# 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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**Background: Individuals with recent HCV infection may benefit from shortened duration therapy. These studies evaluated the efficacy and safety of response-guided regimens with pegylated interferon-α2a and ribavirin for people with recent HCV infection.**

**Methods: Participants with recent hepatitis C (duration of infection ≤18 months) enrolled in the ATAHC II (pegylated interferon-α2a ± ribavirin) and DARE-C I (pegylated interferon-α2a, 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 end point was sustained virological response at 12 weeks (SVR12) by intention-to-treat. Logistic regression analyses were used to identify predictors of SVR.**

**Results: A total of 82 participants (62% HIV-positive) were enrolled in ATAHC II (treated, *n*=52) and 14 (79% HIV-positive) in DARE-C I. The predominant modes 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-α2a and ribavirin. Response-guided therapy for recent hepatitis C infection could be considered in the absence of available interferon-free therapies. ClinicalTrials.gov registry (ATAHC II: NCT01336010; DARE-C I: NCT01743521).**

## Introduction

The management of recent (acute or early chronic) HCV infection is not standardized regarding the optimal regimen and treatment duration [1], particularly as the therapeutic landscape changes with the advent of interferon (IFN)-free direct-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 monotherapy (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-α2a and ribavirin (RBV) for individuals with recent HCV infection. The Directly-acting Antiviral Based Therapy for Recently Acquired Hepatitis C (DARE-C I), a substudy of ATAHC II, assessed the efficacy and safety of response-guided therapy with PEG-IFN-α2a, RBV and telaprevir for individuals with recent genotype-1 (G1) HCV infection.

## 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-α2a (180 μg/week) and RBV (G1: 1,000 mg/day if <75 kg, 1,200 mg/day if ≥75 kg; G2/3: 800 mg/day).

Enrolled participants were assessed for treatment eligibility. Participants who were eligible and consented to treatment were stratified by HIV status and estimated duration of infection at baseline. Participants with acute (estimated duration of infection ≤6 months) HCV monoinfection received PEG-IFN; participants with early chronic infection (estimated duration 6–18 months) and HIV coinfection 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 Additional file 1.

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

*Study design*

A substudy of ATAHC II, DARE-C I assessed the efficacy and safety of response-guided therapy with PEG-IFN-α2a (180 μg/week), weight-based RBV (1,000 mg/day if <75 kg, 1,200 mg/day if ≥75 kg) and telaprevir (1,125 mg twice daily or 1,125 mg 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).

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

| Study and HCV RNA BLoD at indicated week | 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 |

BLoD, below limit of detection; G, genotype; PEG-IFN, pegylated interferon-α2a; RBV, ribavirin; TVR, telaprevir.

*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 Additional file 1.

### 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 6 months of enrolment and either documented recent HCV seroconversion (anti-HCV antibody negative result in the 24 months prior to enrolment) or acute clinical hepatitis (jaundice or alanine aminotransferase [ALT] greater than 10× the upper limit of normal) 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 LLoD. An end-of-treatment response (ETR) was defined as serum HCV RNA below the LLoD 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 virological 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 virological control was defined as a confirmed HIV RNA of at least 400 copies/ml in individuals on cART. For further study definitions, see Additional file 1.

### Study outcomes for ATAHC II and DARE-C I

The primary efficacy end point was sustained virological response at 12 weeks (SVR12), defined as serum HCV RNA below the limit of detection at 12 weeks following end of treatment. Secondary virological end points included a rapid virological response (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 end points, means and proportions with two-sided 95% CIs were determined, and were unadjusted for multiple comparisons. Continuous variables were analysed using ANOVA methods or non-parametric equivalents. Binary end points were analysed using $\chi^2$ 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, USA).

