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HCV reinfection incidence among individuals treated for recent infection

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Background and aims

One challenge to HCV elimination through therapeutic intervention is reinfection. The aim of this analysis was to calculate the incidence of HCV reinfection among both HIV-positive and negative individuals treated for recent HCV infection (estimated infection duration <18 months).

Methods

Individuals with recent HCV infection who achieved an end-of-treatment response in four open-label studies between 2004 and 2015 in Australia and New Zealand were assessed for HCV reinfection, confirmed by sequencing of the Core-E2 and/or NS5B regions. Reinfection incidence was calculated using person-time of observation. Exact Poisson regression analysis was used to assess factors associated with HCV reinfection.

Results

The cohort at-risk for reinfection (n=120; 83% male; median age 36 years) was composed of HIV-positive men-who-have-sex-with-men (53%) and people who inject drugs (current 49%, ever 69%). Total follow-up time at-risk was 135 person-years (median 1.08 years, range 0.17, 2.53). Ten cases of HCV reinfection were identified, for an incidence of 7.4 per 100 py (95% CI 4.0, 13.8). Reinfection incidence was significantly higher amongst participants who reported injection drug use at end of or post-treatment, irrespective of HIV status (15.5 per 100 py, 95% CI 7.8, 31.1). In adjusted analysis, factors associated with reinfection were older age (aIRR 5.3, 95% CI 1.15, 51.5, p=0.042) and injection drug use at end of or post-treatment (aIRR 7.9, 95%CI 1.6, 77.2, p=0.008).

Conclusions

High reinfection incidence following treatment for recent HCV infection in individuals with ongoing risk behaviour emphasises the need for post-treatment surveillance, harm reduction strategies and education in at-risk populations.

Key words: Hepatitis C infection; HIV; recent; acute; reinfection; treatment

Highly effective, well tolerated interferon-free direct-acting antivirals (DAA) have revolutionised hepatitis C virus (HCV) therapeutics (1), with daily fixed-dose combination DAA regimens providing cure in greater than 95% of individuals with chronic infection (2, 3). The availability of DAA therapy has led to significant therapeutic optimism with the possibility of broad treatment uptake and subsequent HCV elimination (4-7). One challenge to HCV elimination though therapeutic intervention is reinfection.

There is concern that HCV reinfection may compromise the individual and population level benefits of HCV treatment in some populations with the risk of reinfection cited as a reason for not offering treatment to people who inject drugs (PWID) (8, 9). However, in general, the

incidence of HCV reinfection in PWID treated for chronic HCV infection ranges between one and five per 100 py (summarised in **Supplementary Table 1**). Reinfection incidence following treatment in individuals with HIV/HCV co-infection is varied, with high incidence reported in some cohorts of HIV-positive men-who-have-sex-with-men (MSM) (10-12). There is uncertainty around these reinfection estimates due to sample size, retrospective study designs, exclusion of recent PWID from trials, varied definitions for recent injection drug use and time at-risk for reinfection, and the inability to accurately distinguish relapse from reinfection.

Mathematical modelling suggests that substantial reductions in HCV incidence and prevalence could be achieved by targeted DAA treatment scale-up amongst those at highest risk of ongoing transmission, including PWID and HIV-positive MSM with recently diagnosed HCV infection (5, 13-15). Despite the high cost of DAA therapy, treating recent PWID and HIV-positive MSM with early liver disease appears to be cost-effective compared to delaying until cirrhosis, given the reduction in liver-related complications and additional benefit of averting secondary infections (6, 7, 16). However, ongoing risk behaviours associated with HCV transmission may contribute to reinfection and compromise the population-level benefits of Treatment as Prevention (5, 17, 18). Few studies have evaluated the incidence of HCV reinfection following treatment of recent HCV infection (summarised in **Supplementary Table 1**) (11, 12, 19), a high-risk group for onward transmission and of importance as DAA treatment access expands to traditionally marginalised populations. The aim of this analysis was to calculate the incidence of HCV reinfection among individuals treated for recent HCV infection (estimated infection duration <18 months) and assess clinical and behavioural factors associated with reinfection.

Methods

Study participants

Individuals with recent HCV infection (infection duration <18 months) who received treatment in four prospective open-label studies (ATAHC I, ATAHC II, DARE-C I and DARE-C II) between 2004 and 2015 in Australia and New Zealand were assessed for HCV reinfection (20-22) (**Figure 1**). The primary endpoints of these studies (20-22) and an analysis of HCV superinfection and reinfection in treated and untreated participants in ATAHC I (19) have been presented or published previously.

