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Antiviral Therapy

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Antiviral Therapy 2016; 10.3851/IMP3035

Submission date 5th November 2015
Acceptance date 2nd February 2016
Publication date 11th February 2016

ISSN 1359-6535

Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP3035

Original article

Short duration response-guided treatment is effective for most individuals with recent hepatitis C infection: the ATAHC II and DARE-C I studies

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Abstract

Background: Individuals with recent hepatitis C virus infection may benefit from shortened duration therapy. These studies evaluated the efficacy and safety of response-guided regimens with pegylated-interferon alfa-2a and ribavirin for people with recent HCV infection.

Methods: Participants with recent hepatitis C (duration of infection ≤18months) enrolled in the ATAHC II (pegylated-interferon alfa-2a +/- ribavirin) and DARE-C I (pegylated-interferon alfa-2a, ribavirin and telaprevir) studies were included for analysis. Treatment duration was response-guided (ATAHC II: 8, 16, 24 or 48 weeks; DARE-C I: 8, 12 or 24 weeks) and dependent on time to first undetectable HCV RNA using Roche Taqman HCV RNA testing. The primary efficacy endpoint was SVR12 by intention-to-treat. Logistic regression analyses were used to identify predictors of SVR.

Results: Eighty-two participants (62% HIV-positive) were enrolled in ATAHC II (treated, n=52) and 14 (79% HIV-positive) in DARE-C I. The predominant modes

Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP3035

of HCV acquisition were injecting drug use (ATAHC II: 55%, DARE-C I: 36%) and sexual intercourse with a partner of the same sex (ATAHC II 39%, DARE-C I 64%). SVR12 was 71% in both ATAHC II (37/52) and DARE-C I (10/14) with 56% in ATAHC II receiving shortened therapy (8 or 16 weeks). SVR was associated with a rapid virological response (odds ratio 10.80; p=0.001).

Conclusions: The majority of participants were able to receive short duration response-guided therapy with pegylated-interferon alfa-2a and ribavirin. Response-guided therapy for recent hepatitis C infection could be considered in the absence of available interferon-free therapies.

Accepted 2 February 2016, published online 11 February 2016

Running head: Treatment for recent HCV

Introduction

The management of recent (acute or early chronic) hepatitis C virus (HCV) infection is not standardised with uncertainty regarding the optimal regimen and treatment duration [1], particularly as the therapeutic landscape changes with the advent of interferon (IFN)-free directly-acting antiviral (DAA) therapy [2–4].

Enhanced responsiveness with IFN-based therapy in recent HCV means that treatment duration can be shortened [1]. Previous studies have demonstrated the efficacy of IFN mono-therapy (standard or pegylated [PEG-IFN]) for 4, 12 and 24 weeks [5–10] with previous international guidelines recommending 24 weeks of therapy [2,11]. Shorter treatment durations result in fewer adverse events, better quality of life, less frequent dose reductions and increased likelihood of optimal adherence [7,8].

As with chronic HCV, response-guided therapy may be appropriate. The Australian Trial in Acute Hepatitis C II (ATAHC II) evaluated the efficacy and safety of response-guided therapy with PEG-IFN alfa-2a and ribavirin (RBV) for individuals with recent HCV infection. The Directly-acting Antiviral Based Therapy for Recently Acquired Hepatitis C (DARE-C I), a sub study of ATAHC II, assessed the efficacy and safety of response-guided therapy with PEG-IFN alfa-2a, RBV and telaprevir for individuals with recent genotype 1 (G1) HCV infection.

Patients and Methods

Australian Trial in Acute Hepatitis C II (ATAHC II)

Study design

ATAHC II was a prospective study of the natural history and treatment outcomes of recent HCV infection (estimated duration of infection ≤18 months) following response-guided therapy with PEG-IFN alfa-2a (180mcg/week) and RBV (G1: 1000mg/day if <75kg, 1200mg/day if ≥75kg; G2/3: 800mg/day).

Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP3035

Enrolled participants were assessed for treatment eligibility. Participants who were eligible and consented for treatment were stratified by HIV status and estimated duration of infection at baseline. Participants with acute (estimated duration of infection ≤6 months) HCV mono-infection received PEG-IFN; participants with early chronic infection (estimated duration 6-18 months) and HIV co-infection received PEG-IFN and RBV. Treatment duration was dependent on time to first HCV RNA below the limit of detection using COBAS Taqman HCV RNA assay, version 2.0 (lower limit of quantitation [LLoQ], 25 IU/mL; lower limit of detection [LLoD] 15 IU/mL; Roche Diagnostics, Branchburg, NJ, USA) (**Table 1**). Participants who were ineligible or declined treatment were followed in the untreated arm.

Setting and participants

Adults (age ≥16 years) with recent HCV were eligible for study inclusion. Participants were screened and enrolled between August 2011 and July 2014 through an Australian network of tertiary hospitals (n=6) and general practice/primary care clinics (n=1) with the last participant completing 12 weeks post treatment follow up in May 2015. Details regarding inclusion and exclusion criteria and study assessments are provided in the *Supplementary Appendix*.

Directly-acting Antiviral Based Therapy for Recently Acquired Hepatitis C (DARE-C I)

Study design

A sub-study of ATAHC II, DARE-C I assessed the efficacy and safety of response-guided therapy with PEG-IFN alfa-2a (180mcg/week), weight-based RBV (1000mg/day if <75kg, 1200mg/day if ≥75kg) and telaprevir (1125mg twice daily or 1125 three times daily if receiving efavirenz) for individuals with recent G1 HCV infection (estimated duration of infection 6-18 months). Treatment duration was dependent on time to first HCV RNA below the limit of detection using COBAS Taqman HCV RNA assay (**Table 1**).

Setting and participants

Adults (age ≥18 years) with recent G1 HCV infection, HCV RNA ≥10,000 IU/mL, and hepatitis B surface antigen negative were eligible for enrolment. Patients were screened and enrolled between April 2013 and May 2014 at two tertiary hospitals in the ATAHC II network. Details regarding inclusion and exclusion criteria and study assessments are provided in the *Supplementary Appendix*.

Study Definitions for ATAHC II and DARE-C I

Recent 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 24 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 [12], with estimated duration

of infection less than 18 months at screening. The duration of HCV infection at screening and baseline was calculated from the estimated date of infection.

HCV virological suppression was defined as HCV RNA below the lower limit of detection. An end-of-treatment response (ETR) was defined as serum HCV RNA below the lower limit of detection at the end of treatment. HCV RNA recurrence was defined as detectable HCV RNA following HCV virological suppression. Participants with recurrence had HCV RNA sequencing performed on the first available detectable HCV RNA sample and the first available detectable HCV RNA sample indicating HCV RNA recurrence. HCV virologic failure was defined as non-response (failure of virological suppression on-treatment with quantifiable HCV RNA at all time points between baseline and end of treatment), breakthrough (an increase from non-quantifiable to quantifiable HCV RNA or to at least 1 $\log_{10}$ above nadir while on treatment) or post-treatment relapse (the presence of quantifiable HCV RNA after an ETR, confirmed by homologous virus on sequencing of Core-E2 and/or NS5B regions as described previously) [13,14]. Reinfection was defined by the detection of infection with an HCV strain that was distinct from the primary infecting strain.

Loss of HIV virologic control was defined as a confirmed HIV RNA of at least 400 copies/mL in individuals on cART. For further study definitions, see *Supplementary Appendix*.

Study Outcomes for ATAHC II and DARE-C I

The primary efficacy endpoint was SVR12, defined as serum HCV RNA below the limit of detection at 12 weeks following end of treatment. Secondary virological endpoints included a rapid virological response (RVR, defined as serum HCV RNA below the LLoQ prior to or at week 4 of treatment), ETR and SVR24 (defined as serum HCV RNA below the limit of detection at 24 weeks following end of treatment. SVR12 results for participants with HCV G1 in ATAHC II were compared with DARE-C I. SVR24 results for participants in ATAHC II were compared to the historical controls in ATAHC I (PEG-IFN +/- RBV for 24 weeks) [10].

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 II: NCT01336010; DARE C I: NCT01743521).

Statistical analysis

Evaluation of HCV treatment response was based on intention-to-treat (ITT) analyses that included all participants who received at least one dose of PEG-IFN. Additional per protocol analyses included all adherent individuals with follow-up virological data to week 12 post treatment.

For all endpoints, means and proportions with two-sided 95% confidence intervals (CI) were determined, and were unadjusted for multiple comparisons. Continuous variables were analysed

using ANOVA methods or non-parametric equivalents. Binary endpoints were analysed using chi-square methods or logistic regression. A Cox proportional hazards model was used to assess factors associated with time to first HCV RNA below the limit of detection and logistic regression analyses were used to identify baseline and on-treatment predictors of HCV treatment response. Potential predictors were determined *a priori* and included participant enrolment, virological and on-treatment characteristics. The multivariate model for predictors of treatment response and HCV clearance were determined using a backwards stepwise approach, considering factors that were significant at the 0.2 level in univariate analysis. The final models included factors that remained significant at the 0.05 level. All p-values are two-sided. Analyses were performed using STATA version 14.0 (Stata Corporation, College Station, TX).

