Reinfection incidence and risk among people treated for recent hepatitis C virus infection

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Objective: Reinfection poses a challenge to hepatitis C virus (HCV) elimination. This analysis assessed incidence of, and factors associated with reinfection among people treated for recent HCV (duration of infection <12 months).

Methods: Participants treated for recent HCV (primary infection or reinfection) in an international randomized trial were followed at 3-monthly intervals for up to 2 years to assess for reinfection. Reinfection incidence was calculated using person-time of observation. Factors associated with HCV reinfection were assessed using Cox proportional hazards regression analysis.

Results: Of 222 participants treated for recent HCV, 196 (62% primary infection, 38% reinfection) were included in the cohort at risk for reinfection, of whom 87% identified as gay or bisexual men, 71% had HIV and 20% injected drugs in the month prior to enrolment. During 198 person-years of follow-up, 28 cases of HCV reinfection were identified among 27 participants, for an incidence of 14.2 per 100 person-years [95% confidence interval (CI) 9.8–20.5]. Reinfection was associated with prior HCV reinfection [adjusted hazards ratio (aHR) 2.42; 95% CI 1.08–5.38], injection drug use posttreatment (aHR 2.53; 95% CI 1.14–5.59), condomless anal intercourse with casual male partners (aHR 3.32; 95% CI 1.14–9.65) and geographic region (United Kingdom, aHR 0.21; 95% CI 0.06–0.75). Among gay and bisexual men (GBM), reinfection was also associated with sexualized drug use involving injecting posttreatment (aHR 2.97; 95% CI 1.10–8.02).

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Received: 25 January 2023; revised: 5 April 2023; accepted: 11 April 2023.

DOI:10.1097/QAD.0000000000003651

Conclusion: High reinfection incidence following treatment for recent HCV among people with ongoing sexual and drug use risk behaviour highlights the need for posttreatment surveillance, rapid retreatment of reinfection and targeted harm reduction strategies.

AIDS 2023, **37**:1883–1890

Keywords: acute, gay and bisexual men, hepatitis C virus, HIV, people who inject drugs

Introduction

Globally, 57 million people are living with hepatitis C virus (HCV) infection, with 1.5 million newly infected each year [1,2]. Key populations include people who inject drugs (PWID) and gay and bisexual men (GBM) with HIV [3–5]. The WHO 2030 elimination targets include an 80% reduction in HCV incidence, with a specific target among PWID [1]. With no vaccine, direct-acting antiviral (DAA) therapy and optimized prevention will be the foundation for elimination efforts.

Reinfection may pose a challenge to elimination [6,7]. Posttreatment HCV reinfection incidence has been estimated at four to six per 100 person-years among people with HIV [8], GBM with HIV [8] and people reporting recent injection drug use [9]. However, most studies have been among people treated for chronic HCV, with limited exploration in the context of recent HCV and contemporary sexual and drug use behaviours [10]. The objectives of this analysis were to assess the incidence of, and factors associated with reinfection among people treated for recent HCV infection.

Methods

Design

The Recently Acquired HCV Infection Trial (REACT) was a randomized trial evaluating efficacy of sofosbuvir-velpatasvir for 6 or 12 weeks among people with recent HCV (duration of infection <12 months) [11].

Posttreatment visits (including HCV RNA testing) occurred 3-monthly up to 2 years to evaluate treatment response and assess reinfection. Participants with detectable HCV RNA after end of treatment had more intensive follow-up with monthly visits for 6 months. Retreatment could be offered at the discretion of the investigator.

Participants completed behavioural questionnaires at pretreatment and posttreatment visits, including demographics, HIV and drug treatment history, drug use behaviours (injection and noninjection), testing and diagnosis of sexually transmitted infections and sexual behaviours [GBM only; casual male partners, condomless anal intercourse, group sex, sexualized drug use ('chemsex')].

Definitions, population and outcomes

Participants were included in this analysis if they received recent HCV treatment, had end of treatment response and at least one posttreatment assessment for HCV reinfection. The primary outcome was reinfection following treatment. End of treatment response was HCV RNA below lower limit of quantitation (LLoQ) and SVR12 HCV RNA below LLoQ at least 12 weeks posttreatment. Reinfection was defined by: presence of quantifiable HCV RNA after end of treatment response with detection of HCV strain distinct from primary infecting strain (heterologous virus on sequencing) or presence of quantifiable HCV RNA after SVR12 (with or without sequence data) [12,13]. For HCV RNA testing and sequencing methodology, see Supplementary Material, http://links.lww.com/QAD/C931.

