Reasons for not commencing direct-acting antiviral treatment despite unrestricted access for individuals with HIV and hepatitis C virus: a multinational, prospective cohort study

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Summary

Background Individuals with HIV and hepatitis C virus (HCV) who remain untreated with direct-acting antivirals can contribute to HCV transmission and HCV-related mortality. We aimed to compare rates of uptake of direct-acting antivirals following unrestricted access to this treatment in high-income countries and examine factors associated with remaining untreated.

Methods This multinational, prospective cohort study used data from the International Collaboration on Hepatitis C Elimination in HIV Cohorts (InCHEHC). We analysed data from nine observational cohorts participating in the InCHEHC, including data from six high-income countries (Australia, Canada, France, the Netherlands, Spain, and Switzerland). We included individuals aged 18 years and older, with HIV and HCV (ie, HCV-RNA positive without evidence of spontaneous clearance) during unrestricted access to interferon-free direct-acting antiviral treatment in each country. We calculated the cumulative proportion of participants who remained untreated with direct-acting antivirals, with follow-up starting after the date of unrestricted access or cohort inclusion, whichever occurred most recently. Factors associated with the commencement rate of direct-acting antiviral treatment were assessed using competing-risks regression with the Fine-Gray method.

Findings The date of unrestricted access to direct-acting antiviral treatment for people with HIV ranged from Nov 1, 2014, in France to Nov 1, 2017, in Switzerland. We included 4552 individuals with HIV–HCV, mainly men who have sex with men (MSM; n=2156 [47%]) and people who inject or have injected drugs (n=1453 [32%]). 1365 (30%) of 4552 participants remained untreated with direct-acting antivirals. For individuals treated with direct-acting antivirals, median time from start of follow-up to treatment was 5 months (IQR 2–12). For individuals who were not treated with direct-acting antivirals, median follow-up was 22 months (8–30). Being linked to care in Australia, France, or the Netherlands, on antiretroviral therapy, having undetectable HIV RNA, and shorter duration since first positive HCV test were independently associated with higher commencement rate of direct-acting antiviral treatment. Compared with MSM, male heterosexuals and females with unknown or other routes of HIV transmission (ie, neither injection drug use nor heterosexual transmission) had lower rates of commencement.

Interpretation Despite unrestricted access, almost a third of individuals with HIV–HCV remained untreated with direct-acting antivirals during follow-up, with variation in commencement rate of HCV treatment between countries and key populations. Increased efforts are required to reach the remaining individuals with HIV who are HCV-viraemic to achieve HIV–HCV micro-elimination.

Funding None.

Introduction

According to the most recent global estimates, 38 million people are living with HIV and approximately 2·3 million have HIV and hepatitis C virus (HCV).[1,2] Since access to highly effective[3] direct-acting antiviral therapy for the treatment of HCV has become unrestricted in many high-income settings, there have been rapid increases in coverage of HCV treatment[4,5] and subsequent sharp decreases in HCV incidence[6–8] and in the proportion of HCV-viraemic individuals[4,9,10] among people with HIV in some countries.

Nevertheless, treatment uptake has decreased after the initially rapid uptake reached a large part of the population in need of treatment.[4,5] The fact that some individuals remain untreated even in the context of unrestricted access suggests there are still barriers to

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Research in context

Evidence before this study

We searched PubMed without language restrictions using the terms "HCV" or "hepatitis C", "HIV", "DAA" or "direct-acting antivirals", "uptake" or "initiation", and "universal" or "unrestricted" for articles published between Jan 1, 2013, and June 20, 2022. The search found 31 articles. Articles that included adults with HIV and hepatitis C virus (HCV) and described uptake of direct-acting antiviral treatment following universal access or factors associated with absence of uptake of direct-acting antiviral treatment during universal access were selected. Various studies reported rapid uptake of direct-acting antiviral treatment following universal access for individuals with HIV–HCV. All these studies used data from a single national or regional cohort, whereas data on uptake of direct-acting antiviral treatment and reasons for absence of uptake had yet to be compared across settings in large, international cohorts. The factors associated with uptake of direct-acting antiviral treatment were also examined in several of these studies, yet findings were frequently inconsistent with respect to several characteristics, such as key population (eg, men who have sex with men and people who inject or have injected drugs), age, and alcohol use.

Added value of this study

Our study included data from nine observational cohorts within six high-income countries on three continents. This broad geographical range allowed for both large sample sizes and the opportunity to compare differences in uptake of direct-acting antiviral treatment in the context of different health-care settings. It also provided robust identification of factors associated with commencement rate of direct-acting antiviral treatment that are not exclusively country-specific. We found significant differences between countries in the rate of commencement of direct-acting antiviral treatment following universal access, which indicates potential differences in access to care and barriers to treatment. Furthermore, we found considerable variation between key populations regarding the rate of commencement of direct-acting antiviral treatment. Finally, multiple indicators of lower engagement in HIV care were independently associated with a lower rate of commencement of direct-acting antiviral treatment, suggesting an overlap between groups receiving suboptimal care for both HIV and HCV.

Implications of all the available evidence

Universal access to direct-acting antiviral treatment in high-income countries was followed by a rapid uptake of among individuals with HIV–HCV. Nevertheless, significant differences in the rate of commencement of direct-acting antiviral treatment exist between countries. These differences seem unlikely to be due to differences in the distribution of key populations, but rather differences in access to care and barriers to treatment. Alternate modalities to facilitate access to direct-acting antiviral treatment, including the availability of pathways to decentralised direct-acting antiviral care, are needed to ensure all individuals with HIV–HCV are treated.

direct-acting antiviral treatment. Because individuals who remain untreated can contribute to ongoing HCV transmission and are at risk of HCV-related mortality, accelerating their treatment uptake is essential to achieving HIV–HCV micro-elimination.

