Behavioural trajectories following DAA treatment for HCV among people with HIV: findings from an international consortium of prospective cohort studies

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See related paper on page 519

Objective: Examine the proportion of people with HIV engaging in behaviours associated with hepatitis C virus (HCV) infection after successful direct-acting antiviral (DAA) treatment and establish longitudinal patterns of behavioural risk over time.

Design: Multinational, prospective cohort study (International Collaboration on Hepatitis C Elimination in HIV Cohorts).

Methods: Individuals with HIV successfully treated with DAAs and ≥2 follow-up visits with behavioural data were included. Changes in the proportion of any risk behaviour after treatment, which included sexual and drug use behaviours, were analysed using logistic regression with generalized estimating equations. We identified distinct trajectories of any risk behaviour over time using group-based trajectory models (GBTM).

Results: Of the 1,477 individuals included, 487 (33.0%) were people who inject drugs, 378 (25.6%) were men who have sex with men and 442 (29.9%) were both. During a median 2.7 years (IQR = 1.6–3.9) of follow-up, the proportion engaging in any risk behaviour slightly decreased over time (adjusted odds ratio per half year = 0.97, 95% confidence interval = 0.95–0.99). GBTM revealed four distinct behavioural trajectories: consistently low (n = 433, 29.3% of total population), moderate at baseline and increasing (n = 119, 8.1%), high at baseline and decreasing (n = 184, 12.5%) and consistently high (n = 741, 50.2%).

Conclusions: Despite slight decreases in behaviours following successful DAA treatment, half of individuals had a consistently high probability of behaviours that put them at risk of HCV reinfection over time. As reinfections comprise a growing proportion of

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new incident HCV cases, these findings underscore the importance of ongoing primary prevention measures alongside testing and retreatment to eliminate HCV.

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Introduction

An estimated 2.2 million people are living with human immunodeficiency virus (HIV)/hepatitis C virus (HCV) co-infection worldwide [1,2]. In people with HIV, new HCV infections are more common among men who have sex with men (MSM) and people who inject drugs (PWID) [1]. It is estimated that, when HCV is left untreated, approximately 20–30% of people with chronic HCV infection develop HCV-related liver complications after 25–30 years [3]. In 2023, around 250 000 people died due to liver complications caused by HCV worldwide [4]. As such, MSM and PWID with HIV are considered priority populations for HCV elimination.

In countries with unrestricted access to highly effective, all-oral based, direct-acting antiviral (DAA) treatment, strong decreases in HCV prevalence and incidence among individuals with HIV were observed [5,6]. These declines could help curb the HCV epidemic in these individuals due to a treatment as prevention effect [5]. A study conducted among MSM with HIV in the Netherlands reported a reduction in behaviours associated with HCV following interferon-based treatment, while among MSM treated with DAAs, no such reductions were observed [7]. However, given the ease of HCV treatment with DAA formulations, relative to interferon-based treatments, less emphasis may be placed on primary preventive measures as part of the ongoing public health response to HCV elimination [8–10]. Further complicating this issue is the fact that viral clearance following HCV treatment does not confer protection against HCV reinfection [11]. If there are limited reductions in these behaviours, incidence of HCV reinfection could rebound (i.e., risk compensation).

In this study, we aimed to examine the proportion of people with HIV engaging in any behaviour associated with HCV acquisition following successful DAA treatment. We then intended to examine longitudinal patterns of behavioural risk and to evaluate the sociodemographic and clinical correlates of these patterns. Examining changes in behaviours following treatment could help identify those at risk of subsequent HCV infection and the need for increased testing and behavioural interventions.

Methods

Study design and setting

Data from the International Collaboration on Hepatitis C Elimination in HIV Cohorts (InCHEHC) were used [12]. Within this cohort, data from 11 different cohorts of people with HIV at risk of HCV infection or coinfected with HCV were pooled from six high-income countries (Australia, Canada, France, the Netherlands, Spain and Switzerland). Members from each cohort prepared and submitted data to the coordinating centre (Burnet Institute, Australia) based on the HIV Cohorts Data Exchange Protocol (HICDEP), including sociodemographic, HIV and HCV clinical and behavioural data, when available [12]. For the current analysis, we included data from six InCHEHC cohorts of five countries that collected data on drug use and sexual risk behaviours (Supplementary Table 1, http://links.lww.com/QAD/D728). Ethical 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. No additional consent was needed from cohort participants to be included in the InCHEHC study.

Eligibility criteria

For the current analysis, we included all people with HIV enrolled in the InCHEHC study if they met the following criteria: aged 18 years or older, were successfully treated with DAAs [i.e., achieved sustained virological response (SVR) 12 weeks after the end of treatment either for primary HCV infection or HCV reinfection], and had at least two follow-up study visits with behavioural data after treatment within $\geq$6 months apart following treatment completion. SVR was defined as having at least one HCV-RNA negative test at least 12 weeks after the end date of DAA treatment.