Statistical analysis

Reinfection incidence was calculated using person-time of observation and reported as number of reinfections per 100 person-years follow-up. Confidence intervals (CI) were calculated using Poisson distribution. Date of HCV reinfection was estimated as mid-point between last negative HCV RNA posttreatment and first positive HCV RNA posttreatment [14]. Time at risk commenced at end of treatment, and was censored at date of reinfection, death, loss to follow-up, or last negative HCV RNA.

Cox proportional hazards regression analysis was used to estimate hazard ratios and 95% CIs to evaluate factors associated with reinfection, using time-dependent covariates for behavioural factors. Population attributable risk and 95% CIs were calculated to quantify the proportional reduction expected in number of HCV reinfections if a modifiable risk factor (identified in the adjusted Cox models) was eliminated. Analysis was performed using STATA (StataCorp, College Station, Texas, USA).

Results

Participant disposition

Between March 2017 and July 2019, 222 participants with recent HCV commenced sofosbuvir-velpatasvir,

with 196 (88%) included in population at risk for reinfection (Supplementary Figure 1, http://links.lww.com/QAD/C931). Following treatment, 189 (85%) achieved end of treatment response, 22 (10%) had no posttreatment follow-up and 11 (5%) had virological failure. Of 11 with virological failure, seven received retreatment, achieved an end of treatment response and were subsequently included. Total follow-up time was 198 person-years (median follow-up 12 months [IQR 7–17], median posttreatment visits 5 [IQR 3–7]).

The enrolment characteristics of cohort at-risk for reinfection are shown in Table 1. Most were male individuals (96%), identified as gay or bisexual (87%) and

Table 1. Demographic and clinical characteristics of participants at-risk for reinfection.

	Participants without reinfection ($n=169$)	Participants with reinfection ($n=27$)	Total ($n=196$)
Male gender [*n* (%)]	163 (96)	26 (96)	189 (96)
Age [*n* (%)]			
Less than 35 years	28 (17)	4 (15)	32 (16)
35–44 years	56 (33)	8 (30)	64 (33)
45–54 years	59 (35)	10 (37)	69 (35)
55 years or older	26 (15)	5 (19)	31 (16)
Sexual orientation [*n* (%)]			
Bisexual	4 (2)	1 (4)	5 (3)
Gay	141 (83)	24 (89)	165 (84)
Heterosexual/straight	23 (14)	2 (7)	25 (13)
Unavailable	1 (1)	0 (0)	1 (1)
Race [*n* (%)]			
Asian	6 (4)	3 (11)	9 (5)
Black	4 (2)	0 (0)	4 (2)
White	143 (85)	21 (78)	164 (84)
Mixed race	7 (4)	2 (7)	9 (5)
Other	6 (4)	0 (7)	6 (3)
Unavailable	169 (100)	1 (4)	4 (2)
Country of residence [*n* (%)]			
Australia	13 (8)	3 (11)	16 (8)
Canada	14 (8)	2 (7)	16 (8)
Germany	42 (25)	11 (41)	53 (27)
Netherlands	22 (13)	5 (19)	27 (14)
New Zealand	2 (1)	0 (0)	2 (1)
Switzerland	11 (7)	0 (0)	11 (6)
United Kingdom	54 (32)	3 (11)	57 (29)
United States of America	11 (7)	3 (11)	14 (7)
Tertiary education [*n* (%)]	23 (14)	1 (4)	24 (12)
Full or part-time employment [*n* (%)]	113 (67)	14 (52)	127 (65)
History of incarceration [*n* (%)]	21 (12)	2 (7)	23 (12)
Harmful alcohol consumption [*n* (%)]	10 (6)	0 (0)	10 (5)
HIV infection [*n* (%)]	117 (69)	23 (85)	140 (71)
On combination antiretroviral therapy [*n* (%)][b]	117 (100)	23 (100)	140 (100)
Nadir $CD4^+$ <200 cells/μl [*n* (%)][b]	23 (20)	1 (4)	24 (17)
STI in the past 12 months [*n* (%)][c]	78 (46)	22 (82)	100 (51)
Injection drug use [*n* (%)]			
Injected ever	88 (52)	15 (56)	103 (53)
Injected in the last 6 months	53 (31)	11 (41)	64 (33)
Injected in the last month	33 (20)	6 (22)	39 (20)
Treated HCV infection at enrolment [*n* (%)]			
Primary infection	111 (66)	10 (37)	121 (62)
Reinfection	58 (34)	17 (63)	75 (38)
Mode of HCV transmission[a] [*n* (%)]			
Injection drug use	32 (19)	3 (11)	35 (18)
Sexual exposure with person of the same sex	124 (73)	23 (85)	147 (75)
Sexual exposure with person of opposite sex	8 (5)	1 (4)	9 (5)
Other	5 (3)	0 (0)	5 (3)
HCV genotype [*n* (%)]			
1a	108 (64)	15 (56)	123 (63)
1b	4 (2)	0 (0)	4 (2)
2	4 (2)	1 (4)	5 (3)
3	28 (17)	3 (11)	31 (16)
4	24 (14)	8 (30)	32 (16)
Unavailable	1 (1)	0 (0)	1 (1)

