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

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Summary

Background Reinfection after successful treatment with direct-acting antivirals is hypothesised to undermine efforts to eliminate hepatitis C virus (HCV) infection among people with HIV. We aimed to assess changes in incidence of HCV reinfection among people with HIV following the introduction of direct-acting antivirals, and the proportion of all incident cases attributable to reinfection.

Methods We pooled individual-level data on HCV reinfection in people with HIV after spontaneous or treatment-induced clearance of HCV from six cohorts contributing data to the International Collaboration on Hepatitis C Elimination in HIV Cohorts (InCHEHC) in Australia, Canada, France, the Netherlands, Spain, and Switzerland between Jan 1, 2010, and Dec 31, 2019. Participants were eligible if they had evidence of an HCV infection (HCV antibody or RNA positive test) followed by spontaneous clearance or treatment-induced clearance, with at least one HCV RNA test after clearance enabling measurement of reinfection. We assessed differences in first reinfection incidence between direct-acting antiviral access periods (pre-direct-acting antiviral, limited access [access restricted to people with moderate or severe liver disease and other priority groups], and broad access [access for all patients with chronic HCV]) using Poisson regression. We estimated changes in combined HCV incidence (primary and reinfection) and the relative contribution of infection type by calendar year.

Findings Overall, 6144 people with HIV who were at risk of HCV reinfection (median age 49 years [IQR 42–54]; 4989 [81%] male; 2836 [46%] men who have sex with men; 2360 [38%] people who inject drugs) were followed up for 17 303 person-years and were included in this analysis. The incidence of first HCV reinfection was stable during the period before the introduction of direct-acting antivirals (pre-introduction period; 4·1 cases per 100 person-years, 95% CI 2·8–6·0). Compared with the pre-introduction period, the average incidence of reinfection was 4% lower during the period of limited access (incidence rate ratio [IRR] 0·96, 95% CI 0·78–1·19), and 28% lower during the period of broad access (0·72, 0·60–0·86). Between 2015 and 2019, the proportion of incident HCV infections due to reinfection increased, but combined incidence declined by 34%, from 1·02 cases per 100 person-years (95% CI 0·96–1·07) in 2015 to 0·67 cases per 100 person-years (95% CI 0·59–0·75) in 2019.

Interpretation HCV reinfection incidence and combined incidence declined in people with HIV following direct-acting antiviral introduction, suggesting reinfection has not affected elimination efforts among people with HIV in InCHEHC countries. The proportion of incident HCV cases due to reinfection was highest during periods of broad access to direct-acting antivirals, highlighting the importance of reducing ongoing risks and continuing testing in people at risk.

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Introduction

Approximately 58 million people live with hepatitis C virus (HCV) globally,[1] which causes an estimated 290 000 deaths annually.[2] In 2013, highly effective (≥95%) direct-acting antiviral therapies revolutionised HCV treatment.[3] In 2016, this led WHO to set ambitious targets to eliminate HCV as a public health threat. Global targets include reducing HCV incidence by 30% in 2020 and by 80% in 2030 (compared with 2015).[4]

HCV infection is more common among people with HIV than individuals without HIV, making them a key target population for HCV elimination.[3,4] However, before direct-acting antivirals were available, modelling studies in Switzerland and the UK had projected increases in

Research in context

Evidence before this study

People with HIV are a key target population for hepatitis C virus (HCV) elimination. Reinfection after successful HCV treatment can make it difficult to reduce HCV incidence and therefore attain incidence reduction targets. We searched PubMed, without any restrictions, from database inception to Sept 29, 2022, to identify relevant English language publications relating to HCV reinfection incidence among people with HIV. We used the search terms: ("hepatitis C" OR "HCV") AND ("reinfection" OR "re-infection") AND ("incidence" OR "rate" OR "trends") AND ("treatment" OR "direct acting antivirals") AND "HIV". Relevant publications were also obtained from coauthors and collaborators. Most countries have implemented direct-acting antiviral therapies in two phases: first, restricted to people with moderate or severe liver disease (limited access to direct-acting antivirals) and second, broad availability for people with chronic HCV. Previous single-country studies have reported mixed results, including decreased, stable, and increased incidence of HCV reinfection among people with HIV after the introduction of direct-acting antivirals. HCV testing frequency and classification methods for reinfection and time at risk varied between studies. Most of these results were descriptive with no statistical testing, with a small number of studies assessing differences in incidence based on two timepoints, or an insufficient number of timepoints or power for any meaningful interpretation of changes over time. We did not find any published multicountry analysis that investigated incidence of HCV reinfection before or during periods of access to direct-acting antivirals.

Added value of this study

This is the first study to measure how access to direct-acting antivirals affected the incidence of HCV reinfection among people with HIV across a range of countries. This multinational longitudinal study, with a sample size of 6144 people with HIV at risk of reinfection and 17 303 person-years of follow-up, demonstrated that incidence of HCV reinfection was stable before the introduction of direct-acting antivirals at approximately four cases per 100 person-years. On average, incidence was 4% lower during the period in which access to direct-acting antivirals was limited and the CI for the incidence rate ratio was consistent with an increase or decrease in HCV incidence during this time period. The incidence of HCV reinfection was on average 28% lower during the period when there was broad access to direct-acting antivirals than before the introduction of direct-acting antivirals, which suggests a clinically significant reduction. Between 2010 and 2019, the proportion of all incident HCV infections that were due to reinfection increased and was highest during the period of broad access in all countries. Combined HCV incidence, including primary and reinfection, declined by 34% from 1·02 cases per 100 person-years (95% CI 0·96–1·07) in 2015 to 0·67 cases per 1000 person-years (0·59–0·75) in 2019.