Study variables

Sociodemographic variables included age, assigned sex at birth, country of cohort enrolment and key population. To define key population, individuals were classified as MSM or PWID based on recorded mode of HIV and HCV transmission, data on sexual orientation (when available) and reported recent sexual and injecting drug use (IDU) behaviours during follow-up. Subsequently,

individuals classified as both MSM and PWID were classified as MSM+PWID. Clinical data included time since HIV diagnosis (at DAA completion), $CD4^+$ cell count, HIV-RNA and HIV antiretroviral treatment (time-updated). Data related to HCV infection included HCV-RNA testing and results, HCV treatment (time-updated) and liver fibrosis stage based on liver stiffness measured by transient elastography (FibroScan at DAA completion). HCV-RNA status (positive vs. negative) was defined based on a qualitative RNA or antigen test, or if there was no qualitative test result available, a quantitative RNA test result. Quantitative HCV-RNA test results were classified as positive if the result was greater than or equal to the lower limit of detection, or 15 copies per mL if the lower limit of detection was unknown. Reinfection was defined as having quantifiable HCV-RNA following successful treatment with DAAs.

Behavioural data were collected using self-reported questionnaires. These data included any recent (i.e., occurring within a maximum of up to twelve months) substance use, IDU, other recreational drug use (hereafter referred to as non-IDU), condomless anal sex (CAS) with any partner, and CAS with any casual partner (all yes/no). Data on non-IDU was inferred from the variables any substance use and IDU where individuals who did report any substance use but no IDU, were considered as non-IDU.

Statistical analysis

Follow-up began at the date of DAA treatment completion (baseline) until the date of last study visit with available behavioural data or date of HCV reinfection diagnosis, whichever occurred first. For individuals who became reinfected and were retreated, follow-up recommenced after the date of successful completion of their subsequent DAA therapy. We censored follow-up time at 5 years given the few individuals contributing follow-up after this time point.

We described the characteristics of the study population at baseline by country of enrolment using medians [interquartile ranges (IQR)] for continuous variables, and counts (%) for categorical variables.

We defined any behavioural risk as a composite endpoint of the following behaviours associated with HCV infection: any substance use (including both IDU and non-IDU), IDU, non-IDU, CAS with any partner, and CAS with any casual partner [13–15]. We modelled the probability of any behavioural risk during follow-up using Generalized Estimating Equations (GEE) for logistic regression accounting for clustering within individuals. We added time in intervals of 6 months as a covariate to calculate odds ratios (ORs), and their corresponding 95% confidence intervals (CIs), of changes in odds of outcome for each interval relative to the prior interval. Models were adjusted for the time-updated covariates age at visit, the number of HCV reinfections (i.e., 0 or $\geq$1) and DAA availability (i.e., in calendar period of restrictive or broad access). Start dates of restrictive and broad DAA access varied by country (Supplementary Table 1, http://links.lww.com/QAD/D728). We then modelled the probability of each individual behaviour over time, separately, using the same adjusted GEE model for logistic regression as described above. From these models, we plotted the marginal probabilities of each outcome over follow-up time along with its 95% CI.

To identify specific patterns of behaviours, we used group-based trajectory modelling (GBTM) to establish distinct longitudinal behavioural trajectories of the probability of any behavioural risk over time [16]. We ran a series of group-based trajectory models with increasing numbers of groups (i.e., $k=1, 2, \cdots, 5$) using the "traj" plug-in in Stata. We modelled time as a cubic function for all trajectories. For each outcome, the final number of groups was determined by selecting the model with the lowest Bayesian Information Criterion (BIC), highest entropy values (increased probability of clear group assignment), and all trajectories having a marginal prevalence of >5% (Supplementary Table 2, http://links.lww.com/QAD/D728). Group-based trajectories and observed group probabilities were plotted using the "trajplot" command. Using the final models, participants were then assigned to the trajectory in which they had the highest *a posteriori* probability of membership. We then compared the characteristics of the study population between trajectory groups using the Kruskall–Wallis test for continuous variables and Pearson X^2 or Fisher's exact test for categorical variables.

These models were also run separately for each individual behaviour as an outcome. To assess which of the individual behaviours were driving the classification of any behavioural risk, we also compared group membership from the model for any behavioural risk associated with HCV acquisition with the membership from the model of each individual behaviour using Spearman's correlation coefficient.

We conducted two sensitivity analyses. First, to assess the influence of behavioural trajectories in only MSM and only PWID, we excluded individuals who were MSM+PWID or other and reran the analysis per key population for any risk behaviour. Second, to assess the effect of differences in data collection periods (i.e., every 6 vs. 12 months), we combined consecutive six-monthly visits into twelve-monthly visits when appropriate and limited analysis to behaviours occurring in the preceding twelve months. If the last study visit did not occur on a 12-monthly visit, it was removed from the sensitivity analysis.

Statistical analyses were performed using Stata (version 17.0, College Station, TX, USA).