Recent primary HCV infection was defined as initial detection of serum anti-HCV antibody and/or HCV RNA within six months of enrolment and either (i) documented recent HCV seroconversion (anti-HCV antibody negative result in the 18 [DARE-C II] or 24 [ATAHC, ATAHC II, DARE-C I] months prior to enrolment) or (ii) acute clinical hepatitis (jaundice or alanine aminotransferase [ALT] greater than 10 times the upper limit of normal [ULN]) within the previous 12 months with the exclusion of other causes of acute hepatitis, with estimated duration of HCV infection less than 12 [DARE-C II] or 18 [ATAHC, ATAHC II, DARE-C I] months at screening.

HCV RNA testing and sequencing

The presence of HCV RNA was assessed at all scheduled study visits (see *Supplementary Material*). In ATAHC I, HCV RNA was assessed using a qualitative HCV RNA assay (Versant transcription-mediated amplification [TMA]; Bayer, Australia; LLoD 10 IU/ml) and if positive, a quantitative HCV RNA assay (Versant HCV RNA 3.0; Bayer, Australia; LLoD 615 IU/ml). In ATAHC II, DARE-C I and DARE-C II, HCV RNA was assessed using a quantitative HCV RNA assay (COBAS Taqman 2.0; Roche Diagnostics, USA; LLoD 15 IU/mL). Population-based HCV RNA sequencing was performed on the first available pre-treatment quantifiable HCV RNA sample and the first available quantifiable HCV RNA sample following HCV RNA recurrence using an in-house assay with methods described previously (23, 24). See *Supplementary Material* for more details.

Study definitions and outcomes

An end-of-treatment response (ETR) was defined as HCV RNA below the lower limit of detection, target not detected (LLoD, TND). HCV RNA recurrence was defined as quantifiable HCV RNA following ETR. Post-treatment relapse was defined as the presence of quantifiable HCV RNA after an ETR, confirmed as homologous virus on sequencing of Core-E2 and/or NS5B regions as described (23, 24). Confirmed reinfection was defined by the presence of quantifiable HCV RNA after an ETR with detection of an HCV strain that was distinct from the primary infecting strain (heterologous virus on sequencing). Possible reinfection was defined by the presence of quantifiable HCV RNA after an ETR without sequence data, but occurring after post treatment week 24 and with documentation of HCV RNA TND at post treatment week 12 or 24 to exclude post-treatment relapse. Persistent reinfection was defined by the presence of quantifiable HCV RNA in a repeated sample taken at least 12 weeks after HCV RNA recurrence.

The time at risk for reinfection was calculated from the date of end of treatment in individuals with an ETR to date of reinfection or last undetectable HCV RNA. The estimated date of reinfection was calculated as the midpoint between the dates of the last undetectable HCV RNA test and the first quantifiable HCV RNA test during follow-up. The primary study outcome was HCV reinfection incidence.

Study oversight

All study participants provided written informed consent before study procedures. The study protocols were approved by St Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), as well as local ethics committees at all study sites. The studies were conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines. The studies were registered with clinicaltrials.gov registry (ATAHC I: NCT00192569; ATAHC II: NCT01336010; DARE-C I: NCT01743521; DARE-C II: NCT02156570).

Statistical analysis

In the cohort at-risk for reinfection (ETR without post-treatment relapse), categorical parameters were summarised as number and proportion and continuous variables were summarised by either mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Reinfection incidence was calculated using person-time of observation. Confidence intervals (CI) for rates were calculated using Poisson distribution.

Exact Poisson regression analysis was used to assess factors associated with HCV reinfection, with time at risk (years) as the exposure variable. In unadjusted analyses, potential predictors were determined *a priori* and included sex, age at study enrolment, income, education level, social functioning score at enrolment (median), mode of HCV acquisition (injection drug use, sexual, other), HIV infection, injection drug use (ever, previous 6 months at enrolment, previous 30 days at enrolment), and injection drug use at end of and/or post-treatment. Social functioning was calculated using a validated scale from the Opiate Treatment Index (25) and addressed employment, residential stability, interpersonal conflict and social support (higher score reflects poorer social functioning, range score 0-48). All variables with $p<0.2$ in univariate analysis were considered in multivariate regression models using a backwards stepwise approach. Statistically significant differences were assessed at $p<0.05$; p-values were two-sided. Additional models assessed factors associated with reinfection among lifetime PWID (participants who reported injection drug use at least once) and HIV-positive MSM. See *Supplementary Material* for more details.

