

CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Effective Treatment of Injecting Drug Users With Recently Acquired Hepatitis C Virus Infection

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BACKGROUND & AIMS: Patients with acute hepatitis C virus (HCV) infection who receive treatment achieve high rates of sustained virologic response (SVR), but few studies have examined outcomes among injecting drug users (IDUs). We evaluated the efficacy of treatment of recent HCV infection in IDUs with acute and early chronic HCV. **METHODS:** We analyzed data from the Australian Trial in Acute Hepatitis C—a prospective study of the natural history and treatment outcomes of patients with recent HCV infection. Participants eligible for the study had their first anti-HCV antibody–positive test result within the past 6 months and either acute clinical HCV within the past 12 months or documented anti-HCV seroconversion within 24 months. Participants with HCV received pegylated interferon- α -2a (180 μ g/wk, n = 74); those with HCV/human immunodeficiency virus (HIV) co-infection received pegylated interferon- α -2a (180 μ g/wk) with ribavirin (n = 35) for 24 weeks. **RESULTS:** From June 2004 to February 2008, 167 participants were enrolled in the Australian Trial in Acute Hepatitis C; 79% had injected drugs in the previous 6 months. Among 74 with only HCV, the SVRs were 55% and 72% by intention-to-treat and per-protocol analysis, respectively. In multivariate analyses, baseline factors independently associated with lower SVR included decreased social functioning and current opiate pharmacotherapy. Adherent participants had higher SVR rates (63% vs 29%; $P = .025$). Of the 35 participants with HCV/HIV co-infection, the SVRs were 74% and 75% by intention-to-treat and per-protocol analysis, respectively. **CONCLUSIONS: Treatment of recent HCV infection among IDUs, including those with HIV co-infection, is effective. Strategies to engage socially marginalized individuals and increase adherence should improve treatment outcomes in this population.**

An estimated 75% of people with acute hepatitis C virus (HCV) infection progress to chronic infection¹ and experience an increased risk of impaired quality of life² and progressive liver disease.³ Several studies have shown that treatment based on interferon- α in acute HCV infection can yield much higher levels of sustained virologic response (SVR) than the treatment of chronic HCV infection.⁴⁻¹⁰

Although these findings are encouraging, questions remain about the most effective treatment strategies in recent HCV infection. For example, data are very limited on the feasibility and outcome of treatment for acute HCV in injecting drug users (IDU), even though they represent the population group at greatest risk for infection in many countries. Most acute HCV treatment studies have been performed in settings where injecting drug use is uncommon,^{4,8,10} or have chosen to predominantly recruit participants whose infection was acquired through other modes of percutaneous exposure.^{7,9}

Another important issue is timing: because the majority of people who spontaneously clear virus after acute HCV infection do so within 16 weeks of symptomatic presentation (20–24 weeks after infection),^{4,8,11} it appears reasonable to delay therapeutic intervention for this time period to avoid unnecessary treatment.^{12,13} On the other hand, treatment strategies for individuals with asymptomatic presentation but evidence of recent infection through anti-HCV antibody seroconversion are less

Abbreviations used in this paper: ATACH, Australian Trial in Acute Hepatitis C; HIV, human immunodeficiency virus; IDU, injection drug user; SVR, sustained virologic response.

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certain. Repeat HCV screening is common among IDUs, but the variability of testing intervals means that many of those with diagnosed recent HCV infection will have early chronic HCV infection.

The Australian Trial in Acute Hepatitis C (ATAHC) study was designed specifically to investigate HCV treatment in people whose infection was acquired recently through injecting drug use. Here we report on the treatment outcomes, and the role and predictors of treatment adherence in determining these outcomes.

Materials and Methods

Study Design

The ATAHC was a multicenter, prospective cohort study of the natural history and treatment of recent HCV infection. Study recruitment commenced in June 2004 through an Australian network of tertiary hospitals (n = 13) and general practice/primary care clinics (n = 3). Recent infection included participants with either acute or early chronic HCV infection with the following eligibility criteria.

Initial positive anti-HCV antibody within 6 months of enrollment; and either (1) acute clinical hepatitis C infection, defined as symptomatic seroconversion illness or alanine aminotransferase (ALT) level greater than 10 times the upper limit of normal (>400 IU/mL) with exclusion of other causes of acute hepatitis, at most 12 months before the initial positive anti-HCV antibody; or (2) asymptomatic hepatitis C infection with seroconversion, defined by a negative anti-HCV antibody in the 2 years before the initial positive anti-HCV antibody.

Other eligibility criteria included being age 16 years or older, having a negative pregnancy test, and the ability to provide written informed consent. All participants with detectable HCV RNA at screening or baseline were assessed for HCV treatment eligibility. HCV treatment was not offered to people who had positive serology for anti-hepatitis A virus immunoglobulin (Ig)M, hepatitis B surface antigen, or anti-hepatitis B core IgM; concurrent additional causes of liver disease; or other standard laboratory-based exclusion criteria for interferon therapy. Having received investigational drugs within the previous 6 weeks was also an exclusion criterion for treatment. Heavy alcohol intake and active illicit drug use were not exclusion criteria, however, a drug and alcohol assessment was performed for treatment suitability.

People diagnosed with recent HCV infection at one of the participating sites who satisfied these inclusion and exclusion study criteria were invited to participate in the study, regardless of their or their doctors' intentions regarding treatment. Participants were followed up from baseline at 4 weekly intervals to week 12, then at 12 weekly intervals for up to 144 weeks.

All study participants provided written informed consent before study procedures. The study protocol was approved

by St Vincent's Hospital, Sydney Human Research Ethics Committee (primary study committee), as well as through local ethics committees at all study sites, and was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines. The study was registered with clinicaltrials.gov registry (NCT00192569).

HCV Treatment and Virologic Assessment

Participants who began HCV treatment received pegylated interferon (PEG-IFN)-alpha 2a 180 µg weekly for 24 weeks. Because of nonresponse at week 12 in the initial 2 participants with HCV/human immunodeficiency virus (HIV) co-infection, the study protocol was amended to provide PEG-IFN and ribavirin combination therapy for 24 weeks in this group. Ribavirin was prescribed at a dose of 1000–1200 mg for those with genotype 1 infection and 800 mg in those with genotype 2/3. Medical supervision of PEG-IFN injections was not mandatory but was available for use on a case-by-case basis.

The presence of HCV RNA was assessed at all scheduled study visits (including screening, baseline, and weeks 4, 8, 12, and 24 on-treatment), with a qualitative HCV-RNA assay (TMA assay; Versant, Bayer, Australia; lower limit of detection, 10 IU/mL) and if positive a quantitative HCV-RNA assay (Versant HCV RNA 3.0; Bayer, Australia; lower limit of detection, 615 IU/mL). HCV genotype (Versant LiPa2; Bayer, Australia) was assessed for participants with detectable HCV-RNA at screening. A questionnaire was administered at screening and every 12 weeks through follow-up evaluation to obtain information on injection of illicit drugs, social functioning (Opiate Treatment Index Social Functioning Scale),¹⁴ and psychological parameters (Mini-International Neuropsychiatric Interview¹⁵ and the Depression Anxiety Stress Scale¹⁶). Adverse events were collected on all treated participants from the commencement of treatment to week 48.