Implications of all the available evidence

Since the introduction of direct-acting antivirals, people previously living with HIV and HCV were treated for HCV in unprecedented numbers. Although HCV treatment is curative, those who have been treated continue to be at risk of HCV reinfection. In our study, the incidence of HCV reinfection and combined HCV incidence declined, consistent with a treatment-as-prevention effect, suggesting that HCV reinfection is not a major threat to the achievement of HCV elimination targets among people with HIV in International Collaboration on Hepatitis C Elimination in HIV Cohort countries. However, HCV reinfection cases accounted for an increasing proportion of combined incidence during the period of broad access to direct-acting antivirals, highlighting the importance of risk-reduction interventions and routine testing for people with a previous infection. Expanded access to direct-acting antiviral therapies remains a high priority in countries that do not yet have broad access to direct-acting antivirals.

HCV reinfections due to ongoing HCV-related risk behaviour among people with HIV who had been previously HCV infected, undermining the achievement of HCV incidence reduction targets among people with HIV.[5,6] Concerns regarding reinfection after treatment continue to fuel a reluctance to treat people with ongoing risk factors in some settings.[7,8]

Using data from the International Collaboration on Hepatitis C Elimination in HIV Cohorts (InCHEHC) among people with HIV in high-income countries with high treatment uptake, we previously showed that broad access to direct-acting antiviral therapies was associated with a treatment as prevention effect for primary HCV incidence, but found no evidence of a decrease in incidence during the period of limited access to direct-acting antivirals (ie, treatment restricted to people with advanced liver disease).[9] However, the effect of access to direct-acting antivirals on reinfection incidence is less clear. Empirical single-country studies measuring changes in incidence of HCV reinfection in people with HIV in high-income countries after the introduction of direct-acting antivirals have reported mixed results, including decreased,[10,11] stable,[12,13] and increased incidence.[14,15] Most studies did not include data for periods before the introduction of direct-acting antivirals hindering comparisons, compared reinfection rates by the treatment regimen rather than time period, compared only two timepoints, or did not have sufficient statistical power. Considering the population at risk of HCV reinfection has grown substantially due to high uptake of direct-acting antiviral treatment, it is crucial to understand changes in re-infection incidence after the introduction of direct-acting antivirals and whether reinfection is likely to undermine elimination efforts.

Using data from InCHEHC, we aimed to assess changes in incidence of HCV reinfection during periods

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See Online for appendix

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of limited and broad access to direct-acting antivirals in people with HIV, and to assess changes in the proportion of overall incident HCV infections due to reinfection by calendar year between 2010 and 2019 in people with HIV, overall and by country.

Methods

Study design and participants

The InCHEHC Collaboration is a consortium of 11 prospective cohorts of people with HIV with or without HCV co-infection from Australia, Canada, France, the Netherlands, Spain, and Switzerland. The InCHEHC cohorts collect sociodemographic and clinical data, including longitudinal HCV antibody and RNA testing, HIV viral load, CD4 cell count, and HIV treatment. We prepared individual cohort data and submitted these to the coordinating centre (Burnet Institute, Melbourne, VIC, Australia) based on the HIV Cohorts Data Exchange Protocol format for HIV collaborations.

The current analysis included data from eight InCHEHC cohorts that include data on HCV reinfections. These cohorts have broad coverage of people with HIV in the respective countries (Australia, the Netherlands, Switzerland) or subregions thereof (France), or broad coverage of a specific subpopulation of people with HIV (people with HIV with HCV antibodies [Canada], people with HIV diagnosed after 2004 [Spain]; appendix p 11). Six cohorts also have data on primary HCV infections. All cohorts received approval from their regulatory or national ethics committees (appendix p 22). Ethical approval for InCHEHC was obtained from the Alfred Hospital Ethics Committee (Melbourne, VIC, Australia). No additional consent was needed from cohort participants to be included in the InCHEHC study.

Participants were eligible if they had evidence of an HCV infection (HCV antibody or RNA positive test) followed by spontaneous clearance or treatment-induced clearance, with at least one HCV RNA test after clearance enabling measurement of reinfection. We defined treatment clearance as sustained virological response (negative HCV RNA result at least 12 weeks after direct-acting antiviral or combined direct-acting antiviral and PEG-interferon treatment or 24 weeks after PEG-interferon treatment). We defined spontaneous clearance as two consecutive undetectable HCV RNA tests, at least 28 days apart, following HCV infection in participants without a recorded HCV treatment.

Procedures

We defined HCV reinfection as a positive RNA test following spontaneous clearance or sustained virological response. 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 per mL if the lower limit of detection was unknown.

We estimated the date of reinfection as the midpoint between the first HCV RNA positive test following spontaneous clearance or sustained virological response, indicating reinfection, and the previous HCV RNA negative test.

We restricted measurements to the study period (2010–19). Follow-up began on Jan 1, 2010, or on the date of the first negative test indicating spontaneous or treatment clearance, whichever occurred later. Follow-up ended at HCV reinfection or, if no reinfection was observed, the last HCV RNA test during the study period. For analyses restricted to the first reinfection, only the first follow-up period was included in analysis if there were multiple spontaneous or treatment clearances.