Results

ATAHC II

Participant disposition and overview of the study population

Between August 2011 and July 2014, 112 individuals were screened and 82 enrolled (**Figure 1**). Participants were predominantly male (89%) with G1 (51%) and G3 (46%) infection. HIV co-infection was documented in 62%. Diagnosis of recent HCV occurred in the context of acute clinical hepatitis in 68% (n=56) and asymptomatic anti-HCV antibody seroconversion in 32% (n=26). In those with acute clinical hepatitis, a symptomatic seroconversion illness was reported in 43% (n=35, including 17 with jaundice) and ALT >400 IU/mL in 59% (n=48). The predominant modes of acquisition were injecting drug use (IDU, 55%, n=45) and sexual intercourse with a partner of the same sex (39%, n=32; all were men-who-have-sex-with-men [MSM]). Other modes of acquisition included heterosexual contact (5%, n=4) and other forms of percutaneous exposure (1%, n=1). The enrolment characteristics of treated (n=52) and untreated (n=30) participants are shown in **Table 2**.

Seventy-six percent (n=62) of participants had ever injected drugs with current IDU (within the last 6 months) reported by 56% (n=46). Among participants who reported IDU ever, median age at first injecting was 27 years (IQR 21-34), with older age at first injecting in those with HIV (median age 29 vs 23 years; p=0.012). Of those reporting IDU within the last 6 months (n=46), 65% had injected in the previous month with methamphetamine (83%), heroin (7%) and other opiates (10%) most often injected.

Participants with HIV (n=51) were older, more likely to have acquired HCV through sexual exposure (p=0.002), be in full or part-time employment (p=0.001) and have better social functioning (p=0.007).

Thirty participants were enrolled in the untreated arm. The reasons for not receiving treatment were PEG-IFN and/or RBV ineligibility (63%, n=19), patient choice (40%, n=12), inability to attend study visits (10%, n=3) and needle phobia (3%, n=1). The percentage total is greater than 100%, as more than one reason was identified for three individuals. Participants in the untreated arm were more

likely to be unemployed, previously incarcerated, have injected drugs and report psychiatric co-morbidity (**Table 2**).

As one participant with undetectable HCV RNA at screening was ineligible, the uptake of HCV treatment was 64% (52/81). In the untreated arm, spontaneous clearance was observed in 14% (4/29).

Efficacy of response-guided PEG-IFN and RBV

In the treated cohort, SVR12 by ITT was 71% (37/52; 95% CI 57%, 83%), with no difference by HIV status (HCV mono-infection, SVR12 73% [11/15]; HIV/HCV co-infection, SVR12 70% [26/37]; p=0.825) (**Figure 2**). Treatment discontinuation due to virological non-response or early treatment discontinuation (prior to duration allocation) occurred in 19% (n=10). By treatment duration (n=42), SVR12 was 85% (11/13) in those receiving 8 weeks, 100% (16/16) in those receiving 16 weeks, 73% (8/11) in those receiving 24 weeks and 100% (2/2) in those receiving 48 weeks. The majority (n=29, 56%) achieved a rapid virological response and received shortened therapy (8 or 16 weeks). In those who achieved a rapid virological response, SVR12 was 93% (27/29). SVR12 was lower in those with G1 (61%; 17/28) as compared with other the HCV genotypes (G2 100%, 1/1; G3 82%, 18/22; G4 100%, 1/1; G1 versus non-G1, p=0.073). In those receiving 8 weeks, SVR12 was 86% in G1 (6/7) and 83% in G3 (5/6). In those receiving 16 weeks, SVR12 was 100% in G1 (8/8), 100% in G3 (7/7) and 100% in G4 (1/1). In those receiving 24 weeks, SVR12 was 25% in G1 (1/4), 100% in G2 (1/1) and 100% in G3 (6/6). In those receiving 48 weeks, SVR12 was 100% in G1 (2/2). SVR12 by per-protocol analysis was 76% (37/49). HCV RNA was below the LLoQ in 27%, 56%, 69%, 77% and 83% at weeks 2, 4, 6, 8 and end of treatment, respectively.

SVR24 by ITT was 69% (34/49). Three participants with undetectable HCV RNA at SVR12 did not reach the SVR24 time point due to study closure. Efficacy data from ATAHC II was compared to historical data from ATAHC I [10]. In those with HCV mono-infection, SVR24 by ITT in ATAHC II (73%) was higher, though not statistically different, when compared with ATAHC I (55%; 24 weeks PEG-IFN) (risk difference 0.18, 95% CI -0.07, 0.43; p=0.200). In those with HIV/HCV co-infection, SVR24 by ITT in ATAHC II (68%) was similar to ATAHC I (74%; 24 weeks PEG-IFN and RBV) (risk difference -0.07, 95% CI -0.28, 0.15; p=0.543).

Virological Failure, Relapse and Reinfection

Treatment discontinuation was noted in 19% due to virological non-response (n=6), medical contraindication to treatment continuation (n=1), and clinician decision (n=3) (including one participant with HCV RNA <15 IU/mL at baseline and HCV RNA undetectable at week 2). No on-treatment virological breakthrough was noted.

Virological suppression on treatment was documented in 83% (43/52) with recurrent HCV viraemia in 21% (9/43); relapse was demonstrated in six (with recurrence of viraemia at 12 and 24 weeks post treatment in five and one individuals, respectively) and reinfection in three participants (with recurrence of viraemia at one and two years post treatment in one and two individuals,

respectively) (**Figure 3**). HCV reinfection incidence in the treated cohort was 7.5 per 100 person years (py) (95% CI 1.6, 20.4).

Treatment adherence

Adherence to therapy was high with PEG-IFN 80/80 (≥80% of doses for ≥80% of treatment period) and 100/100 (100% of doses for 100% of treatment period) adherence 100% and 95%, respectively (mean on-treatment PEG-IFN adherence 99.97% [SD 0.2]) and RBV 80/80 and 100/100 adherence 94% and 67%, respectively (mean on-treatment RBV adherence 95.3% [SD 18.7]). HIV/HCV co-infected participants were more likely to be RBV adherent than HCV mono-infected participants (RBV 80/80 100% vs 79%, p=0.004; RBV 100/100 76% vs 43%, p=0.027). PEG-IFN 80/80 adherence was better with response guided therapy in ATAHC II as compared with ATAHC I (100% vs 82%; p=0.001).

Factors associated with time to first HCV RNA below the limit of detection and SVR

A Cox proportional hazards model was used to assess factors associated with time to first HCV RNA below the limit of detection. Higher baseline HCV RNA level (≥400,000 IU/mL) was negatively associated with time to HCV RNA below the limit of detection (HR 0.34, 95% CI 0.18, 0.64; p=0.001) (*Supplementary Appendix*).

Participant characteristics and on-treatment factors were evaluated as predictors of SVR with logistic regression analysis. Rapid virological response was the only factor associated with SVR (OR 10.80; 95% CI 2.51, 46.43; p=0.001) (*Supplementary Appendix*).

Safety

The safety profile was consistent with the known side effects of PEG-IFN alfa-2a and RBV (*Supplementary Appendix*). At least one clinical adverse event was reported by 51 participants (98%). Most adverse events were of mild (75%) or moderate (24%) severity. PEG-IFN and RBV dose modification were required for toxicity in 6% (neutropenia, n=3) and 2% (anaemia, n=1), respectively. In those with HIV infection, median change in CD4 count at end of treatment was $119x10^6$/L (IQR 47–234) with no loss of HIV virological control.

Three serious adverse events (SAE) were reported: anxiety requiring hospitalisation in an individual with a psychiatric history (possibly related to study drug administration); attempted suicide in an individual with a psychiatric history (possibly related to study drug administration); and sialolithiasis requiring hospitalisation (unrelated to study drug administration). No decompensated liver disease or death occurred.

DARE-C I

Patient disposition and overview of the study population

Between April 2013 and May 2014, 14 participants (79% HIV-positive) were enrolled (**Figure 1**). Enrolment characteristics are shown in **Table 1**. Forty six percent (n=6) had ever injected drugs.

Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP3035

Amphetamines were the most commonly injected drug ever (29%) and within the last 6 months (21%).