HCV, hepatitis C virus; STI, sexually transmitted infection.
[a]Clinician determined mode of HCV transmission.
[b]Among people with HIV infection.
[c]Including syphilis ($n=22$), *Chlamydia trachomatis* infection ($n=12$), *Neisseria gonorrhoeae* infection ($n=11$).

had HIV infection (71%). Injection drug use ever and within 1 month of enrolment was reported by 53 and 20%, respectively. Median age at injecting initiation was 36 years (range 14–61 years), higher among GBM (46 vs. 20 years). Injection drug use following treatment was reported by 40% ($n = 80$), among whom 81% reported injecting amphetamines and 34% use of unsterile needles/syringes. Among GBM ($n = 169$), condomless anal intercourse with casual male partners and group sex were reported by 82 and 63% prior to enrolment, and 87 and 58% during follow-up, respectively. Sexualized drug use ('chemsex') in month prior to enrolment and during follow-up was reported by 30% (involving injection drug use, 19%) and 47% (involving injection drug use, 34%).

Hepatitis C virus reinfection incidence

Twenty-eight cases of HCV reinfection were identified among 27 participants, a reinfection incidence of 14.2 per 100 person-years (95% CI 9.8–20.5) (Fig. 1, Supplementary Table 1, http://links.lww.com/QAD/C931). HCV reinfection incidence was 17.2 per 100 person-years (95% CI 11.5–25.7) among people with HIV. Reinfection incidence was higher among participants treated for recent reinfection (25.6 per 100 person-years, 95% CI 16.2–40.7) compared with recent primary infection (7.8 per 100 person-years, 95% CI 4.2–14.6), and among participants who injected posttreatment (21.1 per 100 person-years, 95% CI 13.1–33.8) compared with those who did not (9.4 per 100 person-years, 95% CI 5.2–16.9).

Among GBM ($n = 169$), 25 cases of reinfection were identified among 24 participants, a reinfection incidence of 14.4 per 100 person-years (95% CI 9.7–21.3) (Supplementary Table 2, http://links.lww.com/QAD/C931). Among PWID ($n = 82$; GBM 79%), 17 cases of reinfection were identified among 16 participants, a reinfection incidence of 21.1 per 100 person-years (95% CI 13.1–33.9) (Supplementary Table 3, http://links.lww.com/QAD/C931).

Clinical characteristics and outcomes

Among participants with reinfection ($n = 27$; 89% GBM, 85% HIV), 44, 59 and 63% reported injection drug use, 'chemsex' and condomless anal intercourse with casual male partners during follow-up, with 30% reporting injecting and sexual risk behaviours. One participant was diagnosed with two episodes of reinfection. Demographic, behavioural and virological characteristics of participants with reinfection are included in Supplementary Table 4, http://links.lww.com/QAD/C931 and Supplementary Figure 4, http://links.lww.com/QAD/C931.

Median time to HCV reinfection from end of treatment was 7 months (range 1–18). Median ALT at end of treatment and reinfection diagnosis were 23 U/l (range 9–46 U/l) and 53 U/l (range 13–459 U/l), respectively, with an increase in ALT of greater than 50% between end of treatment and reinfection diagnosis in 68%. Normal ALT (<30 U/l) at reinfection diagnosis was seen in 29%; however, only one had persistently normal ALT throughout.

Retreatment for reinfection was initiated in 18 of 28 cases (64%), with glecaprevir-pibrentasvir 8 weeks ($n = 12$), sofosbuvir-velpatasvir 12 weeks ($n = 5$) and grazoprevir-elbasvir 12 weeks ($n = 1$); 13 achieved SVR, one was reinfected again (3 months following retreatment) and outcome unknown in four (study close). Median time to retreatment initiation from reinfection diagnosis was 17 weeks (range 2–33). Of 10 reinfection cases that remained untreated (HIV, $n = 7$), all appeared to persist with no evidence of spontaneous clearance.