Statistical analysis

To assess the association between restricted and broad access to direct-acting antivirals and first HCV reinfection incidence per person we defined three periods of access to direct-acting antivirals: pre-introduction of direct-acting antivirals, limited access to direct-acting antivirals (access restricted to people with moderate or severe liver disease and other priority groups; appendix p 11), and broad access to direct-acting antivirals (access for all patients with chronic HCV). The pre-direct-acting antiviral period started on Jan 1, 2010. We defined the start date of limited and broad access to direct-acting antivirals in each country as the first day of the calendar month when the specified level of access to direct-acting antivirals commenced in each country, which ranged from January, 2014 to January, 2015, for limited access and November, 2015 to November, 2017, for broad access (appendix p 11).

To explore differences between the population at risk of reinfection in the three access periods, we described baseline characteristics by the period first at risk. Most data included in the analysis were routinely collected clinical data; previous research has found that re-infection incidence can be influenced by differences in testing intervals.[16] Therefore, we assessed the monthly probability of testing in each country, defined as the number of HCV RNA tests divided by the number of people at risk of reinfection in that month.

To estimate changes in the average predicted incidence during each direct-acting antiviral access period, we used a Poisson regression model with a fixed effect for direct-acting antiviral period and a random intercept for country (average incidence per period model). This was implemented by splitting data for each country into the country-specific direct-acting antiviral periods.

To account for trends in incidence of HCV reinfection before the introduction of direct-acting antivirals, we also assessed whether the rate of change of HCV reinfection incidence (slope) differed by access period using a Poisson

regression model with a random intercept for country. The slope in each access period was common across countries, but the timing of the access periods varied between countries, depending on the country-specific timing of policy changes (appendix pp 3–5).

For these analyses, only the first reinfection per person was included. To estimate the contribution of reinfections to overall HCV incidence, we measured the combined (ie, primary and reinfection) HCV incidence by calendar year, including first and subsequent reinfections. Participant eligibility, follow-up, and case definitions for primary HCV incidence have been described previously (appendix p 2).[9] Participant eligibility, follow-up, and case definitions for subsequent reinfections are in the appendix (p 2). We restricted this analysis to the six cohorts with primary HCV incidence data (appendix p 11). We calculated the absolute number of incident infections per year and classified them by infection type (primary infection *vs* first, second, third reinfection). We calculated the proportion of infections due to each infection type per year by dividing the number of each infection type by the total infections. To describe annual changes in the combined HCV reinfection incidence per person over time, we used Poisson regression models that allowed HCV incidence to vary smoothly over calendar years using restricted cubic splines with three knots. Knots were placed at the 10th, 50th, and 90th percentiles of follow-up time.

We also did sensitivity analyses (appendix p 16) to assess changes in the rate of HCV reinfection through an interrupted time series model: modifying the change in slope model to allow the slope in broad direct-acting antiviral access period to vary between countries; including a period of limited access to direct-acting antivirals for Australia; excluding Australia and Spain from the analysis considering the absence of a limited access period in Australia and contrasting trends in reinfection incidence in Spain relative to the other countries before the introduction of direct-acting antivirals; defining spontaneous clearance as a single HCV RNA negative test after a HCV antibody or HCV RNA positive test; and restricting reinfections to individuals with evidence of HCV RNA of more than 100 copies per mL.

Furthermore, to assess the impact of potential within-person correlation on combined HCV incidence estimates per calendar year, we compared crude incidence rates and Poisson CIs to estimates from a generalised estimating equations model with independent correlation structure and robust CIs.

All statistical analyses were done using R statistical software (version 4.1.2), using *lme4* and *geepack* packages to fit regression models.

Role of the funding source

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

Results

Of 104747 people with HIV included in InCHEHC, 17501 had at least one HCV antibody or RNA positive test, indicating previous or present HCV infection. 14854 (85%) of 17501 people had one subsequent RNA test after the initial HCV positive test date, 7896 (53%) of whom had evidence of spontaneous or treatment clearance, and 6668 (84%) of 7896 with clearance had at least one follow-up visit after spontaneous or treatment clearance. Overall, 6144 (92%) of 6668 people with follow-up data contributed time at risk of reinfection during the study period (figure 1).

At baseline, 6144 participants were identified as at risk of HCV reinfection: median age was 49 years (IQR 42–54),

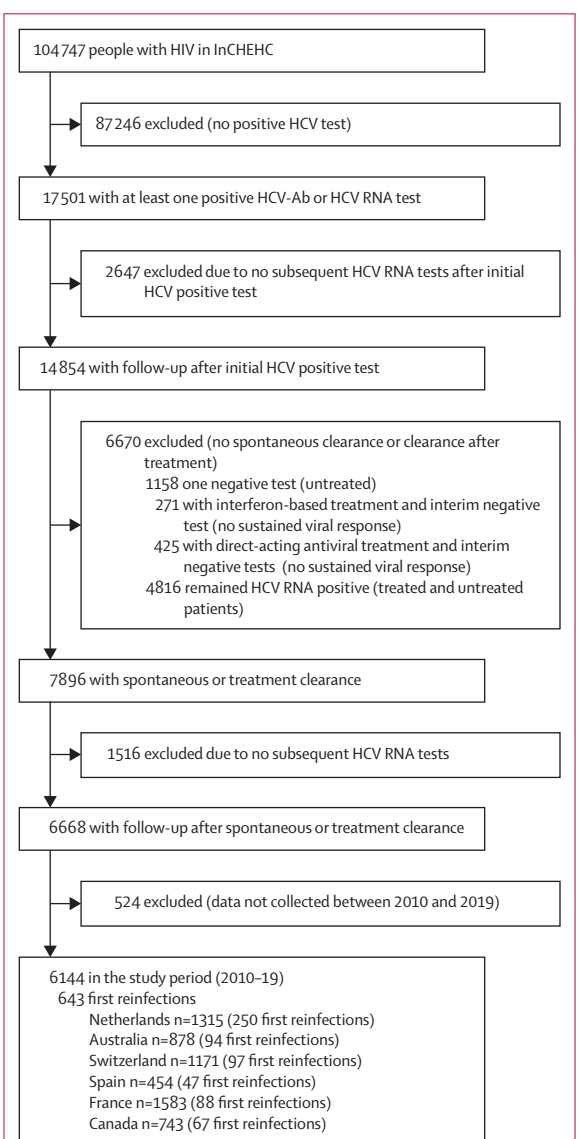


Figure 1: **Participant selection**
InCHEHC=International Collaboration on Hepatitis C Elimination in HIV Cohorts. HCV=hepatitis C virus. Ab=antibody.