Efficacy of response-guided PEG-IFN, RBV and telaprevir

SVR12 by ITT was 71% (10/14) (**Figure 2**). By treatment duration, SVR12 was 71% (5/7) in those receiving PEG/RBV/telaprevir for 8 weeks, 100% (3/3) in those receiving PEG/RBV/telaprevir for 12 weeks and 100% (2/2) in those receiving PEG/RBV/telaprevir for 12 weeks + PEG/RBV for 12 weeks (24 weeks). In those with HIV, SVR12 was 73% (8/11) (**Figure 2**). Rapid virological suppression was demonstrated in the majority with HCV RNA below the LLoQ in 36%, 50%, 57%, 71%, 86%, 86% and 86% at weeks 1, 2, 3, 4, 6, 8 and end of treatment, respectively. There was no difference in SVR12 ITT between G1-infected participants in ATAHC II and DARE C I (61% vs 71%; risk difference -0.11, 95% CI -0.41, 0.19; p=0.494).

Virological Failure, Relapse and Reinfection

Treatment failure was observed in 29%: 7% (n=1) early treatment discontinuation (day 3), 7% (n=1) non-response, 14% (n=2) relapse.

Reinfection was documented in one HIV-positive male participant with recurrence of HCV viraemia between post-treatment week 12 and post-treatment week 24. High-risk sexual behaviour was described with no history of IDU. The combined reinfection incidence in treated HIV-positive participants in ATAHC II and DARE-C I was 11.8 per 100 py (95% CI 3.3, 27.5).

Treatment adherence

As with ATAHC II, adherence was high with PEG-IFN 100/100 adherence 100% and RBV 80/80 and 100/100 adherence 100% and 50%, respectively (mean on-treatment RBV adherence 98.9% [SD 1.6]). Telaprevir 80/80 and 100/100 adherence were 100% and 64% (mean on-treatment telaprevir adherence 98.9% [SD 1.7]).

Safety

Multiple adverse events were documented in all participants with the most common being fatigue (73%) and rash (50%) (*Supplementary Appendix*). Two SAEs were reported: skin cancer (SCC/BCC) requiring hospitalisation and axillary abscess requiring hospitalisation. Adverse events requiring medical intervention, treatment cessation or dose modification occurred in 36% (n=5), with dose reduction of PEG-IFN and RBV in one (7%) and three (21%) individuals, respectively.

The addition of telaprevir was associated with excess haematological toxicity. Mean decrease in haemoglobin at end of treatment was 33 g/L (SD 18) in participants receiving PEG-IFN, ribavirin and telaprevir as compared with 20 g/L (SD 15) in participants receiving PEG-IFN and ribavirin (p=0.007). Anaemia (haemoglobin less than 100 g/L) developed on treatment in 5 participants (36%) receiving PEG-IFN, ribavirin and telaprevir as compared with 3 (6%) receiving PEG-IFN and ribavirin (p=0.008).

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DOI: 10.3851/IMP3035

Discussion

Within ATAHC II and DARE-C I, the majority of participants with recent HCV infection were able to receive short duration (8-16 weeks) response-guided therapy, with the overall SVR similar to that observed with previously recommended 24 week regimens [10]. The recent development of highly curative and safe IFN-free DAA regimens for chronic HCV infection, with treatment duration generally 12 weeks [15–21], offers significant promise. However, due to high drug pricing, access to IFN-free DAA therapy is restricted, even in high-income settings: by and within countries, by fibrosis stage and by former or current substance misuse [4,22]. While many individuals with diagnosed recent HCV infection are keen for treatment [10], access to IFN-free therapy will be denied for most due to mild fibrosis and/or recent drug use. This study demonstrates that recent HCV infection can be effectively and safely treated with short course PEG-IFN and RBV; a response-guided strategy could be considered for motivated individuals wishing to trial therapy at this initial assessment, with treatment cessation at week four if HCV RNA remains detectable. Population-level HCV treatment as prevention strategies will be enhanced by early detection and increased HCV treatment uptake for those with recent HCV infection.

Very limited evidence exists for the use of DAAs in recent HCV infection [23]. Telaprevir, in combination with PEG and RBV, demonstrated improved efficacy in chronic G1 HCV as compared with PEG-IFN and RBV [24,25]. In the DARE-C I study, response-guided therapy with PEG-IFN, RBV and telaprevir was effective in the majority (regardless of HIV co-infection) although similar to that observed with PEG-IFN and RBV alone. Despite the short treatment duration, the side-effect profile, drug-drug interactions and treatment complexity seen with this regimen indicates that the addition of telaprevir offers no significant benefit.

Over the last decade, increasing HCV transmission has been observed in HIV-positive men-who-have-sex-with-men, largely associated with sexual and non-IDU behaviour [26–32]. In comparison with ATAHC I [10], a greater proportion of participants in ATAHC II and DARE-C I were HIV-positive while the proportion reporting IDU remained the same, highlighting the changing patterns of HCV transmission in Australia. Reinfection rates following treatment of acute or recent HCV infection in this population are varied. In a recent meta-analysis, the incidence of viral recurrence (late relapse or reinfection) following SVR in those with HIV was 4.8 per 100 py (95% CI 4.0, 5.7) [33]. The reinfection rate post SVR of 11.8 per 100 py in ATAHC II and DARE-C I is similar to that seen in recent HIV-positive cohorts in high-income settings [33–36]. Multiple reinfections in individuals with ongoing high risk behaviour emphasise the need for continued surveillance and prevention strategies [35,36]. Despite concerns regarding adherence and reinfection, HCV treatment with interferon-containing and interferon-free regimens is feasible and successful in those populations considered to be “high-risk”, including people who inject drugs and people receiving opiate substitution therapy [37–39]. As such, HCV treatment should not be delayed, but rather, should occur in concert with education and harm minimisation.

Limitations of these studies are noted. Although ATAHC II is one of the larger studies in recent HCV infection, the sample size means that Cox proportional hazards and logistic regression analyses were limited to assessment of key virological and treatment factors. DARE-C I was designed as a proof-of-concept study to determine the feasibility of this strategy, and despite the small enrolled population, the tolerability of the regimen was poor.

With advances in HCV therapeutics, management strategies for recent HCV infection will evolve rapidly over the next few years. With IFN-free DAA therapy now the standard-of-care for chronic HCV infection, the “efficacy advantage” of early treatment in recent HCV infection may be reduced (and possibly eliminated) [40]. The paradigm of shortened therapy in recent HCV infection using IFN-free DAA combinations remains uncertain and requires evaluation.

Acknowledgements

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. The Burnet Institute receives funding from the Victorian Operational Infrastructure Support Program. Research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under award R01DA015999 and Janssen-Cilag Pty Ltd. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Jason Grebely and Gail Matthews are supported through NHMRC Career Development Fellowships. Gregory Dore and Andrew Lloyd are supported through NHMRC Practitioner Fellowships.

Disclosures

MM has received speaker payments from Abbvie.

MH has received funding for investigator initiated research from Gilead Sciences and Abbvie. The Burnet Institute has received un-tied educational grant funding from Gilead Sciences.

DS: No conflict

KP: No conflict

TAA: No conflict

JG is a consultant/advisor and has received research grants from Abbvie, Bristol Myers Squibb, Gilead Sciences and Merck.

BY: No conflict

LM: No conflict

DI: No conflict

AL: No conflict

AT: No conflict

JS: No conflict

PH has received speaker payments from Roche.

GJD is an advisory board member and has received honoraria from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb and Abbvie, has received research grant funding from Roche, Merck, Janssen, Gilead, Bristol-Myers Squibb, Vertex, Boeringher Ingelheim and Abbvie, and travel sponsorship from Roche, Merck, Janssen, Gilead, and Bristol-Myers Squibb.

GVM has received research funding, advisory board payments and speaker payments from Gilead and research funding and speaker payments from Janssen.

Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP3035

Financial support:

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. The Burnet Institute receives funding from the Victorian Operational Infrastructure Support Program. Research reported in this publication was supported by the National Institute on Drug Abuse of the National Institutes of Health under award R01DA015999 and Janssen-Cilag Pty Ltd. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Jason Grebely and Gail Matthews are supported through NHMRC Career Development Fellowships. Gregory Dore and Andrew Lloyd are supported through NHMRC Practitioner Fellowships. None of the authors has commercial relationships that might pose a conflict of interest in connection with this manuscript.

Authors contributions:

GVM, GJD, MH, DS, KP, TAA, JG, DI, AL, AT, JS and PH were involved in study concept and design. MM, GVM, GJD, MH, DS, DI, AL and JS were involved in acquisition of data. MM, GVM and GJD were involved in analysis and interpretation of data. MM drafted the manuscript with critical revision of the manuscript for important intellectual content by all authors. MM and KP performed the statistical analysis. BY and LM performed administrative and technical support. GVM and GJD provided overall study supervision. All authors have seen and approved the final version of the manuscript.

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Figure Legends

Figure 1. Patient disposition.

(A) ATAHC II. (B) DARE C I.

[1] Of those excluded and enrolled into another study (n=6), 5 were enrolled into DARE-C I.

