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Response to treatment following recently acquired hepatitis C virus infection in a multi-centre collaborative cohort

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Abstract

Pegylated-interferon therapy is highly effective in recently acquired HCV. The optimal timing of treatment, regimen and influence of host factors remain unclear. We aimed to measure sustained virological response (SVR) during recent HCV infection and identify predictors of response. Data were from five prospective cohorts of high-risk individuals in Australia, Canada, Germany, and the United States. Individuals with acute or early chronic HCV who commenced pegylated-interferon therapy were included. The main outcome was SVR, and predictors were assessed using logistic regression. Among 516 with documented recent HCV infection, 237 were treated (pegylated-interferon n=161; pegylated-interferon/ribavirin n=76) (30% female, median age 35 years, 56% ever injected drugs, median duration of infection 6.2 months). Sixteen percent (n=38) were HIV/HCV co-infected. SVR among those with HCV mono-infection was 64% by intention-to-treat; SVR was 68% among HCV/HIV co-infection. Independent predictors of SVR in HCV mono-infection were duration of HCV infection (the odds of SVR declined by 8% per month of infection, aOR 0.92, 95% CI 0.85–0.99, p=0.033), *IFNL4* genotype (adjusted OR 2.27, 95%CI 1.13–4.56, p=0.021), baseline HCV RNA <400,000 IU/ml (aOR 2.06, 95%CI 1.03–4.12, p=0.041) and age ≥40yrs (versus <30: aOR 2.92, 95%CI 1.31–6.49, p=0.009), with no difference by drug regimen, HCV genotype, symptomatic infection, or gender. The effect of infection duration on odds of SVR was greater among genotype-1 infection. Interferon-based HCV treatment is highly effective in recent HCV infection. Duration of infection, *IFNL4* genotype and baseline HCV RNA levels can predict virological response and may inform clinical decision making.

Keywords

acute infection; Hepatitis C virus; recently acquired infection; virological response

INTRODUCTION

Infection with hepatitis C virus (HCV) progresses to chronic infection in 75% of cases, often leading to cirrhosis and hepatocellular carcinoma (1). Interferon-alfa-based treatment of acute HCV infection can yield high sustained virological response (SVR) rates (2–5). The ideal time point for initiating treatment has not been firmly established, and uncertainty remains about optimal regimen and whether response can be predicted by host or viral genotype. Despite advances in direct acting agents for chronic HCV infection, none have been studied or licenced in acute HCV (5). Given the burden of HCV-related morbidity and mortality globally (1), and that interferon-based therapies are likely to remain the standard of care and most widely accessible therapy for some time (particularly in low- and middle-income countries) (5), a better understanding of treatment response during acute HCV infection is important.

The majority of people who spontaneously clear HCV following acute infection do so within six months (6). Therefore, it has become standard practice to delay therapeutic intervention

three to six months after diagnosis to avoid unnecessary treatment (4, 7). Host genetic factors, such as polymorphisms of *interferon lambda-4* gene (*IFNL4*; also known as *interleukin-28B* [*IL28B*] or *interferon lambda-3* (8)), are established predictors of virological clearance (6) and response in chronic HCV treatment (9). During recent HCV infection, genetic variations in *IFNL4* region have been associated with symptomatic infection and spontaneous clearance (10, 11). Yet amongst small cohorts of acute HCV infection, *IFNL4* genotype has not been established as a predictor of SVR.

Studying acute HCV treatment has been limited by low detection rates of acute HCV cases, difficulty reaching the key affected population of people who inject drugs (PWID) due to social marginalisation, and the nature of interferon-based treatment. While demonstrating high SVR, the relatively small sample size of previous studies has limited statistical power to explore predictors of treatment response. The International Collaboration of Incidence HIV and Hepatitis C in Injecting Cohorts (InC³) Study (6) and the German Network for Competence on Viral Hepatitis (Hep-Net) (3) provide data from ten well-characterised, international cohorts of people with recently acquired HCV infection, and provides an opportunity to assess treatment response in a large number of individuals followed prospectively. The aims of this study were to describe SVR and time to HCV clearance and examine virological, genetic and treatment-based predictors of treatment response.

METHODS

The InC³ Study (12) and the Hep-Net Acute HCV III Study (3) have been previously described; five of the ten cohorts in these collaborations offered or collected information on treatment of recently acquired HCV. Data were included from four InC³ collaboration cohorts evaluating treatment response following recent HCV infection in Australia (Australian Trial in Acute Hepatitis C, and Hepatitis C Incidence and Transmission Study-Prison), Canada (St. Luc HEPCO Cohort) and the United States (Boston Acute HCV Study: Transmission, Immunity and Outcomes Network). The Hep-Net collaboration includes one prospective multi-centre study in Germany evaluating acute HCV treatment. For this current study, individuals receiving at least one dose of anti-viral treatment for documented recently acquired HCV were included.