In several national and regional cohort studies, factors associated with an absence of direct-acting antiviral treatment uptake in individuals with HIV–HCV included having a risk factor for HIV other than identifying as men who have sex with men (MSM), having detectable HIV RNA, and infrequent attendance at health-care clinics.[4,9,11,12] However, some factors for remaining untreated, such as older age, history of injection drug use, and severe alcohol use have been identified within only specific cohorts. Although the reasons for these inconsistent findings are unclear, they could be in part due to differences in statistical methods, definitions, study populations, or health-care systems. Given these differences, the results from these studies are difficult to reliably compare. Analyses in a large, multinational collaboration of cohorts could allow a more robust identification of factors associated with the absence of direct-acting antiviral commencement, particularly in relation to differences between regions and health-care systems.

Therefore, the aim of our study was to determine the rate at which individuals with HIV–HCV in six high-income countries remained untreated with direct-acting antivirals over time following unrestricted access to these drugs. Additionally, we examined demographic and clinical factors associated with absence of direct-acting antiviral uptake in the context of unrestricted availability of these drugs.

Methods

Study design and setting

This multinational, prospective cohort study used data from the International Collaboration on Hepatitis C Elimination in HIV Cohorts (InCHEHC). This consortium pooled prospectively collected data from 11 cohorts of people with HIV from six high-income countries (Australia, Canada, France, the Netherlands, Spain, and Switzerland) using a standard operating procedure based on the HIV Cohorts Data Exchange Protocol.[13] For the current analysis, data from nine observational cohorts from these six countries were used (table 1). Two cohorts were excluded due to overlap between participants or because only those who initiated treatment were included. The CEASE and HEPAVIH cohorts collected data using clinical report forms. All other cohorts obtained data from medical records. Behavioural data were collected via surveys. Ethics approval for the InCHEHC coordination centre was granted by the Alfred Hospital Human Research Ethics Committee (approval number 662/18). All cohorts

received approval from regulatory or national ethics committees (appendix p 20).

Participants

We included all people with HIV enrolled in InCHEHC who were aged 18 years and older and were known to be HCV-RNA positive following the introduction of unrestricted access to direct-acting antivirals in the country or region of their cohort (ie, last known HCV RNA before unrestricted access to direct-acting antiviral treatment was positive or a recorded HCV-RNA positive test after unrestricted access date). Unrestricted access to direct-acting antiviral treatment was defined as the date of lifting restrictions by liver fibrosis stage, risk group, and substance use on access to interferon-free direct-acting antiviral regimens for the treatment of HCV infection in people with HIV. We excluded individuals without at least one HIV-related or HCV-related visit after unrestricted access to direct-acting antiviral treatment, individuals with definitive or presumed spontaneous HCV clearance (defined in appendix p 4), and individuals whose last HCV-RNA result before unrestricted access was positive, but had initiated direct-acting antiviral treatment before unrestricted access and had sustained viral response after the date of unrestricted access. As access to health care and reasons to remain untreated with direct-acting antivirals were likely to have been affected by the COVID-19 pandemic, we chose to include data until Feb 1, 2020, for the two cohorts providing data from after this date. Data on sex and gender were taken from case report forms or medical records. The need for additional informed consent for participation in the InCHEHC study was waived by the Alfred Hospital Human Research Ethics Committee.

See Online for appendix

Covariables

We collected demographic variables (age, gender, and region of origin), HIV-related variables (mode of HIV transmission, HIV RNA, CD4-cell count, and antiretroviral therapy [ART] history), and liver-related variables (HCV RNA, HCV treatment history, liver stiffness measurements, and liver-related laboratory tests) from all nine included cohorts. For six cohorts, behavioural variables and socioeconomic variables were available. Individuals were classified as MSM on the basis of assumed mode of HIV or HCV transmission or sexual orientation. Individuals were classified as people who inject or have injected drugs on the basis of assumed mode of HIV or HCV transmission. Subsequently, individuals classified as both MSM and people who inject

	InCHEHC participants (n)	Cohort type	Included in main analysis (n)	Key populations*	Date of unrestricted access to direct-acting antivirals†	Date of limited access to direct-acting antivirals	Data updated until
Australia							
ACCESS	22 033‡	Nationwide health surveillance network including people with HIV	684	MSM 61%, PWID data not available	March 1, 2016	None	July 13, 2021§
CEASE	402‡	Cohort of individuals with HIV–HCV from multiple Australian states	246	MSM 84%, PWID 10%	March 1, 2016	None	July 24, 2018
Canada							
CCC0	2032	Nationwide cohort of individuals with HIV–HCV	459	MSM 23%, PWID 54%	Quebec July 1, 2016¶, British Columbia and Ontario March 1, 2017¶	Nov 21, 2013	June 1, 2021§
France							
Aquitaine	9296	Cohort of people with HIV from 13 sites in southwest France	396	MSM 41%, PWID 20%	Nov 1, 2014‖	Jan 1, 2014	July 13, 2021§
HEPAVIH	1723‡	Nationwide cohort of individuals with HIV–HCV	564	MSM 16%, PWID 63%	Nov 1, 2014‖	Jan 1, 2014	Nov 6, 2019
SAIDCC	7466‡	Single centre cohort	109	MSM 54%, PWID 5%	Nov 1, 2014‖	Jan 1, 2014	Dec 31, 2017
Netherlands							
ATHENA	24785	Nationwide cohort of people with HIV	1044	MSM 61%, PWID 3%	Nov 1, 2015	Nov 1, 2014	Feb 1, 2020
Spain							
CORIS	16725	Nationwide cohort of people with HIV	609	MSM 77%, PWID 7%	June 1, 2017	Jan 1, 2015	Dec 30, 2019
Switzerland							
SHCS	20740	Nationwide cohort of people with HIV	441	MSM 45%, PWID 19%	Nov 1, 2017	April 1, 2014	Jan 31, 2020

HCV=hepatitis C virus. MSM=men who have sex with men. PWID=people who inject or have injected drugs. *MSM with a history of injecting drug use were considered part of the MSM key population. †Defined as the date of lifting all restrictions on access to direct-acting antivirals for treatment of HCV infection in people with HIV, except for restrictions on decentralised direct-acting antiviral prescriptions. ‡Overlap between ACCESS and CEASE (n=161), overlap between HEPAVIH and SAIDCC (n=98). §As access to health care and therefore reasons to remain untreated with direct-acting antivirals were affected by the COVID-19 pandemic, we chose to include data until Feb 1, 2020. ¶Canadian date of unrestricted access varies per province. Due to privacy regulations, province was only known for those living in Quebec, Ontario, or British Columbia. ‖In France, individuals with HIV and HCV had unrestricted access to direct-acting antivirals on this date before unrestricted access in the general population.