Results

Characteristics of the study population

Of 33,105 individuals with HIV, 2,510 (7.6%) received treatment with DAAs. Of 2,510 individuals, 2,153 (85.8%) were successfully treated. Overall, 1,477 (68.6%) of 2,153 had at least two study visits with behavioural data ≥6 months apart following treatment completion and were included in the analysis (Fig. 1). Of those, DAAs were used to treat primary HCV infection in 1,393 (94.3%) and HCV reinfection in 84 (5.7%).

At DAA treatment completion, median age was 51 years (IQR = 45–56) (Table 1). Most participants were assigned male at birth (n = 1,110, 75.2%) and one third belonged to the PWID key population (n = 487, 33.0%). In addition, 1,397 (94.6%) had an HIV RNA viral load below 50 copies/ml (i.e., undetectable). At baseline, the proportion of participants who were MSM was the highest in the Netherlands [20 (83.3%) of 24 participants] and lowest in Canada [73 (13.2%) of 552 participants]. Participants in France had the highest median years since HIV diagnosis [25.1 years (IQR = 16.1–29.2)].

Changes in behaviours following successful direct-acting antiviral treatment

During follow-up, participants had a median of four visits (IQR = 3–6). Median follow-up was 2.7 years (IQR = 1.6–3.9), totalling 4,062.7 person-years of follow-up. After adjusting for age, number of previous HCV

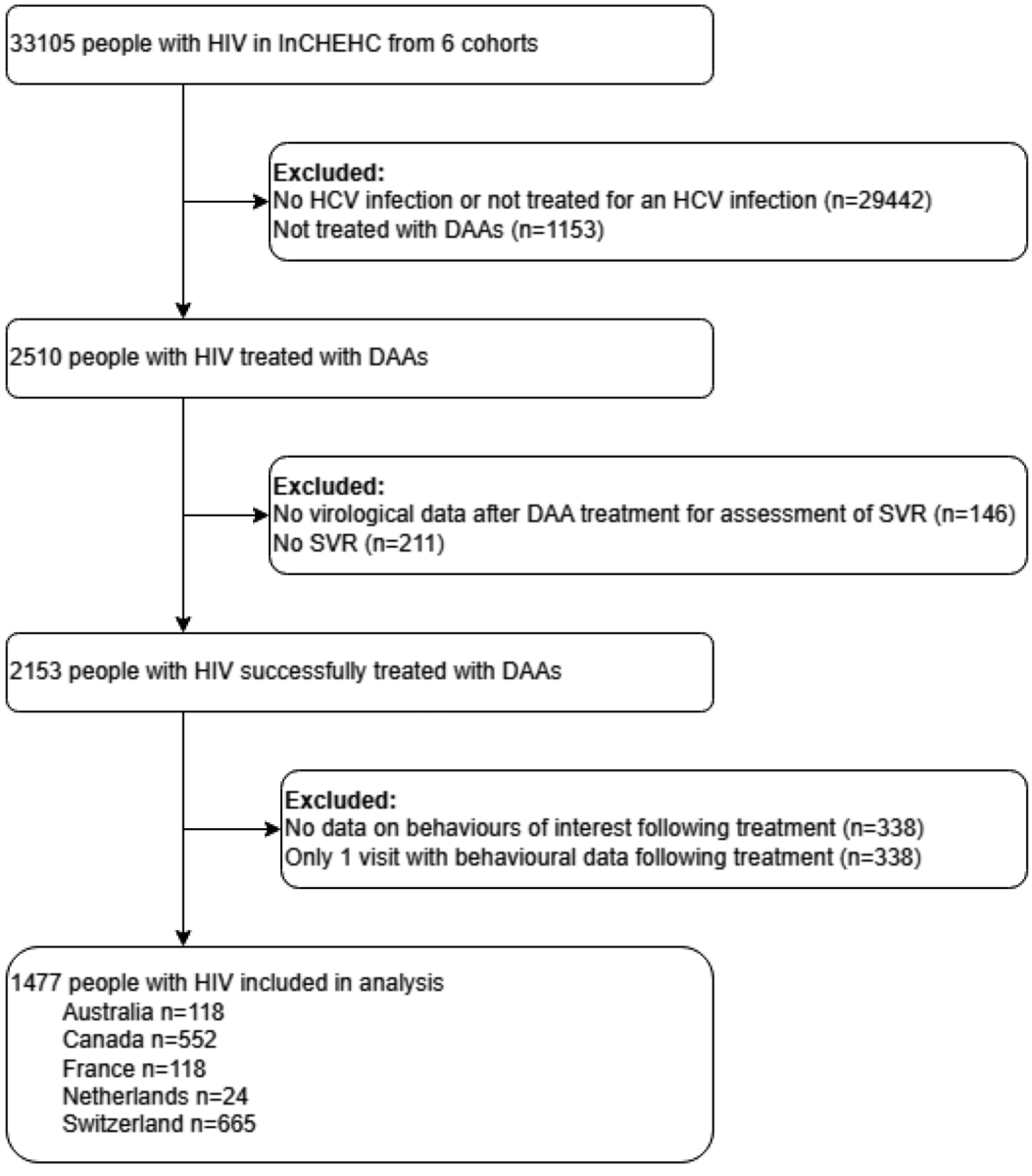

Fig. 1. Flowchart of individuals included in analysis. DAA, direct-acting antiviral; HCV, hepatitis C virus; HIV, human immunodeficiency virus; InCHEHC, International Collaboration on Hepatitis C Elimination in HIV Cohorts; SVR, sustained virologic response.