Documented recently acquired HCV infection was based on either of the following criteria: (1) Acute clinical HCV infection, defined as symptomatic seroconversion illness or medically documented jaundice or alanine aminotransferase (ALT) level greater than ten times the upper limit of normal with exclusion of other causes of acute hepatitis, and HCV RNA detection or high-risk exposure (injecting drug use, or proven/very probable percutaneous or sexual exposure to HCV) within the preceding four months; or (2) Asymptomatic HCV infection with seroconversion, defined by a negative anti-HCV test in the two years prior to the initial positive anti-HCV antibody or HCV RNA test. All participants provided written informed consent and their protocols were approved by local institutional review boards.

HCV treatment and virological testing

All participants were treated using pegylated interferon (PEG-IFN)-alfa 2a (180µg weekly) or PEG-IFN-2b (1.5µg/kg weekly) alone or in combination with ribavirin (RBV, 800–1200mg daily) for a planned duration of 24 weeks in most (>95%) participants. PEG-IFN/RBV was used in HCV mono-infection at four sites, primarily where estimated duration of infection was >6 months; at one site immediate PEG-IFN initiation was randomised, compared to three-month deferred treatment (3). Clinical characteristics including gender, age, HIV and hepatitis B virus status, serum ALT, route of HCV acquisition, and injecting drug behaviour were collected and reported in a standardised manner. Virological testing was performed using different platforms at each site, but applied consistently within each cohort. Qualitative HCV RNA testing was performed using Versant TMA (Bayer, Australia, lower limit of detection [LLOD] <10IU/ml), COBAS Amplicor HCV Test v2 (Roche Diagnostics, Germany, LLOD <50 IU/ml) or COBAS AmpliPrep/COBAS Taqman (Roche, USA, LLOD <15 IU/ml). Quantitative HCV RNA was performed using Versant HCV RNA 3.0 (Bayer, lower limit of quantification [LLOQ] <615 IU/ml), COBAS AmpliPrep/COBAS Taqman (Roche Diagnostics, Germany LLOQ <15 IU/ml) or an in-house polymerase chain reaction assay (LLOQ<1000 IU/ml). HCV genotype was determined by line-probe assay (Versant LiPa1/LiPa2; Bayer, Australia) or HCV sequencing. *IFNL4* genotype was determined by sequencing of the rs12979860 or rs8099917 single-nucleotide polymorphism (6, 13, 14).

Study definitions

Recently acquired HCV infection included acute (<6 months) and early chronic (6–24 months) infection. The estimated date of infection was defined using a hierarchy favouring symptomatic infection over asymptomatic antibody or RNA seroconversion dates. For cases of acute symptomatic HCV, date of infection was calculated as six weeks prior to onset of acute clinical symptoms, where jaundice or ALT elevation (>400 IU/ml) was recorded (15). The estimated date of infection for cases of acute asymptomatic HCV was calculated as the mid-point between last negative anti-HCV antibody and first positive anti-HCV antibody, except for participants who were anti-HCV antibody negative and HCV RNA positive at the diagnosis date of infection, where infection date was estimated four weeks prior (16–18). In a small number of cases (n=19) where other definitions could not be applied, participants with a high-risk HCV exposure within four months prior to first diagnosis had date of infection estimated from the date of exposure (3).

The estimated duration of infection at baseline was calculated as the time between estimated date of infection and date of treatment commencement. Adherence to treatment protocol was defined as receiving at least 80% of scheduled PEG-IFN or RBV doses or at least 80% of scheduled treatment period, and finishing study follow up at week 24. Among untreated participants, spontaneous clearance was defined as two negative HCV RNA tests greater than four weeks apart. Time to RNA clearance was estimated as the mid-point between last positive and first negative HCV RNA test among participants with spontaneous clearance and treatment-induced clearance.

Study Outcomes

The primary study outcome was the proportion of subjects achieving SVR, defined as undetectable HCV RNA at 24 weeks post-treatment. Secondary end-points included proportion with treatment response at weeks four (rapid virological response, RVR) and twelve (early virological response, EVR), and the time to HCV RNA clearance comparing treated and untreated participants with recent HCV infection. The primary outcome was assessed by intention-to-treat analysis including all participants receiving at least one PEG-IFN dose, with a secondary analysis examining adherent participants completing study follow up and achieving SVR (per-protocol analysis).

Statistical analysis

Categorical characteristics of participants with and without treatment outcome were compared using χ^2 test and Fisher's exact test, as appropriate. Predictors of treatment response were analysed using univariable and multivariable random-effects logistic regression models to estimate crude and adjusted odds ratios (OR) with 95% confidence intervals. Key hypotheses under investigation were that shorter duration of infection (19), HCV genotype (1 versus non-1) (20), favourable *IFNL4* genotype (rs12979860 CC versus non-CC) (11, 13, 21), and combination therapy (PEG-IFN+RBV versus PEG-IFN)(22) would improve SVR stratified by HIV status. Potential predictors for exploration and adjustment were identified *a priori* including age (categorised as <30, 30–40 and >40 years), gender, weight (<75kg), baseline HCV RNA level (<400,000IU/ml), clinical presentation (symptomatic versus asymptomatic), duration of treatment, prior injecting drug use and cohort site.