Study Definitions

The presentation of recent HCV 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 level greater than 400 IU/mL at or before the time of diagnosis. Asymptomatic infection included participants with anti-HCV antibody seroconversion but no acute clinical symptoms or documented peak ALT level greater than 400 IU/mL. The estimated date of infection for acute clinical infection was calculated as 6 weeks before onset of seroconversion illness if present or 6 weeks before the first ALT reading greater than 400 IU/mL. The estimated date of infection for asymptomatic infection was calculated as the midpoint between the last negative anti-HCV anti-

body and the first positive anti-HCV antibody test result. For participants who were anti-HCV antibody negative and HCV-RNA positive at screening, the estimated date of infection was designated to be 6 weeks before screening.

Adherence was defined as the receipt of at least 80% of scheduled PEG-IFN alfa-2a doses and therapy for 80% of the scheduled treatment period. For participants in whom therapy was terminated at 12 weeks because of virologic nonresponse, the scheduled treatment period was defined as 12 weeks. HCV relapse and breakthrough were distinguished from reinfection by the detection of HCV-RNA with a viral sequence that differed from that of the initial infection, as confirmed by viral sequence analysis.¹⁷

Study Outcomes

Evaluation of HCV treatment response was based on intention-to-treat analyses that included all participants who received at least one injection of PEG-IFN therapy. Additional per-protocol analyses included all adherent individuals with follow-up virologic data (\geq week 48). Primary end points for treatment were the proportion of participants with undetectable qualitative HCV-RNA rates at weeks 4 (rapid virologic response), 12, 24 (end-of-treatment response), and 48 (SVR). If HCV RNA had not been assessed at week 48, the result of the next available HCV-RNA assessment was used to calculate SVR. HCV treatment outcomes were assessed separately in participants with and without HIV infection.

Statistical Analyses

Logistic regression analyses were used to identify predictors of HCV treatment response. Potential predictors were determined a priori and included sex, age, weight, education, employment, accommodation, social functioning, methadone or buprenorphine treatment, mental health status (depression and suicidality, based on the Mini-International Neuropsychiatric Interview), ethnicity, injecting drug use characteristics, alcohol consumption, estimated duration of HCV infection, presentation (acute clinical, asymptomatic), peak and baseline ALT level, baseline HCV-RNA levels, and HCV genotype. Social functioning was calculated using a validated scale from the Opiate Treatment Index¹⁴ that addresses employment, residential stability, and interpersonal conflict. The scale also addresses social support, and the role of drug use in the participant's social networks, and a higher number means poorer functioning. This scale has been validated among opiate users in Australia (range, 0–48).¹⁴ Current depression and suicide risk were evaluated using the Mini-International Neuropsychiatric Interview.¹⁵

Additional analyses were performed to evaluate the time to clearance among treated and untreated groups and the impact of treatment on clearance of HCV infec-

tion. Among untreated subjects, spontaneous HCV clearance was defined as 2 consecutive negative qualitative tests for HCV-RNA over an interval of 4 or more weeks. The estimated date of spontaneous clearance was determined by calculating the midpoint between the date of the last HCV-RNA qualitative positive test and the first qualitative HCV-RNA negative test. Among treated participants, the estimated date of initial HCV clearance (in those with subsequent SVR) was determined by calculating the midpoint between the date of the last HCV-RNA qualitative positive test and the first qualitative HCV-RNA negative test. Kaplan-Meier analyses were used to estimate the time to spontaneous HCV clearance and initial HCV clearance (in those with subsequent SVR). The impact of treatment on HCV clearance was evaluated using Cox Proportional Hazards Analyses, while adjusting for factors associated with spontaneous HCV clearance and SVR. These factors included sex, age, history of injecting, estimated duration of HCV infection, presentation (acute clinical, asymptomatic), peak ALT level, baseline HCV-RNA levels, HCV genotype, and HIV infection.

The multivariate model for predictors of treatment response and HCV clearance were determined using a forward stepwise approach, considering factors that were significant at the 0.10 level in univariate analysis. The final models included only factors that remained significant at the 0.05 level. All analyses were performed using the statistical packages SAS 9.1 (SAS Institute, Cary, NC) and STATA (Stata Corporation, College Station, TX).

Results

Over the period June 2004 through February 2008, 200 people with recent HCV infection were screened for potential inclusion in the study (Figure 1). Ultimately, 167 participants were enrolled through tertiary hospitals ($n = 150$) or through general practice or primary care clinics ($n = 17$). Of those who consented to enroll, 4 participants did not return for a subsequent baseline visit and were excluded from further analysis, leaving a total participant population of 163.

Diagnosis of recent HCV infection was on the basis of acute clinical hepatitis in 61% (99 of 163), which included symptomatic seroconversion illness in 41% (67 of 163, including 36 with jaundice) and ALT level greater than 400 IU/mL in 20% (32 of 163). Diagnosis of recent HCV infection was on the basis of anti-HCV antibody seroconversion in the absence of an acute clinical presentation in 39% (64 of 163). Overall, anti-HCV antibody seroconversion was documented in 86% ($n = 140$). The enrollment characteristics of treated ($n = 111$) and untreated ($n = 52$) participants, with the latter group stratified by HCV-RNA status (35 positive, 17 negative) at screening, are shown in Table 1.

For the majority of participants, injecting drug use was recorded as the most likely mode of HCV acquisition