Table 1. Baseline sociodemographic and clinical characteristics at the start of follow-up among participants successfully treated with DAAs and enrolled in InCHEHC.

Characteristic	Total (*N* = 1477)	Australia (*N* = 118)	Canada (*N* = 552)	France (*N* = 118)	Netherlands (*N* = 24)	Switzerland (*N* = 665)
Age (years)	51 (46–56)	50 (43–56)	51 (46–56)	51 (48–55)	49 (44–55)	52 (46–56)
Sex assigned at birth[a]						
Female	364 (24.6)	3 (2.5)	150 (27.2)	27 (22.9)	0 (0.0)	184 (27.7)
Male	1,110 (75.2)	115 (97.5)	339 (72.3)	91 (77.1)	24 (100.0)	481 (72.3)
Key population						
MSM	378 (25.6)	58 (49.2)	73 (13.2)	17 (14.4)	20 (83.3)	210 (31.6)
PWID	487 (33.0)	10 (8.5)	215 (39.0)	81 (68.6)	0 (0.0)	181 (27.2)
MSM+PWID	442 (29.9)	43 (36.4)	187 (33.9)	6 (5.1)	4 (16.7)	202 (30.4)
Other/unknown	170 (11.5)	7 (5.9)	77 (14.0)	14 (11.9)	0 (0.0)	72 (10.8)
Years since HIV diagnosis[a]	18.2 (10.5–25.6)	15.4 (9.0–23.9)	15.9 (9.2–21.1)	25.1 (16.1–29.2)	12.5 (8.7–17.4)	20.1 (11.9–27.4)
$CD4^+$ T-cell count, cells per μl[a]	584 (407–813)	652 (450–811)	512 (320–750)	623 (446–864)	610 (552–830)	620 (456–838)
HIV-RNA status[a]						
Detectable	74 (5.0)	7 (5.9)	34 (6.2)	8 (6.8)	2 (8.3)	23 (3.5)
Undetectable[b]	1,397 (94.6)	111 (94.1)	512 (92.8)	110 (93.2)	22 (91.7)	642 (96.5)
Ever prescribed ART[a]	914 (61.9)	114 (96.6)	497 (90.0)	64 (54.2)	24 (100.0)	215 (32.3)
Liver stiffness[c]						
F0–F2 (<9.5 kPa)	797 (54.0)	91 (77.1)	263 (47.6)	0 (0.0)	15 (62.5)	428 (64.4)
F3–F4 (≥9.5 kPa)	304 (20.6)	18 (15.3)	121 (21.9)	0 (0.0)	0 (0.0)	165 (24.8)
Unknown	376 (25.5)	9 (7.6)	168 (30.4)	118 (100.0)	9 (37.5)	72 (10.8)

Presented are *n* (%) or median (IQR).
[a]Three participants with missing data on sex at birth (*n* = 3 Canada); 20 participants with missing data on years since HIV diagnosis (*n* = 4 Australia, *n* = 16 Canada); 6 participants with missing data on $CD4^+$ cell count (*n* = 6 Australia); 6 participants with missing data on HIV-RNA status (*n* = 6 Canada); 217 participants with missing data on ART (*n* = 3 Australia, *n* = 6 Canada, *n* = 208 Switzerland).
[b]Defined as ≤50 copies per mL or below the detection limit of the used assay.
[c]Measured by transient elastography (FibroScan).
ART, antiretroviral therapy; DAA, direct-acting antiviral; HIV, human immunodeficiency virus; InCHEHC, International Collaboration on Hepatitis C Elimination in HIV Cohorts; kPa, kilopascal; MSM, men who have sex with men; PWID, people who inject or have injected drugs; RNA, ribonucleic acid.

reinfections and DAA availability, any risk behaviour slightly decreased during follow-up [adjusted odds ratio (aOR) = 0.97, *P* = 0.004] (Table 2). Decreases were also observed with any substance use (aOR = 0.97, *P* = 0.02) and non-IDU (aOR = 0.97, *P* = 0.045); but there was no evidence for decreases in IDU (aOR = 0.98, *P* = 0.23), CAS with any partner (aOR = 1.01, *P* = 0.55) or CAS with any casual partner (aOR = 1.01, *P* = 0.53) (Table 2). Supplementary Figure 1, http://links.lww.com/QAD/D728 presents the proportion of participants reporting each behavioural outcome over time.