	Total (n=6144)	Pre-introduction of direct-acting antivirals (n=2560)	Limited access to direct-acting antivirals (n=1897)	Broad access to direct-acting antivirals (n=1687)
Sex at birth*				
Male	4989 (81%)	2037 (80%)	1485 (79%)	1467 (87%)
Female	1137 (19%)	517 (20%)	403 (21%)	217 (13%)
Age, years	48·6 (42·2–54·0)	45·5 (39·7–50·2)	51·8 (46·1–55·6)	49·6 (42·6–55·5)
Risk group				
MSM and PWID	277 (5%)	116 (5%)	111 (6%)	50 (3%)
PWID	2083 (34%)	850 (33%)	884 (47%)†	349 (21%)
MSM	2559 (42%)	1074 (42%)	519 (27%)	966 (57%)
Other or unknown	1225 (20%)	520 (20%)	383 (20%)	322 (19%)
Clearance of previous infection‡				
Spontaneous	1883 (31%)	1187 (46%)	298 (16%)	398 (24%)
After treatment	4261 (69%)	1373 (54%)	1599 (84%)	1289 (76%)
Time since HIV diagnosis, years§	12·5 (5·8–21·9)	10·3 (4·5–19·4)	19·7 (10·4–26·7)	8·9 (5·6–17·9)
Time since first HCV diagnosis, years	6·7 (1·8–14·5)	4·4 (1·4–11·1)	13·1 (4·3–19·6)	5·3 (1·5–11·4)
CD4 count, cells per μL¶‖	580 (410–795)	520 (369–693)	608 (423–845)	651 (480–880)
HIV viral load suppressed‖**				
Yes	4997 (81%)	1927 (75%)	1803 (95%)	1267 (75%)
No	483 (8%)	339 (13%)	80 (4%)	64 (4%)
Unknown	664 (11%)	294 (11%)	14 (1%)	356 (21%)
Fibrosis-4‖				
<1·45	2210 (36%)	929 (36%)	585 (31%)	696 (41%)
>1·45	1735 (28%)	647 (25%)	679 (36%)	409 (24%)
Unknown	2199 (36%)	984 (38%)	633 (33%)	582 (34%)
Country				
Australia	878 (14%)	379 (15%)	0 (0%)	499 (30%)
Canada	743 (12%)	234 (9%)	288 (15%)	221 (13%)
France	1583 (26%)	617 (24%)	864 (46%)	102 (6%)
Spain	454 (7%)	160 (6%)	178 (9%)	116 (7%)
Switzerland	1171 (19%)	496 (19%)	463 (24%)	212 (13%)
Netherlands	1315 (21%)	674 (26%)	104 (5%)	537 (32%)

Data are n (%) or median (IQR). HCV=hepatitis C virus. MSM=men who have sex with men. PWID=people who inject drugs. *Data missing for 18 participants. †There was not a period of limited access in Australia, thus the observed proportion of people who inject drugs in the limited access period was high; HIV transmission in Australia is uncommon among people who inject drugs and data on drug use were not collected in the ACCESS surveillance system. ‡Spontaneous clearance was defined as two HCV RNA negative tests at least 28 days apart where there is no evidence of treatment; missing treatment data might 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 might result in additional missing treatment data if the HCV-treating practice was not part of the ACCESS network. §Data missing for 32 participants. ¶Data missing for 127 participants. ‖Measurement within 1 year of baseline analysis (before or after); where multiple measurements were available per person, the closest to the date at risk of reinfection was used. **<200 copies per mL.

Table 1: **Baseline characteristics of participants at risk of HCV reinfection, by access period (n=6144)**

4989 (81%) were male, 2836 (46%) were men who have sex with men (MSM), and 2360 (38%) were people who inject drugs (table 1). The median time between HIV diagnosis and baseline was 13 years (IQR 6–22); 4997 (91%) of 5480 had a HIV RNA viral load of less than 200 copies per mL. The median CD4 count was 580 cells per μL (IQR 410–795; table 1). A Fibrosis-4 (Fib-4) score measurement was available for 3945 (64%) of 6144 participants within 1 year of baseline analysis (before or after), of whom 2210 (56%) had Fib-4 score of less than 1·45 (ie, excluding advanced liver fibrosis).

Of 6144 participants at risk of reinfection, 4261 (69%) cleared their first observed HCV infection after antiviral treatment, whereas 1883 (31%) had spontaneous clearance of infection. Median time from first HCV positive test to baseline for this reinfection analysis was 7 years (IQR 2–15; table 1).

Time from both HIV diagnosis and first positive HCV test to start of follow-up was longer in people who started their reinfection risk period during the limited access period than those who started during the broad access period (median time from HIV diagnosis: 19·7 years [IQR 10·4–26·7] *vs* 10·3 years [4·5–19·4]; median time from first HCV positive test: 13·1 years [4·3–19·6] *vs* 4·4 years [1·4–11·1]; table 1).

