-Western France). Covers 85% of PLHIV living in Nouvelle Aquitaine.	1987	✓
				SAIDCC	Single-site (Paris) hospital and clinic-recruited prospective cohort. Includes 35% in COREVIH Ile de France Centre.	1992	✓
				HEPAVIH	Nationwide multi-site prospective study of people with HIV and HCV antibodies. Participants recruited from hospitals and HIV cohorts (29 sites). Coverage of PHIV in France is unknown.	2005	
The Netherlands	November 2014	Moderate to severe fibrosis	November 2015	ATHENA	Nationwide prospective cohort includes 98% PHIV in care in the Netherlands	1998	✓
Spain	January 2015	Severe fibrosis and those with high risk of transmission such as MSM with ongoing risk behaviour	June 2017	CORIS	Multi-centre prospective cohort study of people diagnosed with HIV after 2004 in 28 hospital-based sites. Coverage of PHIV in care in Spain: 12% (~15,000 of ~130,00 in care)	2004	✓
Switzerland	April 2014	Severe fibrosis or defined extrahepatic manifestation	November 2017	Swiss HIV cohort study (SHCS)	Nationwide prospective cohort involving 71% PHIV on ART in Switzerland (59% of estimated total population of people living with HIV)	1988	✓

Abbreviations: NA: not applicable, PHIV: people with HIV, ACCESS: Australian Collaboration for Coordinated Enhanced Sentinel Surveillance; co-EC: Eliminating hepatitis C transmission by enhancing care and treatment among HIV co-infected individuals; ATHENA: AIDS Therapy Evaluation in the Netherlands; SAIDCC: Saint-Antoine Infectious Disease Clinical Cohort; CoRIS: The cohort of Spanish HIV research network; AQUITAINE: ANRS CO3 AQUITAINE / AquiVIH-NA; HEPAVIH: Clinical Centres Collaborations of Subjects Co-infected with HIV and HCV.