Trajectories of behaviour changes following successful direct-acting antiviral treatment

In GBTM analyses, four distinct trajectories for any risk behaviour were identified: one with a group mean probability below 0.20 throughout follow-up [termed herein as "consistently low" (27.8%)], one with a group mean probability around 0.80 at baseline with a decreasing probability during follow-up ["high decreasing", (16.4%)], one with a group mean probability around 0.40 at baseline with an increasing probability during follow-up ["moderate increasing", 11.6%)] and one with

Table 2. Population-averaged changes in drug use and sexual behaviours following successful DAA treatment for HCV infection among InCHEHC participants.

Behaviours[a]	Number of individuals analysed (*n*)	Total number of observations	Median follow-up time (IQR)	aOR (95% CI)	*P*
Any risk behaviour	1,477	6,997	2.7 (1.6–3.9)	0.97 (0.95–0.99)	0.004
Individual behaviours					
Any substance use	1,454	6,930	2.8 (1.6–3.9)	0.97 (0.95–1.00)	0.02
IDU	1,433	6,794	2.7 (1.5–3.9)	0.98 (0.94–1.01)	0.23
Non-IDU	1,236	5,837	2.8 (1.6–3.9)	0.97 (0.95–1.00)	0.045
CAS with any partner	629	2,416	2.4 (1.4–3.5)	1.01 (0.97–1.06)	0.55
CAS with any casual partner	629	2,416	2.4 (1.4–3.5)	1.01 (0.97–1.06)	0.53

The estimated adjusted odds ratio indicates the average behaviour change for each 6-montly interval relative to the prior interval. Odds ratios were adjusted for age, number of HCV reinfections and DAA availability (all as time-varying covariates).
[a]Behaviours occurring within a maximum of up to 12 months.
aOR, adjusted odds ratio; CAS, condomless anal sex; CI, confidence interval; HCV, hepatitis C virus; IDU, injecting drug use; InCHEHC, International Collaboration on Hepatitis C Elimination in HIV Cohorts; IQR, interquartile range.