In addition to hypothesised predictors of treatment response, other variables that were significant at the 0.20 level in the univariable analysis were considered as covariates in multivariable random-effects logistic regression. A backwards stepwise approach sequentially eliminated variables subject to the result of a likelihood ratio test, and the final model was evaluated using a Hosmer-Lemeshow goodness-of-fit test. We controlled for unobserved heterogeneity across cohort sites by including site as a random-effects term in multivariable models. Sensitivity analyses were performed to assess the definition of duration of HCV infection (reordering the definition hierarchy to seroconversion then symptomatic infection) and interactions (effect modification) between hypothesised predictors on SVR (gender and *IFNL4* genotype; gender and HCV genotype; HCV genotype and *IFNL4* genotype; and seroconversion illness and *IFNL4* genotype).

Time to HCV RNA clearance comparing treated and untreated participants was evaluated using Kaplan-Meier analyses to account for anticipated spontaneous clearances masked by successful treatment. Treated participants who did not achieve SVR were considered not to have cleared, regardless of any on-treatment virological suppression. For comparison with time to clearance in treated participants, untreated were included if they remained viraemic three months after estimated date of infection, approximating earliest treatment initiation. Cox proportional hazards analyses modelled time to HCV clearance by treatment status adjusted for gender, age, HCV genotype, symptomatic seroconversion, HCV RNA level,

and *IFNL4* genotype. Hazard proportionality assumptions were assessed using scaled Schoenfeld residuals.

Differences were considered significant at the 0.05 level using two-sided p values. All analyses were conducted using Stata (v13.1, Stata Corporation, College Station, TX, United States).

RESULTS

Participant characteristics

Between 2004 and 2010, 516 cases of recent HCV infection were observed. Of these, 85 spontaneously cleared HCV infection, 194 had persisting untreated viraemia and 237 received at least one dose of PEG-IFN. Overall, 75% (178/237) completed >80% of planned treatment and were assessed at 24 weeks post-treatment follow-up. HCV treatment was initiated during acute HCV (0–6 months) in 46% (n=109), and early chronic HCV (6–24 months) in 49% (n=116), with 5% (n=12) having an unknown date of infection. Date of HCV infection was estimated by acute symptomatic illness in 48% (114/237), asymptomatic HCV-antibody seroconversion midpoint in 36% (86/237), HCV-antibody negative/RNA positive in 3% (6/237), or by high-risk HCV exposure in 8% (19/237).

The median age of treated participants was 35 years, 70% (n=166) were male, and the median duration of HCV at treatment commencement was 6.2 months (interquartile range [IQR], 3.5–8.7) (Table 1). Among those with available data (n=155), a history of injecting drug use was reported by 86% (n=133). Overall, 62% had genotype-1 infection, 37% had genotype-2 or -3 infection (Table 1). HCV genotype distribution was similar between those with and without HIV co-infection.

Treated participants were older (35 versus 28 years, $p<0.001$), and more likely to have HIV co-infection (16% versus 4%, $p<0.001$) and symptomatic HCV infection (59% versus 42%, $p<0.001$), compared with untreated individuals. A similar proportion of treated and untreated participants had the favourable CC allele (53% versus 49%, $p=0.502$).

Treatment disposition

Treatment outcomes were analysed separately for HIV/HCV co-infected individuals given systematic differences in treatment regimen and HIV inclusion criteria across sites. All 38 HIV/HCV co-infected participants received PEG-IFN+RBV for 24 weeks. In contrast, those with HCV mono-infection (n=197) received PEG-IFN alone for 16 weeks (n=9, 4%) or 24 weeks (n=152, 78%), or PEG-IFN+RBV for 24 weeks (n=32, 16%) or 48 weeks (n=4, 2%). In contrast to HCV mono-infected participants, treated HIV co-infected participants were older (41 versus 33 years, $p=0.002$), predominantly male (97% versus 64%, $p<0.001$), and be more likely to have asymptomatic infection (47% versus 33%, $p<0.001$) compared to HCV mono-infected participants.

HCV mono-infection treatment outcomes

Among HCV mono-infected participants, 78% (153/197) completed at least 80% of planned treatment duration and PEG-IFN doses. Overall, undetectable HCV RNA at weeks 4, 12 and

end of treatment were observed in 87 (44%), 138 (70%), and 139 (71%), respectively. In the intention to treat population, SVR was 64% (126/197), compared to 83% (122/147) among the per-protocol population (Figure 1). Lower SVR in the intention to treat population are accounted for primarily by poor adherence (n=16), early discontinuation for medical reasons (n=10) or incomplete follow up (n=14).

In unadjusted analysis, SVR was more likely among older participants (>40 years versus <30 years), Hep-Net site participants versus other sites, those with shorter duration of infection, and favourable *IFNL4* genotype (Table 2). Data on injecting behaviour were not collected at one site (n=82, 35%), and complete treatment success among those few (n=6) HCV monoinfected individuals who reported never injecting drugs prevented inclusion of injecting drug use in the adjusted model. Gender, drug regimen (PEG-IFN versus PEG-IFN/RBV) and length of treatment, symptomatic infection and peak ALT were not associated with SVR.