[2] ATAHC II non-responder: Participants receiving PEG-IFN with or without RBV who do not achieve an HCV RNA below the limit of detection (LLoD <15 IU/ml on Roche TaqMan) after 12 weeks of treatment

[3] Early treatment discontinuation: Treatment ceased prior to allocation of treatment duration

[4] DARE C I non-responder: Participants in whom therapy was terminated at week 4 due to HCV RNA >1000 IU/mL or week 8 due to detectable HCV RNA.

Figure 2. Primary and secondary efficacy endpoints by study (intention-to-treat population).

(A) ATAHC II – response-guided PEG-IFN and ribavirin. (B) DARE C-I – response-guided PEG-IFN, ribavirin and telaprevir.

Abbreviations: End of treatment response (ETR); sustained virological response (SVR)

Figure 3. ATAHC II: Viral kinetics and outcome in participants with recurrence of HCV viraemia (relapse or reinfection).

(A) Relapse (n=6). (B) Re-infection (n=3). Grey lines indicate individuals with HIV/HCV co-infection. Black lines indicate individuals with HCV mono-infection. Note, in (A), two individuals demonstrated spontaneous clearance of HCV viraemia following relapse (at SVR24 and FU2).

Abbreviations: SVR – sustained virological response, FU 1 – follow up 1 year post end of treatment, FU 2 – follow up 2 years post end of treatment

Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP3035

Table 1. Treatment allocation in ATAHC II and DARE C I

Study	HCV RNA BLoD at:	Treatment duration (weeks)	Treatment regimen
ATAHC II	Week 2	8	PEG-IFN +/- RBV
	Week 4	16	PEG-IFN +/- RBV
	Week 6	24	PEG-IFN +/- RBV
	Week 8	32 (24 for G2/3)	PEG-IFN +/- RBV
	Week 12	48 (24 for G2/3)	PEG-IFN +/- RBV
DARE-C I	Week 2	8	PEG-IFN/RBV/TVR
	Week 4	12	PEG-IFN/RBV/TVR
	Week 8	24	PEG-IFN/RBV/TVR for 12 weeks followed by PEG-IFN/RBV for 12 weeks

Abbreviations: BLoD, below limit of detection; PEG-IFN, pegylated interferon alfa-2a; RBV, ribavirin; TVR, telaprevir

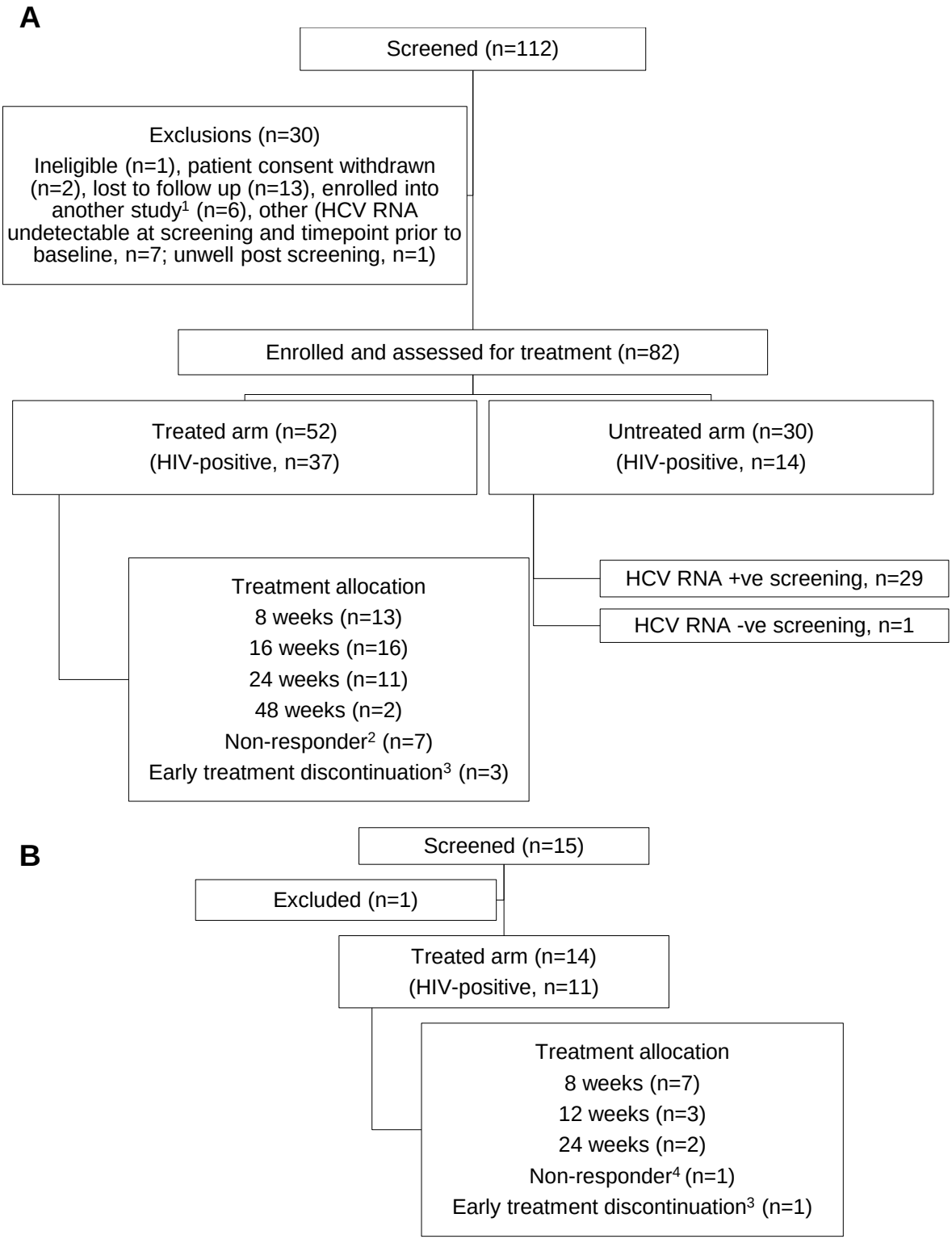
Table 2. Participant enrolment characteristics – by study and treatment allocation

Enrolment characteristics	ATAHC II			DARE-C I
	Overall (n=82)	**Treated (n=52)**	**Untreated (n=30)**	**Overall (n=14)**
Age (years), mean (SD)	39 (10)	41 (10)	36 (9)	48 (11)
Male, n (%)	73 (89)	48 (92)	25 (83)	14 (100)
Weight (kg), mean (SD)	77 (13)	79 (13)	74 (12)	77 (13)
BMI (kg/m^2), mean (SD)	25 (3)	25 (3)	24 (3)	24 (3)
Caucasian ethnicity, n (%)	67 (82)	44 (85)	23 (77)	14 (100)
Higher education or qualification[a], n (%)	51 (62)	36 (69)	15 (50)	8 (57)
Full or part time employment, n (%)	40 (49)	33 (63)	7 (23)	7 (50)
Incarceration ever, n (%)	5 (6)	1 (2)	4 (13)	0
Social functioning score, median (IQR)	12 (7-17)	10 (6-14)	15 (10-19)	13 (9-16)
Psychiatric history, n (%)	46 (56)	23 (44)	23 (77)	10 (71)
Current major depression, n (%)	16 (20)	11 (21)	5 (17)	5 (36)
Injecting drug use, n (%)				
Ever	62 (76)	34 (65)	28 (93)	6 (43)
Current [b]	46 (56)	22 (42)	24 (80)	3 (21)
Opioid substitution therapy, n (%)				
Ever	10 (12)	7 (13)	3 (10)	1 (7)
Current	6 (7)	3 (6)	3 (10)	0
HIV infection, n (%)	51 (62)	37 (71)	14 (47)	11 (79)
CD4 count (10^6/L), median (IQR)	610 (441-754)	512 (399-692)	723 (624-860)	464 (376-626)
HIV VL ≤50 copies/mL at screening, n (%)	33 (65) [c]	21 (57) [c]	12 (86)	8 (73)
On cART, n (%)	46 (90)	32 (86)	14 (100)	11 (100)
Mode of HCV acquisition, n (%)				
Injecting drug use	45 (55)	22 (42)	23 (77)	5 (36)
Sexual exposure – same sex	32 (39)	26 (50)	6 (20)	9 (64)
Sexual exposure – opposite sex	4 (5)	3 (6)	1 (3)	0
Other	1 (1)	1 (2)	0	0
Acute HCV (<6 months)[d], n (%)	20 (38)	40 (49)	19 (63)	0
Estimated duration of infection (weeks)				
At screening, median (IQR)	26 (14-35)	28 (19-39)	18 (9-29)	32 (26–40)
At baseline, median (IQR)	36 (27-46)	37 (30-46)	32 (25-49)	41 (36-56)
Presentation of recent HCV, n (%)				
Acute clinical illness – symptomatic	35 (43)	22 (42)	13 (43)	5 (36)
Jaundice [e]	17 (49)	11 (50)	6 (46)	2 (40)
Nausea/vomiting	12 (34)	8 (32)	4 (31)	2 (40)
Abdominal pain	13 (37)	8 (32)	5 (38)	3 (60)
Fever	10 (29)	6 (27)	4 (31)	3 (60)
Acute clinical illness - ALT >10x ULN	48 (59)	32 (62)	16 (53)	10 (71)