Factors associated with hepatitis C virus reinfection

Reinfection was associated with prior HCV reinfection (vs. primary infection; aHR 2.42, 95% CI 1.08–5.38), injection drug use posttreatment (vs. no; aHR 2.53, 95% CI 1.14–5.59), condomless anal intercourse with casual male partners (aHR 3.32, 95% CI 1.14–9.65) and geographic region (vs. Germany, Netherlands and Switzerland; United Kingdom, aHR 0.21, 95% CI 0.06–0.75) (Supplementary Table 5, http://links.lww.com/QAD/C931). Population attributable risk for injecting drug use was 0.22 (95% CI 0.07–0.35) and for condomless anal intercourse with casual male partners was 0.53 (95% CI 0.18–0.74).

Among GBM, reinfection was associated with prior HCV reinfection (aHR 2.43; 95% CI 1.05–5.65), injection drug use posttreatment (aHR 2.53, 95% CI 1.07–6.00) and geographic region (United Kingdom, aHR 0.21, 95% CI 0.06–0.74). Population attributable risk for injecting drug use was 0.20 (95% CI 0.05–0.83). In a second adjusted model, reinfection was associated with 'chemsex' involving injection drug use posttreatment (aHR 2.97, 95% CI 1.10–8.02), but not 'chemsex' without injecting drug use (Supplementary Table 2, http://links.lww.com/QAD/C931). Population attributable risk for 'chemsex' was 0.35 (95% CI 0.12–0.52). Among PWID, reinfection was associated with prior HCV reinfection (aHR 3.92; 95% CI 1.28–12.04) and geographic region (United Kingdom, aHR 0.11, 95% CI 0.01–0.82) (Supplementary Table 3, http://links.lww.com/QAD/C931).

Discussion

In this international cohort composed predominantly of GBM with HIV from high-income countries, high reinfection incidence was observed among people treated for recent HCV infection, two to three times greater than