Predictors independently associated with improved SVR included age >40 years (versus <30: adjusted odds ratio [aOR] 2.92, 95% confidence interval [CI] 1.31–6.49, p=0.009), *IFNL4* favourable CC genotype (versus CT/TT: aOR 2.27, 95%CI 1.13–4.56, p=0.021) and low baseline HCV RNA level <400,000IU/ml (versus >400,000IU/ml: aOR 2.06, 95%CI 1.03–4.12, p=0.041). Duration of HCV infection also independently predicted SVR; for each month since estimated infection, the odds of SVR declined by 8% (aOR 0.92, 95%CI 0.85–0.99, p=0.033; linearity assumptions verified graphically). SVR was 72%, 68%, 57%, respectively, when duration of infection was <3 months, 3 to 6 months, or >6 months from estimated infection date.

While not independently predicting SVR, HCV genotype had a significant effect modification on the association between duration of infection with SVR (p=0.043) and potentially modified the association between *IFNL4* genotype and SVR (p=0.099). Duration of infection more strongly predicted SVR among HCV genotype-1 individuals (aOR 0.84 per month of infection, 95% CI 0.75–0.95) than non-genotype-1 (aOR 0.97, 95% CI 0.84–1.14) (Figure 2). *IFNL4* genotype tended to predict SVR more strongly among genotype-1 infected individuals (aOR 4.13, 95% CI 1.52–11.24) than non-genotype-1 infection (aOR 1.30, 95% CI 0.41–4.14). Among HCV genotype-1 monoinfected individuals, SVR was 75% among those with favourable *IFNL4* genotype compared to SVR 50% among *IFNL4* unfavourable (non-CC) (Figure 3). There was no interaction between *IFNL4* and gender on SVR.

In sensitivity analyses, the results did not change significantly when the methodology for estimating the date of infection was modified.

HCV/HIV co-infection treatment outcomes

Among HCV/HIV co-infected individuals, 79% (30/38) completed at least 80% of planned treated duration and PEG-IFN doses. Undetectable HCV RNA at weeks 4, 12 and end of treatment were observed in 17 (45%), 30 (79%), and 29 (76%), respectively. In the ITT population, SVR was 68% (26/38), compared to 83% (24/29) among the per-protocol population (Figure 1). Most of the treated HIV infected individuals were recruited in the

Australian ATACH cohort (36 out of 38), who have been previously well characterised (2, 23).

In unadjusted analysis, SVR was more likely among HCV non-genotype-1 infection (92%) compared with genotype-1 infection (53%, $p=0.038$) (Supplementary Table 1). There was no difference in SVR between injectors and non-injectors (64% versus 75%, $p=0.459$). There was no association between SVR and other predictors of treatment response in the univariable model. Of note, all HCV/HIV co-infected individuals received combined PEG-IFN and RBV therapy, and all but one individual were male, limiting exploration of these factors as predictors of response. In models adjusted for age and site, there remained an association between SVR and HCV genotype (genotype non-1 versus genotype-1: aOR 0.09, 95% CI 0.01–0.84, $p=0.035$) in those with HIV/HCV co-infection. Sensitivity analyses substituted other *a priori* predictors into the adjusted model, including *IFNL4* genotype, symptomatic infection, and HCV RNA, but none provided better fit of the data or affect the observed association between SVR and HCV genotype.

Effect of HCV treatment on clearance

Given the observation that duration of infection was associated with treatment response, time to HCV clearance was assessed using Kaplan-Meier analyses (Figure 4). At 6, 12, 18 and 24 months after estimated date of infection, clearance had occurred spontaneously in 11%, 18%, 22% and 22% cumulative of untreated participants, compared to 29%, 60%, 71%, 78% of treated participants, respectively. In Cox proportional hazards regression, treatment was independently associated with HCV RNA clearance (adjusted hazard ratio [aHR] 5.00, 95% CI 3.29–7.60, $p<0.001$) adjusted for age, gender, HCV genotype and *IFNL4* genotype (Table 3). Gender interacted significantly with the effect of treatment on HCV monoinfection RNA clearance (Treatment v no treatment aHR among males: 8.38, 95% CI 4.46–15.75; aHR among females: 2.47, 95% CI 1.38–4.45); interaction term $p=0.034$, Figure 4). Cox proportional hazards assumptions were not violated ($p=0.229$).

DISCUSSION

This study describes the virological outcomes and independent predictors of treatment response in a large multi-country sample of people with recent HCV infection followed over time. The findings reinforce that treatment of recent HCV with PEG-IFN is effective, including among people who inject drugs and those with HIV co-infection. This study demonstrated for the first time that variations in the *IFNL4* gene are associated with acute treatment response to PEG-IFN-based therapy in genotype-1 infection. There was no improvement in SVR when RBV was added to PEG-IFN in recent HCV mono-infection independent of duration of infection. Finally, this study also provides important evidence for commencing PEG-IFN treatment during acute rather than early chronic HCV infection given declining SVR over time, particularly among HCV genotype-1 infected individuals, after taking into account age, HCV RNA level and *IFNL4* genotype in clinical decisions.