Analysis was performed using STATA version 14.0 (StataCorp, College Station, TX).

Results

Participant disposition

Between 2004 and 2015, 278 participants with recent HCV infection were enrolled in Australia and New Zealand with 196 participants included in the intention-to-treat population; 82 participants were enrolled into the untreated arms of ATAHC I and II (**Figure 1**). An end of treatment response (ETR) was documented in 77% (n=151). Six participants (4%) were lost to follow up (LTFU) after ETR. Viral recurrence following ETR was seen in 35 (23%), confirmed by sequencing as relapse in 25 (17%) and reinfection in 10 (6%). Participants with relapse and LTFU after ETR were excluded from subsequent analysis.

The enrolment characteristics of the cohort at-risk for reinfection (n=120; male 83%; median age 36 years, IQR 29-46) are shown in **Table 1**. HIV co-infection was documented in 53%; all of whom identified as MSM. Injection drug use ever prior to enrolment, within six months and within 30 days of enrolment was reported by 69%, 49% and 43%, respectively. Of those participants who reported injection drug use within 30 days of enrolment (n=52), the drugs most commonly injected were amphetamines (61%) and heroin or other opiates (29%) (**Supplementary Table 2**). Injection drug use at end of or post treatment was reported by 38% (n=45). Among those reporting injection drug use during follow-up, 71% (n=32) reported predominantly injecting amphetamines and 22% (n=10) reported use of unsterile needles and/or syringes. Different drug use behaviours were observed among participants with HIV/HCV co-infection as compared with HCV mono-infection; while participants with HIV/HCV co-infection were less likely to have ever injected drugs (61% vs 80%; p=0.021), those who did were older at commencement of injection drug use (30 years [IQR 25, 41] vs 23 years [IQR 18, 30]; p<0.001) (**Supplementary Table 3**).

Total follow-up time post treatment was 141 person-years (py; median 1.22 py, range 0.19, 2.53). Total follow-up time at-risk for reinfection (censured at estimated date of reinfection) was 135 py (median 1.08 years, range 0.17, 2.53).

HCV reinfection among participants treated for recent HCV infection

Ten cases of HCV reinfection were identified (eight confirmed, two possible), with persistent reinfection in five and spontaneous clearance in three cases (**Figure 2**). Reinfection outcome was indeterminate in two cases due to lack of on-study follow-up testing. Of the ten participants (seven HIV-positive MSM) with reinfection, eight reported injection drug use during follow up; one HIV-positive MSM who reported never injecting drugs prior to study enrolment subsequently injected anabolic steroids during follow-up. The remaining two cases occurred in HIV-positive MSM who denied ever injecting drugs. Detailed demographic and clinical characteristics of the ten participants with reinfection are displayed in **Table 2.**

Among eight cases of confirmed reinfection, median estimated time to HCV reinfection was 35 weeks (range 9 - 81 weeks) from end of treatment. The shortest time to reinfection was noted in an HIV-positive MSM following short duration interferon-free DAA therapy who reported high-risk drug and sexual behaviour. Despite confirmation of sustained virological response at week 4 post treatment (SVR4, HCV RNA TND), HCV RNA was quantifiable at post treatment week 12 with an HCV genotype switch from 3a (screening) to 1a (post treatment week 12) in association with an acute clinical illness and transaminitis (ALT 910 U/L). Amongst participants with confirmed reinfection, median ALT at end of treatment and following diagnosis of reinfection were 25 U/L (range 15 – 83 U/L) and 192 U/L (range 15 – 1135 U/L), respectively.

Low level quantifiable HCV RNA was detected in the two cases of possible reinfection and as such, reinfection could not be confirmed by sequencing. Estimated time to possible reinfection was 31 and 64 weeks from end of treatment, respectively. In the first case, quantifiable HCV RNA (3.87 $\log_{10}$ IU/mL) was detected at a single time point at post treatment week 36 (TND at post treatment week 24) and was repeatedly negative between post treatment weeks 48 and 120. In the second case, quantifiable HCV RNA (2.18 $\log_{10}$ IU/mL) was detected at post treatment week 72 (TND at post treatment week 48) and was repeatedly negative subsequent to this.