Table 1: **Profiles of the cohorts included in the current analysis**

or have injected drugs were classified as belonging to the MSM key population, because MSM who reported ever injecting drugs have more in common with MSM than heterosexual people who inject or have injected drugs regarding potential determinants of commencement of direct-acting antiviral treatment (ie, socioeconomic status, age, HCV infection duration, and somatic and psychosocial comorbidities). Additional definitions of covariables are given in the appendix (p 4).

Statistical analysis

For HCV-RNA positive individuals included in the cohort before unrestricted access to direct-acting antiviral treatment, start of follow-up was defined as the date of unrestricted access for the given country. For individuals who became HCV-RNA positive after unrestricted access to direct-acting antiviral treatment, start of follow-up was defined as the date of first HCV-RNA positive test result. For individuals who were HCV-RNA positive at inclusion in the cohort after unrestricted access to direct-acting antiviral treatment, start of follow-up was defined as the date of inclusion in the cohort. Follow-up continued until commencement or prescription of direct-acting antiviral treatment, last HIV-related or HCV-related visit, loss to follow-up, moving abroad, cohort exit, study end, or death, whichever occurred first. Included individuals with unsuccessful treatment with direct-acting antivirals or reinfection after successful treatment did not recontribute to follow-up. Additionally, individuals with reinfection following spontaneous clearance after unrestricted access to direct-acting antiviral treatment did not contribute to follow-up.

Individuals were classified as being either treated or untreated with direct-acting antivirals on the basis of whether or not direct-acting antiviral treatment was initiated following unrestricted access. Demographic and clinical characteristics were summarised using descriptive statistics at the most recent time at which participants were HCV-viraemic. This was defined as direct-acting antiviral commencement for treated individuals and the end of follow-up for untreated individuals. The most recent value before these timepoints were used, including data from before the analysis follow-up period. If only values after this timepoint were available, or no values were available, the characteristics were considered missing.

The primary outcome was the cumulative proportion of individuals who remained untreated with direct-acting antivirals. Time until uptake of direct-acting antivirals was summarised, stratified by country, using survival curves calculated by the Kaplan-Meier method. Differences between the stratified curves were compared for statistical significance using the log-rank test. To identify factors associated with uptake of direct-acting antivirals over time, a Fine-Gray competing-risks regression was used to calculate subdistribution hazard ratios (HRs) and 95% CIs comparing the rates of initiating treatment with direct-acting antivirals across levels of determinants at the most recent point where participants were HCV-viraemic, with the competing risk being death. To avoid using a particular country as a reference category, uptake of direct-acting antivirals per country was compared with the grand mean using effect coding. Factors included in the analysis were selected on the basis of assumed clinical relevance, previous literature, and availability of data. All factors included in the unadjusted analysis were included for the multivariable analysis. To assess whether the country affected the relationship between explanatory variable and uptake of direct-acting antiviral treatment, interaction terms between country and each variable included in the final model were added to the multivariable model separately. Additionally, interaction between country and the natural logarithm of follow-up time was analysed. A p value less than 0·05 based on the Wald test for the interaction term was considered significant. The analysis of determinants was additionally stratified for the key populations of MSM and people who inject or have injected drugs. The ACCESS cohort did not have information on the status of people who inject or have injected drugs and hence for Australia only data from CEASE could be used for the people who inject or have injected drugs group. As a prespecified sensitivity analysis, we reanalysed the data with the start of follow-up defined as the date of first official limited access to direct-acting antiviral treatment per country (ie, official access limited to specific subgroups, such as individuals with cirrhosis, not compassionate use only). This analysis aimed to assess whether differences in the rate of commencement of direct-acting antiviral treatment between countries might be explained by treatment commencement during the period of limited access to direct-acting antivirals. Data were analysed using R (version 4.1.2).

Role of the funding source

There was no funding source for this study.

Results

The date of unrestricted access to direct-acting antiviral treatment for people with HIV ranged from Nov 1, 2014, in France to Nov 1, 2017, in Switzerland (table 1). 104 943 people with HIV from Australia, Canada, France, the Netherlands, Spain, and Switzerland participating in the InCHEHC cohort were assessed for eligibility (appendix p 5). Of these, 17 983 (17%) ever had HCV, with documentation of a positive HCV-antibody, HCV-RNA, or HCV-genotype result. At the time of or after unrestricted access to direct-acting antiviral treatment, 4552 individuals were HCV-RNA positive and were included in the analysis. Of these, 3226 (71%) were included at the time of unrestricted access to direct-acting antiviral treatment. HCV was diagnosed after the date of unrestricted access in 857 (19%) individuals and 469 (10%) individuals entered

the cohort after the date of unrestricted access with a known HCV infection. 198 (4%) of 4552 participants fulfilled acute HCV diagnosis criteria and had acute HCV diagnosis less than 6 months from start of follow-up. Median follow-up duration was 7 months (IQR 2–20). Absolute number of direct-acting antiviral treatment initiations per country between 2011 and 2019 are shown in the appendix (p 6).