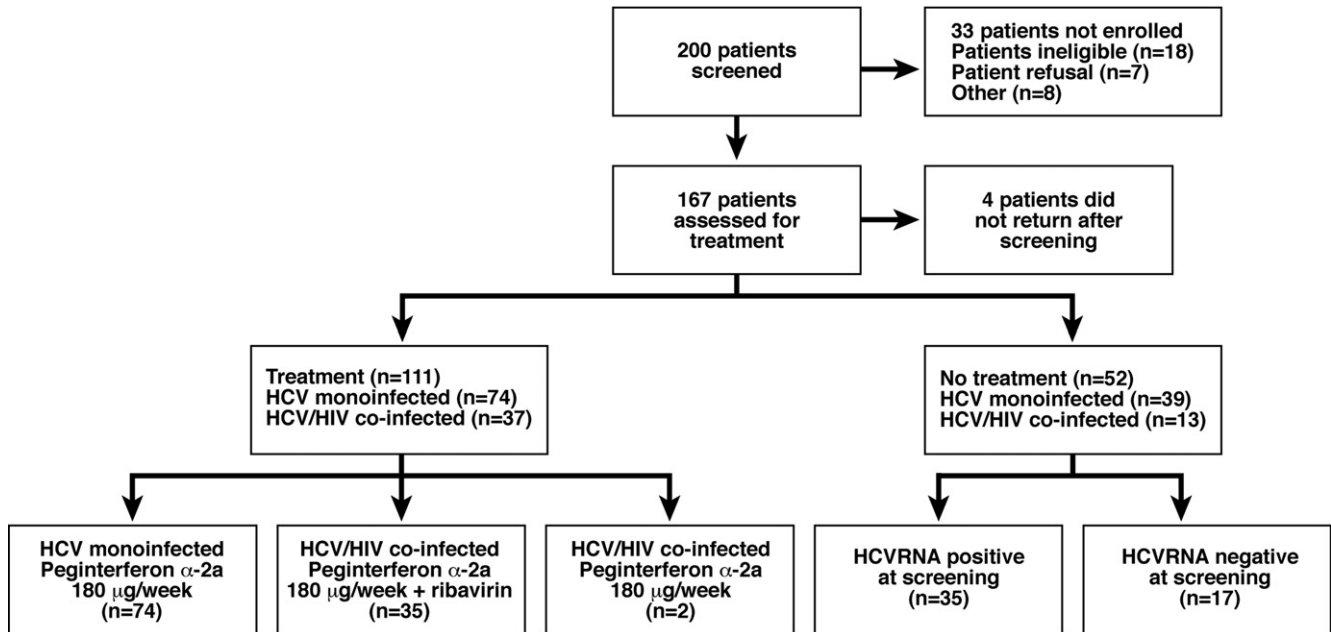


Figure 1. Overview of study population. At least 1 dose of PEG-IFN was administered to 111 participants. Two HCV/HIV coinfecting participants received PEG-IFN monotherapy (both nonresponders) before a protocol amendment in which HCV/HIV participants then received PEG-IFN and ribavirin combination therapy.

($n = 119$; 73%). Other modes of reported HCV acquisition included male-to-male sexual contact ($n = 24$; 15%), heterosexual contact ($n = 5$; 3%), body piercing ($n = 1$; 1%), medical procedure ($n = 1$; 1%), occupational needle stick ($n = 1$; 1%), tattoos ($n = 1$; 1%), and other forms of percutaneous exposure ($n = 1$; 1%). In 6% of participants ($n = 10$), no risk factor could be identified.

The study population had a low proportion of participants who were in full-time or part-time employment (39%) or who had completed tertiary education (22%). Social functioning was low, with a median score of 13 (interquartile range, 8–18; possible range, 0–48). Overall, 125 (77%) participants had ever injected illicit drugs and 39 (24%) reported having ever received methadone or buprenorphine treatment. Among participants who reported injection drug use ever, recent injecting was common, with 42% (53 of 125) injecting in the previous month and an additional 37% (46 of 125) in the period 1–6 months before screening. Among those having reported injection drug use in the past 6 months, the drugs most often injected were methamphetamine (48%) and heroin (39%).

HCV Treatment Uptake

Because the 17 participants with undetectable HCV-RNA at screening were ineligible for treatment, the uptake of HCV treatment was 76% (111 of 146) among those who were eligible on the basis of positive HCV-RNA. Uptake was 76% (74 of 97) in participants without HIV and 76% (37 of 49) among those with HIV infection.

Among participants with detectable HCV-RNA positive at screening or baseline and therefore potentially

eligible for treatment ($n = 146$), untreated participants had slightly poorer social functioning (ie, higher scores, 15 vs 11), lower tertiary education (9% vs 29%), and were less frequently in full-time or part-time employment (26% vs 47%) when compared with treated participants. A greater proportion of untreated participants also had current major depression (26% vs 7%) and reported injection drug use in the past month (50% vs 37%). Untreated participants had a shorter estimated duration of infection at screening (19 vs 25 wk), lower peak ALT level (393 vs 479 IU/L) or screening ALT level (104 vs 185 IU/L), and lower median HCV-RNA level at screening (3.3 vs 5.0 \log_{10} HCV RNA).

HCV Treatment Outcomes

Because of the different treatment regimens used, treatment outcomes were assessed separately for HCV mono-infected participants receiving PEG-IFN monotherapy ($n = 74$) and the HCV/HIV co-infected participants receiving PEG-IFN and ribavirin combination therapy ($n = 35$). The initial 2 participants with HCV/HIV co-infection treated with PEG-IFN monotherapy were excluded from outcome analyses (both were nonresponders at week 12).

Among treated participants, those with HCV/HIV co-infection were older, more likely to be male (100% vs 62%), more likely to have acquired HCV through sexual contact (63% vs 5%), and had better social functioning (ie, lower scores, 8 vs 14; Table 2).

As shown in Figure 2, 77% of HCV mono-infected participants (57 of 74) received at least 80% of PEG-IFN alfa-2a doses and therapy for 80% of the scheduled treat-

Table 1. Enrollment Characteristics of Participants (n = 163)^{c,d}

	Total study population	Treated	Untreated	
			HCV-RNA positive at screening	HCV-RNA negative at screening
Total participants, n	163	111	35	17
Male, n (%)	116 (71)	83 (75)	23 (66)	10 (59)
Age, y, mean ± SD	34.3 ± 9.9	34.5 ± 10.4	34.9 ± 8.9	31.9 ± 8.5
Weight, kg, mean ± SD	73.2 ± 14.1	72.6 ± 11.7	70.6 ± 12.8	82.7 ± 24.5
BMI, kg/m ² , mean ± SD	24.0 ± 4.3	23.7 ± 3.3	23.3 ± 4.1	27.7 ± 8.1
Caucasian ethnicity, n (%)	149 (91)	99 (89)	34 (97)	16 (94)
Tertiary education or greater, n (%)	35 (22)	32 (29)	3 (9)	0 (0)
Full-time or part-time employment, n (%)	63 (39)	52 (47)	9 (26)	2 (12)
Methadone or buprenorphine treatment				
Ever (not current)	17 (10%)	12 (11%)	4 (11%)	1 (6%)
Current	22 (14%)	12 (11%)	6 (17%)	4 (24%)
Social functioning score, median (IQR)	13 (8–18)	11 (6–17)	15 (10–19)	18 (13–20)
Current major depression, n (%)	19 (12)	8 (7)	9 (26)	2 (12)
Injection drug use ever, n (%)	125 (77)	84 (76)	30 (86)	11 (65)
Last time injected, n (%) ^a				
Within the past month	53 (42%)	31 (37%)	15 (50%)	7 (64%)
1–6 months ago	46 (37%)	35 (42%)	9 (30%)	2 (18%)
>6 months ago	25 (20%)	18 (21%)	5 (17%)	2 (18%)
Estimated duration of infection at screening (wk), median (range)	25 (6–74)	25 (6–74)	19 (7–62)	26 (15–66)
Presentation of recent HCV, n (%)				
Acute clinical (symptomatic)	67 (41)	46 (41)	12 (34)	9 (53)
Acute clinical (ALT level, >400 IU/mL)	32 (20)	24 (22)	6 (17)	2 (12)
Asymptomatic seroconversion	64 (39)	41 (37)	17 (49)	6 (35)
Symptoms and signs in acute clinical (symptomatic) cases, n (%) ^b				
Jaundice	36 (54)	24 (52)	5 (42)	7 (78)
Nausea	45 (67)	29 (63)	8 (67)	8 (89)
Abdominal pain	42 (63)	30 (65)	8 (67)	4 (44)
Hepatomegaly	16 (24)	11 (24)	4 (33)	1 (11)
HIV infection, n (%)	50 (31)	37 (33)	12 (34)	1 (6)
ALT level, IU/L				
Peak ALT level before enrollment, median (IQR)	468 (175–1206)	479 (207–1179)	393 (114–1174)	382 (44–2206)
ALT level at screening, median (IQR)	118 (52–312)	185 (70–403)	104 (39–155)	27 (20–49)
HCV-RNA level, IU/L				
Log ₁₀ HCV-RNA level at screening, median	4.5	5.0	3.3	<1.0
<400,000 IU/mL, n (%)	119 (73)	73 (66)	29 (83)	17 (100)
HCV genotype, n (%)				
Genotype 1	76 (47)	63 (57)	13 (37)	0 (0)
Genotype 2	6 (4)	4 (4)	2 (6)	0 (0)
Genotype 3	56 (34)	40 (36)	16 (46)	0 (0)
Genotype 4	1 (1)	0 (0)	1 (3)	0 (0)
Genotype missing	24 (15)	4 (4)	3 (9)	17 (100)