Among all participants at-risk for reinfection, reinfection incidence was 7.4 per 100 py (95% CI 4.0, 13.8) (**Table 3** and **Supplementary Table 4**), for a projected cumulative reinfection incidence of 7.2% at one year and 14.5% at two years from end of treatment (**Supplementary Figure 1**). The incidence of HCV reinfection was 4.5 per 100 py (95% CI 1.4, 13.9) amongst those with HCV mono-infection, compared to 10.3 per 100 py (95% CI 4.9, 21.7) in those with HIV/HCV co-infection (p=0.232). The incidence of HCV reinfection was 8.5 per 100 py (95% CI 4.2, 16.9) in those who had ever injected drugs, compared to 4.9 per 100 py (95% CI 1.2, 19.8) in those who had never injected drugs (p=0.532). HCV reinfection incidence was significantly higher amongst participants who reported injection drug use at end of and/or post treatment (15.5 per 100 py, 95% CI 7.8, 31.1) as compared with those who did not inject drugs during follow up (2.6 per 100 py, 95% CI 0.6, 10.3) (p=0.023).

Risk factors for HCV reinfection following treatment for recent infection

Factors associated with HCV reinfection were assessed using exact Poisson regression analysis (**Table 4**). In adjusted analysis, factors independently associated with reinfection included older age (aIRR 5.42, 95% CI 1.06, 52.93, p=0.040) and injection drug use at end of and/or post-treatment (aIRR 7.86, 95%CI 1.54, 76.79, p=0.008) (**Table 4**). Factors associated with reinfection were unchanged when the analysis was limited to those with confirmed reinfection (**Supplementary Table 5**).

Factors associated with HCV reinfection were also assessed amongst lifetime PWID (n=84; 46% HIV-positive MSM) and HIV-positive MSM (n=64). Among lifetime PWID, 54% reported injection drug use at end of and/or post-treatment. Median age at first injection drug use was 25 years (IQR 20-34), significantly older among those with reinfection (35 years [IQR 30-46] vs 25 years [IQR 20-32]; p=0.013). Median duration of injection drug use at enrolment was 5.5 years (IQR 2.2, 11.0), with shorter duration and more recent onset of injection drug use among those with reinfection (2.8 years [IQR 0.5, 5.2] vs 6.2 years [IQR

2.6, 12.5]; p=0.046). In unadjusted analysis, HCV reinfection in PWID was associated with methamphetamine injecting during follow up (p=0.010) and use of unsterile needles and/or syringes during follow up (p=0.002). On multivariate analysis, reinfection was associated with older age (aIRR 23.26, 95% CI 2.49, 319.35, p=0.003), shorter duration of injection drug use (duration >5.5 years: aIRR 0.05, 95% CI 0.00, 0.59; p=0.010) and use of unsterile needles and/or syringes during follow up (aIRR 43.27, 95%CI 5.52, 368.14, p<0.001) (**Supplementary Table 6**). Among HIV-positive MSM, injection drug use at end of and/or post-treatment was reported by 23% (ever injection drug use 61%); this was the only factor associated with HCV reinfection in this sub-group (aIRR 8.19, 95%CI 1.34, 85.99, p=0.019; adjusted for age) (**Supplementary Table 7**).

Discussion

This analysis assessed HCV reinfection incidence amongst individuals treated for recent HCV infection (duration of infection <18 months) who achieved an end-of-treatment response. High levels of risk behaviour associated with HCV transmission were reported, including 38% reporting injection drug use at end of and/or post treatment, predominantly methamphetamine. Ten cases of reinfection were identified for an overall reinfection incidence of 7.4 per 100 py. All cases occurred in men, the majority of whom were HIV-positive MSM (n=7) and reported injection drug use at end of and/or post treatment (n=8). Two cases occurred in HIV-positive MSM who denied ever injecting drugs.

The incidence of reinfection following treatment for recent HCV infection reported in this analysis is consistent with previous studies amongst HIV-positive MSM and PWID (reinfection incidence: 9.6 – 15.2 per 100 py) (10-12), and expands upon the previous analysis limited to the predominantly HCV mono-infected ATAHC I cohort (19). The higher incidence of HCV reinfection in this and other acute cohorts contrasts with the majority of published studies in individuals treated for chronic HCV infection (summarised in **Supplementary Table 1**). In a recent meta-analysis, Simmons et al (26) examined the risk

of HCV recurrence following interferon-based treatment-induced SVR in three different populations, defined by their perceived risk of reinfection – HCV mono-infected "low risk" (no recognised risk factors for reinfection), HCV mono-infected "high risk" (former or recent injection drug use, incarceration, MSM) and HIV/HCV co-infection. Reinfection incidence was 0.0 per 100 py (95% 0.0, 0.0) in those deemed "low risk", 1.9 per 100 py (95% CI 1.1, 2.8) in those deemed "high risk" and 3.2 per 100 py (95% CI 0.0, 12.3) in those with HIV/HCV co-infection. However, the proportion of "high risk" or HIV/HCV co-infected individuals continuing to engage in behaviours which facilitated HCV transmission and placed them at risk of reinfection was unclear.