1365 (30%) of 4552 included individuals remained untreated during follow-up (table 2), with 1745 (42%) of 4132 remaining untreated after 1 year of follow-up, 828 (22%) of 3771 remaining untreated after 2 years of follow-up, and 298 (9%) of 3422 remaining untreated after 3 years of follow-up. For individuals treated with direct-acting antivirals, median time from start of follow-up to treatment was 5 months (IQR 2–12). For individuals who were not treated with direct-acting antivirals, median follow-up was 22 months (8–30). Time to commencement of direct-acting antiviral treatment differed significantly between the six countries (figure; log-rank test p<0·0001). After 2 years since unrestricted access to direct-acting antiviral treatment, 1609 (35%) of 4552 participants were untreated in the pooled database, which was highest in Spain (338 [56%] of 609) and Switzerland (247 [56%] of 441) and lowest in the Netherlands (193 [18%] of 1044). Lower rates of direct-acting antiviral commencement were observed for individuals with start of follow-up in more recent calendar years (subdistribution HR 0·84 [95% CI 0·82–0·86]). During follow-up, 129 (3%) participants were censored because of a recorded death.

In multivariable analysis, being linked to care in Australia, France, or the Netherlands, ever having been prescribed ART, having a higher CD4 count, and ever having been treated for HCV before unrestricted access to direct-acting antiviral treatment were associated with an increased rate of treatment commencement during unrestricted access (table 3). Compared with identifying as an MSM, being a heterosexual man, a woman with an unknown HIV transmission route, or a woman with an HIV transmission route that was through neither heterosexual contact nor injecting drug use were associated with a lower rate of commencement of direct-acting antiviral treatment. Additionally, longer duration since the first positive HCV test, detectable or missing HIV-RNA status, and missing non-invasive parameters of liver fibrosis were associated with a lower rate of treatment commencement. There was evidence that the association between receiving HCV treatment before unrestricted access to direct-acting antiviral treatment or liver fibrosis stage and rates of commencement of direct-acting antiviral treatment were different across countries (p for interaction <0·0001 for both; stratified results for these factors are in appendix p 9). The interaction between country and natural logarithm of time was statistically significant (p<0·0001), indicating that differences in effect size between countries varied over time.

	Untreated with direct-acting antivirals (n=1365)	Treated with direct-acting antivirals (n=3187)
Sex at birth		
Female	290 (21%)	536 (17%)
Male	1075 (79%)	2651 (83%)
Age, years	51 (44–57)	51 (44–55)
HIV key population*		
MSM	536 (39%)	1620 (51%)
PWID	478 (35%)	975 (31%)
Heterosexual	149 (11%)	242 (8%)
Other or unknown	202 (15%)†	350 (11%)†
Country		
Australia	285 (21%)	645 (20%)
Canada	151 (11%)	308 (10%)
France	194 (14%)	875 (27%)
Netherlands	156 (11%)	888 (28%)
Spain	333 (24%)	276 (9%)
Switzerland	246 (18%)	195 (6%)
Ever prescribed ART	1107 (81%)	2810 (88%)
HIV-RNA status		
Undetectable‡	959 (70%)	2646 (83%)
Detectable	261 (19%)	315 (10%)
Missing	145 (11%)	226 (75%)
CD4 count, cells per µL	617 (360–825)	633 (451–848)
Ever diagnosed with AIDS	287 (21%)	565 (18%)
Ever treated for HCV before unrestricted access to direct-acting antiviral treatment	294 (22%)	794 (25%)
Years since first positive HCV test	8 (3–14)	6 (1–13)
HCV reinfection before unrestricted access to direct-acting antiviral treatment	82 (6%)	200 (6%)
Liver stiffness measurement		
F0–F2 (<9·5 kPa)	380 (28%)	993 (31%)
F3–F4 (≥9·5 kPa)	107 (8%)	276 (9%
Missing	878 (64%)	1918 (60%)
FIB-4 score		
<2·67	786 (58%)	1603 (50%)
≥2·67	219 (16%)	385 (12%)
Missing	360 (26%)	1199 (38%)

Data are n (%) or median (IQR). Characteristics were summarised at the start of direct-acting antiviral therapy for treated individuals and at the most recent outpatient clinic visit for untreated individuals. ART=antiretroviral therapy. HCV=hepatitis C virus. FIB-4=Fibrosis-4. MSM=men who have sex with men. PWID=people who inject or have injected drugs. *The ACCESS cohort includes data on sexual orientation but not on HIV or HCV transmission route; therefore, HIV key population for ACCESS participants is classified as either MSM or other or unknown. †Untreated with direct-acting antivirals: unknown (n=167), unspecified sexual contact (n=20), non-haemophilia-related transfusion (n=12), haemophilia-related transfusion (n=1), perinatal (n=1), needle accident (n=1). Treated with direct-acting antivirals: unknown (n=231), non-haemophilia-related transfusion (n=45), unspecified sexual contact (n=41), haemophilia-related transfusion (n=24), needle accident (n=5), perinatal (n=2), tattoo (n=2). ‡Defined as ≤50 copies per mL or below the detection limit of the used assay.

Table 2: **Characteristics of participants by direct-acting antiviral treatment status**

Before unrestricted access to direct-acting antiviral treatment, several countries had limited access to this treatment, mostly restricted by liver fibrosis stage, with the date of its implementation ranging from Nov 21, 2013, in Canada to Jan 1, 2015, in Spain (table 1). Australia never had a period of limited access, thus access date was taken as the primary analysis for Australia. In the