***Table S2**: Baseline characteristics of 6144 participants at risk of reinfection by country*

Characteristic	Total (N=6144)	Australia (N=878)	Canada (N=743)	France (N=1583)	Spain (N=454)	Switzerland (N=1171)	the Netherlands (N=1315)
Time period first at risk of reinfection							
Pre DAA access	2560 (42%)	379 (43%)	234 (31%)	617 (39%)	160 (35%)	496 (42%)	674 (51%)
Limited DAA access	1897 (31%)	0 (0%)	288 (39%)	864 (55%)	178 (39%)	463 (40%)	104 (8%)
Broad DAA access	1687 (27%)	499 (57%)	221 (30%)	102 (6%)	116 (26%)	212 (18%)	537 (41%)
Sex at birth[a]							
Male	4989 (81%)	846 (97%)	537 (73%)	1184 (75%)	374 (82%)	841 (72%)	1207 (92%)
Female	1137 (19%)	28 (3%)	194 (27%)	397 (25%)	80 (18%)	330 (28%)	108 (8%)
Age, yrs							
Median (IQR)	48.6 (42.2, 54.0)	47.1 (40.2, 53.8)	50.3 (43.6, 55.6)	51.0 (45.8, 54.9)	46.0 (39.4, 51.4)	48.3 (42.3, 53.7)	45.9 (38.9, 52.1)
Risk group							
MSM+PWID	277 (5%)	0 (0%)[b]	92 (12%)	49 (3%)	0 (0%)	136 (12%)	0 (0%)
PWID	2083 (34%)	0 (0%)[b]	391 (53%)	856 (54%)	187 (41%)	499 (43%)	150 (11%)
MSM	2559 (42%)	682 (78%)	115 (15%)	315 (20%)	165 (36%)	308 (26%)	974 (74%)
Other/Unknown	1225 (20%)	196 (22%)	145 (20%)	363 (23%)	102 (22%)	228 (19%)	191 (15%)
Clearance type (previous infection)							
Spontaneous clearance	1883 (31%)	599 (68%)[c]	167 (22%)	269 (17%)	155 (34%)	402 (34%)	291 (22%)
Treatment clearance	4261 (69%)	279 (32%)	576 (78%)	1314 (83%)	299 (66%)	769 (66%)	1024 (78%)
Time since HIV diagnosis, yrs[d]							
Median (IQR)	12.5 (5.8, 21.9)	5.2 (2.2, 7.6)	14.4 (8.3, 19.8)	22.0 (14.6, 26.7)	6.5 (2.6, 11.2)	18.0 (9.9, 24.5)	8.9 (4.6, 15.7)
Time since first HCV diagnosis, yrs							
Median (IQR)	6.7 (1.8, 14.5)	2.0 (0.7, 5.0)	12.4 (6.7, 17.8)	13.4 (6.2, 19.7)	2.9 (1.2, 6.9)	10.2 (3.8, 16.7)	2.3 (1.1, 7.7)
CD4 cell count[ef]							
Median (IQR)	580 (410, 795)	605 (442, 826)	511 (340, 736)	586 (409, 806)	542 (369, 803)	585 (425, 809)	580 (430, 780)
HIV viral load supressed[fg]							
Yes	4997 (81%)	228 (26%)	668 (90%)	1474 (93%)	376 (83%)	1091 (93%)	1160 (88%)
No	483 (8%)	44 (5%)	65 (9%)	87 (5%)	74 (16%)	72 (6%)	141 (11%)
Unknown	664 (11%)	606 (69%)	10 (1%)	22 (1%)	4 (1%)	8 (1%)	14 (1%)
Fibrosis-4[f]							
<1.45	2210 (36%)	19 (2%)	373 (50%)	220 (14%)	251 (55%)	658 (56%)	689 (52%)
>1.45	1735 (28%)	15 (2%)	353 (48%)	380 (24%)	147 (32%)	483 (41%)	357 (27%)
Unknown	2199 (36%)	844 (96%)	17 (2%)	983 (62%)	56 (12%)	30 (3%)	269 (20%)

Abbreviations: HCV: Hepatitis C virus; IQR: interquartile range; PWID: people who inject drugs; MSM: men who have sex with men. [a]Data on sex at birth were missing for 18 participants. [b]HIV transmission in Australia uncommon in PWID and PWID status not collected in the ACCESS surveillance system. [c]Spontaneous clearance is defined as two HCV RNA negative tests at least 28 days apart where there is no evidence of treatment. Missing treatment data may lead to misclassification of treatment clearance as spontaneous clearance. In Australia, due to health system differences, participants are more likely to access HIV care at a different practice to where they access HCV treatment, which may result in additional missing treatment data if the HCV-treating practice is not part of the ACCESS network. [d]Data on date of HIV diagnosis were missing for 32 participants. [e]Data on CD4 were missing for 127 participants. [f]Measurement within one year of first at risk of reinfection. Where multiple measurements were available per person, the closest to the date at risk of reinfection was used. [g]<200 copies/mL.

***Table S3**: Follow up, reinfection events, and HCV RNA testing among 6144 participants at risk of reinfection, by country*

Characteristic	Total (N=6144)	Australia (N=878)	Canada (N=743)	France (N=1583)	Spain (N=454)	Switzerland (N=1171)	the Netherlands (N=1315)
Time at risk (years)[a]							
Median (IQR)	2.1 (0.9, 3.9)	2.0 (1.1, 3.2)	2.3 (1.0, 4.1)	2.1 (1.0, 3.9)	1.2 (0.5, 2.5)	2.3 (1.0, 5.0)	2.0 (0.8, 4.0)
Number of reinfection events							
Events	643	94	67	88	47	97	250
Number of tests per person during follow-up							
Median (IQR)	3.0 (2.0, 4.0)	3.0 (2.0, 5.0)	4.0 (2.0, 6.0)	3.0 (2.0, 4.0)	3.0 (2.0, 3.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Test interval (years)							
Median (IQR)[b]	0.9 (0.5, 1.5)	0.8 (0.5, 1.3)	0.7 (0.5, 1.0)	1.0 (0.6, 1.5)	0.7 (0.4, 1.4)	1.0 (0.5, 2.2)	0.8 (0.5, 1.6)

Abbreviations: HCV: Hepatitis C virus; IQR: interquartile range

[a]Time between HCV clearance and last HCV RNA negative test or estimated reinfection date.