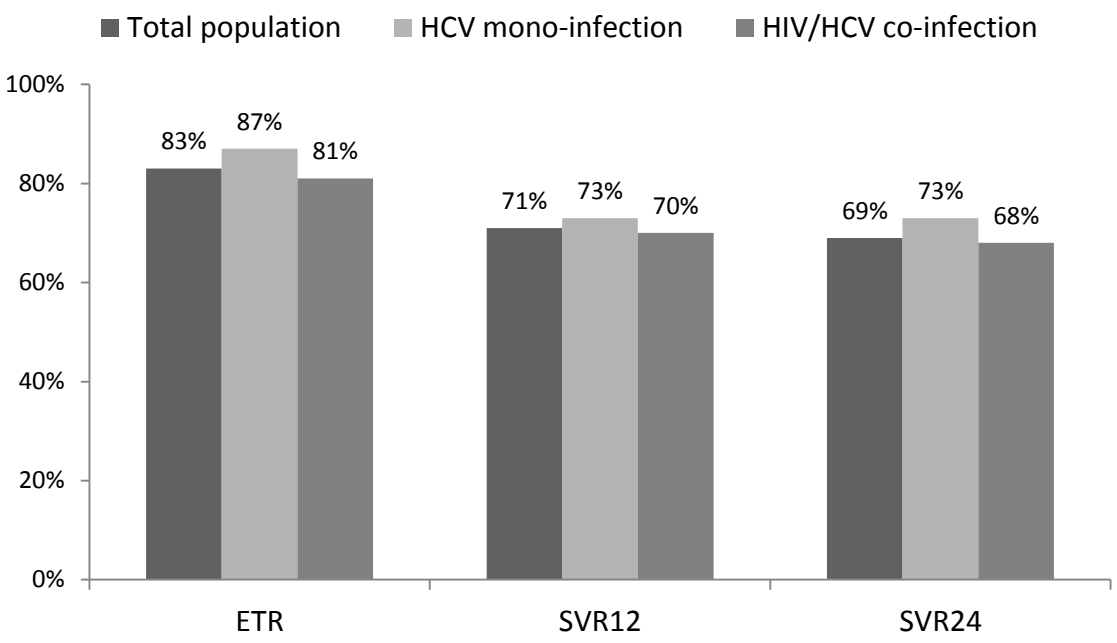
Publication: Antiviral Therapy; Type: Original article
DOI: 10.3851/IMP3035

Asymptomatic seroconversion	26 (32)	15 (29)	11 (37)	2 (14)
ALT (U/L), median (IQR)				
Peak ALT prior to enrolment	621 (218-1129)	621 (232-1110)	575 (169-1247)	623 (156-925)
ALT at screening	135 (81-354)	127 (83-360)	142 (70-349)	116 (53–151)
Log_{10} HCV RNA at screening, median (IQR)	5.7 (4.6-6.5)	5.9 (5.1-6.6)	4.7 (2.9-5.9)	6.3 (6.2-6.8)
HCV RNA <400,000 IU/mL, n (%)	38 (46)	19 (37)	19 (63)	5 (36)
HCV genotype (and subtype), n (%)				
Genotype 1	42 (51)	28 (54)	14 (47)	14 (100)
1a	41 (98)	28 (100)	13 (93)	13 (93)
1b	1 (2)	0	1 (7)	1 (7)
Genotype 2	1 (1)	1 (2)	0	
Genotype 3	38 (46)	22 (42)	16 (53)	
Genotype 4	1 (1)	1 (2)	0	

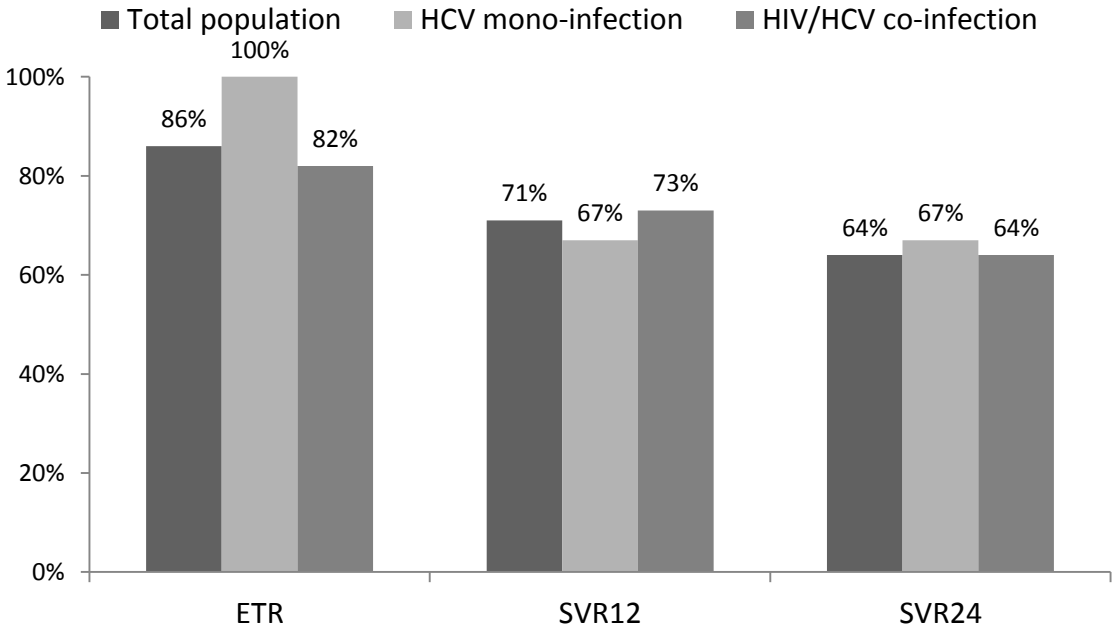
[a] Completed higher technical qualification/TAFE/College/university degree
[b] Current injecting drug use refers to use within 6 months of screening
[c] Recent diagnosis of HIV infection (within 2 years of study enrolment), n=11 (22%), with 10 enrolled in the treated arm. HIV RNA <50 copies/mL at screening in only 18% (2/11) with a recent HIV diagnosis compared with 78% (31/40) in those without (p<0.001).
[d] Acute HCV infection (duration of infection <6 months) at screening
[e] Denominator = number of people with acute clinical (symptomatic) illness
Abbreviations: cART – Combination antiretroviral therapy


A
Screened (n=112)
Exclusions (n=30)
Ineligible (n=1), patient consent withdrawn (n=2), lost to follow up (n=13), enrolled into another study[1] (n=6), other (HCV RNA undetectable at screening and timepoint prior to baseline, n=7; unwell post screening, n=1)
Enrolled and assessed for treatment (n=82)
Treated arm (n=52)
(HIV-positive, n=37)
Untreated arm (n=30)
(HIV-positive, n=14)
Treatment allocation
8 weeks (n=13)
16 weeks (n=16)
24 weeks (n=11)
48 weeks (n=2)
Non-responder[2] (n=7)
Early treatment discontinuation[3] (n=3)
HCV RNA +ve screening, n=29
HCV RNA -ve screening, n=1
B
Screened (n=15)
Excluded (n=1)
Treated arm (n=14)
(HIV-positive, n=11)
Treatment allocation
8 weeks (n=7)
12 weeks (n=3)
24 weeks (n=2)
Non-responder[4] (n=1)
Early treatment discontinuation[3] (n=1)

A


Total population
HCV mono-infection
HIV/HCV co-infection
100%
80%
60%
40%
20%
0%
83%
87%
81%
71%
73%
70%
69%
73%
68%
ETR
SVR12
SVR24