## Results

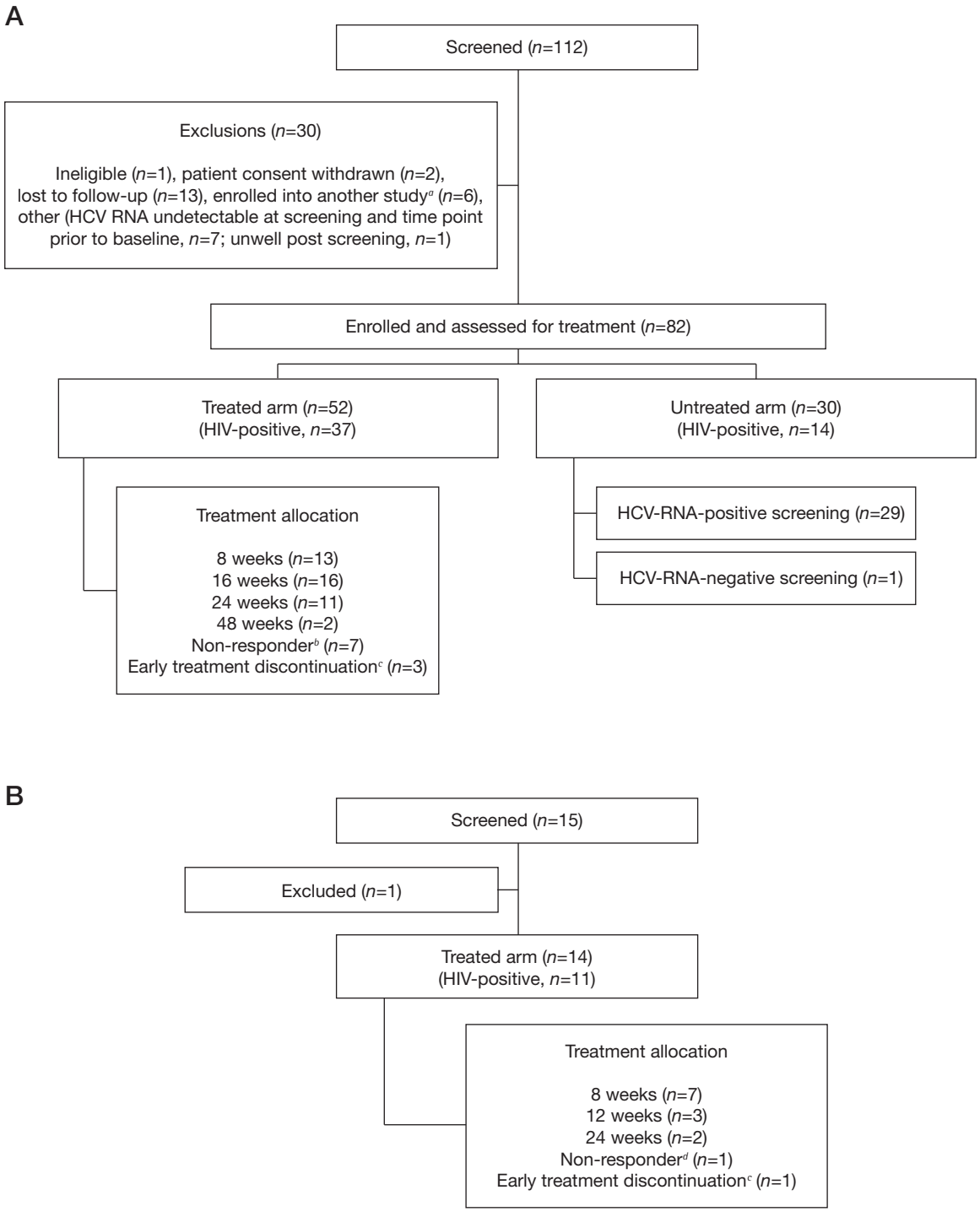
### ATAHC II

*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 coinfection 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). 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.