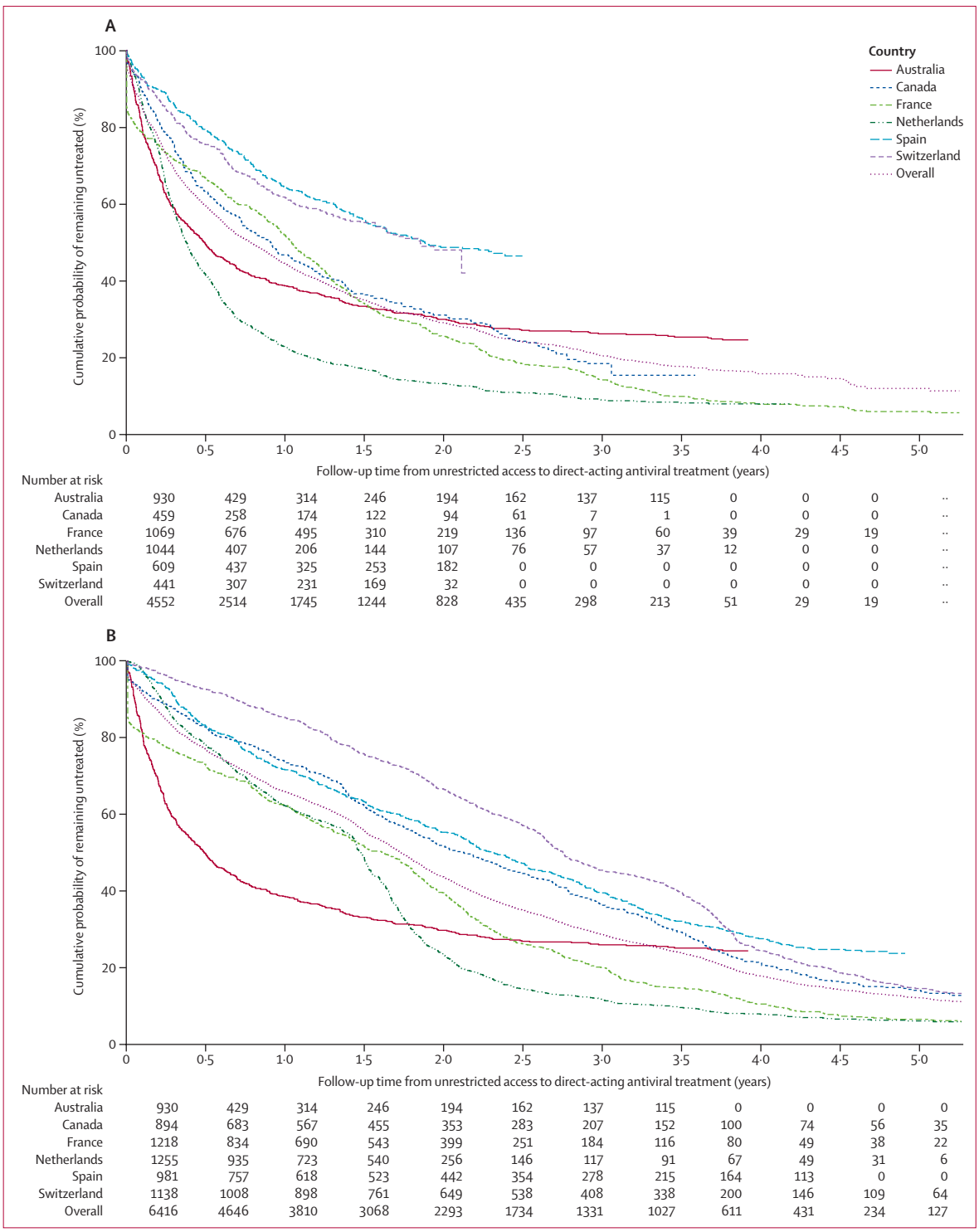

Figure: **Commencement of direct-acting antiviral treatment per country**
(A) Commencement of direct-acting antiviral treatment following unrestricted access or cohort inclusion if occurred afterwards. (B) Commencement of direct-acting antiviral treatment following official limited access or cohort inclusion if occurred afterwards. Data from the International Collaboration on Hepatitis C Elimination in HIV Cohorts including the following cohorts: ACCESS (Australia), CEASE (Australia), CCC0 (Canada), Aquitaine (France), HEPAVIH (France), SAIDCC (France), ATHENA (the Netherlands), CORIS (Spain), SHCS (Switzerland). Log-rank test for both analyses p<0·0001.

sensitivity analysis basing the start of follow-up on the date of limited access to direct-acting antiviral treatment, 6416 individuals were included (appendix p 7). Median follow-up duration was 17 months (IQR 5–32). 1686 (26%) individuals remained untreated with direct-acting antivirals during follow-up (appendix p 10). During follow-up in this analysis, the rate of commencement of direct-acting antiviral treatment varied significantly between countries (p<0·0001; figure), yet the cumulative proportion remaining untreated by the end of follow-up was similar between countries. In multivariable analysis, factors associated with the rate of commencement of direct-acting antiviral treatment were similar to the analyses basing the start of follow-up on the date of unrestricted access to treatment (appendix p 11). The main differences between the main analysis and the sensitivity analysis were that in the sensitivity analysis, belonging to the key population of people who inject or have injected drugs was significantly associated with a lower rate of commencement of direct-acting antiviral treatment and that having advanced liver fibrosis or cirrhosis was significantly associated with a higher rate of commencement of direct-acting antiviral treatment.

1839 individual treated with direct-acting antivirals and 876 untreated individuals were included in the six cohorts with available behavioural data (appendix p 12). Risk behaviours associated with HCV transmission, such as injection drug use, needle or syringe sharing, and condomless sex, were common to both the treated and untreated groups. In the six cohorts with behavioural data, 118 (20%) of 604 people with HIV who were not treated with direct-acting antivirals reported recent injecting drug use and 56 (88%) of 64 MSM who were not treated with direct-acting antivirals reported recent condomless sex.