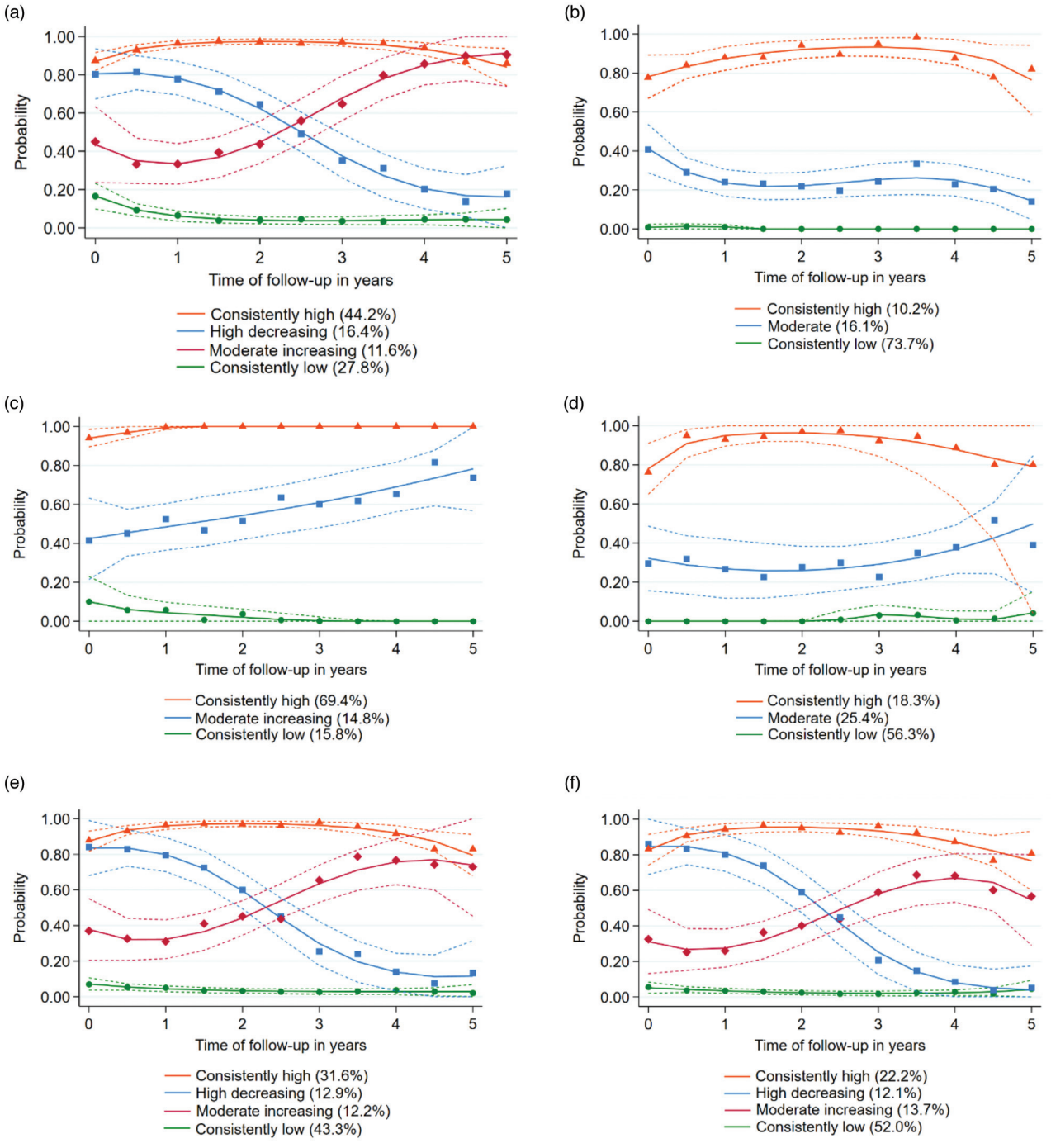

Fig. 2. Trajectories of behavioural outcomes following successful DAA treatment among InCHEHC participants. Behavioural trajectories for (a) any risk behaviour, (b) IDU, (c) CAS with any partner, (d) CAS with any casual partner, (e) any substance use, (f) non-IDU. Plotted symbols indicate the observed group mean probability of risk behaviour per six months; the plotted lined indicates the trajectory; dashed lines indicate the 95% confidence intervals of the trajectory.
CAS, condomless anal sex; DAA, direct-acting antiviral; IDU, injecting drug use; InCHEHC, International Collaboration on Hepatitis C Elimination in HIV Cohorts.

a group mean probability above 0.80 throughout follow-up ["consistently high", (44.2%)] (Fig. 2a). At baseline, those assigned to the "consistently high" profile were the youngest ($P < 0.001$), more recently received an HIV diagnosis ($P < 0.001$) and least often had an undetectable HIV viral load ($P = 0.035$), compared to the other profiles (Table 3). Individuals with "consistently low" risk behaviour least often belonged to the MSM or PWID key populations ($P < 0.001$). However, the differences between profiles were often numerically minimal.

Table 3. Sociodemographic and clinical characteristics at baseline according to any risk behaviour trajectory.

	Trajectory[a]				
	Consistently low ($n=433$)	Moderate increasing ($n=119$)	High decreasing ($n=184$)	Consistently high ($n=741$)	*P*
Age (years)	53 (49–57)	52 (47–55)	51 (47–56)	51 (44–55)	0.001
Country					<0.001
Australia	32 (7.4)	4 (3.4)	6 (3.3)	76 (10.3)	
Canada	155 (35.8)	48 (40.3)	91 (46.5)	258 (34.8)	
France	29 (6.7)	5 (4.2)	8 (4.4)	76 (10.3)	
Netherlands	1 (0.3)	1 (0.8)	0 (0.0)	22 (3.0)	
Switzerland	216 (49.9)	61 (51.3)	79 (42.9)	309 (41.7)	
Sex assigned at birth[b]					0.47
Male	321 (74.1)	88 (74.0)	132 (71.7)	569 (76.8)	
Female	110 (25.4)	31 (26.1)	52 (28.3)	171 (23.1)	
Key population					<0.001
MSM	88 (20.3)	36 (30.3)	41 (22.3)	213 (28.7)	
PWID	172 (39.7)	40 (33.6)	62 (33.7)	213 (28.7)	
MSM+PWID	51 (11.8)	37 (31.1)	71 (38.6)	283 (38.2)	
Other/Unknown	122 (28.2)	6 (5.0)	10 (5.4)	32 (4.3)	
Years since HIV diagnosis[b]	20.0 (12.0–26.6)	19.5 (12.5–26.0)	18.4 (10.6–24.4)	16.2 (9.6–25.0)	<0.001
$CD4^+$ T-cell count, cells per μl[b]	578 (415–803)	567 (360–813)	549 (360–820)	600 (415–813)	0.74
HIV-RNA status[b]					0.035
Detectable	11 (2.5)	7 (5.9)	9 (4.9)	47 (6.3)	
Undetectable[c]	422 (97.5)	112 (94.1)	174 (94.6)	689 (93.0)	
Ever prescribed ART[b]	260 (60.1)	64 (53.8)	115 (62.5)	475 (64.1)	0.52
Liver stiffness[d]					0.07
F0–F2 (<9.5 kPa)	242 (55.9)	58 (48.7)	95 (51.6)	402 (54.3)	
F3–F4 (≥9.5 kPa)	94 (21.7)	35 (29.4)	41 (22.3)	134 (18.1)	
Missing	97 (22.4)	26 (21.9)	48 (26.1)	205 (27.7)	
HCV reinfection IR per 100 PY (95%CI)	0.24 (0.03–0.71)	0.26 (0.01–1.25)	0.35 (0.04–1.25)	1.28 (0.84–1.90)	0.003