B


Total population
HCV mono-infection
HIV/HCV co-infection
100%
80%
60%
40%
20%
0%
86%
100%
82%
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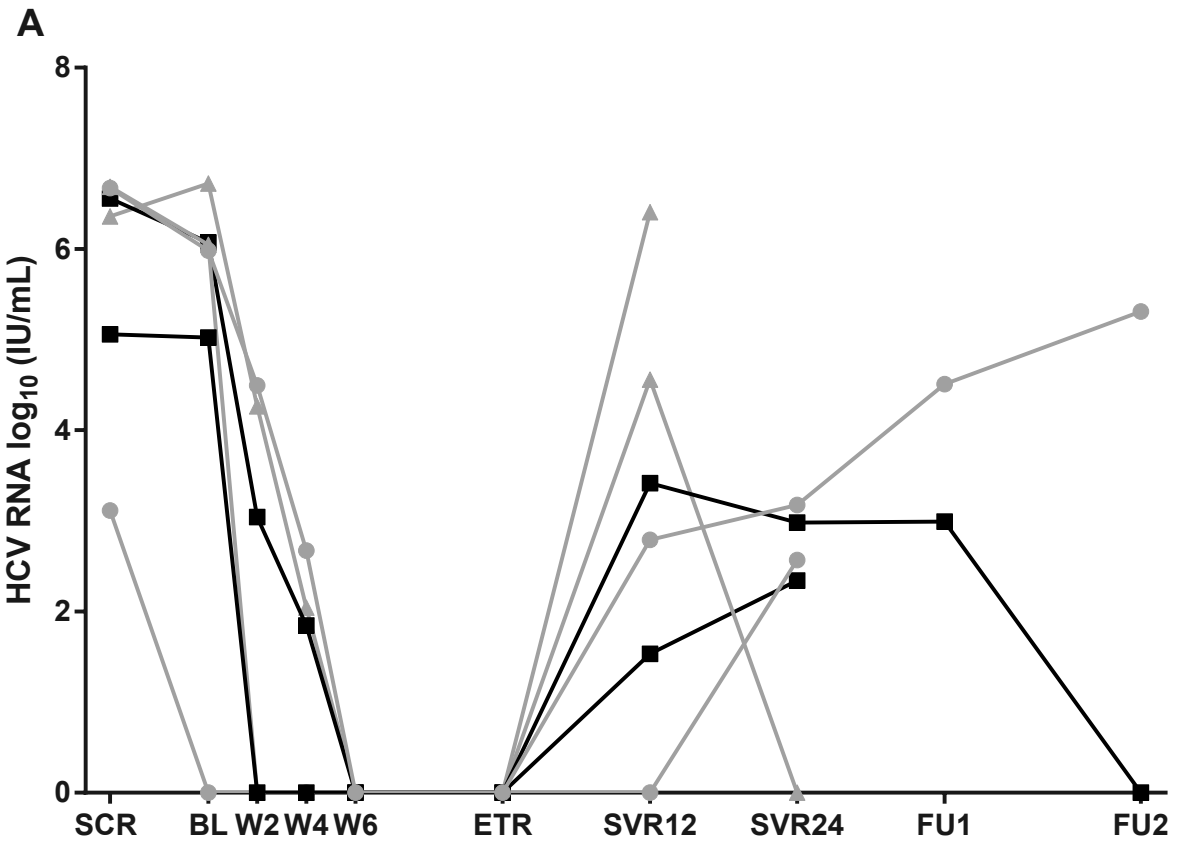
73%
64%
67%
64%
ETR
SVR12
SVR24


A
8
6
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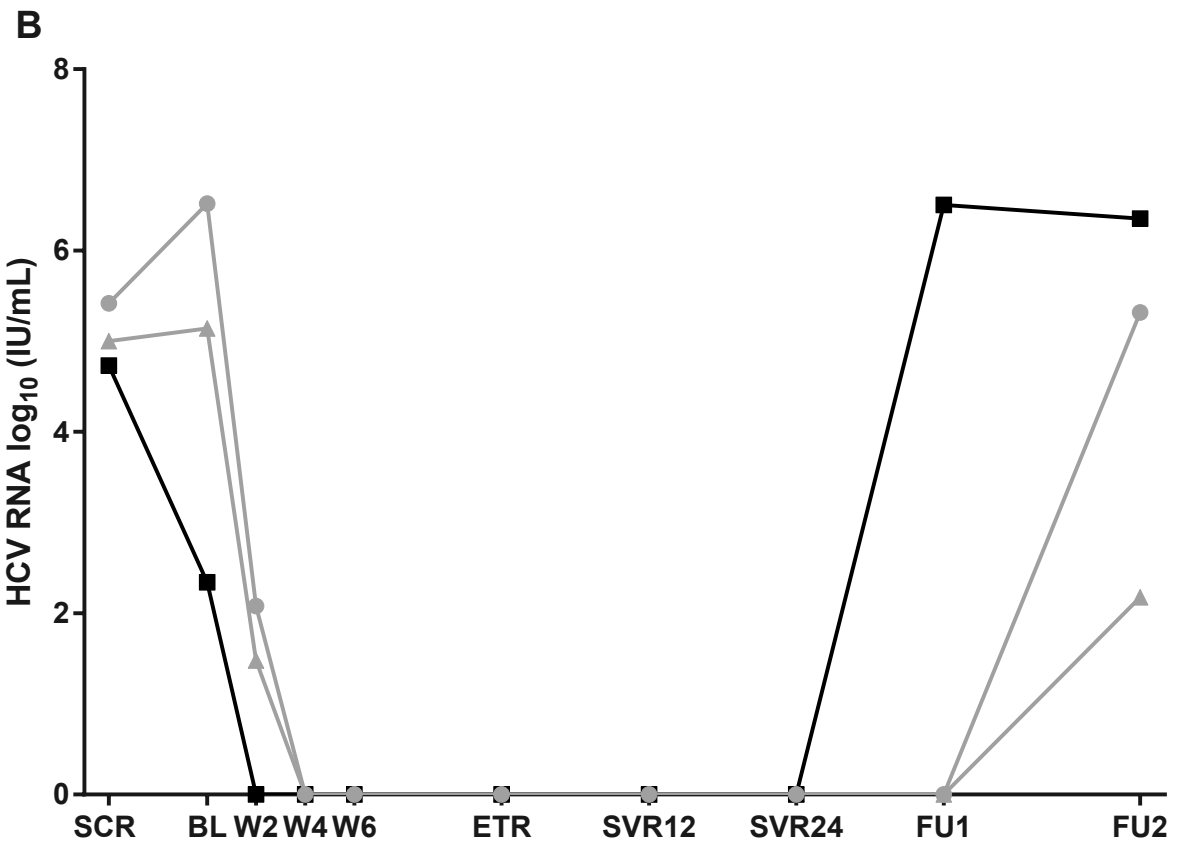
2
0
HCV RNA log10 (IU/mL)
SCR
BL
W2
W4
W6
ETR
SVR12
SVR24
FU1
FU2


B
8
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HCV RNA log10 (IU/mL)
SCR
BL
W2
W4
W6
ETR
SVR12
SVR24
FU1
FU2

Supplementary Appendix

Short duration response-guided treatment is effective for most individuals with recent hepatitis C infection: the ATAHC II and DARE-C I studies

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Methods

ATAHC II

Inclusion and exclusion criteria

Adults (age ≥16 years) with recent HCV infection were eligible for study inclusion. Participants with detectable HCV RNA at screening were assessed for treatment eligibility.

Exclusion criteria for enrolment in the treatment arm included: age 16-18 years; pregnant women or male partners of pregnant women; breast feeding; systemic anti-viral, anti-neoplastic or immunomodulatory therapy ≤6 months prior to first dose of study drug; any investigational drug ≤6 weeks prior to first dose of study drug; positive anti-HAV IgM Ab or anti-HBc IgM Ab at screening; alternative aetiology of chronic liver disease; decompensated liver disease; active thyroid disease; severe retinopathy; severe seizure disorder; immunologically mediated disease, chronic pulmonary disease with functional limitation, severe cardiac disease, organ transplantation (apart from corneal, skin or hair graft), malignancy, or other severe illness (including psychiatric) which would make the participant unsuitable; and the following lab values at screening: neutrophil count <1500 cells/mm^3, platelet count <90,000 cells/mm^3, creatinine >1.5 times the upper limit of normal, haemoglobin <12 g/dL in women or <13 g/dL in men. Heavy alcohol intake and active illicit drug use were not exclusion criteria. A drug and alcohol assessment was performed at screening to determine treatment suitability.

Study assessments

In the treated arm, study visits were undertaken at baseline, day 1 and weeks 2, 4, 6, 8, 12, 16, 20 and 24, depending on treatment duration, and post-treatment weeks

12, 24, 48 and 72, until the individual completed study follow-up or the study closed (May 2015). In the untreated arm, study visits were undertaken at baseline and weeks 4, 8, 12, 24, 48, 72 and 96, until the individual completed study follow-up or the study closed (May 2015). The presence of HCV RNA was assessed at all scheduled study visits. HCV GT was assessed at screening. Adverse events were recorded on all treated participants from screening until week 12 post treatment. Questionnaires were administered at screening and every 12 weeks through follow-up to obtain information on illicit drug use, social functioning (Opiate Treatment Index Social Functioning Scale (1)) and psychological parameters (Mini-International Neuropsychiatric Interview (2) and the Depression Anxiety Stress Scale (3)). Adherence to therapy was assessed at clinical review and by self-reported questionnaire.

DARE-C I

Inclusion and exclusion criteria

Adults (age ≥18 years) with recent genotype 1 HCV infection, HCV RNA ≥10,000 IU/mL at screening and baseline and hepatitis B sAg negative were eligible for enrolment and treatment commencement.