Time until commencement of direct-acting antiviral treatment differed significantly between key populations (log-rank test p<0·0001; appendix p 8). In total, 536 (25%) of 2156 included MSM and 478 (33%) of 1453 included people who inject or have injected drugs remained untreated with direct-acting antivirals during follow-up (appendix p 13). For individuals treated with direct-acting antivirals, median time from inclusion to commencement of treatment was 4 months (IQR 1–8) for MSM and 8 months (2–17) for people who inject or have injected drugs (Mood's median test p<0·0001). In competing-risk regression stratified by key population (MSM *vs* people who inject or have injected drugs), characteristics associated with higher rates of commencement of direct-acting antiviral treatment in both key populations were being linked to care in Australia or France, undetectable HIV-RNA status, and fewer years since the first positive HCV test (table 4). Having received HCV treatment before unrestricted access to direct-acting antiviral treatment and older age were associated with a higher rate of commencement of direct-acting antivirals among MSM only, whereas younger age and higher CD4 counts were associated with higher rates of commencement among people who inject or have injected drugs only.

	Univariable analysis, subdistribution HR (95% CI)	Multivariable analysis, adjusted subdistribution HR (95% CI)
Age, per 10 years	0·95 (0·91–0·98)	0·99 (0·95–1·03)
Gender and HIV key populations		
MSM	1 (ref)	1 (ref)
PWID, male	0·70 (0·64–0·77)	0·92 (0·82–1·02)
PWID, female	0·69 (0·61–0·77)	0·94 (0·83–1·08)
Heterosexual, male	0·60 (0·50–0·73)	0·68 (0·56–0·83)
Heterosexual, female	0·64 (0·54–0·76)	0·86 (0·72–1·02)
Other or unknown, male	0·72 (0·63–0·82)	0·89 (0·77–1·03)
Other or unknown, female	0·66 (0·53–0·81)	0·74 (0·58–0·93)
Country*		
Australia	1·25 (1·15–1·36)	1·65 (1·43–1·89)
Canada	1·02 (0·92–1·12)	0·91 (0·82–1·02)
France	1·34 (1·26–1·43)	1·42 (1·31–1·54)
Netherlands	1·82 (1·69–1·94)	1·55 (1·45–1·68)
Spain	0·57 (0·51–0·63)	0·48 (0·43–0·54)
Switzerland	0·57 (0·50–0·65)	0·63 (0·55–0·73)
Ever prescribed ART versus never prescribed ART	1·55 (1·40–1·71)	1·18 (1·05–1·32)
HIV-RNA status		
Undetectable (<50 copies per mL)	1 (ref)	1 (ref)
Detectable	0·61 (0·54–0·69)	0·64 (0·56–0·72)
Missing	0·75 (0·65–0·86)	0·60 (0·49–0·72)
CD4 count, square root	1·01 (1·01–1·02)	1·01 (1·00–1·01)
Ever diagnosed with AIDS versus never diagnosed with AIDS	0·84 (0·77–0·92)	0·93 (0·85–1·03)
Ever treated for HCV before unrestricted direct-acting antiviral access versus never treated for HCV	1·13 (1·04–1·22)	1·25 (1·14–1·36)
HCV reinfection versus primary infection before unrestricted direct-acting antiviral access	1·07 (0·93–1·24)	0·90 (0·77–1·04)
Years since first positive HCV test, per year	0·98 (0·97–0·98)	0·97 (0·97–0·98)
Liver fibrosis stage†		
No advanced fibrosis	1 (ref)	1 (ref)
Advanced fibrosis or cirrhosis	0·92 (0·84–1·00)	0·97 (0·88–1·07)
Missing	0·91 (0·82–1·01)	0·76 (0·63–0·92)

Parameter estimates obtained from competing-risks regression analysis using the Fine-Gray method. ART=antiretroviral therapy. HCV=hepatitis C virus. HR=hazard ratio. MSM=men who have sex with men. PWID=people who inject or have injected drugs. *To avoid using a particular country as a reference category, uptake of direct-acting antiviral treatment per country was compared with the grand mean using effect coding. †Advanced fibrosis or cirrhosis defined as a liver stiffness measurement ≥9·5 kPa or Fibrosis-4 score ≥2·67.

Table 3: **Factors associated with rate of commencement of direct-acting antiviral treatment (n=4552)**

Discussion

The advent of highly effective direct-acting antiviral therapy has resulted in a global effort to pursue HIV–HCV micro-elimination. In this unique, multinational cohort collaboration we assessed factors associated with the rate of commencement of direct-acting antiviral treatment following unrestricted access among individuals with HIV–HCV in several high-income countries. Despite

	MSM (n=2156), adjusted subdistribution HR* (95% CI)	PWID (n=1453), adjusted subdistribution HR* (95% CI)
Age, per 10 years	1·06 (1·01–1·12)	0·85 (0·77–0·94)
Female versus male sex	Not included	1·00 (0·88–1·15)
Country†		
Australia	1·82 (1·56–2·14)	2·16 (1·45–3·20)
Canada	0·94 (0·77–1·14)	0·98 (0·81–1·17)
France	1·25 (1·08–1·44)	1·55 (1·35–1·77)
Netherlands	1·68 (1·51–1·87)	1·10 (0·92–1·31)
Spain	0·54 (0·46–0·63)	0·41 (0·34–0·51)
Switzerland	0·52 (0·41–0·66)	0·68 (0·53–0·87)
Ever prescribed ART versus never prescribed ART	1·09 (0·89–1·34)	1·24 (1·05–1·46)
HIV-RNA status		
Undetectable (<50 copies per mL)	1 (ref)	1 (ref)
Detectable	0·77 (0·65–0·92)	0·53 (0·41–0·67)
Missing	0·60 (0·48–0·75)	2·65 (1·97–3·58)
CD4 count, square root	1·00 (0·99–1·01)	1·01 (1·00–1·02)
Ever diagnosed with AIDS versus never diagnosed with AIDS	0·94 (0·79–1·11)	0·87 (0·76–1·01)
Ever treated for HCV before unrestricted direct-acting antiviral access versus never treated for HCV	1·38 (1·20–1·58)	1·06 (0·92–1·21)
HCV reinfection versus primary infection	0·97 (0·82–1·16)	0·80 (0·54–1·20)
Years since first positive HCV test, per year	0·94 (0·93–0·96)	0·99 (0·98–1·00)
Liver fibrosis stage‡		
No advanced fibrosis	1 (ref)	1 (ref)
Advanced fibrosis or cirrhosis	0·90 (0·76–1·06)	1·11 (0·96–1·29)
Missing	0·73 (0·59–0·90)	1·98 (1·08–3·62)