All are presented as *n* (%) or median (IQR) unless otherwise indicated.
[a]Participants were assigned to a trajectory based on the highest posterior probability of belonging to a given class.
[b]Three participants with missing data on sex at birth ($n=2$ consistently low and $n=1$ consistently high); 20 participants with missing data on HIV diagnosis ($n=7$ consistently low, $n=2$ moderate increasing, $n=3$ high decreasing and $n=8$ consistently high); 6 participants with missing data on $CD4^+$ T-cell count ($n=3$ consistently low and $n=3$ consistently high); 6 participants with missing data on HIV-RNA status ($n=1$ high decreasing and $n=5$ consistently high); 217 participants with missing data on ever prescribed ART ($n=76$ consistently low, $n=22$ moderate increasing, $n=27$ high decreasing and $n=92$ consistently high).
[c]Defined as ≤50 copies per mL or below the detection limit of the used assay.
[d]Measured by transient elastography (FibroScan®).
ART, antiretroviral therapy; DAA, direct-acting antiviral; HIV, human immunodeficiency virus; kPa, kilopascal; MSM, men who have sex with men; NA, not accessed; PWID, people who inject or have injected drugs; RNA, ribonucleic acid.

When looking at individual behaviours, most GBTM analyses identified three profiles of consistently low, moderate and consistently high behavioural risk [for outcomes IDU (Fig. 2b), CAS with any partner (Fig. 2c) and CAS with any casual partner (Fig. 2d)]. Only any substance use (Fig. 2e) and non-IDU (Fig. 2f) had the same four profiles as in the main analysis. The group-based trajectories of any risk behaviour were most strongly correlated with any substance use (= 0.73, $P<0.001$) and least correlated with CAS with any casual partner (= 0.29, $P<0.001$) (Supplementary Table 3, http://links.lww.com/QAD/D728). For most of the outcomes, younger age at baseline was associated with a higher risk of being in the "consistently high" profile [for outcomes any substance use (Supplementary Table 4, http://links.lww.com/QAD/D728), IDU (Supplementary Table 5, http://links.lww.com/QAD/D728), non-IDU (Supplementary Table 6, http://links.lww.com/QAD/D728) and CAS with any casual partner (Supplementary Table 7, http://links.lww.com/QAD/D728)]. Compared to the "consistently low" profiles, other behavioural profiles more often included PWID or MSM+PWID for drug use outcomes [i.e., any substance use (Supplementary Table 4, http://links.lww.com/QAD/D728), IDU (Supplementary Table 5, http://links.lww.com/QAD/D728) and non-IDU (Supplementary Table 6, http://links.lww.com/QAD/D728)] and MSM or MSM+PWID for sexual behavioural outcomes [i.e., CAS with any casual partner (Supplementary Table 7, http://links.lww.com/QAD/D728) and CAS with any partner (Supplementary Table 8, http://links.lww.com/QAD/D728)].

Sensitivity analysis

In sensitivity analysis where we restricted analysis to MSM ($n=378$), we found no changes in any risk behaviour following successful DAA treatment (aOR = 1.02, $P=0.44$) (Supplementary Table 9, http://links.lww.com/QAD/D728 and Supplementary Figure 2A, http://links.lww.com/QAD/D728). GBTM revealed two distinct trajectories: one group with a "consistently low" (35.0%) profile and one group with a "consistently high" (65.0%) profile (Supplementary Figure 3A, http://links.lww.

com/QAD/D728). When restricting analyses to PWID ($n = 487$), we observed a slight decrease in any risk behaviour during follow-up after successful DAA treatment (aOR = 0.95, $P = 0.01$) (Supplementary Table 9, http://links.lww.com/QAD/D728 and Supplementary Figure 2B, http://links.lww.com/QAD/D728). GBTM analyses revealed four distinct trajectories of "consistently low" (29.8%), "moderate increasing" (16.4%), "high decreasing" (14.6%) and "consistently high" (39.2%) among PWID (Supplementary Figure 3B, http://links.lww.com/QAD/D728). In sensitivity analysis limited to behaviours occurring in the preceding twelve months ($n = 912$), no changes in any risk behaviour following successful DAA treatment were observed (aOR = 1.00, $P = 0.82$) (Supplementary Table 9, http://links.lww.com/QAD/D728 and Supplementary Figure 2C, http://links.lww.com/QAD/D728). GBTM revealed two distinct trajectories: one group with a "consistently low" (37.7%) profile and one group with a "consistently high" (62.3%) profile (Supplementary Figure 3C, http://links.lww.com/QAD/D728).

Discussion

In this international, longitudinal cohort of individuals with HIV who acquired HCV, we assessed longitudinal drug use and sexual behaviours following successful HCV treatment with DAAs. Over time, there were overall slight decreases in behaviours associated with HCV. However, after identifying four distinct trajectories of any risk behaviour, half of individuals had a "consistently high" probability of engaging in drug use and sexual behaviours following treatment. Apart from being slightly younger and more recently diagnosed with HIV, individuals with a high probability risk behaviour had no discernible characteristics compared to other trajectory groups.