There have been several recent advances in chronic HCV treatment and it is expected that new direct acting antiviral therapies will be highly efficacious when studied in acute HCV infection (5, 7). However, resource limitations, cost-effectiveness and licensing restrictions

could mean that PEG-IFN-monotherapy – particularly among HCV mono-infected individuals with favourable treatment response characteristics – remains a default treatment approach in many settings, particularly in low- and middle-income countries. As such, this study makes significant contribution to the appropriate targeting of treatment to those with predictors of SVR and demonstrates benefits of early treatment initiation following acute HCV.

A meta-analysis found PEG-IFN therapy initiated at 12 weeks following infection yield a pooled SVR of 82%, compared with treatment started at 12–24 weeks (66% SVR) and >24 weeks (62% SVR), but heterogeneity in effect estimates, study methodology, and no head-to-head comparison of treatment duration limit those findings (24, 25). The current study's results were consistent with SVR 72%, 68%, 57% at less than 3 months, 3–6 months, and greater than six months after infection, indicating acute treatment is superior to early chronic treatment for HCV genotype-1 infection. However, this study includes a large sample size and similar study definitions applied across sites to provide a robust estimate of the virological consequence of deferring recently acquired HCV therapy. To our knowledge, this is the largest cohort of patients treated with acute HCV infection worldwide to date.

The observation that the effect of duration of infection on SVR was enhanced in HCV genotype-1 infection may be consistent with emerging prospective data indicating genotype-1 (6, 20, 26), rather than genotype-3 (27), infected individuals have higher rates of spontaneous clearance, since some treated individuals may have gone on to spontaneously clear. Higher spontaneous clearance of genotype-1 may also explain the observation that HCV genotype does not appear to predict SVR in recent infection, unlike in chronic infection. However, this study found substantially higher HCV RNA clearance using PEG-IFN-monotherapy compared with no treatment from three months after estimated infection, independent of factors associated with spontaneous clearance. This provides evidence to support current guidelines and previous research that generally recommend treatment initiation three months after estimated date of HCV infection (3, 7, 28). The effect of male gender increasing likelihood of treatment-induced clearance compared to spontaneous clearance is also consistent with previous research that demonstrated an association between female gender and spontaneous clearance (29, 30). The relative effect of male gender versus female gender on treatment-induced clearance is best demonstrated in the Kaplan-Meier curve (Figure 4): the effect modification of gender on treatment-induced clearance appears primarily due to differential spontaneous clearance probabilities between females and male. Female and male treated groups appear have similar likelihood of clearance.

IFNL4 genotype is strongly associated with SVR in chronic HCV infection (9, 14). It is the strongest predictor of PEG-based treatment response in genotype-1 infection (21), and its effect in HCV genotypes 2, 3 and 4 infection is weaker but still significant (31–33). Smaller studies have failed to detect a relationship between *IFNL4* genotype and SVR in recently acquired infection treatment previously – including among individual InC3 sites (10, 22). The large sample size in this analysis allowed an independent effect of *IFNL4* genotype in recent infection to be demonstrated for the first time. While the effect modification of HCV genotype on *IFNL4* genotype did not reach statistical significance here, it is plausible and

consistent that genotype-1 and favourable *IFNL4* genotype combined will strongly predict SVR in recent infection.

Low baseline HCV RNA level (less than 400,000IU/ml) predicts improved SVR in chronic HCV mono-infection (34, 35). This is consistent with our findings, despite some variations in quantitative HCV RNA platforms used in this study. The observation that older age (>40 compared with <30 years) is independently associated with SVR among HCV mono-infected is contradictory to other data indicating lower SVR with advancing age in chronic HCV (36, 37). While age might be a surrogate for undiagnosed cirrhosis in long-standing HCV infection, and hence results in lower SVR (38), in recent infection HCV-mediated fibrosis should be absent or minimal. In this cohort where a large proportion report injecting drug use, age is more likely to be a proxy for adherence and social stability which could both increase SVR (2). In a per-protocol analysis to explore the effect of unmeasured confounders affecting adherence, the relationship between age and SVR was no longer statistically significant (age >40yrs versus <30yrs: aOR 2.09, 95% CI 0.52–8.41).