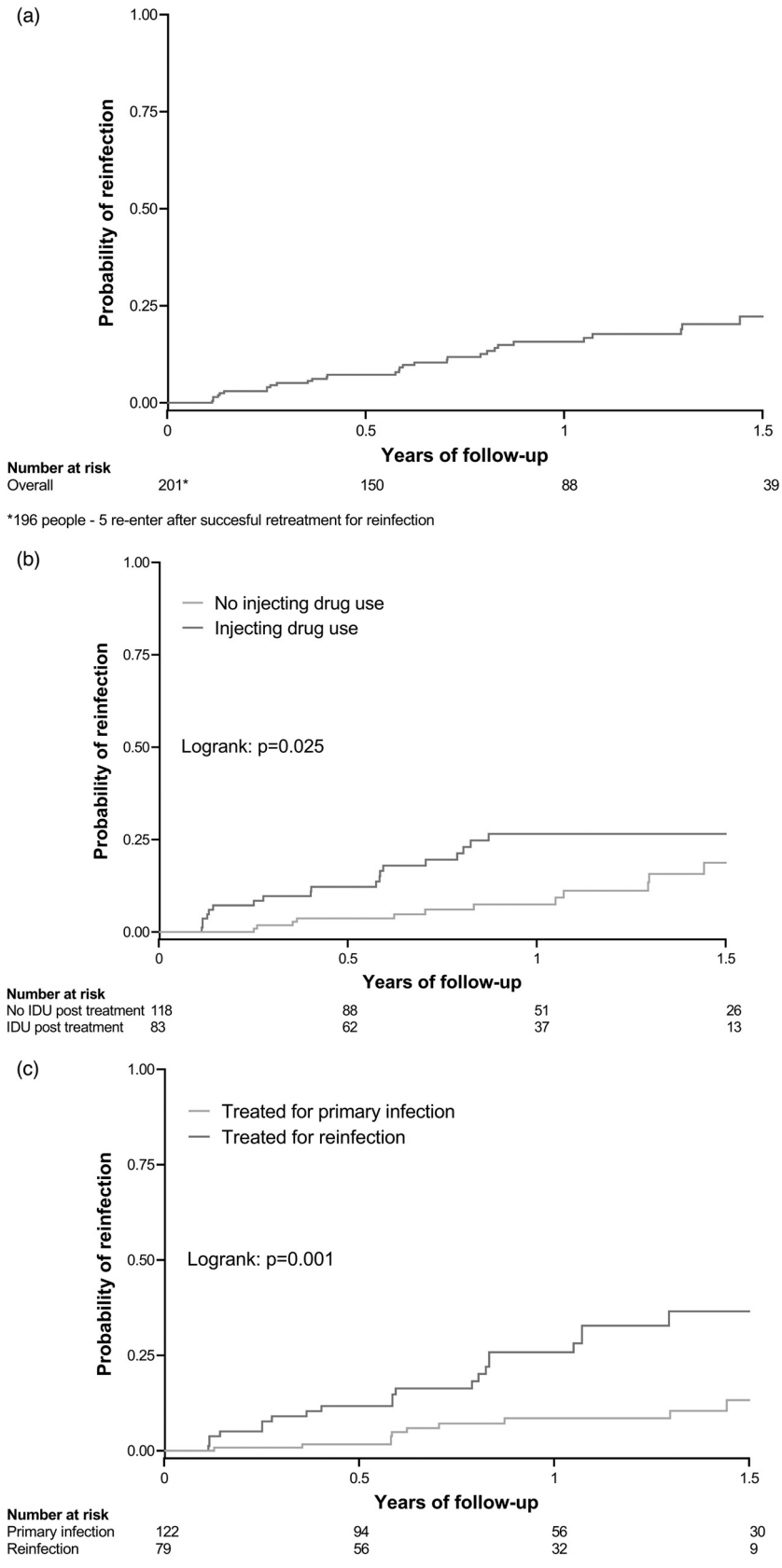

Fig. 1. Kaplan–Meier curves of time to reinfection following treatment for recent hepatitis C virus infection in the overall population (a), and stratified by injection drug use post treatment (b) and HCV infection type at enrolment (primary vs. reinfection) (c).

contemporary reinfection estimates among at-risk populations treated for chronic HCV [8,9,15–17]. Reinfection was associated with a previous diagnosis of HCV reinfection, injection drug use posttreatment, condomless anal intercourse with casual male partners and geographic region. Although many participants diagnosed with reinfection were successfully retreated, one-third remained untreated at end of follow-up. Elimination strategies will be enhanced by diagnosis and treatment of recent HCV [18]; however, high reinfection incidence highlights the need for enhanced surveillance, tailored prevention strategies and rapid access to retreatment.

HCV reinfection incidence was significantly higher among people who reported injecting drug use following treatment, including among GBM reporting 'chemsex' involving injection drug use ('slamming', 'slamsex'). One-third reported needle/syringe sharing, higher than other studies of reinfection following recent (22%) and chronic (6%) infection among PWID [14,19]. For PWID, access to harm reduction interventions known to reduce risk is essential [17,20]. However, different PWID populations require nuanced approaches. GBM who engage in sexualized injecting (and noninjecting) drug use involving stimulants or psychotropics are at higher risk of HCV (re) infection but may not engage with traditional harm reduction and prevention messaging, given a focus on people who inject opioids [10]. Although GBM in high-income countries are often engaged with healthcare, disclosure of behaviours associated with HCV transmission may be limited because of fear of stigma [21,22]. Targeted strategies should enable individuals to form and maintain safe sexual and injecting practices.

Condomless anal sex with casual male partners, recent HCV reinfection at enrolment and geographic region were also associated with reinfection. Although modelling of micro-elimination strategies supports behavioural risk reduction (and condomless anal sex had the greatest population attributable risk) [18], empirical evidence demonstrating the effectiveness of sexual behavioural interventions for HCV prevention among GBM are lacking [22–25]. People at risk for reinfection are recommended to have at least annual HCV RNA testing [13]. Given the high observed reinfection incidence (particularly those with repeated infection) and short median time to reinfection posttreatment, more frequent monitoring should be considered, providing an opportunity for early intervention and interruption of transmission. In addition, differences in healthcare and harm reduction provision, DAA scale-up and access (including for retreatment) and regional HCV RNA prevalence may have influenced reinfection risk [2,4,26–30].

Our study highlights that screening for and treatment of HCV reinfection, education focused on reinfection prevention and access to safe sex and harm reduction services are essential.

Acknowledgements

The REACT study group includes members of the Protocol Steering Committee; Coordinating Centre, The Kirby Institute, UNSW Sydney; and Study Site Principal Investigators.