76% (*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 versus 23 years; *P*=0.012). Of those reporting IDU within the last 6 months (*n*=46), 65% had injected in the previous month with

**Figure 1.** Patient disposition




**(A)** ATAHC II. **(B)** DARE-C I. [a]Of those excluded and enrolled into another study (*n*=6), 5 were enrolled into DARE-C I. [b]ATAHC II non-responder: participants receiving pegylated interferon with or without ribavirin who do not achieve an HCV RNA level below the limit of detection (<15 IU/ml on Roche TaqMan) after 12 weeks of treatment. [c]Early treatment discontinuation: treatment ceased prior to allocation of treatment duration. [d]DARE-C I non-responder: participants for whom therapy was terminated at week 4 due to HCV RNA >1,000 IU/ml or week 8 due to detectable HCV RNA.

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

| Enrolment characteristics | ATAHC II | | | DARE-C I: overall (*n*=14) |
|---|---|---|---|---|
| | Overall (*n*=82) | Treated (*n*=52) | Untreated (*n*=30) | |
| Mean age, years (SD) | 39 (10) | 41 (10) | 36 (9) | 48 (11) |
| Male, *n* (%) | 73 (89) | 48 (92) | 25 (83) | 14 (100) |
| Mean weight, kg (SD) | 77 (13) | 79 (13) | 74 (12) | 77 (13) |
| Mean BMI, kg/m$^2$ (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 |
| Median social functioning score (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 | | | | |
| Ever, *n* (%) | 62 (76) | 34 (65) | 28 (93) | 6 (43) |
| Current[b], *n* (%) | 46 (56) | 22 (42) | 24 (80) | 3 (21) |
| Opioid substitution therapy | | | | |
| Ever, *n* (%) | 10 (12) | 7 (13) | 3 (10) | 1 (7) |
| Current, *n* (%) | 6 (7) | 3 (6) | 3 (10) | 0 |
| HIV infection, *n* (%) | 51 (62) | 37 (71) | 14 (47) | 11 (79) |
| Median CD4$^+$ T-cell count, 10$^6$/l (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 | | | | |
| Injecting drug use, *n* (%) | 45 (55) | 22 (42) | 23 (77) | 5 (36) |
| Sexual exposure – same sex, *n* (%) | 32 (39) | 26 (50) | 6 (20) | 9 (64) |
| Sexual exposure – opposite sex, *n* (%) | 4 (5) | 3 (6) | 1 (3) | 0 |
| Other, *n* (%) | 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 | | | | |
| Acute clinical illness – symptomatic, *n* (%) | 35 (43) | 22 (42) | 13 (43) | 5 (36) |
| Jaundice[e], *n* (%) | 17 (49) | 11 (50) | 6 (46) | 2 (40) |
| Nausea/vomiting[e], *n* (%) | 12 (34) | 8 (32) | 4 (31) | 2 (40) |
| Abdominal pain[e], *n* (%) | 13 (37) | 8 (32) | 5 (38) | 3 (60) |
| Fever[e], *n* (%) | 10 (29) | 6 (27) | 4 (31) | 3 (60) |
| Acute clinical illness – ALT >10×ULN, *n* (%) | 48 (59) | 32 (62) | 16 (53) | 10 (71) |
| Asymptomatic seroconversion, *n* (%) | 26 (32) | 15 (29) | 11 (37) | 2 (14) |
| Median ALT | | | | |
| Peak ALT prior to enrolment, U/l (IQR) | 621 (218–1,129) | 621 (232–1,110) | 575 (169–1,247) | 623 (156–925) |
| ALT at screening, U/l (IQR) | 135 (81–354) | 127 (83–360) | 142 (70–349) | 116 (53–151) |
| Median $\log_{10}$ HCV RNA at screening, IU/ml (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) | | | | |
| Genotype 1, *n* (%) | 42 (51) | 28 (54) | 14 (47) | 14 (100) |
| 1a, *n* (%) | 41 (98) | 28 (100) | 13 (93) | 13 (93) |
| 1b, *n* (%) | 1 (2) | 0 | 1 (7) | 1 (7) |
| Genotype 2, *n* (%) | 1 (1) | 1 (2) | 0 | – |
| Genotype 3, *n* (%) | 38 (46) | 22 (42) | 16 (53) | – |
| Genotype 4, *n* (%) | 1 (1) | 1 (2) | 0 | – |

[a]Completed higher technical qualification/Technical and Further Education (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. ALT, alanine aminotransferase; BMI, body mass index; cART, combination antiretroviral therapy; ULN, upper limit of normal.