Parameter estimates obtained from a competing-risks regression analysis using the Fine-Gray method. ART=antiretroviral therapy. HCV=hepatitis C virus. HR=hazard ratio. MSM=men who have sex with men. PWID=people who inject or injected drugs. *Only the results of the multivariable analyses are shown. Both univariable and multivariable HRs are shown in the appendix (p 14). †To avoid using a particular country as a reference category, uptake of direct-acting antiviral treatment per country was compared with the grand mean using effect coding. ‡Advanced fibrosis or cirrhosis defined as a liver stiffness measurement ≥9·5 kPa or Fibrosis-4 score ≥2·67.

Table 4: **Factors associated with rate of commencement of direct-acting antiviral treatment for MSM and PWID**

direct-acting antivirals being available with unrestricted access for several years (range 2–5 years), 30% of HCV-viraemic individuals with HIV included in this study remained untreated during follow-up. Significant differences in rates of uptake of direct-acting antiviral treatment were observed between countries, indicating potential differences in access to care and barriers to treatment. Furthermore, several factors associated with rates of commencement of treatment were found, with partially different risk profiles for untreated people who inject or have injected drugs and MSM.

Several indicators of engagement in HIV care and HIV treatment adherence were independently associated with a lower rate of commencement of direct-acting antiviral treatment, including having a detectable HIV RNA and a lower CD4 count. Additionally, lower rates of commencement were observed in individuals with missing HIV-RNA data or missing data on liver fibrosis parameters, which could also be considered proxies for lower engagement in care. Hence, these results indicate an overlap between groups not consistently engaged in care and treatment for both HIV and HCV and are in line with two previous studies that reported an association between lower frequency of visits and absence of treatment uptake.[9,11] As untreated HIV is associated with an accelerated progression of HCV-related liver fibrosis,[14] treatment of both HIV and HCV is of particular importance in these individuals.

Our findings showed variation between key populations regarding the commencement rate of direct-acting antiviral treatment. Compared with MSM, all other key populations had a lower rate of commencement. Additionally, for individuals who were treated with direct-acting antivirals, median time from inclusion to treatment was significantly longer in people who inject or have injected drugs than in MSM. This might indicate differences in access to health care between key populations. Several patient, provider, and structural level barriers have been identified that might affect treatment uptake among people who inject or have injected drugs, including experiences of stigma against this population in health-care settings, perceptions that sobriety is required for treatment access, and competing responsibilities due to comorbidities, including mental illness.[15] Additionally, because the duration of infection is generally much longer among people who inject or have injected drugs than among MSM, the former might have had more negative experiences with interferon in the past and hence a more negative attitude towards HCV treatment. Furthermore, among people with HIV, belonging to the key population of people who inject or have injected drugs is associated with an increased risk of becoming lost to follow-up.[16] However, in multivariable analysis, statistical significance was only observed for men with heterosexual HIV transmission and women with a route of HIV transmission other than injecting drug use or heterosexual sex, or an unknown route of HIV transmission. Of note, in the ACCESS cohort, accounting for 74% of inclusions from Australia, participants could not be assigned to the key populations of heterosexual people or people who inject or have injected drugs due to an absence of data on HIV or HCV transmission route. As Australia was the country with the highest rate of commencement of direct-acting antiviral treatment, this might have affected the analysis on differences between key populations.

Rates of uptake of treatment also varied across countries. Some of these differences could be explained by differing health-care systems and when restrictions on direct-acting antiviral treatment were lifted. Uptake in Australia peaked very quickly and declined strongly thereafter, probably caused by a warehousing effect greater than in other countries due to relatively late access to direct-acting antivirals but with unrestricted access immediately. Additionally, compared with other countries, a small proportion of individuals who ever tested HCV-RNA positive was treated between 2010 and the introduction of direct-acting antivirals (15% in Australia

versus 26–59% in other countries).[8] The two countries (Switzerland and Spain) with a significantly lower rate of commencement of direct-acting antiviral treatment compared with the population mean had a more gradual lifting of treatment restrictions and a later introduction of unrestricted access to treatment. Consequently, a larger proportion of individuals with HIV–HCV in these countries commenced treatment before unrestricted access,[17,18] and the remaining population who were HCV-viraemic during unrestricted access to direct-acting antivirals might have been a selection of individuals who were less likely to initiate treatment. As an example, in Switzerland, many MSM with HIV–HCV were treated in a trial that finished before unrestricted access to direct-acting antiviral treatment was granted and which was followed by sustained HIV–HCV micro-elimination in this population.[19,20]

This explanation is supported by the fact that the differences among countries became smaller when the rate of commencement of treatment was analysed with follow-up starting at the moment of official limited access to direct-acting antiviral treatment. Also, although country differences in the time to treatment uptake remained after including the limited access period, differences in the proportion of participants who had initiated treatment by the end of follow-up did not. This implies that the differences in time to treatment reflect differences in treatment roll-out where treatment uptake in countries with early unrestricted access peaked very quickly compared with a more gradual uptake in countries with a stepwise release of restrictions. Another factor that could have resulted in differences in commencement rates between countries is varying policies for treatment of acute HCV infection. Because direct-acting antivirals were not officially registered for acute HCV infection, treatment of acute HCV was dependent on local or national policies. Additionally, in some of the participating countries, individuals diagnosed with acute HCV were being proactively enrolled in clinical trials for treatment of acute HCV.[21,22] However, because only 198 (4%) of 4552 participants fulfilled acute HCV diagnosis criteria and had acute HCV diagnosis less than 6 months from start of follow-up, influence was probably minimal. Furthermore, results could have been affected by violation of the proportional hazards assumption, because differences in effect size between countries varied over time.