[b]Median of the mean number of years between tests per person

***Figure S1**: Per-month probability of RNA testing among those at risk of reinfection per country over time*

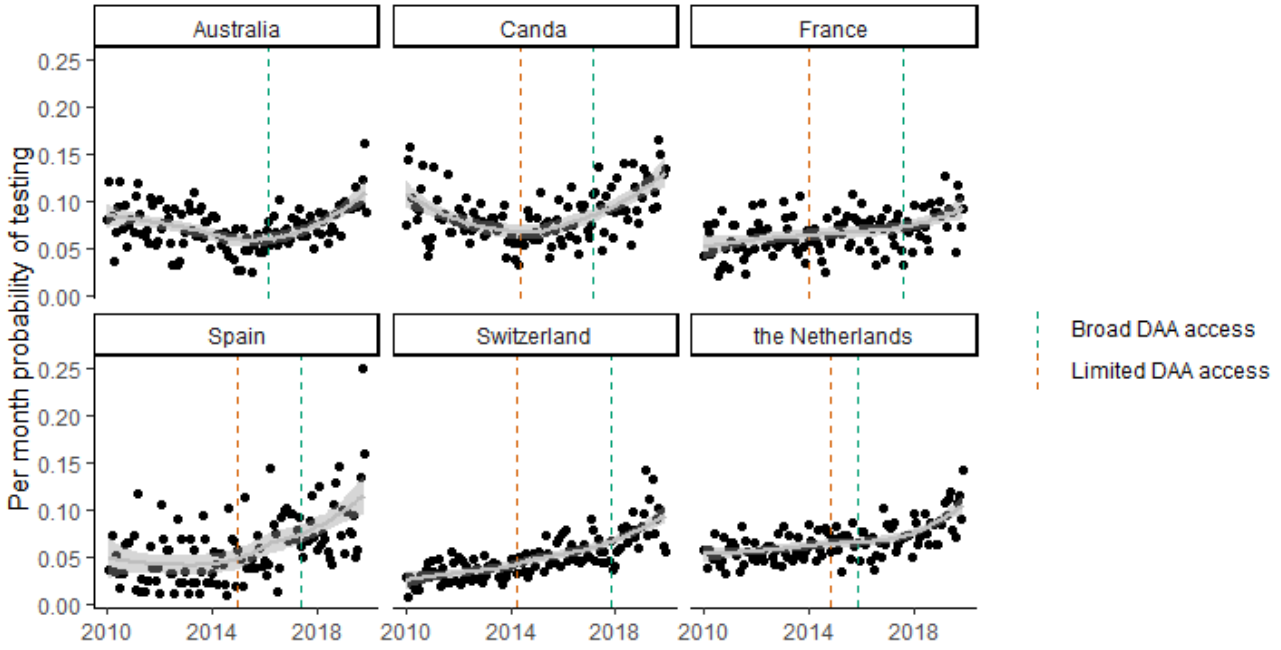


***Figure S2**: Proportion and number of events due to reinfection, including multiple reinfections, in five countries with primary and reinfection data available*