Protocol Steering Committee – Gail Matthews (Protocol Steering Committee chair; The Kirby Institute, UNSW Sydney, Sydney, Australia), Tanya Applegate (The Kirby Institute, UNSW Sydney, Sydney, Australia), Sanjay Bhagani (Royal Free Hospital, London, UK), Julie Bruneau (Centre Hospitalier de l'Université de Montréal, Montréal, Canada), Greg Dore (St Vincent's Hospital and the Kirby Institute, UNSW Sydney, Sydney, Australia), Jordan Feld (Toronto General Hospital, Toronto, Canada), Ed Gane (Auckland City Hospital, Auckland, New Zealand), Jason Grebely (The Kirby Institute, UNSW Sydney, Sydney, Australia), Margaret Hellard (The Alfred Hospital and Burnet Institute, Melbourne, Australia), Arthur Kim (Massachusetts General Hospital, Boston, USA), Pip Marks (The Kirby Institute, UNSW Sydney, Sydney, Australia), Marianne Martinello (The Kirby Institute, UNSW Sydney, Sydney, Australia), Kathy Petoumenos (The Kirby Institute, UNSW Sydney, Sydney, Australia), Andri Rauch (Bern Inselspital, Bern, Switzerland), Jürgen Rockstroh (University Clinic Bonn, Bonn, Germany), Marc van der Valk (Amsterdam University medical Centers, The Netherlands).

Coordinating Centre, The Kirby Institute, UNSW Sydney, Sydney, Australia – Gail Matthews (Coordinating Principal Investigator), Pip Marks (Clinical Trials Manager), Sophia Amjad (Study Coordinator), Elise Tu (Study Co-ordinator), Kathy Petoumenos (Statistician) and Mahshid Tamaddoni (Systems and Data Manager).

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Lugano, Switzerland), Maria Christine Thurnheer (Bern Inselspital, Bern, Switzerland); The Netherlands – Marc van der Valk (Amsterdam University medical Centers, The Netherlands); United Kingdom – Sanjay Bhagani (Royal Free Hospital, London, UK), Yvonne Gilleece (Brighton and Sussex University Hospitals, Brighton, UK), Mark Nelson (Chelsea and Westminster Hospital, London, UK), Andrew Ustianowski (Pennine Acute Hospitals, Manchester, UK); United States of America – Arthur Y Kim (Massachusetts General Hospital, Boston, USA), Juhi Moon (Johns Hopkins University, Baltimore, USA).

The authors would like to thank the study participants for their contribution to the research. The authors would also like to acknowledge the work undertaken by the Study Site Coordinators.

Site Co-ordinators and Site Co-investigators – Australia – Karen Chronister and Rosie Gilliver (Kirketon Road Centre, Sydney, Australia), Catherine Ferguson (Royal Adelaide Hospital, Adelaide, Australia), Michelle Hagenauer (The Alfred Hospital, Melbourne, Australia), Joanne Patterson (Royal Melbourne Hospital, Melbourne, Australia), Alison Sevehon (St Vincent's Hospital, Sydney, Australia); Canada – Rachel Bouchard and Barbara Kotsoros (Centre Hospitalier de l'Université de Montréal, Montréal, Canada), Orlando Cerocchi (Toronto General Hospital, Toronto, Canada), Bruce Ganase and Marianne Harris (St Paul's Hospital, Vancouver, Canada), Marion Selfridge (Cool Aid Community Health Centre, Victoria, Canada); Germany – Christina Appelhans and Annette Haas (Infektio-Research GmbH, Frankfurt, Germany), Brigitta Becker, Karina Mohrmann and Angelika Saidi (University Clinic Bonn, Bonn, Germany), Christoph Gerlach and Christine Monnich (Zentrum für Infektiologie Berlin-Prenzlauer Berg, Berlin, Germany), Reinhold Schröder (Praxis Dr Cordes, Berlin, Germany); New Zealand – Genevieve Morris and Victoria Oliver (Auckland City Hospital, Auckland, New Zealand); Switzerland – Christine Bruelisauer, Daniela Hirter, Melanie Lacalamita, Manuela Manz, and Pia Scherler (Bern Inselspital, Bern, Switzerland), Selma Calcagnile and Paola Messina (Fondazione Epatocentro Ticino, Lugano, Switzerland), Christina Grube (University Hospital Zurich, Zurich, Switzerland); The Netherlands – Hadassa Porretta, Martine Peters and Jeltje Helder (Amsterdam University Medical Centers, The Netherlands); United Kingdom – Tanya Adams (Brighton and Sussex University Hospitals, Brighton, UK), Anne Carroll, Parizade Raymode and Eric Witele (Royal Free Hospital, London, UK), Serge Fedele, Lester Macabodbod, Thomas Morrish, and Orla Thunder (Chelsea and Westminster Hospital, London, UK), Valerie George and Gabriella Lindergard (Pennine Acute Hospitals, Manchester, UK); United States of America – Fiona Evans and Jenna Gustafson (Massachusetts General Hospital, Boston, USA), Stephanie Katz, Stacey Reece and Mark Sulkowski (Johns Hopkins University, Baltimore, USA).