IQR, interquartile range.

^aAmong those having reported injecting ever.^bDenominator is in total number of participants reporting documented illness.^cExcludes 4 participants with no follow-up after screening, ^dat time of screening.

ment period. Adherence to therapy was not achieved in 23% (17 of 74) (Supplementary Figure 1). These subjects discontinued treatment prematurely, either because of side effects (n = 4), death (n = 1), lost to follow-up evaluation or unwillingness to continue in the study (n = 8), late discontinuation at 15 weeks with virologic non-response (n = 1), and testing HCV-RNA positive at screening but negative at treatment commencement (2 participants after week 2 injection, and 1 participant after week 6 injection).

In HCV mono-infected participants, 46% (34 of 74) and 66% (49 of 74) had undetectable HCV-RNA (<10 IU/mL) at weeks 4 and 12, respectively, and an end-of-treatment response was achieved in 69% (51 of 74). Among adherent participants with follow-up virologic data (per-protocol analysis group) (n = 50), 41 (82%) achieved an end-of-treatment response (Figure 3). SVR was 55% by intention-to-treat and 72% by per-protocol analysis.

In univariate analysis, SVR occurred more frequently in participants with better social function (ie, lower scores),

Table 2. Baseline Characteristics Among Treated HCV and HCV/HIV-Infected Participants With Recently Acquired HCV Infection (n = 109)

	HCV infected	HCV/HIV infected
Total participants, n	74	35
Male, n (%)	46 (62)	35 (100)
Age, y, mean \pm SD	31.0 \pm 9.0	42.0 \pm 9.5
Age category, n (%)		
\leq 25	18 (24%)	1 (3%)
26–30	21 (28%)	4 (11%)
31–40	24 (32%)	9 (26%)
>40	11 (15%)	21 (60%)
Weight, kg, mean \pm SD	69.5 \pm 11.8	78.1 \pm 9.2
BMI, kg/m ² , mean \pm SD	23.0 \pm 3.6	24.7 \pm 2.3
Caucasian ethnicity, n (%)	63 (85)	34 (97)
Tertiary education or greater, n (%)	13 (18)	17 (49)
Full-time or part-time employment, n (%)	26 (35)	24 (69)
Methadone or buprenorphine treatment, n (%)		
Ever (not current)	12 (16%)	0 (0%)
Current	12 (16%)	0 (0%)
Social functioning score, median (IQR)	14 (9–19)	8 (4–13)
Current major depression, n (%)	7 (10)	1 (3)
Mode of infection, n (%)		
Injecting drug use	62 (84)	13 (37)
Sexual exposure with person(s) of same sex	1 (1)	21 (60)
Sexual exposure with person(s) of opposite sex	3 (4)	0 (0)
Other	8 (11)	1 (3)
Injection drug use ever, n (%)	63 (85)	19 (54)
Age at first injection drug use, mean \pm SD ^a	23.0 \pm 8.5	33.8 \pm 10.3
Last time injected, n (%) ^{a,b}		
Within the past month	27 (43)	4 (21)
1–6 months ago	25 (40)	9 (47)
>6 months ago	11 (18)	6 (32)
Drug(s) injected most frequently, (%) ^{b,c}	Opiates (50)	Methamphetamine (87)
Number of days drinking in past month, mean \pm SD ^b	5.6 \pm 6.7	7.4 \pm 8.9
Estimated duration of infection, wk, median (range)		
Screening	28 (7–74)	17 (6–64)
Baseline	34 (18–84)	30 (10–93)
Presentation of recent HCV, n (%) ^b		
Acute clinical (symptomatic)	30 (41)	15 (43)
Acute clinical (ALT level, >400 IU/mL)	13 (18)	11 (31)
Asymptomatic seroconversion	31 (42)	9 (26)
Symptoms in acute clinical (symptomatic) cases, n (%) ^{b,d}		
Jaundice	18 (60)	6 (40)
Nausea	20 (67)	9 (60)
Abdominal pain	19 (63)	11 (73)
Hepatomegaly	8 (27)	3 (20)
ALT level, IU/L		
Peak before screening, median (IQR)	427 (182–1161)	557 (286–1151)
At screening, median (IQR)	132 (64–312)	254 (131–630)
At baseline, median (IQR)	120 (52–215)	130 (99–422)
HCV-RNA level, IU/L		
Log ₁₀ HCV-RNA level at baseline, median	5.0	5.8
<400,000 IU/mL, n (%)	52 (70)	16 (46)
HCV genotype, n (%)		
Genotype 1	41 (54)	19 (56)
Genotype 2	1 (1)	3 (8)
Genotype 3	29 (39)	12 (34)
Missing	3 (4)	1 (3)

NOTE. Two HCV/HIV co-infected participants receiving PEG-IFN monotherapy were excluded from this analysis.

IQR, interquartile range.

^aAmong those having reported injecting ever.^bAt time of screening.^cAmong those having injected in the past 6 months.^dDenominator is in total number of participants reporting documented illness.