When assessing suitability for HCV therapy, certain populations, including PWID and people with HIV/HCV co-infection, have been considered "high-risk", primarily based on the apparent potential for reinfection (26). However, these populations are heterogeneous with different levels of risk attributable to specific subgroups. Sub-populations of PWID include those who report injecting an illicit drug at least once (lifetime PWID), those who have ceased injecting drug use (former PWID) and those who continue to inject drugs (recent PWID, with definitions of "recent" varying between one to 12 months) (27). Understanding the definitions for different PWID populations is crucial to accurately define reinfection risk following therapy. Similarly, not all people with HIV/HCV co-infection demonstrate contemporary behaviours placing them at risk of reinfection. While the internationally observed increase in HCV incidence in HIV-positive MSM has been associated with sexual risk behaviour and recreational drug use (10), as with primary HCV infection (28, 29), HIV-positive MSM who inject drugs are at significantly higher risk of HCV reinfection than HIV-positive MSM who do not inject drugs. As exemplified in this cohort, populations at high risk of reinfection, such as PWID and HIV-positive MSM, are not mutually exclusive. While often discussed as separate cohorts, it is important to remember that there is significant overlap.

The risk of HCV reinfection following treatment is significantly higher in those who report ongoing behaviour facilitating HCV transmission, with reinfection incidence ranging between 0.0 – 33.0 per 100 py in PWID treated for chronic HCV infection who reported ongoing injection drug use (19, 30-36). Similarly, in this cohort, HCV reinfection incidence was significantly higher amongst participants who reported injection drug use during follow up as compared with those who did not. However, reinfection was not associated with injection drug use prior to or at commencement of therapy. Particularly in the setting of interferon-based therapy, there may have been considerable selection bias in those PWID deemed suitable, or willing, for treatment. While injecting risk behaviour among PWID appeared to decline during and after interferon-based treatment (37), it is possible that expanded HCV treatment access and DAA therapeutic optimism may be associated with increased risk behaviour, as seen among MSM following the introduction of HIV combination antiretroviral therapy (38).

Reinfection was associated with injection drug use following treatment and older age, the latter appearing to be related to older age and shorter time since injecting onset among PWID with reinfection. Recent onset of injection drug use has been associated with HCV acquisition, though typically among young PWID (39-45). The increased risk of reinfection seen with injection drug use post treatment in association with use of unsterile needles and syringes highlights the need for education and broad access to harm reduction and prevention strategies in concert with HCV treatment. For PWID, access to interventions known to prevent HCV infection, including OST and high coverage needle and syringe access programs (42, 46-49), will be crucial. However, differences in drug use and sexual behaviours among cohorts of HIV-positive MSM as compared with HCV mono-infected populations may necessitate different public health strategies. Much of the literature surrounding HCV acquisition and prevention among PWID focusses on individuals who

inject opiates (42, 46-49). Older age at injecting onset, increasing use of stimulant drugs (largely amphetamines) and the phenomena of 'chemsex' (illicit drug use before or during sex, by both injecting and non-injecting routes of administration) may necessitate a different approach in MSM (50-54). Evidence supporting sexual behavioural interventions for HCV prevention among MSM is lacking. With serosorting of sexual partners by HIV-status and increasing use of pre-exposure prophylaxis to prevent HIV transmission in HIV-negative MSM, there is the potential for increased sexual risk behaviour and transmission of HCV among MSM populations (52, 55, 56). With DAA treatment scale-up among traditionally marginalised or "high-risk" populations, implementation and evaluation of novel prevention strategies should be a priority.

This study has a number of strengths, including the prospective design, inclusion of active PWID and HIV/HCV co-infected MSM, robust definition of follow up time at-risk for reinfection and use of viral sequencing to accurately delineate relapse and reinfection. The inclusion of a relatively large at-risk population, and documentation of ten cases of reinfection, provided sufficient power to evaluate associations. The prospective design allowed for serial HCV RNA measurements, improving the accuracy of the date of HCV reinfection estimation. Time at-risk for reinfection was calculated from date of end of treatment, where previous analyses have calculated time at-risk from date of SVR. In the era of DAA therapy, reinfection incidence rates will need to be calculated from end of treatment and sequencing used to accurately determine the aetiology of post-treatment HCV RNA recurrence to avoid misclassification, with reinfection occurring prior to the primary endpoint (SVR12) also seen in DAA registration trials (57, 58). However, the sequencing methodology used in this analysis could be considered suboptimal, given the inherent limitations of population-based (Sanger) sequencing, including poor sensitivity to detect minor variants and inability to detect mixed infection (9). Use of next-generation sequencing (NGS) could provide additional clarity in classification of post-treatment viral recurrence.