We would like to acknowledge the contributions of Brendan Jacka, Maria Martinez and Andrey Verich, Kirby Institute, UNSW Sydney, Sydney for their assistance with RNA extraction, sequencing and phylogenetic analysis.

Funding: the REACT study was funded by National Institutes of Health (R01DA040506). Study medication was provided by Gilead Sciences Inc. The Kirby Institute is funded by the Australian Government Department of Health and Ageing. The views expressed in this publication do not necessarily represent the position of the Australian Government.

Author's contributions: M.M. and G.V.M. proposed the study analysis. G.V.M. and G.D. designed the REACT study. G.V.M., G.D., M.V.d.V., J.R., P.I., M.N., T.L., M. H., C.C., J.M., S.B., J.F., A.R., J.B., A.K., M.H., and E. G. were involved in participant recruitment and data collection. G.V.M., G.D., M.V.d.V., J.R., S.B., J.F., A.R., J.B., A.K., M.H., E.G., J.G., and M.M. provided study governance through the Protocol Steering Committee. E.T. oversaw study coordination. J.M.C. conducted the data analysis, with oversight from M.M. and G.V.M. M. M. drafted the manuscript with critical revision of the manuscript for important intellectual content by all authors. All authors have seen and approved the final version of the manuscript.

Clinical trial registration: clinicaltrials.gov Identifier NCT02625909.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. *Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022–2030* Editor: World Health Organization: Global HIV HaSTIP. Geneva, Switzerland: World Health Organization; 2022.
2. Polaris Observatory HCV Collaborators. **Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study.** *Lancet Gastroenterol Hepatol* 2022; **7**:396–415.
3. Martinello M, Hajarizadeh B, Grebely J, Dore GJ, Matthews GV. **Management of acute HCV infection in the era of direct-acting antiviral therapy.** *Nat Rev Gastroenterol Hepatol* 2018; **15**:412–424.
4. Jin F, Dore GJ, Matthews G, Luhmann N, Macdonald V, Bajis S, *et al*. **Prevalence and incidence of hepatitis C virus infection in men who have sex with men: a systematic review and meta-analysis.** *Lancet Gastroenterol Hepatol* 2021; **6**:39–56.
5. Degenhardt L, Peacock A, Colledge S, Leung J, Grebely J, Vickerman P, *et al*. **Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review.** *Lancet Glob Health* 2017; **5**:e1192–e1207.