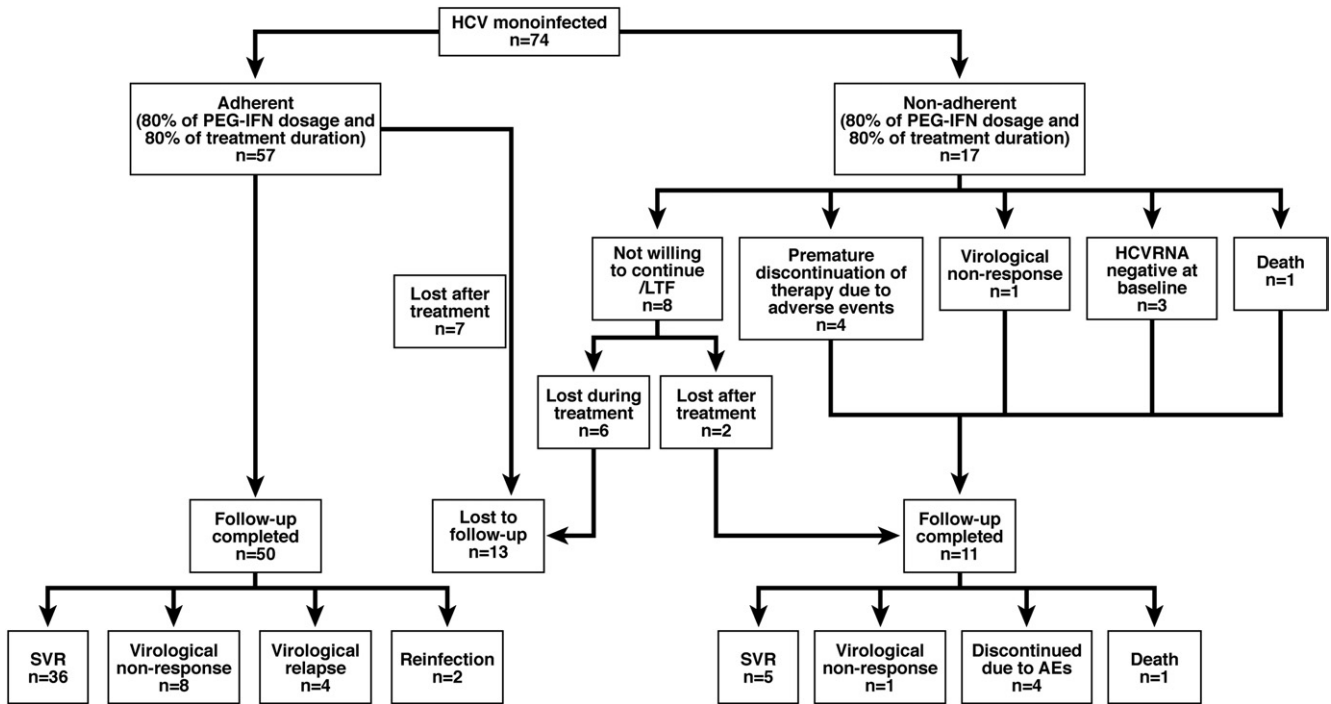


Figure 2. Overview of HCV mono-infected participant population.

those not currently receiving methadone or buprenorphine treatment, and those not having used injection drugs ever (Table 3). Although participants reporting ever having injected drugs had a lower frequency of SVR than those who never injected (48% vs 91%; $P = .030$), SVR was not associated with either the duration of abstinence from injection drug use or the frequency of injection drug use at baseline among those who injected (Table 3).

There was no association between baseline HCV-RNA level ($P = .93$) or HCV genotype ($P = .65$) and SVR. However, among the per-protocol group, a trend toward lower SVR was seen in those with genotype 1 and high baseline viral load (HCV-RNA level, $\geq 400,000$; 54%) compared with those with genotype 1 with low baseline viral load (HCV-RNA level, $< 400,000$) and genotypes 2/3 with low (HCV-RNA level, $< 400,000$) and high (HCV-RNA

level, $\geq 400,000$) baseline viral loads (75%, 80%, and 75%, respectively; $P = .61$) (Supplementary Figure 2).

In multivariate analysis, the only factors associated with SVR were social functioning (odds ratio, 0.21; 95% confidence interval, 0.07–0.64; $P = .009$) and drug dependency treatment (odds ratio, 0.12; 95% confidence interval, 0.02–0.54; $P = .004$). Participants with higher social functioning scores and no history of drug dependency treatment had a higher SVR. In a further analysis, including only participants who had ever injected drugs ($n = 63$), the same 2 factors were associated with SVR (data not shown).

Further analyses assessed the role of treatment adherence and injection drug use during treatment as predictors of SVR in HCV mono-infected participants. The SVR rates were higher among adherent participants (63% vs

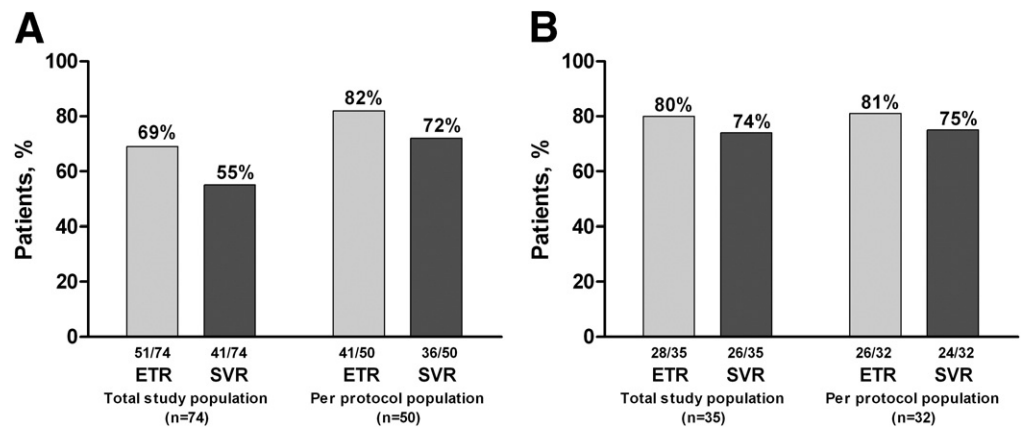


Figure 3. Response rates in (A) HCV mono-infected participants and (B) HCV/HIV co-infected participants in the total study population (intent-to-treat) and per-protocol population.