There are other limitations to this study. Firstly, duration of follow up was limited to that stipulated in the original trial protocol, ranging from 48 to 120 weeks post treatment. Two cases of confirmed reinfection were of indeterminate outcome as reinfection occurred at the last study visit. Given the follow up time, it is also possible that some participants were not followed for a sufficient time to allow for spontaneous clearance of reinfection. Additionally, while the cohort at-risk for reinfection was sizeable, the total follow up time post treatment was impacted by short individual follow up time, which could bias reinfection incidence, by creating a "cohort effect" in which those individuals at very high risk are reinfected early, while overall risk reduces over time. Secondly, due to the intervals between HCV RNA tests (12-24 weeks during follow up), some reinfections with rapid clearance may have been missed and as such, the reported reinfection incidence is an underestimate (59). However, this would not have impacted detection of persistent HCV reinfection. Thirdly, sexual behaviour was not collected, and as such, this could not be included in the model. However, the association between ongoing infecting drug use and reinfection in HIV-positive MSM highlights the overlap in these populations. Lastly, only six percent of the cohort received an interferon-free DAA regimen. Data is being to emerge on reinfection following treatment of chronic HCV infection with DAA therapy. In the C-EDGE COSTAR trial among people receiving OST, six cases of reinfection were identified at or prior to post treatment week 24, with five cases of reinfection detected at post treatment week eight (reinfection incidence 4.6 per 100 py, 95% CI 1.7, 10.0) (57). Urine drug screen was positive both during and following treatment in five of the six cases. The incidence of reinfection following DAA-based treatment needs careful evaluation as access to treatment among populations at-risk of ongoing transmission increases.

The treatment paradigm for individuals with HCV infection is evolving rapidly (2, 3, 58, 60). The potential for broad access to highly effective, well tolerated interferon-free DAA regimens has stimulated discussion around HCV treatment-as-prevention. HCV treatment-as-prevention strategies will be enhanced by early diagnosis and increased treatment uptake

in recent HCV infection, in order to reduce transmission amongst at-risk populations (5, 13). The significant risk for HCV reinfection following treatment in individuals with ongoing high risk behaviour emphasises the need for post-treatment surveillance, harm reduction strategies and education (12, 61), but must not be considered an impediment to treatment, if HCV elimination is to be achieved.

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

Variables	Overall N=120	HCV Reinfection N=10	No reinfection [a] N=110
Age at enrolment, median (IQR)	36 (29-46)	44 (36-49)	35 (24-46)
Gender			
Male	100 (83)	10 (100)	90 (82)
Female	19 (16)	0	19 (17)
Transgender	1 (1)	0	1 (1)
Full or part-time employment	68 (56)	5 (50)	63 (57)
Tertiary education or greater, n (%)	70 (58)	8 (80)	62 (56)
Social functioning score, median (IQR)	11 (6-16)	16 (12-17)	11 (6-15)
HIV infection, n (%)	64 (53)	7 (70)	57 (52)
On cART, n (%)	52 (81)	5 (71)	47 (82)
IDU, n (%)			
Ever prior to enrolment	83 (69)	7 (70)	77 (69)
Previous 6 months prior to enrolment	59 (49)	6 (60)	53 (48)
Previous 30 days prior to enrolment	52 (43)	6 (60)	46 (42)
Age at first IDU, median (IQR)	25 (20-34)	35 (30-46)	25 (20-32)
OST, n (%)			
Ever prior to enrolment	14 (12)	1 (10)	13 (13)
At enrolment	6 (5)	1 (10)	5 (5)
Mode of primary HCV acquisition, n (%)			
IDU	66 (55)	6 (60)	60 (55)
Sexual exposure	51 (43)	4 (40)	47 (43)
Other	3 (3)	0	3 (3)
Weeks between estimated date of HCV infection and treatment commencement, median (IQR)	36 (30-46)	34 (27-52)	37 (30-46)
HCV treatment			
PEG ± RBV	103 (86)	8 (80)	95 (86)
PEG-IFN + RBV + telaprevir	10 (8)	1 (10)	9 (8)
Sofosbuvir + RBV	7 (6)	1 (10)	6 (5)
Treatment weeks, median (IQR)	24 (16-24)	20 (8-24)	24 (16-24)
Time at risk of reinfection (years), median (IQR)	1.08 (0.59, 1.50)	0.67 (0.35, 1.23)	1.19 (0.60, 1.52)