This analysis has several limitations. Treatment data was merged from five cohorts but primarily came from two cohorts. Variations in study measurement and assessment introduce heterogeneity into any merged analysis, which cannot be completely adjusted for despite statistical corrections. Several variables of clinical interest relating to injecting drug use, substance use and behaviour were differentially collected across sites, precluding their use in the analysis. Similarities in treatment length (95% received 24 weeks PEG-IFN) limit our ability to comment on differences treatment duration, although recent randomised trial data indicate equivalent response at 12 and 24 weeks in acute HCV mono-infection (39). While there was no apparent additional benefit of RBV to PEG-IFN in HCV mono-infection, the small numbers receiving combination therapy (n=36) limits power to detect small differences. Considered in light of other recent randomised data and additional toxicity from RBV use, there is no indication for combination PEG-IFN/RBV in acute HCV mono-infection (39). The small number of HCV/HIV co-infected participants limits our ability to generalise predictors of treatment response seen here to other settings. Nevertheless, the SVR of 68% (and 83% among adherent participants) is an impressive treatment response compared to chronic HCV treatment in HIV co-infection (40), and particularly considering delays before new HCV antivirals will become accessible for routine use in HIV co-infection. This study's strengths are that it is largest pooled study of acute HCV treatment to date, data were prospectively collected in well characterised cohorts, and statistical adjustment for heterogeneity between study sites was made using a conservative random effects method.

CONCLUSIONS

Recently acquired HCV can be treated successfully with IFN-based therapies. SVR is at least comparable to IFN-based treatment of chronic HCV infection which requires longer and more complex combination therapy. Treatment initiation three months after estimated date of HCV infection is optimal, and offers substantially higher HCV RNA clearance than no treatment, independent of other factors associated with spontaneous clearance. Clinical decisions on whether to offer treatment in recently acquired HCV infection should consider

IFNL4 genotype, HCV RNA level and time since infection, particularly amongst genotype-1 infected individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

HCV	hepatitis C virus
SVR	sustained virological response
PEG-IFN	pegylated-interferon
RBV	ribavirin
PWID	people who inject drugs
InC3	The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts
Hep-Net	The German Network for Competence on Viral Hepatitis
ATAHC	Australian Trial in Acute Hepatitis C
BAHSTION	Boston Acute HCV Study: Transmission, Immunity and Outcomes Network
HEPCO	St. Luc Cohort, HEPCO
HITS-p	Hepatitis C Incidence and Transmission Study – prison
LLOQ	lower limit of quantification
LLOD	lower limit of detection
IQR	interquartile range
N/A	not applicable
OR	odds ratio

aOR	adjusted odds ratio
HR	hazard ratio
aHR	adjusted hazard ratio

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Figure 1. Treatment response rates at end of treatment (ETR) and SVR
(A) HCV monoinfected. (B) HCV/HIV co-infected.

Figure 2.
Influence of estimated duration of infection on SVR among HCV monoinfected participants,
by HCV genotype (n=171)

Figure 3.
Influence of *IFNL4* genotype on SVR among HCV monoinfected participants, by HCV genotype (n=164)

Figure 4. Kaplan-Meier survival graph of time to HCV virological clearance among all HCV-infected participants (n=432)

(A) Stratified by treatment. (B) Stratified by treatment and gender (treatment & gender interaction $p=0.034$).

Table 1

Characteristics of participants with recently acquired HCV Infection, excluding spontaneous clearance, by treatment and HIV status

Characteristic at Baseline	Treated, n (column %)			Untreated, n (column %)
	Total	HCV mono-infected	HIV co-infected ^I	
Overall	237	197	38	194
Site				
ATAHC (Australia)	105 (44%)	69 (35%)	36 (95%)	22 (11%)
BAHSTION (USA)	13 (5%)	9 (5%)	2 (5%)	28 (14%)
HEPCO (Canada)	21 (9%)	21 (11%)	0	47 (24%)
Hep-Net (Germany)	94 (40%)	94 (48%)	0	27 (14%)
HITS-P (Australia)	4 (2%)	4 (2%)	0	70 (36%)
Age, years, median (IQR)	35 (27–44)	34 (26–42)	42 (35–48)	28 (23–36) ²
Male Gender	166 (70%)	127 (64%)	37 (97%)	117 (70%)
Weight, kg, median (IQR)	74 (64–83)	72 (61–83)	77 (72–84)	69 (60–81)
Body mass index, kg/m², median (IQR)	23.8 (21.5–25.8)	23.2 (21.1–26.0)	24.7 (23.5–25.6)	22.2 (20.3–25.6)
Ethnicity				
European origin	131 (55%)	92 (47%)	37 (97%)	139 (72%)
Non-European	12 (11%)	11 (5%)	1 (3%)	28 (14%)
Not collected at site	94 (40%)	94 (48%)	0	27 (14%)
Injecting drug use				
Ever	133 (56%)	109 (55%)	22 (58%)	166 (85%)
Never	22 (9%)	6 (3%)	16 (42%)	1 (<1%)
Not collected at site	82 (35%)	82 (42%)	0	27 (14%)
Estimated duration of infection at treatment				
Months, median (IQR)	6.2 (3.5–8.7)	5.8 (3.0–8.7)	7.0 (5.2–9.8)	–
0–3 months	49 (21%)	47 (24%)	2 (5%)	–
3–6 months	60 (25%)	50 (25%)	10 (26%)	–
>6 months	116 (49%)	90 (46%)	24 (63%)	–
Missing	12 (5%)	10 (5%)	2 (5%)	–
Presentation of HCV				
Seroconversion illness	139 (59%)	122 (62%)	17 (45%)	81 (42%)
Jaundice	77/139 (55%)	71/122 (58%)	6/17 (35%)	2/6 ³ (33%)
ALT 400 IU/ml	101/139 (73%)	86/122 (70%)	15/17 (88%)	6/7 ³ (86%)
Asymptomatic infection	83 (35%)	65 (33%)	18 (47%)	56 (29%)
Missing	15 (6%)	10 (5%)	3 (8%)	57 (29%)
HIV co-infection				
Yes	38 (16%)	N/A	38 (100%)	7 (4%)
No	197 (83%)	197 (100%)	N/A	181 (93%)
Missing	2 (1%)	0	0	6 (3%)
HCV RNA screening				