Table 3. Factors Associated With SVR Among HCV Mono-Infected Participants Receiving Treatment for Recently Acquired HCV Infection (n = 74)

	SVR	No SVR	OR	95% CI		P value	P value overall
Sex							
Male	24	23	1.00	—	—	—	—
Female	17	10	1.63	0.62	4.29	.323	—
Age category, y							
≤25	11	13	1.00	—	—	—	—
26–30	15	12	1.48	0.49	4.46	.489	.107
31–40	9	7	1.52	0.43	5.43	.519	—
>40	6	1	7.09	0.74	68.24	.090	—
Weight, kg							
≤75	26	18	1.00	—	—	—	—
>75	13	8	1.125	0.39	3.27	.829	—
Missing	2	7	—	—	—	—	—
Education							
Primary/secondary	26	21	1.00	—	—	—	—
Other (eg, TAFE, tertiary)	15	12	1.01	0.39	2.62	.984	—
Employment							
Full-time/part-time	18	8	1.00	—	—	—	—
Other	23	25	0.41	0.15	1.12	.082	—
Accommodation							
Rental	25	19	1.00	—	—	—	—
Privately owned	13	5	1.98	0.60	6.50	.263	.052
Unstable	3	9	0.25	0.06	1.07	.061	—
Social functioning score							
≤14	24	10	1.00	—	—	—	—
>14	12	19	0.26	0.09	0.74	.011	.011
Missing	5	4	0.52	0.12	2.35	.396	—
Methadone or buprenorphine treatment							
Never	33	17	1.00	—	—	—	—
Ever (not current)	5	7	0.37	0.10	1.33	.128	.009
Current	3	9	0.17	0.04	0.72	.016	—
Current depression at screening							
No	36	29	1.00	—	—	—	—
Yes	5	4	1.01	0.25	4.09	.992	—
Suicidality							
None/low	36	31	1.00	—	—	—	—
Moderate/high	5	2	2.15	0.39	11.89	.379	—
Injection drug use ever							
No	10	1	1.00	—	—	—	—
Yes	31	32	0.10	0.01	0.80	.030	—
Last time injected							
Within the past month	12	15	1.00	—	—	—	—
1–6 months ago	13	12	1.35	0.45	4.03	.586	.021
>6 months ago	6	5	1.50	0.37	6.14	.573	—
Never injected	10	1	12.50	1.40	111.83	.024	—
Injection frequency							
>Daily	8	12	1.00	—	—	—	—
<Daily, >weekly	6	9	1.00	0.25	3.92	1.000	.010
<Weekly	11	6	2.75	0.72	10.48	.138	—
Not injected in past 6 months	4	4	1.50	0.29	7.81	.630	—
Never injected	10	1	15.00	1.59	141.16	.018	—
Missing	2	1	—	—	—	—	—
Drug injected most often in past 6 months							
Heroin/methadone/other opiates	11	13	1.00	—	—	—	—
Methamphetamine	11	9	1.44	0.44	4.76	.545	.495
Other	1	5	0.24	0.02	2.34	.217	—
Not injected in past 6 months	4	4	1.18	0.24	5.86	.838	—
Never injected	10	1	11.82	1.30	107.39	.028	—
Missing	4	1	—	—	—	—	—
Mean number of alcoholic drinks per day							
<4	22	22	1.00	—	—	—	—
≥4	15	11	1.36	0.51	3.62	.534	—
Missing	4	0	—	—	—	—	—

Table 3. Continued

	SVR	No SVR	OR	95% CI	P value	P value overall
Estimated duration of infection at baseline, wk						
≤26	6	11	1.00	—	—	—
27–52	27	10	4.95	1.45	16.96	.011
>52	8	12	1.22	0.32	4.66	.769
Presentation of recent HCV						
Acute clinical	23	20	1.00	—	—	—
Asymptomatic seroconversion	18	13	1.20	0.47	3.06	.814
Peak ALT level before screening, IU/L						
≤400	19	14	1.00	—	—	—
>400	21	18	0.86	0.34	2.19	.751
Missing	1	1	—	—	—	—
ALT level at screening, IU/L						
≤100	17	14	1.00	—	—	—
>100	24	19	1.04	0.41	2.63	.934
HCV-RNA QN at baseline, IU/mL						
<400,000	21	22	1.00	—	—	—
≥400,000	10	10	1.05	0.36	3.03	.932
Genotype/subtype						
Genotype 1	21	20	1.00	—	—	—
Genotypes 2 and 3	17	13	1.25	0.48	3.21	.650
Missing genotype	3	0	—	—	—	—

OR, odds ratio; CI, confidence interval.

29%; $P = .025$). Among those reporting ever having injected drugs ($n = 63$), the SVR rate was similar for those with and without injecting during treatment (53% vs 59%; $P = .76$) and was not related to frequency of injecting.

Among HIV/HCV co-infected participants treated with PEG-IFN and ribavirin ($n = 35$), 91% (32 of 35) were at least 80% adherent. Two of the other 3 stopped treatment prematurely as a result of side effects ($n = 2$), and the third stopped treatment after the week 2 injection because the baseline HCV-RNA was negative, despite the screening assessment having been positive. Undetectable HCV-RNA (<10 IU/mL) was achieved in 34% and 91% at weeks 4 and 12, respectively. At the end of treatment, HCV-RNA was undetectable in 80% (Figure 3). SVR was 74% by intention-to-treat and 75% by per-protocol analysis. There was no association between baseline HCV-RNA level or HCV genotype and SVR.

We also compared the impact of estimated duration of infection at the commencement of treatment on subsequent SVR in HCV mono-infected and HIV/HCV co-infected groups. Among HCV mono-infected participants, SVR was highest in those with an estimated duration of infection of 27–52 weeks (73%; 27 of 37), but was reduced both in those with a duration greater than 52 weeks (40%; 8 of 20) and in those with a duration of 26 weeks or less (35%; 6 of 17) (Supplementary Figure 3). The proportion with 80% or higher adherence was 65%, 86%, and 70% in those with an estimated duration of infection of 26 weeks or less, 27–52 weeks, and more than 52 weeks, respectively. Similarly, the proportion receiving all PEG-IFN injections (24 in total) was 35%, 70%, and 45% in those same groups, respectively. In contrast,

among HIV/HCV co-infected participants, SVR was similar within estimated duration of infection groups of 26 weeks or less (67%; 10 of 15), 27–52 weeks (73%; 11 of 15), and more than 52 weeks (100%; 5 of 5) (Supplementary Figure 1).

Among the combined per-protocol group ($n = 82$; HCV = 50, HCV/HIV = 32), we observed 20 participants with virologic failure, including 11 with nonresponse, 1 with viral breakthrough, and 8 with viral relapse (Supplementary Table 1).

Safety

Adverse events are shown in Table 4. Three deaths occurred among treated participants in this study. The one death during IFN-based treatment occurred at week 4 of therapy, in a man whose cause of death was reported as methamphetamine toxicity with a contribution of arrhythmogenic right ventricular dysplasia. At baseline, he was assessed as having major depressive symptoms but no suicidality. He had no reported history of injection drug use and the mode of HCV acquisition was recorded as unknown. The other 2 deaths occurred at 3 and 4 months after treatment completion, respectively, with the cause of death given as carbon monoxide toxicity with combined drug effect (amphetamines and 3 prescribed medications, including methadone) in one and electrocution in the other. The post-mortem toxicology report in this third case also revealed ongoing polydrug use (ethanol, methamphetamine, methylenedioxymethamphetamine, and cannabinoids.) Both cases showed no major depressive symptoms or suicide risk at baseline.