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).

A total of 30 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 comorbidity (Table 2).

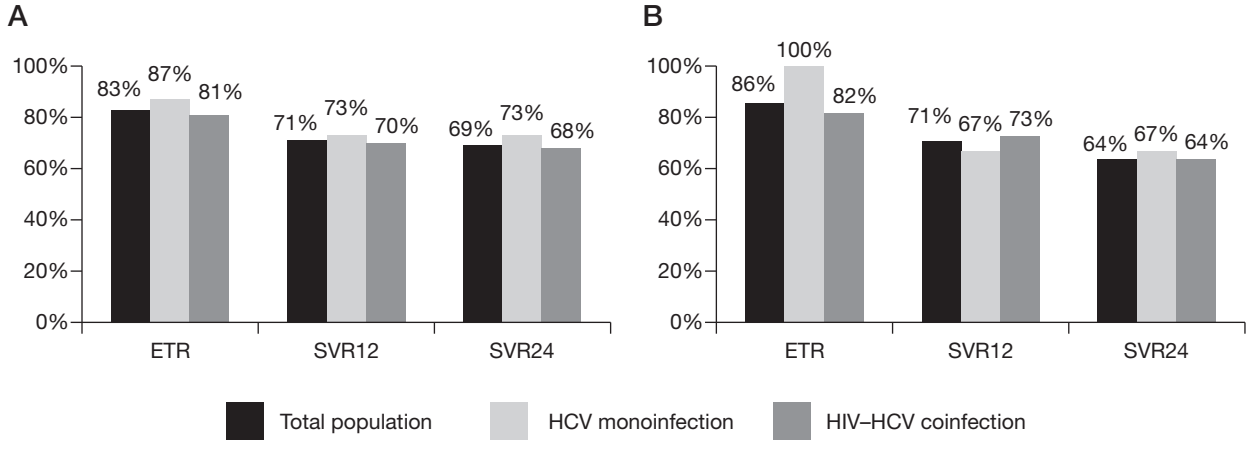
As one participant with undetectable HCV RNA at screening was ineligible, the uptake of HCV treatment was 64% (52/81). In the untreated arm, spontaneous clearance was observed in 14% (4/29).

*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 monoinfection, SVR12 73% [11/15]; HIV–HCV coinfection, 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 monoinfection, 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 coinfection, 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).

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




**(A)** ATAHC II – response-guided pegylated interferon (PEG-IFN) and ribavirin. **(B)** DARE-C I – response-guided PEG-IFN, ribavirin and telaprevir. ETR, end of treatment response; SVR12, sustained virological response at 12 weeks; SVR24, sustained virological response at 24 weeks.

## 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 1 and 2 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) showing adherence of 100% and 95%, respectively (mean on-treatment PEG-IFN adherence 99.97% [SD 0.2]), and RBV 80/80 and 100/100 showing adherence of 94% and 67%, respectively (mean on-treatment RBV adherence 95.3% [SD 18.7]). HIV–HCV-coinfected participants were more likely to be RBV adherent than HCV monoinfected participants (RBV 80/80 100% versus 79%; *P*=0.004; RBV 100/100 76% versus 43%; *P*=0.027). PEG-IFN 80/80 adherence was better with response-guided therapy in ATAHC II as compared with ATAHC I (100% versus 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; Additional file 1).