[a] Includes participants with ETR and no reinfection or relapse

Abbreviations: Injecting drug use (IDU); opiate substitution therapy (OST); pegylated interferon (PEG-IFN); ribavirin (RBV)

Table 2. Detailed demographic, behavioural and virological characteristics of participants with HCV reinfection (n=10)

Gender, age[1]	HIV	Mode of primary HCV	IDU		HCV genotype		Region sequenced	Time between EOT and reinfection (weeks)	ALT		Reinfection outcome
			At screening[2]	During follow-up	Primary	Reinfection			EOT	Reinfection	
Confirmed reinfection											
Male 29	No	IDU	Yes	Yes	3a	1a	E1/HVR1	18	21	53	Spontaneous clearance
Male 49	Yes	IDU	Yes	Yes	3a/1a	3a/1a	Core-E2	81	83	1135	Persistence
Male 36	No	IDU	Yes	Yes	1a	3a	E1/HVR1 Core-E2	30	26	319	Persistence
Male 44	Yes	Sexual	No	No	2a	1a/3a	Core-E2	40	58	565	Indeterminate
Male 50	Yes	Sexual	No	Yes	1a	1a	NS5B	65	18	15	Indeterminate
Male 62	Yes	IDU	Yes	Yes	3a	1a	Core-E2 NS5B	39	15	65	Persistence
Male 45	Yes	Sexual	No	No	1a	1a	Core-E2 NS5B	18	29	54	Persistence
Male 41	Yes	IDU	Yes	Yes	3a	1a	Core-E2 NS5B	9	23	910	Persistence
Possible reinfection											
Male 35	No	IDU	Yes	Yes	3a	NA[3]	InnoLipa	31	15	14	Spontaneous clearance
Male 46	Yes	Sexual	No	Yes[4]	1a	NA[3]	InnoLipa	64	71	43	Spontaneous clearance

[1] Age at study enrolment
[2] IDU within 6 months of study enrolment
[3] Unable to sequence due to low HCV RNA at time of viral recurrence
[4] Anabolic steroids
Abbreviations: ALT, alanine aminotransferase; EOT, end of treatment; IDU, injecting drug use[1] ALT, normal range 0-30 U/L

Table 3. Incidence of HCV reinfection among participants treated for recent HCV infection

Participant type	Cases of reinfection (n)	Participants at risk (n)	Person years follow-up	Incidence/100 person-years	95% CI
Overall					
Confirmed/possible reinfection	10	120	135	7.4	4.0, 13.8
Confirmed reinfection	8	120	135	5.9	3.0, 11.9
Confirmed persistent reinfection	5	120	135	3.7	1.5, 8.9
HCV mono-infection					
Confirmed/possible reinfection	3	56	67	4.5	1.4, 13.9
Confirmed reinfection	2	56	67	3.0	0.7, 11.9
Confirmed persistent reinfection	1	56	67	1.5	0.2, 10.6
HIV/HCV co-infection[#]					
Confirmed/possible reinfection	7	64	68	10.3	4.9, 21.7
Confirmed reinfection	6	64	68	8.9	4.0, 19.7
Confirmed persistent reinfection	4	64	68	5.9	2.2, 15.7
IDU ever					
Confirmed/possible reinfection	8	84	94	8.5	4.2, 16.9
Confirmed reinfection	6	84	94	6.4	2.9, 14.1
Confirmed persistent reinfection	4	84	94	4.2	1.6, 11.3
IDU never					
Confirmed/possible reinfection	2	36	41	4.9	1.2, 19.8
Confirmed reinfection	2	36	41	4.9	1.2, 19.8
Confirmed persistent reinfection	1	36	41	2.5	0.3, 17.5
IDU at end of and/or post-treatment					
Confirmed/possible reinfection	8	45*	52	15.3	7.7, 30.6
Confirmed reinfection	6	45*	52	11.5	5.2, 25.5
Confirmed persistent reinfection	4	45*	52	7.7	2.9, 20.4
No IDU at end of and/or post-treatment					
Confirmed/possible reinfection	2	72*	77	2.6	0.7, 10.4
Confirmed reinfection	2	72*	77	2.6	0.7, 10.4
Confirmed persistent reinfection	1	72*	77	1.3	0.2, 9.2