The characterisation in our study of individuals untreated with direct-acting antivirals highlights several potential obstacles for HIV–HCV micro-elimination. Of the untreated individuals, 8% had advanced fibrosis and in many individuals the fibrosis stage was unknown, indicating a considerable risk of liver-related morbidity and mortality in this group. Furthermore, a substantial proportion of untreated individuals reported behaviour associated with the risk of onward HCV transmission, such as injection drug use and condomless sex. The absence of uptake of direct-acting antiviral treatment could potentially serve as a driving factor for onward transmission of HCV. This issue does not seem to be confined within a specific country,[9] considering that some settings have shown an increase in the proportion of external introductions of HCV infections due to international transmission among MSM.[23] In different analyses of InCHEHC data, a decrease in incidence of primary HCV infections and HCV reinfections was seen.[8] However, because our findings showed that treatment uptake has declined, it is unclear whether these reductions in incidence will be sustained and whether the WHO targets will be reached by 2030.

Our analysis of a large-scale, international collaboration of cohorts allowed us to compare uptake of direct-acting antiviral treatment across several high-income countries, while identifying factors associated with a lower rate of treatment commencement that are not necessarily country specific. Nevertheless, there are several limitations of this study. First, because only cohorts from high-income countries were included, our results are not necessarily generalisable to low-income and middle-income countries. Second, a positive HCV-RNA test was required for inclusion and individuals who tested HCV-antibody positive with missing HCV-RNA status were not included. This selection criterion might have biased the proportion of individuals remaining untreated with direct-acting antivirals. Third, excluding individuals with presumed spontaneous HCV clearance on the basis of only one negative HCV-RNA result might have resulted in incorrectly excluding individuals who did not have definitive spontaneous clearance. Of the 764 individuals excluded because of presumed spontaneous clearance, 65 (9%) had a subsequent HCV-RNA positive test, which could either be due to reinfection or incorrect classification of spontaneous clearance. Importantly, this percentage is in line with the proportion of reinfections following spontaneous clearance reported in literature,[6,24] and therefore the effect of this potential misclassification bias is likely to be minimal.

Fourth, behavioural characteristics were only available for a small number of participants, making it difficult to understand whether these factors affected commencement of direct-acting antiviral treatment or whether untreated individuals were at risk of onwards HCV transmission. Fifth, our study included individuals with a least one visit during the direct-acting antiviral era. Hence, results might not be generalisable to individuals lost to follow-up from regular care and reported rates of treatment commencement might be underestimated. Sixth, 10% of participants were included at cohort entry after the date of unrestricted access with a known HCV diagnosis. An unknown proportion of this group might have already been eligible for direct-acting antiviral treatment before inclusion, thereby artificially reducing follow-up time and consequently the rate of treatment commencement for this group. Seventh, individuals

with reinfection following HCV clearance in the direct-acting antiviral era were not reconsidered in analysis, thus caution is needed when interpreting these findings in the context of reinfection. Finally, due to an absence of data or inconsistencies in reporting data between cohorts, several characteristics known to be associated with poor uptake of direct-acting antiviral treatment were not accounted for in the analysis, including socioeconomic characteristics, incarceration, and frequency of outpatient clinic visits.[9,11,12] Also, treatment adherence was not evaluated and ethnicity data were not available.

In conclusion, of the countries included in this international cohort, most individuals with HIV–HCV commenced treatment with direct-acting antivirals following unrestricted access. However, there remains a substantial group of people with HIV who are HCV-viraemic who have yet to commence direct-acting antiviral treatment despite unrestricted access. As these individuals are likely to contribute to ongoing national and international HCV transmission and are at risk of HCV-related mortality, treating this population might be a crucial step towards achieving HCV elimination. Efforts to increase engagement in care as well as decentralised direct-acting antiviral care pathways are required to increase treatment uptake among the remaining group of people with HIV who are HCV-viraemic.

Contributors

CJI, AB, RS-D, DKvS, CS, MM, JS, MvdV, and GVM conceived and designed the current study. CS, JB, LW, MBK, AR, DS, KL, JSD, MH, MvdV, MS, and GVM collected the data. RS-D, DKvS, and AS managed the data. CJI, AB, RS-D, DKvS, and CS analysed the data. CJI, AB, and CS drafted the first version of the manuscript. CJI, RS-D, and DKvS accessed and verified the underlying data. All authors contributed to the interpretation of results and preparation and review of the manuscript. All authors read and approved the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CJI has received research funding from Gilead, unrelated to this work. MS has received investigator-initiated research funding from Gilead Sciences and AbbVie and consultant fees from Gilead Sciences for activities unrelated to this work. JB has received grants from Gilead, MSD, and ViiV Healthcare; and honoraria for advice or public speaking from Gilead, MSD, Janssen, and ViiV Healthcare. MBK reports grants for investigator-initiated studies from ViiV Healthcare, AbbVie, and Gilead, and consulting fees from ViiV Healthcare, AbbVie, and Gilead, all outside the submitted work. MBK is supported by a Tier I Canada Research Chair. AR reports support to his institution for advisory boards or travel grants from MSD, Gilead Sciences, Pfizer, and AbbVie, and an investigator-initiated trial grant from Gilead Sciences. All remuneration went to his home institution and not to AR personally, and all remuneration was provided outside the submitted work. JS's institution has received research support and consultancy fees from Gilead, and a speaker's fee from Janssen Pharmaceuticals, independent from the submitted work. JSD receives funding from Gilead Sciences and AbbVie, unrelated to this work. MH receives funding from Gilead Sciences and AbbVie unrelated to this work. MvdV reports honoraria or research grants from Gilead, MSD, and ViiV Healthcare, all paid to his institution and outside the submitted work. KL has received research support from MSD unrelated to this work. All other authors report no competing interests.

Data sharing

The data dictionary based on the HIV Cohorts Data Exchange Protocol 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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