Characteristic at Baseline	Treated, n (column %)			Untreated, n (column %)
	Total	HCV mono-infected	HIV co-infected ¹	
Log ₁₀ IU/mL, median (IQR)	5.5 (4.4–6.2)	5.3 (4.3–6.1)	6.2 (5.0–6.5)	5.4 (4.6–6.2)
<400,000 IU/ml	116 (49%)	104 (53%)	12 (32%)	75 (45%)
400,000 IU/ml	103 (43%)	75 (38%)	26 (68%)	55 (34%)
Quantitative RNA missing	18 (8%)	18 (9%)	0	64 (22%)
ALT peak, IU/ml, median (IQR)	569 (250–1236)	535 (216–1198)	685 (285–1514)	265 (133–663)
HCV genotype				
Genotype 1	139 (59%)	113 (57%)	24 (63%)	72 (37%)
Genotype 2	18 (8%)	16 (8%)	2 (5%)	5 (3%)
Genotype 3	65 (27%)	54 (27%)	11 (29%)	74 (38%)
Genotype 4	1 (<1%)	1 (<1%)	0	2 (1%)
Genotype 6	0	0	0	2 (1%)
Mixed genotype	2 (<1%)	2 (1%)	0	9 (5%)
Unknown genotype	12 (5%)	11 (6%)	1 (3%)	30 (20%)
IFNL4 genotype				
CC	112 (47%)	91 (46%)	21 (55%)	69 (36%)
CT	82 (35%)	71 (36%)	11 (29%)	60 (31%)
TT	19 (8%)	13 (7%)	4 (11%)	12 (6%)
Missing	24 (10%)	22 (11%)	2 (5%)	53 (27%)
Treatment regimen				
PEG-IFN	161 (68%)	161 (82%)	0	–
16 weeks	9/161 (6%)	9/161 (6%)	0	–
24 weeks	152/161 (94%)	152/161 (94%)	0	–
PEG-IFN & RBV	76 (32%)	36 (18%)	38 (100%)	–
24 weeks	72/76 (95%)	32/36 (89%)	38 (100%)	–
48 weeks	4/76 (5%)	4/36 (11%)	0	–

¹ HIV status unknown n=2

² Age at time of incident HCV infection among untreated group

³ Details among untreated participants incompletely collected

Table 2
Factors associated with SVR among HCV mono-infection using logistic regression (n=197)

Site	SVR n (%)	Univariable model		Multivariable model ¹	
		OR (95% CI)	p value	aOR (95% CI)	p value
ATAHC (Australia)	37 (54%)	1	–	N/A ¹	–
BAHSTION (USA)	2 (22%)	0.25 (0.05, 1.28)	0.095	–	–
HEPCO (Canada)	13 (62%)	1.40 (0.52, 3.82)	0.505	–	–
Hep-Net (Germany)	72 (77%)	2.83 (1.44, 5.54)	0.002	–	–
HITS-P (Australia)	2 (50%)	0.87 (0.11, 6.50)	0.888	–	–
Age categorised					
30 years	42 (54%)	1	–	1	–
30–40 years	37 (65%)	1.59 (0.79, 3.20)	0.199	1.98 (0.91, 4.29)	0.085
40 years	47 (76%)	2.69 (1.29, 5.58)	0.008	2.92 (1.31, 6.49)	0.009
Gender					
Male	79 (62%)	1	–	1	–
Female	47 (67%)	1.24 (0.67, 2.30)	0.490	1.20 (0.61, 2.39)	0.590
Weight					
75 kg	61 (65%)	1	–	–	–
>75kg	53 (70%)	1.25 (0.65, 2.38)	0.504	–	–
Missing	12 (44%)	0.43 (0.18, 1.03)	0.059	–	–
Injecting drug use ever²					
Yes	54 (50%)	1	–	–	–
No	6 (100%)	N/A ²	–	–	–
Duration of infection					
0–3 months	34 (72%)	1	–	–	–
3–6 months	34 (68%)	0.81 (0.34, 1.94)	0.641	–	–
>6 months	51 (57%)	0.50 (0.23, 1.07)	0.075 ⁴	–	–
Missing	7 (70%)	0.89 (0.20, 3.98)	0.881	–	–
Duration of infection (continuous, per month)	–	0.92 (0.85, 0.99)	0.031	0.91 (0.84, 0.99)	0.033³