The following additional inclusion criteria were required for HIV-positive individuals: 1. HIV >6 months duration, 2. CD4 count >200 cells/mm^3 and HIV viral load <50 copies/ml on stable combination antiretroviral therapy (cART) or 3. CD4 count ≥500 cells/mm^3 and HIV viral load <100,000 copies/mL not on cART. The following antiretroviral agents were permitted: tenofovir, lamivudine, emtricitabine, efavirenez, abacavir, raltegravir, etravirine, rilpivirine and ritonavir-boosted atazanavir.

Exclusion criteria were the same as ATAHC II and in addition included: infection with non-GT 1 HCV; injecting drug use (IDU) within the previous 4 weeks; poorly

controlled diabetes mellitus (haemoglobin A1c ≥8.5%); prior treatment with HCV protease or polymerase inhibitors; congenital QT prolongation or family history of congenital QT prolongation or sudden death; pancreatitis; haemophilia or other bleeding disorder; serious bacterial or fungal infection; and the following lab values at screening: potassium <3.5 mmol/L, calculated creatinine clearance <50mL/min.

Study assessments

Study visits were undertaken at baseline, day 1, weeks 1, 2, 3, 4, 6, 8, 12, 16, 20 and 24, depending on treatment duration, and post-treatment weeks 12, 24, 48 and 72. The presence of HCV RNA was assessed at all scheduled study visits. HCV genotype was assessed at screening. Adverse events were collected from screening until week 12 post treatment. The same questionnaires as in ATAHC II were administered at screening and every 12 weeks through follow-up evaluation (1-3).

Study definitions for ATAHC II and DARE C I

Recent 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 24 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 (4), with estimated duration of infection less than 18 months at screening.

The presentation of recent HCV infection at the time of diagnosis was classified as either acute clinical or asymptomatic infection. Acute clinical infection included participants with a documented clinical history of symptomatic seroconversion illness

and those without clinical symptoms but with a documented peak ALT > 400 U/L at or before the time of diagnosis. Asymptomatic infection included participants with anti-HCV Ab seroconversion but no acute clinical symptoms or documented peak ALT > 400 U/L. The estimated date of clinical infection was calculated as six weeks before onset of seroconversion illness or six weeks before the first ALT >400 U/L. The estimated date of asymptomatic infection was calculated as the midpoint between the last negative anti-HCV antibody and the first positive anti-HCV antibody. For participants who were anti-HCV antibody negative and HCV-RNA positive at screening, the estimated date of infection was six weeks before enrolment, regardless of symptom status.

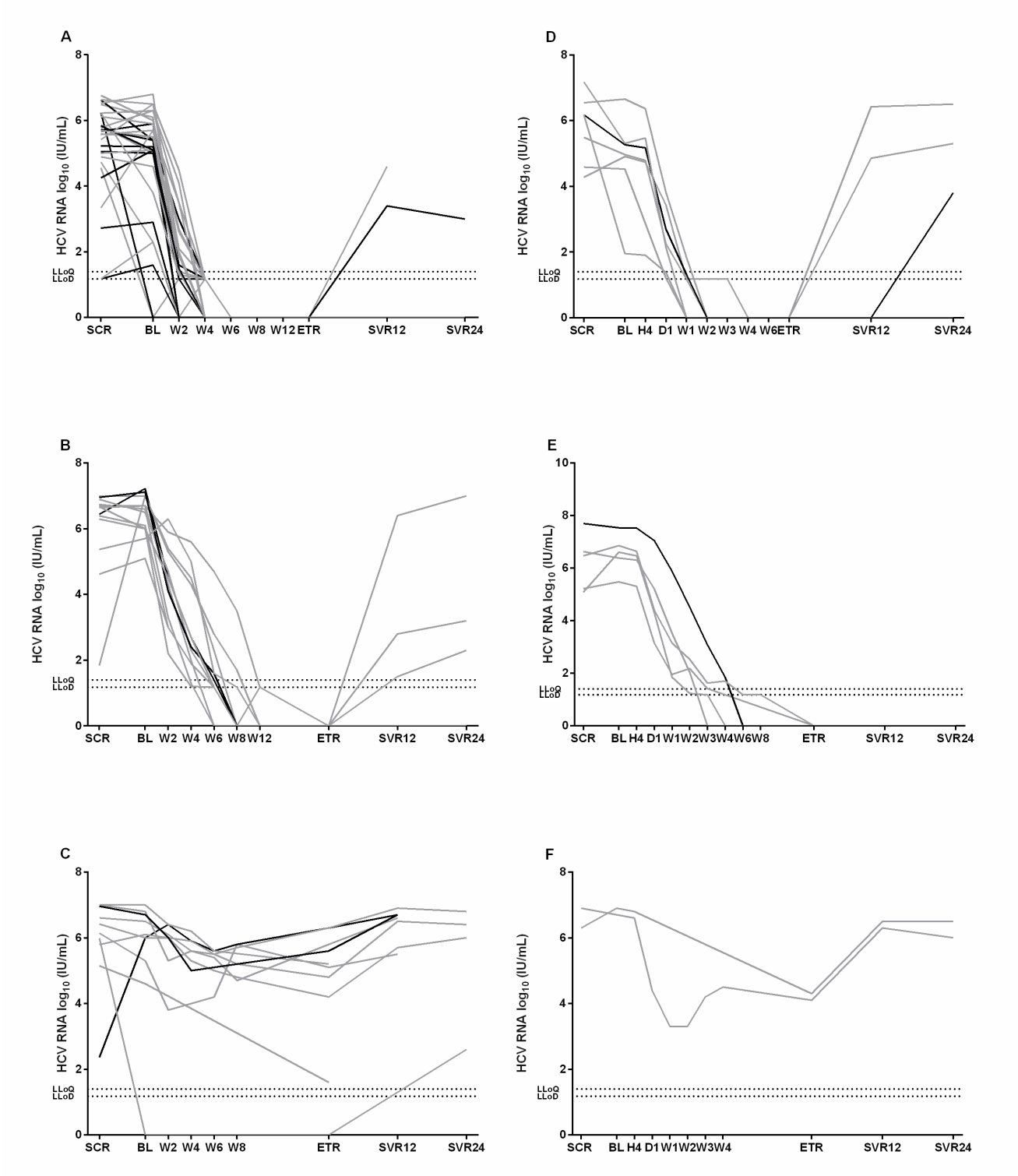
On-treatment adherence was calculated for each medication individually (PEG-IFN, RBV and telaprevir) by subtracting the number of missed doses from the total number of doses prescribed for therapy duration and dividing by the total number of doses prescribed for therapy duration. By pill count and self-reported questionnaire, compliance with each medication was individually calculated at the 80/80 and 100/100 adherence levels, defined as receipt of ≥80% or 100% of scheduled doses for ≥80% or 100% of the scheduled treatment period, respectively.

Statistical analysis

For all endpoints, means and proportions with two-sided 95% confidence intervals (CI) were determined, and were unadjusted for multiple comparisons. Continuous variables were analysed using ANOVA methods or non-parametric equivalents, as appropriate. Binary endpoints were analysed using chi-square methods or logistic regression. A Cox proportional hazards model was used to assess factors associated with time to first HCV RNA below the limit of detection and logistic

regression analyses were used to identify baseline and on-treatment predictors of HCV treatment response. Potential predictors were determined *a priori* and included participant, virological and treatment characteristics including sex, age, weight, education, employment, accommodation, social functioning, opioid substitution therapy, mental health status (depression and suicidality, based on the Mini-International Neuropsychiatric Interview(2)), ethnicity, IDU characteristics, alcohol consumption, estimated duration of HCV infection, presentation (acute clinical, asymptomatic), peak and baseline ALT, baseline HCV RNA, and HCV genotype. Social functioning was calculated using a validated scale from the Opiate Treatment Index (1) that addresses employment, residential stability, interpersonal conflict, social support, and the role of drug use in the participant's social networks. A higher value indicates poorer functioning (range: 0– 48). The multivariate model for predictors of treatment response and HCV clearance were determined using a backwards stepwise approach, considering factors that were significant at the 0.2 level in univariate analysis. The final models included only factors that remained significant at the 0.05 level. All p-values are two-sided. All analyses were performed using STATA version 13.0 (Stata Corporation, College Station, TX).

Figures



Supplementary Appendix Figure 1. Viral kinetics and outcome by study and treatment allocation. (A) ATAHC II – 8 and 16 weeks (n=29). (B) ATAHC II – 24 and 48 weeks (n=13). (C) ATAHC II – Non-response and early treatment discontinuation (n=10). (D) DARE-C I – 8 weeks (n=7). (E) DARE-C I – 12 and 24 weeks (n=5). (F) DARE-C I – Non-response and early treatment discontinuation

(n=2). Participants with HIV/HCV co-infection indicated in grey and HCV mono-infection in black.