Table 4. Adverse Events Among Treated HCV and HCV/HIV-Infected Participants With Recently Acquired HCV Infection (n = 109)

	HCV-infected PEG-IFN alfa-2a (n = 74)		HCV/HIV-infected PEG-IFN alfa-2a + ribavirin (n = 35)	
	N	%	N	%
Adverse event grade ^a				
Grade 1	70	94.6	35	100.0
Grade 2	54	73.0	31	88.6
Grade 3	28	37.8	25	71.4
Grade 4	3	4.1	1	2.9
Most frequent adverse event (>10% of patients) ^b				
Fatigue	59	79.7	32	91.4
Headache	57	77.0	27	77.1
Irritability	51	68.9	30	85.7
Myalgia	53	71.6	25	71.4
Insomnia	48	64.9	29	82.9
Anxiety	44	59.5	27	77.1
Disturbance in attention	41	55.4	27	77.1
Arthralgia	41	55.4	23	65.7
Injection site reaction	45	60.8	19	54.3
Nausea	39	52.7	24	68.6
Dry skin	37	50.0	25	71.4
Abdominal pain	37	50.0	22	62.9
Cough	34	45.9	25	71.4
Anorexia	37	50.0	21	60.0
Pruritus	37	50.0	20	57.1
Pyrexia	33	44.6	22	62.9
Diarrhea	35	47.3	19	54.3
Dizziness	32	43.2	20	57.1
Dyspnea	28	37.8	24	68.6
Weight decreased	28	37.8	24	68.6
Pain	29	39.2	22	62.9
Chills	27	36.5	16	45.7
Alopecia	31	41.9	10	28.6
Asthenia	22	29.7	19	54.3
Dermatitis	22	29.7	11	31.4
Depression	17	23.0	4	11.4

^aParticipants can be counted in 1 or more grades.

^bAdverse events reported according to MedDRA preferred terms.

Impact of Treatment on HCV Clearance

Among the 146 participants with detectable HCV-RNA at screening or baseline, 35 were not treated for HCV infection and 12 (34%) of these participants showed spontaneous HCV-RNA clearance. Because the untreated participants differed from the treated participants, particularly with respect to factors associated with spontaneous HCV-RNA clearance (lower screening HCV-RNA level, shorter estimated duration of infection), adjusted analyses were undertaken to examine the impact of treatment on clearance. In the treated group, only participants who subsequently achieved an SVR were considered to have HCV-RNA clearance. The Kaplan-Meier analysis of the impact of treatment on HCV-RNA clearance among untreated

(n = 34) and treated (n = 106) participants with detectable HCV-RNA at screening is shown in Figure 4. In Cox proportional hazards analyses, treatment was associated independently with HCV-RNA clearance (hazard ratio, 4.20; 95% confidence interval, 1.96–9.00; $P < .0001$) after adjusting for sex, age, history of injecting, estimated duration of HCV infection, clinical presentation, peak ALT level, baseline HCV-RNA level, HCV genotype, and HIV infection.

Discussion

This study found that treatment for recent HCV infection is effective in people whose infection was acquired through injection drug use, even in those with HIV co-infection. Further, it appears that treatment with PEG-IFN alone remains effective when commenced at up to 12 months post-HCV infection. The strengths of ATACH were the large study population and recruitment of participants with and without HIV infection through the same recruitment network. The ATACH differed from previous studies in evaluating HCV treatment outcomes across a broad definition of recent HCV infection, which encompassed acute and early chronic disease.

An overall intention-to-treat SVR rate of 55%–74% with PEG-IFN-based therapy for 24 weeks is very encouraging, given the assumptions that often are made about the feasibility of treatment in this population, and the relatively long estimated duration of HCV infection at treatment initiation. The SVR rate of 74% for HIV/HCV co-infected participants who received PEG-IFN and ribavirin combination therapy was particularly impressive. There was a relatively lower SVR rate of 55% among HCV mono-infected participants, largely related to social factors (poorer social functioning leading to suboptimal treatment adherence). In addition, PEG-IFN monotherapy may have been suboptimal for some HCV mono-infected participants including those with genotype 1 and high HCV-RNA level or duration of HCV infection greater than 12 months.

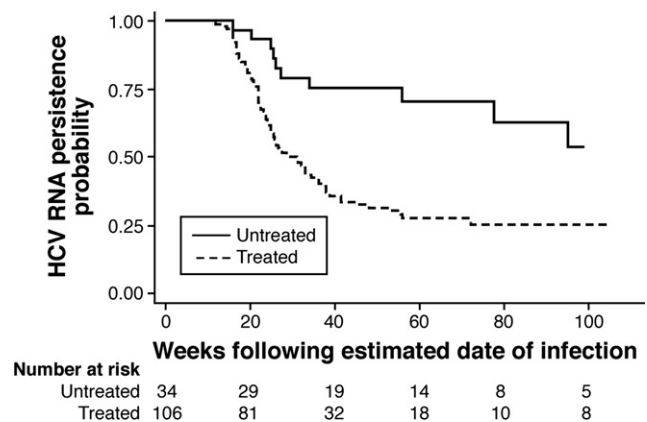


Figure 4. Time to HCV-RNA clearance among treated and untreated participants in the ATACH study.

Previous PEG-IFN-based studies (12–24 wk) in acute HCV infection have shown somewhat higher SVR rates of 57%–88%.^{4,6–8,10,18,19} The ATAHC results differed from most of these investigations in the predominantly injection drug use–related acquisition of the study population and the relatively late enrollment of the participants in the course of their infection. In other studies, mainly made up of cases of acute symptomatic infection, enrollment was within a median of 12 weeks, and many cases may have cleared HCV spontaneously, even without being treated. In contrast, the median estimated duration of HCV infection at treatment commencement was around 30 weeks in the ATAHC, after the time when spontaneous HCV clearance is generally occurs.²⁰

Adherence clearly plays an important role. In the ATAHC, treatment response among HCV mono-infected participants varied considerably by adherence grouping, and the overall SVR of 55% was lower than the rate from a recently reported Italian study (n = 46; 26 IDU; SVR = 72%),¹⁸ in which all injections were medically supervised and adherence was close to 100%. HCV treatment adherence is predictive of chronic HCV treatment outcomes, both in the non-IDU and IDU population.^{21,22} In the ATAHC poor adherence largely was related to loss to follow-up evaluation rather than either missed doses or dose reductions; therefore, strategies to improve engagement for socially marginalized individuals commenced on HCV treatment are required.

Poorer social functioning and current drug dependency treatment were the only factors independently associated with lower SVR among HCV mono-infected participants in this study. The social functioning scale used in this study addresses major aspects of social integration such as employment, residential stability, interpersonal conflict, social support, and the involvement of the participant in drug-using networks. The results from this aspect of the study are and suggest this social functioning scale may be a useful tool for future studies of illicit drug users to assess suitability for treatment initiation. Although current opioid maintenance treatment was associated with reduced response rates to therapy, the numbers of participants in this group was small and further investigations of the involvement of the impact of this variable on SVR are required.