At baseline, the proportion of participants who were male (846 [97%] of 878 participants) and MSM (682 [78%] participants) was highest in Australia, followed by the Netherlands (1207 [92%] of 1315 were male; 974 [74%] of 1315 participants were MSM; appendix p 12). Participants in France and Canada had the highest median age (51 years [IQR 46–55] and 50 years [44–56], respectively) and were more likely to be people who injected drugs (54% and 53%, respectively; appendix p 12).

Overall, participants were followed up for a median of 2 years (IQR 1–4) of reinfection risk between 2010 and 2019; the median follow-up time was shortest in Spain (median 1·2 years [IQR 0·5–2·5]; appendix p 13). The median number of HCV RNA tests during that time was 3 (2–4) and the median interval between HCV RNA tests was 0·9 years (0·5–1·5; appendix p 13). Before the introduction of direct-acting antivirals, the probability of testing was stable in the Netherlands and Spain, decreasing in Australia and Canada, and increasing in France and Switzerland. During the period of limited and broad access to direct-acting antivirals, probability of testing increased in all countries, with the highest probability of testing observed during the broad access period (appendix p 14).

The crude incidence of first HCV reinfection over the study period was 3·7 per 100 person-years (95% CI 3·4–4·0; 643 cases, 17 303 person-years). After adjusting for country, the predicted pooled incidence of first HCV reinfection in the period before the introduction of direct-acting antivirals was 4·6 per 100 person-years (95% CI 4·1–5·1). Incidence of HCV reinfection was 4% lower in the limited access period (incidence rate ratio [IRR] 0·96, 95% CI 0·78–1·19), and 28% lower in the broad access period than the period before the introduction of direct-acting antivirals (0·72, 0·60–0·86; figure 2, table 2).

The incidence of HCV reinfection was stable before the introduction of direct-acting antivirals, with an estimated 1% increase in reinfection incidence per year (IRR 1·04, 95% CI 0·96–1·10). During the period of limited access,

the incidence of reinfection reduced by 18% per year (0·82, 0·72–0·94) compared with the period before access to direct-acting antivirals, which seemed to continue in the broad direct-acting antiviral access period although CIs for the change in slope during broad access crossed 1, indicating that reinfection incidence might have stabilised during this period (IRR relative to the slope for the period before introduction of direct-acting antivirals, 0·90, 0·78–1·04; figure 2, table 2).

Among the six cohorts with primary and reinfection incidence data, 49 413 participants were at risk of primary HCV infection, first reinfection, or subsequent reinfection in five countries. These participants were followed up over 262 125 person-years, during which time 2041 primary infections, 531 first reinfections, and 56 subsequent reinfections were observed. The combined incidence of HCV infection was 1·00 per 100 person-years (95% CI 0·97–1·04), declining 34% from 1·02 per 100 person-years (0·96–1·07) in 2015 to 0·67 per 100 person-years (0·59–0·75) in 2019 (figure 3).

Most incident infections could be attributed to primary infections in all calendar years (figure 3). Overall, the proportion of HCV incident cases due to reinfection was stable between 2010 and 2015 and increased from 23% in 2015 to 41% in 2019. This increase was consistent across all countries (appendix p 15).

Results from sensitivity analyses in which we defined a limited access period for Australia, excluded Australia,