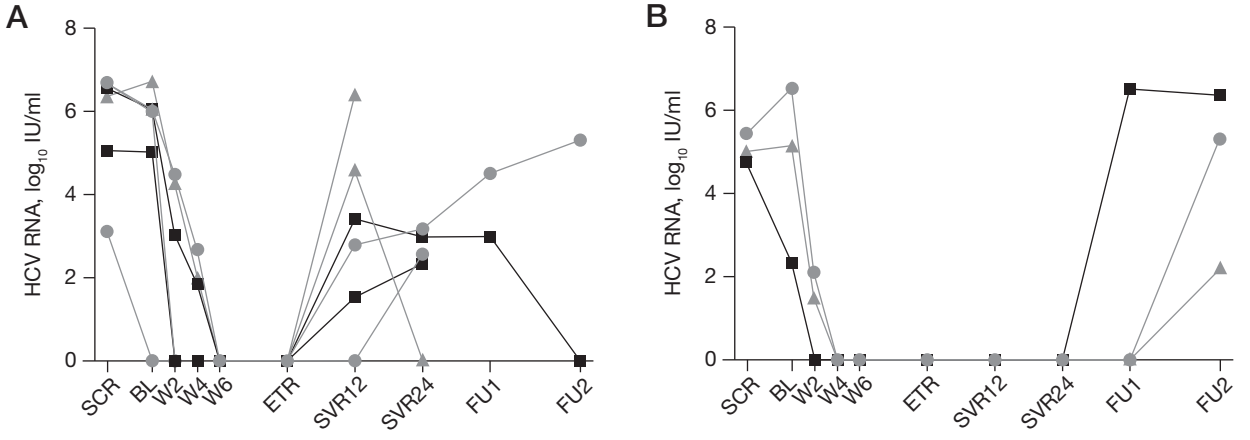
Participant characteristics and on-treatment factors were evaluated as predictors of SVR with logistic regression analysis. Rapid virological response was the only factor associated with SVR (OR 10.80; 95% CI 2.51, 46.43; *P*=0.001; Additional file 1).

## Safety

The safety profile was consistent with the known side effects of PEG-IFN-α2a and RBV (Additional file 1). 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 $CD4^+$ T-cell count at end of treatment was $119\times10^6$/l (IQR 47–234) with no loss of HIV virological control.

Three serious adverse events were reported: anxiety requiring hospitalization in an individual with a psychiatric history (possibly related to study drug administration), attempted suicide in an individual

**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 coinfection. Black lines indicate individuals with HCV monoinfection. Note, in (A) two individuals demonstrated spontaneous clearance of HCV viraemia following relapse (at sustained virological response at 24 weeks [SVR24] and follow-up 2 years post end of treatment [FU2]). BL, baseline; ETR, end of treatment response; FU1, follow-up 1 year post end of treatment; SCR, screening; SVR12, sustained virological response at 12 weeks; W, week.

with a psychiatric history (possibly related to study drug administration) and sialolithiasis requiring hospitalization (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. 46% (*n*=6) had ever injected drugs. 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% versus 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 and 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, showing adherence of 100% and RBV 80/80 and 100/100, showing adherence of 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%; Additional file 1). Two serious adverse events were reported: skin cancer squamous cell carcinoma/basal cell carcinoma (SCC/BCC) requiring hospitalization and axillary abscess requiring hospitalization. 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, RBV and telaprevir as compared with 20 g/l (SD 15) in participants receiving PEG-IFN and RBV (*P*=0.007). Anaemia (haemoglobin less than 100 g/l) developed on-treatment in five participants (36%) receiving PEG-IFN, RBV and telaprevir as compared with three (6%) receiving PEG-IFN and RBV (*P*=0.008).

## 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 4 if HCV RNA remains detectable. Population-level HCV treatment-as-prevention (TasP) 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 coinfection) 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 of late viral recurrence following treatment for acute or chronic HCV infection, the incidence of reinfection following SVR in those with HIV was 3.2 per 100 py (95% CI 0.1, 12.3) [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 emphasize the need for continued surveillance and prevention strategies [35,36]. Despite concerns regarding adherence and reinfection, HCV treatment with IFN-containing and IFN-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 minimization.

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.

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GVM, GJD, MH, DS, KP, TA, 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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## Additional file

Additional file 1: Supplementary material can be found at https://www.intmedpress.com/uploads/documents/3718_Martinello_Addfile1.pdf

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