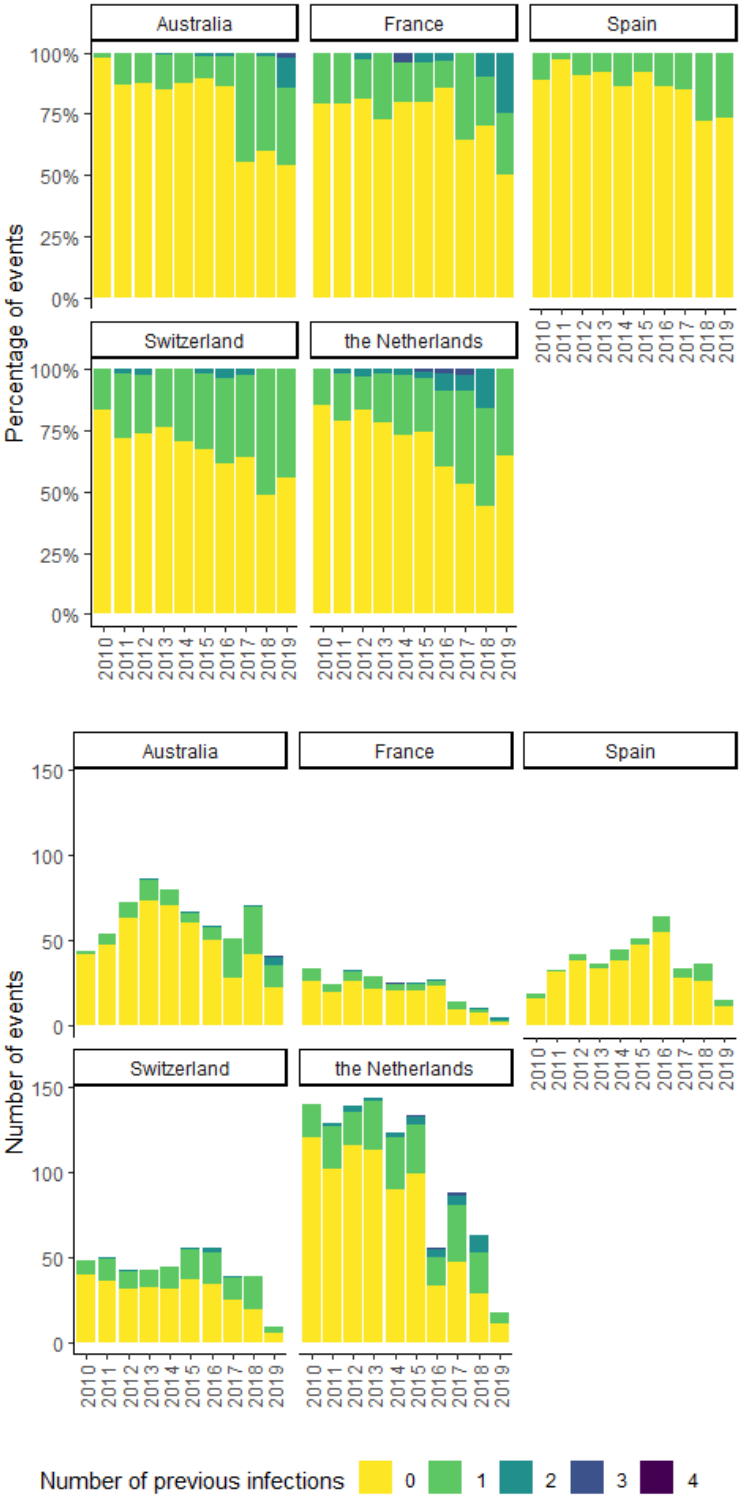


***Table S4**: List of sensitivity analyses and differences relative to the primary analysis*

Label	Domain	Primary analysis	Sensitivity analysis
S1	Regression model to assess change in slope of reinfection incidence	Change of slope at each DAA change point but no change in intercept	Change in slope and intercept at each DAA change point (interrupted time series model)
S2	Regression model to assess change in slope of reinfection incidence	Common slope across countries for each DAA period	Random slope per country for the broad DAA access period, to allow differences between countries in the broad DAA access period.
S3	Spontaneous clearance definition	Two consecutive HCV RNA negative tests ≥28 days apart after an HCV antibody or RNA positive test	One HCV RNA negative test after and HCV antibody or RNA positive test
S4	Australia's limited DAA access period	No period of limited DAA access in Australia (consistent with policy)	Assume a period of limited access prior to broad access given to reflect DAA treatments through compassionate access, clinical trials and overseas buyer schemes at this time.
S5	Inclusion of Spain	Spain included.	Spain excluded.
S6	Inclusion of Australia	Australia included	Australia excluded
S7	Restricting HCV reinfections to those with evidence of HCV RNA viral load ≥ 100 copies/mL	HCV RNA status (positive vs negative) was defined on the basis of a qualitative HCV RNA test, or if there was no qualitative result available, a HCV RNA quantitative test result. Quantitative HCV RNA test results were classified as positive if the result was greater than or equal to the lower limit of detection, or 15 copies/mL if the lower limit of detection was unknown. A reinfection event was defined as one or more HCV RNA positive tests after treatment-induced or spontaneous clearance. In some cases, a reinfection event may consist of a single low positive (<100 copies/mL) HCV RNA.	For the purposes of defining spontaneous clearance and treatment-induced clearance HCV RNA status was defined in the same way as the primary analysis. For the purpose of defining reinfection events, participants were classified as HCV RNA positive on a given date if there was quantitative test undertaken and HCV RNA was greater than or equal to 100 copies/mL. If there was no quantitative test undertaken, positivity was defined on the basis of a positive qualitative HCV RNA result. This meant that events with a single low positive HCV RNA were not classified as reinfections in this sensitivity analysis.