[#]All participants with HIV/HCV are HIV-positive MSM

*Numbers do not equal 120 due to missing data on injecting during follow-up in 3 participants

Abbreviations: Confidence interval (CI)

Table 4. Factors associated with reinfection following treatment for recent HCV infection – Exact Poisson regression analysis

	HCV reinfection N=10	No reinfection N=110	IRR	95% CI	*P*	aIRR	95% CI	*P*
Sex, n (%)					*			
Male	10 (100)	90 (82)	1.00	-				
Female	0	19 (17)	0.37	0.00, 2.28	0.336			
Transgender	0	1 (1)	3.35	0.00, 20.82	1.000			
Age category (divided at median), n (%)								
≤36	**2 (20)**	**54 (49)**	**1.00**	**-**		**1.00**	**-**	
>36	**8 (80)**	**56 (51)**	**3.72**	**0.74, 35.99**	**0.137**	**5.42**	**1.06, 52.93**	**0.040**
Tertiary education, n (%)								
No	2 (20)	48 (44)	1.00	-	-			
Yes	8 (80)	62 (56)	2.79	0.56, 26.97	1.000			
Full or part-time employment, n (%)								
No	5 (50)	47 (43)	1.00	-	-			
Yes	5 (50)	63 (57)	0.84	0.19, 3.64	1.000			
Social functioning score at enrolment, n (%)					*			
≤11	2 (20)	58 (53)	1.00	-				
>11	7 (70)	45 (41)	4.60	0.88, 45.34	0.079			
Missing	1 (10)	7 (6)	3.06	0.05, 58.77	0.730			
Mode of primary HCV acquisition, n (%)								
IDU	6 (60)	60 (55)	1.00	-				
Sexual	4 (40)	47 (43)	0.98	0.20, 4.14	1.000			
Other	0	3 (3)	3.66	0.00, 25.36	1.000			
HIV infection, n (%)								
No	3 (30)	53 (48)	1.00	-				
Yes	7 (70)	57 (52)	2.31	0.53, 13.86	0.351			
Injecting drug use ever at enrolment, n (%)								
No	3 (30)	33 (30)	1.00	-				
Yes	7 (70)	77 (70)	1.04	0.24, 6.26	1.000			
Injection drug use in previous 6 months at enrolment, n (%)					*			
No	4(40)	55 (50)	1.00	-				
Yes	6 (60)	53 (48)	1.40	0.33, 6.76	0.838			
Missing	0	2 (2)	5.98	0.00, 47.84	1.000			
Injection drug use in previous 30 days at enrolment, n (%)								
No	4 (40)	64 (58)	1.00	-				
Yes	6 (60)	46 (42)	2.77	0.64, 12.02	0.195			
IDU at end of treatment and/or post treatment, n (%)					******			******
No	**2 (20)**	**70 (64)**	**1.00**	**-**		**1.00**	**-**	
Yes	**8 (80)**	**37 (34)**	**5.88**	**1.17, 56.82**	**0.027**	**7.86**	**1.54, 76.79**	**0.008**
Missing	**0**	**3 (3)**	**5.51**	**0.00, 71.51**	**1.000**	**5.78**	**0.00, 74.36**	**1.000**

P overall for categorical variables: * ≥0.05, ** 0.001-0.05, *** <0.001
Univariate analysis - P overall: Sex, p=0.281, social functioning score, p=0.079, IDU in previous 6 months, p=0.838, IDU at end of and/or post treatment, p=0.027
Multivariate analysis – P overall: IDU at end of and/or post treatment, p=0.008

Figure legends

Figure 1. Participant disposition.

Participants highlighted in **bold** constitute the cohort at-risk for reinfection.

Figure 2. Viral kinetics on and post-treatment in participants with HCV reinfection.

Panel A: Persistent HCV reinfection. Panel B: Spontaneous clearance of HCV reinfection.

Panel C: Indeterminate HCV reinfection outcome.

Shaded area indicates period on treatment.

LLoQ 25 IU/mL and LLoD 15 IU/mL for COBAS Taqman 2.0, Roche Diagnostics, USA.

Abbreviations: Baseline (BL), end-of-treatment response (ETR), lower limit of detection (LLoD), lower limit of quantitation (LLoQ), week (W), post treatment (PT)