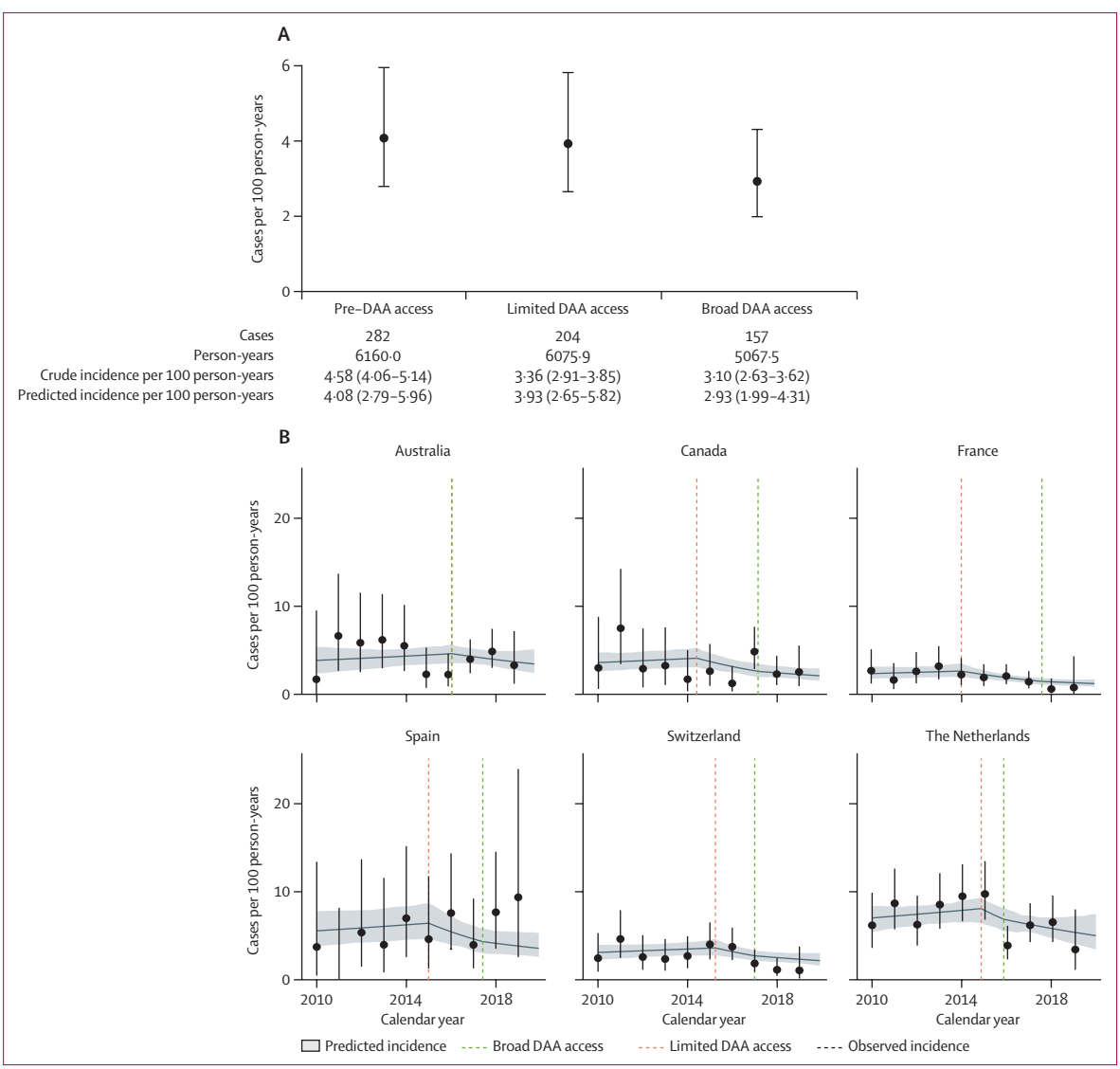


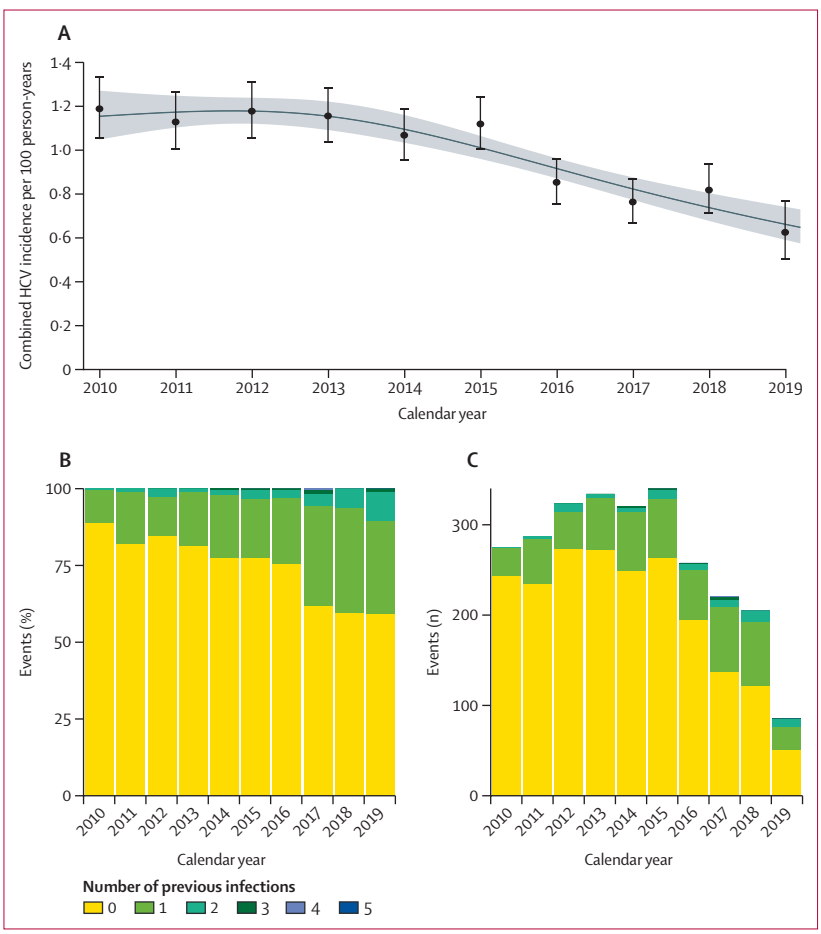
Figure 2: **Predicted incidence of first HCV reinfection in 6144 participants of InCHEHC cohorts before and after the introduction of direct-acting antivirals (limited and direct access periods)**

(A) Overall average incidence per access period (predictions are from the average incidence per period model). (B) Changes in incidence of HCV reinfection by country (predictions are from the change in slope model). Shaded areas show 95% CIs for model-predicted reinfection incidence and error bars show poisson CIs for the observed incidence of reinfection. HCV=hepatitis C virus. InCHEHC=International Collaboration on Hepatitis C Elimination in HIV Cohorts. DAA=direct-acting antivirals.

	Average incidence per direct-acting antiviral access period model	Change in slope model
Intercept, incidence (95% CI)	0·04 (0·03–0·06)	0·04 (0·03–0·06)
Change in incidence associated with limited* access to direct-acting antivirals, IRR (95% CI)	0·96 (0·78–1·19)	..
Change in incidence associated with broad* access to direct-acting antivirals, IRR (95% CI)	0·72 (0·60–0·86)	..
Slope, IRR (95% CI)	..	1·03 (0·96–1·10)
Change in slope* associated with limited direct-acting antiviral access, IRR (95% CI)	..	0·82 (0·72–0·94)
Change in slope* associated with broad direct-acting antiviral access, IRR (95% CI)	-	0·90 (0·78–1·04)
SD of random intercept	0·45	0·37

IRR=incidence rate ratio. *Compared with the period before direct-acting antivirals were introduced.