S8	Total HCV incidence confidence intervals	Poisson confidence intervals, no adjustment for within person correlation in multiple infection per person analysis	Robust sandwich estimator confidence intervals calculated using a GEE model with independent correlation structure

***Table S5**: Sensitivity analysis: Piecewise Exponential Model*

	Main result	S3	S4	S5	S6	S7
N	6144	6278	6144	5690	5266	6125
Cases	643	878	643	596	549	575
Intercept: IR (95% CI)	0.04 (0.03-0.06)	0.07 (0.05-0.11)	0.04 (0.03-0.06)	0.04 (0.03-0.06)	0.04 (0.03-0.06)	0.04 (0.02-0.06)
Limited DAA access: IRR (95% CI)	0.96 (0.78-1.19)	0.91 (0.77-1.07)	0.89 (0.73-1.09)	0.95 (0.76-1.18)	0.95 (0.77-1.18)	0.86 (0.68-1.08)
Broad DAA access: IRR (95% CI)	0.72 (0.60-0.86)	0.51 (0.44-0.60)	0.70 (0.58-0.84)	0.68 (0.56-0.82)	0.69 (0.56-0.84)	0.73 (0.61-0.88)
AIC	6794.9	9448.9	6794.7	6349.2	5848.0	6156.5
BIC	6826.7	9480.6	6826.5	6380.7	5879.2	6188.2

S3: Spontaneous clearance definition defined as a single HCV RNA negative test. S4: Define a limited access period for Australia. S5: Remove Spain from the analysis. S6. Remove Australia from the analysis. S7: Exclude HCV RNA < 100 copies/mL from reinfection classification

CI: Confidence interval

IRR: Incidence rate ratio

IR: Incidence rate

***Table S6**: Sensitivity analysis: association between DAA change points and change in rate of change of HCV incidence*

	Main result	S1	S2	S3	S4
Intercept: IR (95% CI)	0.04 (0.03-0.06)	0.04 (0.03-0.06)	0.04 (0.03-0.06)	0.07 (0.05-0.10)	0.04 (0.03-0.06)
Slope: IRR (95% CI)	1.03 (0.96-1.10)	1.04 (0.96-1.14)	1.02 (0.95-1.10)	0.97 (0.92-1.03)	1.05 (0.98-1.13)
Immediate change associated with limited DAA access: IRR (95% CI)		0.99 (0.73-1.34)			
Immediate change associated with broad DAA access: IRR (95% CI)		0.72 (0.48-1.07)			
Change in slope* associated with limited DAA access: IRR (95% CI)	0.82 (0.72-0.94)	0.85 (0.74-0.98)	0.85 (0.73-1.00)	0.88 (0.79-0.99)	0.79 (0.68-0.92)
Change in slope* associated with broad DAA access: IRR (95% CI)	0.90 (0.78-1.04)	0.99 (0.83-1.17)	0.86 (0.64-1.15)	0.88 (0.78-1.00)	0.90 (0.78-1.03)
AIC	9851.4	9851.3	9855.7	12897.9	9849.4
BIC	9903.0	9923.6	9927.9	12949.5	9901.0