6. Dore GJ, Martinello M, Alavi M, Grebely J. **Global elimination of hepatitis C virus by 2030: why not?** *Nat Med* 2020; **26**:157–160.
7. Martinello M, Bajis S, Dore GJ. **Progress toward hepatitis C virus elimination: therapy and implementation.** *Gastroenterol Clin North Am* 2020; **49**:253–277.
8. Hosseini-Hooshyar S, Hajarizadeh B, Bajis S, Law M, Janjua NZ, Fierer DS, *et al*. **Risk of hepatitis C reinfection following successful therapy among people living with HIV: a global systematic review, meta-analysis, and meta-regression.** *The lancet HIV* 2022; **9**:e414–e427.
9. Hajarizadeh B, Cunningham EB, Valerio H, Martinello M, Law M, Janjua NZ, *et al*. **Hepatitis C reinfection after successful antiviral treatment among people who inject drugs: A meta-analysis.** *J Hepatol* 2020; **72**:643–657.
10. Maxwell S, Shahmanesh M, Gafos M. **Chemsex behaviours among men who have sex with men: a systematic review of the literature.** *Int J Drug Policy* 2019; **63**:74–89.
11. Matthews GV, Bhagani S, Van der Valk M, Rockstroh J, Feld JJ, Rauch A, *et al*. **Sofosbuvir/velpatasvir for 12 vs. 6 weeks for the treatment of recently acquired hepatitis C infection.** *J Hepatol* 2021; **75**:829–839.
12. Lamoury FM, Jacka B, Bartlett S, Bull RA, Wong A, Amin J, *et al*. **The influence of hepatitis C virus genetic region on phylogenetic clustering analysis.** *PLoS One* 2015; **10**:e0131437.
13. **European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series.** *J Hepatol* 2020; **73**:1170–1218.
14. Martinello M, Grebely J, Petoumenos K, Gane E, Hellard M, Shaw D, *et al*. **HCV reinfection incidence among individuals treated for recent infection.** *J Viral Hepat* 2017; **24**:359–370.
15. Liu C-H, Sun H-Y, Peng C-Y, Hsieh S-M, Yang S-S, Kao W-Y, *et al*. **Hepatitis C virus reinfection in people with HIV in Taiwan after achieving sustained virologic response with antiviral treatment: the RECUR Study.** *Open Forum Infect Dis* 2022; **9**:ofac348.
16. Johannesson JM, Fridriksdottir RH, Löve TJ, Runarsdottir V, Hansdóttir I, Löve A, *et al*., Treatment as Prevention for Hepatitis C (TraP Hep C) group. **High rate of hepatitis C virus reinfection among recently injecting drug users: results from the TraP Hep C Program—a prospective nationwide, population-based study.** *Clin Infect Dis* 2022; **75**:1732–1739.
17. Grebely J, Dore GJ, Altice FL, Conway B, Litwin AH, Norton BL, *et al*. **Reinfection and risk behaviors after treatment of hepatitis C virus infection in persons receiving opioid agonist therapy: a cohort study.** *Ann Intern Med* 2022; **175**:1221–1229.
18. Martin NK, Thornton A, Hickman M, Sabin C, Nelson M, Cooke GS, *et al*. **Can hepatitis C virus (HCV) direct-acting antiviral treatment as prevention reverse the HCV epidemic among men who have sex with men in the United Kingdom?** *Epidemiol Model Insights Clin Infect Dis* 2016; **62**:1072–1080.
19. Cunningham EB, Hajarizadeh B, Amin J, Hellard M, Bruneau J, Feld JJ, *et al*. **Reinfection following successful direct-acting antiviral therapy for hepatitis C virus infection among people who inject drugs.** *Clin Infect Dis* 2021; **72**:1392–1400.
20. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, *et al*. **Needle and syringe programmes and opioid substitution therapy for preventing HCV transmission among people who inject drugs: findings from a Cochrane Review and meta-analysis.** *Addiction* 2018; **113**:545–563.
21. Demant D, Carroll J-A, Saliba B, Bourne A. **Information-seeking behaviours in Australian sexual minority men engaged in chemsex.** *Addict Behav Rep* 2022; **16**:100399.
22. Marshall AD, Martinello M, Treloar C, Matthews GV. **Perceptions of hepatitis C treatment and reinfection risk among HIV-positive men who have sex with men and engage in high risk behaviours for hepatitis C transmission: the CEASE qualitative study.** *Int J Drug Policy* 2022; **109**:103828.
23. Lambers F, van der Veldt W, Prins M, Davidovich U, MOSAIC study. **Changing the odds: motives for and barriers to reducing HCV-related sexual risk behaviour among HIV-infected MSM previously infected with HCV.** *BMC Infect Dis* 2018; **18**:678.
24. Prinsenberg T, Illidge J, Zantkuijl P, Bedert M, Prins M, van der Valk M, Davidovich U. **Usability, acceptability, and self-reported impact of an innovative hepatitis C risk reduction intervention for men have sex with men: a mixed methods study.** *PLoS One* 2022; **17**:e0263654.
25. Künzler-Heule P, Fierz K, Schmidt AJ, Rasi M, Bogdanovic J, Kocher A, *et al*. **Response to a sexual risk reduction intervention provided in combination with hepatitis C treatment by HIV/HCV co-infected men who have sex with men: a reflexive thematic analysis.** *BMC Infect Dis* 2021; **21**:319.
26. Martinello M, Yee J, Bartlett SR, Read P, Baker D, Post JJ, *et al*. **Moving towards hepatitis C microelimination among people living with human immunodeficiency virus in Australia: the CEASE Study.** *Clin Infect Dis* 2020; **71**:1502–1510.
27. Garvey LJ, Cooke GS, Smith C, Stingone C, Ghosh I, Dakshina S, *et al*. **Decline in hepatitis C virus (HCV) incidence in men who have sex with men living with human immunodeficiency virus: progress to HCV microelimination in the United Kingdom?** *Clin Infect Dis* 2021; **72**:233–238.
28. Smit C, Boyd A, Rijnders BJA, van de Laar TJW, Leyten EM, Bierman WF, *et al*. **HCV micro-elimination in individuals with HIV in the Netherlands 4 years after universal access to direct-acting antivirals: a retrospective cohort study.** *Lancet HIV* 2021; **8**:e96–e105.
29. Isfordink CJ, Smit C, Boyd A, de Regt MJA, Rijnders BJA, van Crevel R, *et al*., ATHENA observational cohort. **Low hepatitis C virus-viremia prevalence yet continued barriers to direct-acting antiviral treatment in people living with HIV in the Netherlands.** *AIDS* 2022; **36**:773–783.
30. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, *et al*. **Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review.** *Lancet Global Health* 2017; **5**:e1208–e1220.