Table 2: **Changes in incidence of first HCV reinfection and changes in the rate of change (slope) of first HCV reinfection incidence during periods of limited and broad access to direct-acting antivirals compared with the period before the introduction of pre-direct-acting antivirals**



excluded Spain, used an interrupted time series model, and restricted reinfections to individuals with a HCV RNA viral load greater than 100 copies per mL were similar to the main analysis (appendix pp 17–19). However, modifying the spontaneous clearance definition to require one HCV RNA negative test rather than two consecutive tests 28 days apart did affect the results. Using this definition, 235 additional reinfections were more likely to be observed earlier in the observation period, leading to a larger reduction in the average incidence of reinfection during the period of broad access to direct-acting antivirals (IRR 0·51, 95% CI 0·44–0·60; appendix p 17). Robust CIs for combined HCV incidence, accounting for within-individual correlation were almost identical to crude Poisson CIs (appendix p 20).

Discussion

Our analysis, which included data for 6144 people with HIV at risk of HCV reinfection across six countries, found that the incidence of first HCV reinfection decreased after the introduction of direct-acting antivirals. The incidence of first HCV reinfection was on average 28% lower during the period of broad access to direct-acting antivirals than the period before the introduction of direct-acting antivirals. The proportion of all HCV incident cases due to reinfection increased after the introduction of direct-acting antivirals, with 41% of all incident infections in 2019 attributed to reinfection. A 34% decline in combined HCV incidence (including primary infection, first and subsequent reinfections), was observed over the same period.

These findings highlight the importance of monitoring HCV RNA in people who have been cured or had spontaneous clearance of infection to identify reinfections, particularly in the period of broad access to direct-acting antivirals when an increasing proportion of new HCV cases are reinfections. As expected, the incidence of first HCV reinfection remained considerably higher than HCV primary infection incidence among people with HIV, given that those susceptible to reinfection have already been infected previously. This highlights the need for frequent RNA monitoring in individuals who are at continued risk of HCV after treatment. Although frequent testing is recommended for people with HCV-related sexual and injecting risk behaviours,[17,18] the optimal frequency of testing remains unknown, and costs and limits on the number of tests reimbursable per year remain barriers to frequent monitoring in some

Figure 3: **Combined HCV incidence among people with HIV by calendar year (A), and proportion (B) and number (C) of cases due to reinfection and multiple reinfection by calendar year**
Shaded areas show 95% CIs for predicted combined incidence and error bars show observed incidence of combined primary and reinfection incidence. Predictions are from the restricted cubic spline model. HCV=hepatitis C virus.

countries.[19] In addition to monitoring HCV RNA, prevention programmes with continued emphasis on harm reduction and risk reduction counselling for people who inject drugs and MSM at HCV diagnosis and treatment are needed.[5,20] Risk reduction counselling was delivered to MSM during the direct-acting antiviral roll-out in Switzerland through the HCVree trial,[11] in the Netherlands through the NoMoreC project,[21] and informally in other countries, and might have contributed to low incidence of HCV reinfection in this group in addition to a possible treatment-as-prevention effect. It is unclear whether the maintenance of low levels of HCV reinfection in the broad direct-acting antiviral era would have been possible without harm reduction and risk reduction counselling in place. Notably, broad direct-acting antiviral access was defined as access for individuals with chronic HCV. Restrictions on treating acute HCV remained in most countries and might have led to delays in treatment and loss to care. Larger declines in HCV incidence due to a treatment-as-prevention effect might be possible if these restrictions are removed.

Decreasing HCV reinfection and combined (primary and reinfection) incidence following the expansion of access to direct-acting antivirals are reassuring for HCV elimination efforts. Combined HCV incidence, combining primary and reinfection, declined 34% from 1·02 cases per 100 person-years in 2015 to 0·67 cases per 100 person-years in 2019. This is consistent with a treatment-as-prevention effect and suggests that InCHEHC countries are on track to eliminate HCV as a public health threat among people with HIV based on the 2020 progress target established by WHO (ie, 30% reduction in incidence).[4] This demonstrates that the increase in the number of people susceptible to reinfection due to high uptake of direct-acting antiviral treatment has not undermined HCV elimination efforts in InCHEHC countries.

The decline in the incidence of HCV reinfection was lower than the decline in primary infection incidence over the same period (28% *vs* 49%).[9] The proportion of incident cases due to reinfection increased during this time period, with the highest proportion observed during the period of broad access to direct-acting antivirals. This finding was consistent between countries, and was due to increases in the pool of people at risk of reinfection leading to higher numbers of reinfection cases combined with decreases in primary infection cases. This suggests that HCV infections are concentrated in a smaller group of people who have cleared a previous infection. These findings are consistent with predictions from mathematical modelling and single-country studies in the Netherlands, Switzerland, and the UK, which showed large decreases in HCV primary incidence and smaller decreases in reinfection incidence over the same period.[5,6,10,11,22]

The rapid reduction in incidence of reinfection during the period of limited access is likely to be partly attributable to the greater numbers of people with severe liver disease in the group at risk of reinfection during that period. These individuals might be less likely to engage in ongoing behaviours associated with HCV risk and therefore have a lower risk of reinfection. This is consistent with findings from previous research that found low rates of reinfection in the early years of access to direct-acting antivirals, when many countries restricted access to people with moderate and severe liver disease.[23,24] The decrease in incidence of first reinfection was maintained during the period of broad access.