	S5	S6	S7
Intercept: IR (95% CI)	0.04 (0.03-0.06)	0.04 (0.02-0.05)	0.04 (0.02-0.06)
Slope: IRR (95% CI)	1.02 (0.95-1.09)	1.07 (0.99-1.16)	1.00 (0.93-1.07)
Change in slope* associated with limited DAA access: IRR (95% CI)	0.81 (0.71-0.93)	0.78 (0.67-0.91)	0.87 (0.75-1.01)
Change in slope* associated with broad DAA access: IRR (95% CI)	0.90 (0.78-1.05)	0.83 (0.71-0.98)	0.94 (0.81-1.09)
AIC	9149.3	8405.4	8868.9
BIC	9200.6	8456.3	8920.5

S1: Interrupted time series model. S2: Random slope for broad DAA access period model. S2: Spontaneous clearance definition defined as a single HCV RNA negative test. S3: Define a limited access period for Australia. S4: Remove Spain from the analysis. S5. Remove Australia from the analysis. S6: Exclude HCV RNA < 100 copies/mL.

Figure S3: *Predicted incidence of first HCV reinfection in 6144 participants of InCHEHC cohorts prior to and during limited and broad DAA access: Changes in the rate of change by country, sensitivity analysis where Australia was assumed to have a limited access period*