Abbreviations: End of treatment (ETR); sustained virological response (SVR); SCR (screening); BL (baseline, hour 0); H4 (baseline, hour 4); D1 (day 1); W1-12 (week 1-12); LLoQ (lower limit of quantitation); LLoD (lower limit of detection)

Tables

Supplementary Appendix Table 1. Participant enrolment characteristics in ATAHC II by HIV co-infection

Enrolment characteristics	HCV mono-infection (n=31)	HCV/HIV co-infection (n=51)	*P*
Age (years), mean (SD)	36 (9)	41 (8)	0.010
Male, n (%)	22 (71)	51 (100)	<0.001
Weight (kg), mean (SD)	77 (17)	77 (10)	0.983
BMI (kg/m^2), mean (SD)	25 (4)	25 (3)	0.311
Caucasian ethnicity, n (%)	25 (81)	42 (82)	0.846
Higher education or qualification [a], n (%)	15 (48)	36 (71)	0.044
Full or part time employment	8 (24)	32 (63)	0.001
Prison/juvenile justice centre ever, n (%)	4 (13)	1 (2)	0.047
Social functioning score, median (IQR)	15 (9-21)	10 (6-14)	0.007
Current major depression, n (%)	8 (26)	8 (16)	0.262
Injecting drug use ever, n (%) Ever Current [b]	 26 (84) 19 (61)	 36 (71) 27 (53)	 0.220 0.209
In those reporting injecting drug use: Age at first injecting, median (IQR) Last injected within last month, n (%) Last injected between 1-6 months ago, n (%) Last injected >6 months ago, n (%)	 23 (18 – 30) 14 (54) 5 (19) 7 (27)	 29 (25-38) 16 (44) 11 (31) 9 (25)	 0.012
Drug injected most in last month, n (%) Amphetamines Heroin Other opiates	 9 (64) 2 (14) 3 (21)	 16 (100) 0 0	 0.024
Opioid substitution therapy, n (%) Ever Current	 6 (19) 6 (19)	 4 (8) 0	 0.131 0.002
Estimated duration of infection (weeks) At screening, median (IQR) At baseline, median (IQR)	 26 (11-33) 37 (27-43)	 24 (14-40) 33 (27-50)	 0.899 0.899
Acute clinical illness - jaundice +/- ALT >10x ULN Asymptomatic seroconversion	18 (58) 13 (42)	34 (67) 17 (33)	0.950
Mode of HCV acquisition, n (%) Injecting drug use Sexual exposure - same sex Sexual exposure – opposite sex Other	 25 (81) 3 (9) 2 (6) 1 (3)	 20 (39) 29 (57) 2 (4) 0	 0.002

[a] Completed higher technical qualification/TAFE/College/university degree

[b] Current injecting drug use refers to use within 6 months of screening

Supplementary Appendix Table 2. Factors associated with time to first HCV RNA below the limit of detection in ATAHC II on Cox proportional hazards analysis (n=52)

Variable	HR	95% CI	*P*
Sex			
Male	1.00	-	-
Female	3.27	0.91, 11.73	0.069
Social functioning score			
<6	1.00	-	-
7-12	0.75	0.36, 1.55	0.435
>12	1.11	0.54, 2.3	0.777
IDU ever			
No	1.00	-	-
Yes	0.85	0.44, 1.64	0.627
HIV co-infection			
No	1.00	-	-
Yes	0.65	0.34, 1.25	0.195
Presentation of acute HCV			
Asymptomatic seroconversion	1.00	-	-
Acute clinical	1.87	0.93, 3.72	0.080
Peak ALT			
≤400 U/L	1.00	-	-
>400 U/L	0.65	0.34, 1.24	0.189
HCV RNA at baseline			
<400,000 IU/mL	**1.00**	**-**	**-**
≥400,000 IU/mL	**0.34**	**0.18, 0.64**	**0.001**
HCV genotype			
GT 1	1.00	-	-
GT 2	0.94	0.13, 7.06	0.956
GT 3	1.19	0.65, 2.22	0.562
GT 4	1.56	0.21, 11.72	0.666

Supplementary Appendix Table 3. Factors associated with SVR 12 in ATAHC II on logistic regression analysis (n=52)

Variable	SVR	No SVR	OR	95% CI	*P*
Sex					
Male	35	13	1.00	-	-
Female	2	2	0.37	0.05, 2.91	0.346
Social functioning score					
<6	13	4	1.00	-	-
7-12	12	5	0.74	0.16, 3.41	0.698
>12	12	6	0.62	0.14, 2.72	0.523
Injecting drug use - ever					
No	11	6	1.00	-	-
Yes	25	9	0.66	0.19, 2.31	0.516
Injecting drug use - frequency					
Have not injected in past month	13	7	1.00	-	-
Have injected in past month	12	2	3.23	0.56, 18.71	0.191
Never injected	11	6	0.68	0.25, 3.82	0.985
HIV co-infection					
No	11	4	1.00	-	-
Yes	26	11	0.90	0.22, 3.30	0.825
Presentation of acute HCV					
Asymptomatic seroconversion	10	7	1.00	-	-
Acute clinical illness	27	8	2.36	0.68, 8.22	0.177
HCV genotype 1					
No	20	4	1.00	-	-
Yes	11	17	0.31	0.08, 1.15	0.080
HCV RNA at baseline					
<400,000 IU/mL	18	4	1.00	-	-
≥400,000 IU/mL	19	11	0.38	0.10, 1.43	0.153
Rapid virological response					
No	**10**	**12**	**1.00**	**-**	**-**
Yes	**27**	**3**	**10.80**	**2.51, 46.43**	**0.001**

Supplementary Appendix Table 4. Safety – Clinical adverse events and laboratory parameters

Clinical and lab adverse events	ATAHC II					DARE-C I
	All treated (n=52)[a]	Treatment group (weeks)				All treated (n=14)
		8 (n=13)	16 (n=16)	24 (n=11)	48 (n=2)	
Any adverse event, n (%)	347 (100)	88 (25)	117 (34)	82 (24)	19 (6)	103 (100)
Grade 3 or 4, n (%)	4 (1)	0	0	1	1	0
Serious adverse events, n (%)	3 (1)					2 (14)
Adverse events[b]						
Common (>10%), n (%)						
Fatigue	31 (60)	9 (69)	4 (25)	9 (82)	1 (50)	10 (71)
Insomnia	27(52)	6 (46)	9 (56)	6 (55)	2 (100)	6 (43)
Headache	17 (33)	5 (38)	7 (44)	3 (27)	1 (50)	6 (43)
Nausea	17 (33)	5 (38)	6 (38)	3 (27)	2 (100)	5 (36)
Arthralgia	14 (27)	7 (54)	1 (6)	5 (45)	1 (50)	0
Myalgia	14 (27)	4 (31)	3 (19)	4 (36)	1 (50)	4 (29)
Diarrhoea	13 (25)	2 (15)	4 (25)	7 (64)	0	0
Influenza-like illness	9 (17)	2 (15)	4 (25)	1 (9)	0	0
Depressed mood	8 (15)	1 (8)	3 (19)	2 (18)	2 (100)	0
Injection site erythema	8 (15)	1 (8)	0	5 (45)	1 (50)	0
Irritability	8 (15)	2 (15)	3 (19)	1 (9)	1 (50)	3 (21)
Decreased appetite	7 (13)	2 (15)	3 (19)	1 (9)	0	2 (14)
Lethargy	7 (13)	0	4 (25)	3 (27)	0	0
Injection site reaction	6 (12)	0	3 (19)	1 (9)	0	3 (21)
Pruritus	6 (12)	3 (23)	1 (6)	1 (9)	1 (50)	6 (43)
Rash	6 (12)	3 (23)	0	1 (9)	0	7 (50)
Mean on-treatment nadir Hb (g/L), SD	122 (14)	120 (14)	121 (12)	119 (12)	104 (16)	105 (17)
Decrease in Hb >30g/L, n (%)*	24 (46)	6 (46)	8 (50)	7 (64)	2 (100)	12 (86)
Decrease in Hb <100g/L, n (%)	3 (6)	1 (8)	1 (6)	0	1 (50)	5 (36)
Decrease in Hb <85 g/L, n (%)	0	0	0	0	0	2 (14)
Decrease in ANC ≤0.75, n (%)	13 (25)	1 (8)	5 (31)	4 (36)	1 (50)	2 (14)
Decrease in ANC ≤0.5, n (%)	4 (8)	1 (8)	2 (13)	1 (9)	0	1 (7)
Decrease in plt <50, n (%)	0	0	0	0	0	0

[a] Includes individuals with no allocated treatment duration due to early treatment discontinuation and virological non-response

[b] Other common adverse events in DARE-C I included abdominal pain (21%, n=3) and perianal pain/discomfort (21%, n=3)

[c] Decease in Hb >30g/L at any time between baseline and end of treatment

Abbreviations: Haemoglobin (Hb), absolute neutrophil count (ANC), platelet (plt)

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