While the observed incidence of first HCV reinfection per calendar year was consistent with model predictions in most countries, the sensitivity analysis that assumed a period of limited access to direct-acting antivirals in Australia was more consistent with the observed Australian data than the primary analysis (appendix p 19). Although there was not an official period of limited access to direct-acting antivirals in Australia, people did receive direct-acting antiviral therapies before broad access through clinical trials and compassionate access programmes. More data are needed to assess the model predictions for Spain. Notably, the Spanish cohort represents a younger population than the other cohorts (people with HIV diagnosed after 2004) and this population might be at higher risk of HCV reinfection compared with participants from other countries. We did a sensitivity analysis in which Spain was removed from the dataset and the results were not sensitive to this change (appendix pp 16–18).

Previous studies of reinfection vary considerably with respect to classification methods for determining reinfection. This includes classification of HCV RNA as positive or negative and classification of spontaneous clearance (one *vs* two consecutive RNA negative tests). A strength of our comparative analysis is application of consistent definitions to multiple countries. We tested several definitions of HCV RNA negative and positive, and found these had minimal impact on HCV reinfection rates and changes in HCV reinfection rates associated with changes in access to direct-acting antivirals. However, we did observe differences in reinfection rates using different definitions of spontaneous clearance, which might be partly due to misclassification of occurrences of fluctuating HCV RNA as reinfection events when a single negative test was classified as spontaneous clearance.[25] Although we observed an overall decline in incidence associated with access to direct-acting antivirals, differences between countries remain possible. Although clear declines in the incidence of first HCV reinfection were observed in France, the Netherlands, and Switzerland, in Australia, Canada, and Spain, the number of reinfections observed was smaller, leading to broader CIs, making it more difficult to interpret country-specific trends.[9]

This study has some limitations. We could not adjust analyses for recent sexual or injecting behaviours due to variations in data availability between cohorts. Further analysis is warranted to better understand whether the association between changes in access to direct-acting antivirals and relative risk of reinfection is explainable by

differences in recent behaviour. Some studies have shown that condomless sex increased among MSM with HIV in high-income countries during our study period,[26,27] but it is unclear whether there have been changes in injecting drug use. Additionally, HCV testing data were mainly collected prospectively based on routine clinical testing; therefore, the probability that individuals at risk of HCV reinfection received RNA tests varied between countries and within countries over time. The probability of testing among individuals at risk of reinfection increased in all countries during the period of broad access to direct-acting antivirals. Spontaneous clearance of reinfections can be missed due to long testing intervals,[16] and although spontaneous clearance is less common in people with HIV than those without HIV, it is still possible that the incidence of HCV reinfection was overestimated in the period of broad access to direct-acting antivirals relative to earlier periods when testing was less frequent. Therefore, the observed reductions in HCV reinfection might underestimate the true reduction in reinfection incidence associated with access to direct-acting antivirals. Furthermore, we did not include reinfections before sustained virological response and might underestimate the reinfection rate, particularly in the period before direct-acting antivirals were accessible when the time from treatment initiation to sustained virological response was longest. Viral sequencing data were not available to confirm reinfections, so intermittent viraemia might be misclassified as reinfection, particularly after spontaneous clearance.[25] We mitigated this uncertainty by defining spontaneous clearance as two consecutive negative tests. Unsuccessful treatment with direct-acting antivirals is uncommon among people with HIV (approximately 5%) and relapse after sustained virological response is rare.[28,29] Finally, although we analysed changes in incidence of first reinfection associated with access to direct-acting antivirals, there were insufficient events to similarly analyse changes in incidence of subsequent reinfection. Nonetheless, subsequent reinfections were included in our analysis of combined HCV incidence.

Incidence of HCV reinfection declined in people with HIV after the introduction of direct-acting antivirals and was 28% lower during the period of broad access to direct-acting antivirals than the period before direct-acting antivirals were available in Australia, Canada, France, the Netherlands, Spain, and Switzerland. Combined HCV incidence decreased during the same period, consistent with a treatment-as-prevention effect, suggesting that reinfection is not a major threat to the achievement of the WHO elimination goals. The proportion of incident cases due to reinfection increased over the observation period and was highest during the period of broad access to direct-acting antivirals, suggesting that HCV infections are concentrating in a smaller group of previously infected individuals. This highlights the importance of continued monitoring in people at risk of reinfection, and interventions to reduce risk where possible.

Contributors

RS-D and DKvS conceptualised the study and were involved in data visualisation, data curation, project administration, methodology, software, formal analysis, and writing, reviewing, and editing of the manuscript. AB, JY, and TS conceptualised the study and were involved in methodology, and writing, reviewing, and editing of the manuscript. M-BR, CS, and AS were involved in provision of data, data curation, and writing, reviewing, and editing of the manuscript. MvdV, AR, CM, IJ, JB, KL, LW, OL, DS, FB, GVM, RG, JSD, MK, MP, and MS conceptualised the study, were involved in provision of data, and writing, reviewing, and editing of the manuscript. NKM conceptualised the study and was involved in writing, reviewing, and editing of the manuscript. MH conceptualised the study, and was involved in provision of data, supervising the study, funding acquisition, and writing, reviewing, and editing of the manuscript. RS-D and DKvS had access to and verified all of the data, and together with MH had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The data dictionary based on the HIV Cohorts Data Exchange Protocol is available at https://hicdep.org/ is available upon request. Data (analyses) requests are welcome subject to approval by the study steering committee. Requests and enquiries should be directed to the data coordinator, Rachel Sacks-Davis (rachel.sacks-davis@burnet.edu.au).

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