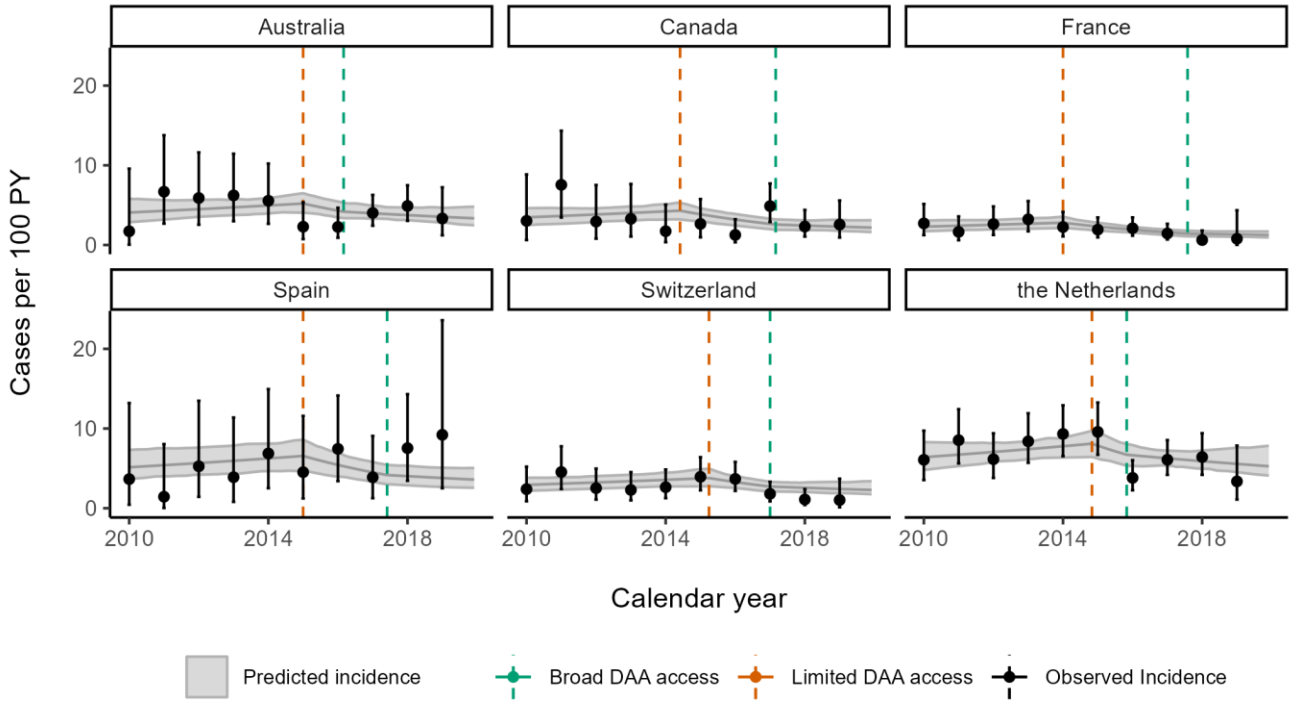
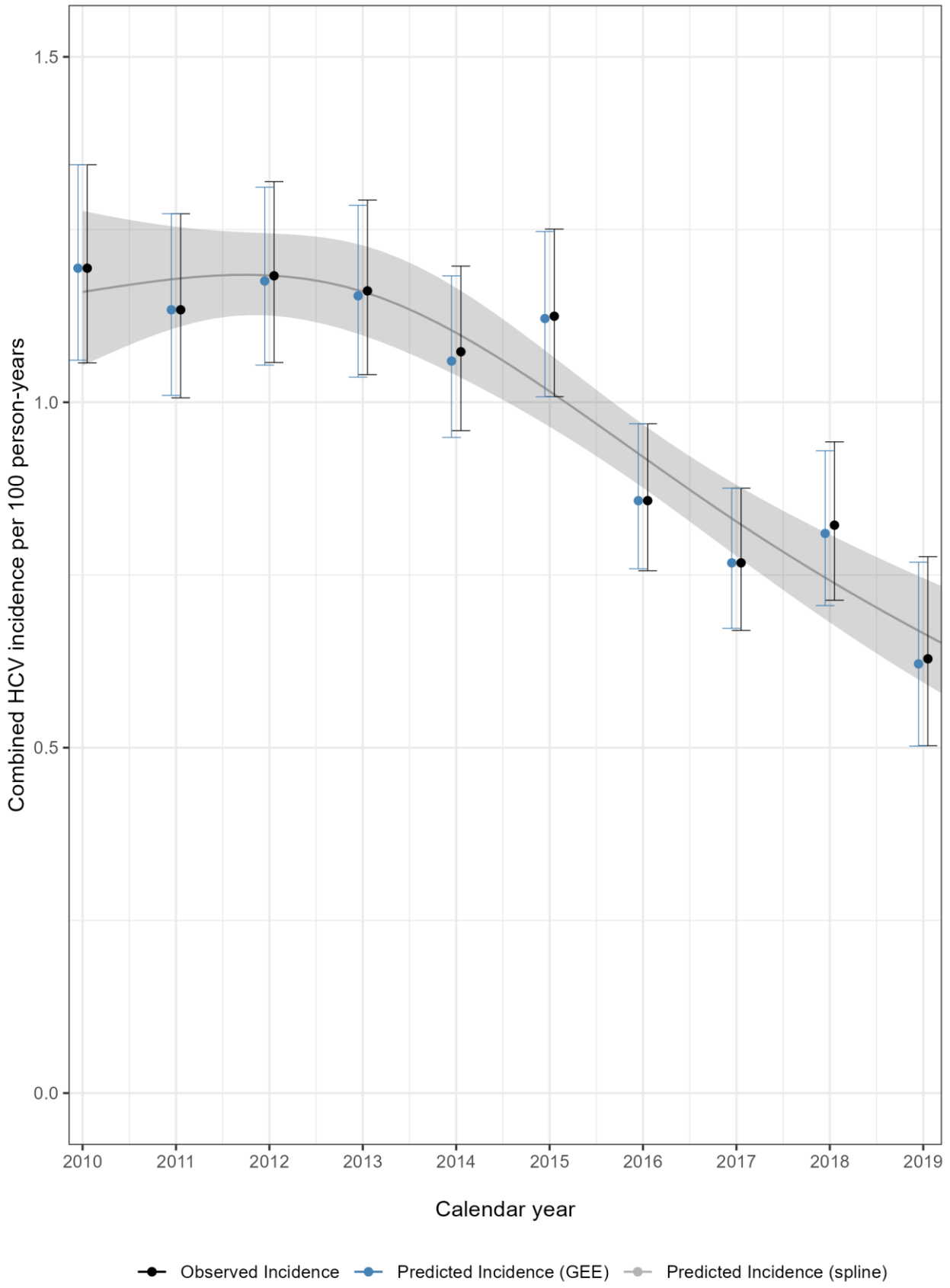