	SVR n (%)	Univariable model		Multivariable model ¹	
		OR (95% CI)	p value	aOR (95% CI)	p value
Presentation of HCV					
Seroconversion illness	80 (66%)	1	–	–	–
Asymptomatic infection	41 (63%)	0.90 (0.48, 1.68)	0.734	–	–
Missing	5 (50%)	0.53 (0.14, 1.92)	0.329	–	–
HCV RNA screening					
400,000 IU/ml	43 (57%)	1	–	1	–
<400,000 IU/ml	72 (69%)	1.67 (0.90, 3.11)	0.102	2.06 (1.03, 4.12)	0.041
Missing	11 (61%)	1.17 (0.41, 3.35)	0.771	–	–
ALT peak					
<400 IU/ml	33 (63%)	1	–	–	–
400 IU/ml	75 (69%)	1.27 (0.63, 2.54)	0.500	–	–
Missing	18 (50%)	0.58 (0.24, 1.37)	0.210	–	–
HCV genotype					
Genotype non-1	45 (62%)	1	–	1	–
Genotype 1	73 (65%)	1.14 (0.62, 2.09)	0.683	1.20 (0.61, 2.38)	0.608
Missing	8 (73%)	1.66 (0.41, 6.78)	0.481	–	–
<i>IFNL4</i> genotype					
CT or TT	47 (56%)	1	–	1	–
CC	66 (73%)	2.08 (1.11, 3.90)	0.023	2.27 (1.13, 4.56)	0.021⁴
Missing	13 (59%)	1.14 (0.44, 2.95)	0.792	–	–
Treatment regimen					
PEG-IFN	103 (64%)	1	–	–	–
PEG-IFN/RBV	23 (64%)	0.99 (0.47, 2.11)	0.992	–	–
Treatment duration					
24 weeks	119 (64%)	1	–	–	–
16 weeks	3 (56%)	0.70 (0.18, 2.71)	0.610	–	–
48 weeks	2 (100%)	N/A	–	–	–

¹ Adjusting for random effects of site, and fixed effects of age, gender, duration of infection, HCV RNA level, HCV genotype, *IFNL4* genotype (n=187).

² Data collected at four of five sites included (n=103).

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³ Interaction between HCV genotype and duration of infection (p=0.043). Duration of infection among genotype-1: aOR 0.84 (95%CI 0.75–0.95); among genotype-non-1, aOR 0.97 (95%CI 0.84–1.14).

⁴ Interaction between HCV genotype and *IFNL4* genotype (p=0.099). *IFNL4* favourable genotype among HCV genotype-1: aOR 4.13 (95%CI 1.52–11.24); among genotype-non-1, aOR 1.30 (95%CI 0.41–4.14).

Table 3

Cox proportional hazards regression of factors associated with time to virological clearance among HCV mono-infected individuals with persisting viraemic three months after estimated date of infection (n=381)

	Univariable model		Multivariable model ¹	
HCV Treatment	HR (95% CI)	p value	aHR (95% CI)	p value
No	1		1	
Yes	5.50 (3.66, 8.26)	<0.001	5.00 (3.29, 7.60) ²	<0.001
Age categorised				
30 years	1	–	1	–
30–40 years	1.49 (0.99, 2.25)	0.058	1.31 (0.86, 1.98)	0.204
40 years	2.29 (1.58, 3.33)	<0.001	1.94 (1.32, 2.84)	0.001
Gender				
Male	1.00	–	1	–
Female	1.56 (1.13, 2.16)	0.008	1.60 (1.15, 2.24)	0.005
Presentation of HCV³				
Asymptomatic infection	1	–	–	–
Seroconversion illness	2.09 (1.44, 3.03)	<0.001	–	–
Missing	0.55 (0.31, 0.98)	0.043	–	–
HCV RNA screening⁴				
<400,000 IU/ml	1	–	–	–
400,000 IU/ml	0.81 (0.57, 1.16)	0.256	–	–
Missing	0.89 (0.55, 1.42)	0.617	–	–
HCV genotype⁵				
Genotype non-1	1	–	1	–
Genotype 1	1.76 (1.24, 2.50)	0.002	1.29 (0.90, 1.85)	0.161
Missing	1.63 (0.93, 2.88)	0.089	–	–
IFNL4 genotype				
CT or TT	1	–	1	–
CC	1.53 (1.08, 2.16)	0.016	1.66 (1.16, 2.36)	0.005

	Univariable model		Multivariable model ¹	
	HR (95% CI)	p value	aHR (95% CI)	p value
Missing ⁶	1.19 (0.69, 2.04)	0.541	–	–

¹ Adjusting for age, gender, seroconversion illness, HCV genotype, *IFNL4* genotype (n=366). Cox proportional hazards assumptions violation test p=0.229.

² Interaction between treatment and gender; p=0.034. Treatment v no treatment aHR among males: 8.38 (95%CI 4.46–15.75); aHR among females: 2.47 (95%CI 1.38–4.45).

³ Omitted from multivariable model due to missing data n=74.

Missing data n=67.

⁵ Missing data n=41.

⁶ Missing data n=62.