The availability of all-oral, highly effective DAA regimens marks a significant breakthrough in HCV treatment. However, those who are cured continue to be at risk of HCV reinfection. Following the availability of DAAs, concerns have arisen that simplified treatment may result in a lower prioritisation of primary prevention measures within the public health response to HCV [10,17]. Several studies have found decreases after DAA treatment in certain risk behaviours, such as IDU and CAS with casual partners, whereas other studies found no such changes [18–20]. Some of the differences between studies could be due to differences in the behaviours measured, including differences in reference periods, and the epidemiological context of HCV, such as variations in primary transmission routes. In addition, previous studies found limited behavioural change before and after DAA treatment among MSM with HIV diagnosed with an HCV infection [7,18]. In our study, we found a slight decrease in the proportion of individuals engaging in any substance use and non-IDU following DAA treatment. IDU and sexual behaviours appeared to remain stable following DAA treatment. These findings highlight that primary prevention remains a key pillar in HCV elimination efforts alongside reinfection surveillance and the availability of retreatment among individuals with a cleared HCV infection.

One issue of modelling a population-averaged assessment in behaviours is that certain patterns of behaviour may be masked. Indeed, group-based trajectory modelling of any risk behaviour revealed four distinct trajectories, whereby roughly one-quarter of included individuals had a "consistently low" risk behaviour probability (29.3% of the total population) and the majority retained a high probability of risk behaviour (50.2%) during follow-up. These groupings were likely largely driven by differences in any substance use and non-IDU, as a majority of individuals also retained a high probability in these drug use behaviours. Interestingly, two trajectories had divergent patterns of change in any risk behaviour, with one profile whose probability decreased and the other increased during follow-up. Increases in risk behaviour could be attributed to initial risk reduction after having received an HCV diagnosis or concerns about potential onward transmission [10,21,22]. However, this interpretation remains speculative. There appeared to be few clinically meaningful factors that could effectively distinguish the trajectories from one another. Nevertheless, for most behaviours, high probability risk behaviour seemed to be the most present among somewhat younger individuals, and individuals belonging to the PWID and MSM+PWID (for drug use behaviours) and the MSM and MSM+PWID key population (for sexual behaviours). We conducted a sensitivity analysis among PWID and MSM separately, finding similar behavioural trajectories among PWID and two trajectories of high and low probability risk behaviour among MSM. When focussing on behaviours occurring in the preceding twelve months, two distinct probability trajectories were identified to be the best-fitting model, likely due to less granular data (i.e., a reduced number of individuals and study visits) included in the analysis.

HCV infection incidence has declined in countries with broad access to DAA treatment [5]. However, the proportion of all incident HCV infections due to reinfection has increased from 23% in 2015 to 41% in 2019 in this cohort [6]. By 2023, one third of all DAAs dispensed in Australia were for retreatment, primarily due to HCV reinfection [23], suggesting that as primary infections decline, reinfections are playing an increasingly important role in the HCV epidemic in the DAA era. While 3 to 6-monthly testing is currently recommended for people with ongoing HCV-related drug use and sexual behaviours following HCV clearance, the optimal testing frequency remains unknown and HCV testing

guidelines often differ between countries [24–26]. Given the limited behavioural change in some of the identified behavioural trajectories, including the consistent high probability of risk behaviours in the majority of individuals, and the varying patterns in behaviours in other trajectories, continuous assessment of behaviours should be encouraged to inform targeted HCV RNA testing strategies.

Strengths of this study included the large scale, international collaboration of cohorts, which allowed us to assess changes in HCV-related behaviours following DAA treatment across several high-income countries. In addition, the large sample size and use of GBTM helped us to identify distinct behavioural trajectories within the population that would have remained unnoticed in smaller studies. Limitations of this study included the relatively low number of individuals included in the analysis from some countries or cohorts, making it difficult to test whether those from certain countries were more likely to belong to a given trajectory compared to others. Second, given the absence of data on receptive needle and syringe sharing, we relied on injecting drug use as a proxy for potential HCV exposure, which may underestimate actual transmission risk. Furthermore, data on other sexual behaviours known to be associated with HCV (including sharing sex toys, and the engagement in group sex activities) were lacking for the majority of participants or were not collected. Third, we had to infer data on non-IDU from the variables any substance use and IDU. The number of individuals engaging in non-IDU might thus be underestimated if those who reported IDU also engaged in non-IDU. Lastly, cohorts included in this international collaboration were all from high-income countries enrolling individuals with HIV who were engaged in care, and therefore findings may not be generalizable to other settings.

In conclusion, although there was an overall slight decrease in any behavioural risk, there were four different trajectories of risk behaviour associated with HCV, the majority of which demonstrated ongoing behaviours following successful DAA treatment. In a setting where the proportion of incident cases due to reinfection increases, albeit in settings of overall lower incidence and prevalence, this highlights the importance of ongoing scale up of primary prevention measures within the overall public health response and timely testing, diagnosis and retreatment initiation. In addition, individuals with consistently high levels of behavioural risk would be ideal candidates for behavioural interventions.

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Conflicts of interest

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