***Figure S4**: Sensitivity analysis 7 showing robust sandwich estimator (GEE) vs standard Poisson confidence intervals for the calculation of combined HCV incidence (primary and reinfection incidence)*



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Cohort name abbreviations:

ACCESS: Australian Collaboration for Coordinated Enhanced Sentinel Surveillance
ATHENA: AIDS Therapy Evaluation in the Netherlands
AQUITAINE: ANRS CO3 AQUITAINE / AquiVIH-NA - prospective clinical based HIV cohort
CCC: Canadian Co-infection Cohort
CEASE: Control and Elimination within AuStralia of HEpatitis C from people living with HIV
Co-EC: Eliminating hepatitis C transmission by enhancing care and treatment among HIV co-infected individuals
CORIS: The cohort of Spanish HIV research network
HEPAVIH: Clinical Centres Collaborations of Subjects Co-infected with HIV and HCV
MOSAIC: MSM Observational Study of Acute Infection with hepatitis C
SAIDCC: Saint-Antoine Infectious Disease Clinical Cohort
SHCS: Swiss HIV cohort Study

4. Participating cohort ethics and funding

Ethics committees

Ethics approval for the coordinating centre was granted by the Alfred Hospital Human Research Ethics Committee. Ethics approval for each cohort has been granted by the following committees: ACCESS: Alfred Hospital Human Research Ethics Committee. ANRS CO13 HEPAVIH: CPP Ile de France III. ANRS CO3 AQUITAINE: CPP Sud-Ouest et Outre-mer III. ATHENA cohort: At initiation, the cohort was approved by the institutional review board of all participating centres. People entering HIV care receive written material about participation in the ATHENA cohort and are being informed by their treating physician of the purpose of collection of data, after which they can consent verbally or elect to opt-out. Data are pseudonymised before being provided to investigators and may be used for scientific purposes. A designated quality management coordinator safeguards compliance with the European General Data Protection Regulation. Canadian Coinfection Cohort: McGill University Health Centre Research Ethics Board. CoRIS: Comité Ético de Investigación Clínica del Hospital General Universitario Gregorio Marañon. MOSAIC: Institutional Review Board of the Academic Medical Center and ethical committees/board of directors of each institute recruiting participants. SAIDCC: Registre général des traitements de l'APHP.

The SHCS was approved by the local ethical committees of the participating centres: Ethikkommission beider Basel ("Die Ethikkommission beider Basel hat die Dokumente zur Studie zustimmend zur Kenntnis genommen und genehmigt."); Kantonale Ethikkommission Bern (21/88); Comité départemental d'éthique des spécialités médicales et de médecine communautaire et de premier recours, Hôpitaux Universitaires de Genève (01–142); Commission cantonale d'éthique de la recherche sur l'être humain, Canton de Vaud (131/01); Comitato etico cantonale, Repubblica e Cantone Ticino (CE 813); Ethikkommission des Kantons St. Gallen (EKSG 12/003); Kantonale Ethikkommission Zürich (KEK-ZH-NR: EK-793), and written informed consent was obtained from all participants.

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