The ATAHC suggests that a delay in commencement of treatment until such time as spontaneous HCV clearance is unlikely, does not seem to influence treatment effectiveness adversely in this population. Although delayed commencement (20 vs 8–12 weeks after acute HCV presentation) produced a lower SVR (76% vs 92%–95%) in a prior randomized controlled trial, this was conducted in a largely non-IDU population.⁴ Estimated duration of HCV infection at commencement of treatment was not a predictor of treatment response in the ATAHC in multivariate analysis, however, within the HCV mono-infected population, lower SVR rates were seen among partici-

pants with short (≤ 26 wk) and longer (> 52 wk) durations of infection. Poorer responses in the most prolonged duration group may reflect suboptimal therapy with PEG-IFN monotherapy, particularly given the favorable responses in the HIV/HCV co-infected group. On the other hand, poorer responses in the short duration of infection group may be driven by poorer adherence among individuals who acquired HCV infection more recently.

For people with both HIV infection and recently acquired HCV, the SVR rate after PEG-IFN and ribavirin combination therapy (74%) confirms the favorable preliminary data reported for the initial 22 co-infected participants.²³ The SVR was higher than other acute HCV studies among co-infected populations with study populations greater than 20 (59%–61%),^{24,25} and considerably higher than that reported for chronic HCV studies of PEG-IFN and ribavirin therapy in this population (26%–40%).^{26,27} It also suggests that 24 weeks is adequate therapy for both acute and early chronic HCV infection, irrespective of HCV genotype and baseline HCV-RNA level.

Despite the somewhat poorer treatment outcomes in HCV mono-infected participants compared with other acute HCV treatment studies, the ATAHC shows that in a setting of predominant injection drug use HCV acquisition participants with acute and early chronic HCV infection can be treated effectively. Although the ATAHC did not contain a randomized control arm without treatment, the comparison of HCV-RNA clearance among treated and untreated groups with adjustment for baseline factors associated with clearance provided further evidence of the beneficial impact of early therapeutic intervention. Improved strategies are required to select individuals for treatment initiation and to enhance treatment adherence and follow-up evaluation, including the potential of supervised therapy, case management, and peer-based support. Ways to improve and support IDUs social functioning before commencing treatment should be explored. Drug rehabilitation and harm reduction strategies that reduce rates of injecting drug use and HCV exposure during injecting also need to be the focus of an overall strategy to enhance HCV treatment outcomes among IDUs, both in the acute and chronic HCV infection setting. Finally, a randomized controlled trial of PEG-IFN vs PEG-IFN and ribavirin therapy in this study population would appear justified based on the data reported here.

ATAHC Study Group

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of

Gastroenterology at www.gastrojournal.org, and at doi: [10.1053/j.gastro.2009.09.019](https://doi.org/10.1053/j.gastro.2009.09.019).

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Conflicts of interest

These authors disclose the following: Gregory Dore, G.M., and J. Kaldor have received research support from Roche Pharmaceuticals; Gregory Dore is on the speaker's bureau for Roche Pharmaceuticals; Gregory Dore and G.M. are members of the advisory board for Roche Pharmaceuticals; Gregory Dore, P. Marks, and B. Yeung have received travel grants from Roche Pharmaceuticals; Gregory Dore is a consultant/advisor for Schering Plough, Tibotec, and Abbott; and G.M. is a consultant/advisor for Schering Plough, Novartis, and Astellar. The remaining authors disclose no conflicts.

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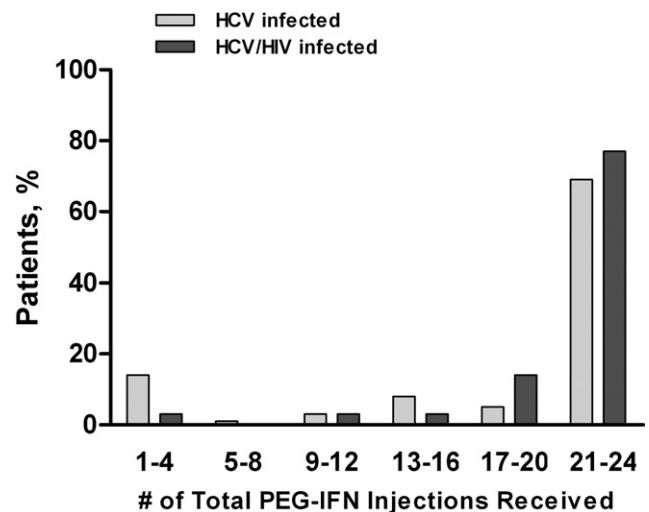
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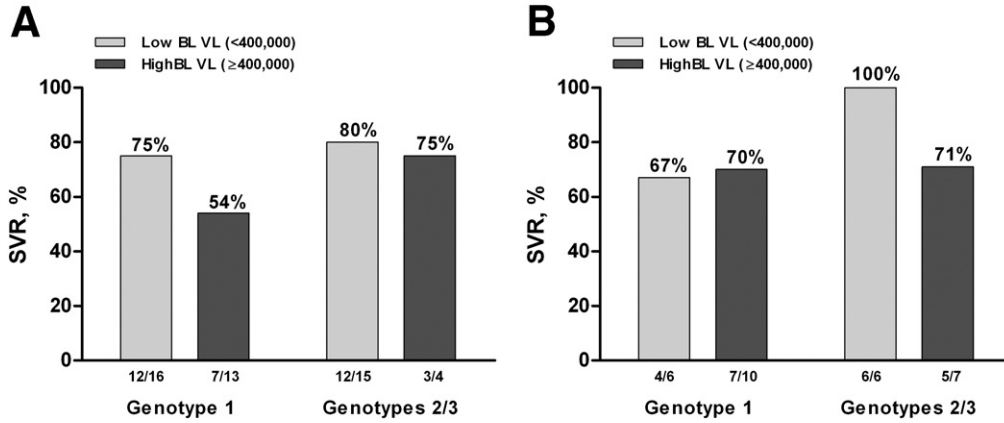
Supplementary Table 1. Characteristics of Participants With Nonresponse (n = 11), Viral Breakthrough (n = 1), and Viral Relapse (n = 8) Among Adherent Participants (n = 82)

ID	Age (Sex)	HIV	Genotype	Baseline HCV-RNA level, IU/mL	Baseline ALT level, IU/mL	Mode of acquisition	Estimated duration of infection at baseline, (w/k)	Last time of injection drug use, mo	Drug most often injected in past 6 months	Injecting drug use during treatment	RVR	cEVR	Outcome
109	35 (M)	No	1a	4,615,385	122	IDU	22	1-6	Heroin	Yes	No	No	Nonresponder, wk 12
110	18 (M)	No	2	10,000	215	IDU	18	1-6	Methamphetamine	Yes	No	No	Nonresponder, wk 12
127	23 (M)	Yes	1a	4,410,661	598	Other	27	Never	NA	No	No	No	Nonresponder, wk 12
606	18 (F)	No	3a	596,154	338	IDU	27	<1	Methamphetamine	Yes	No	No	Nonresponder, wk 12
645	28 (F)	No	1a	286,477	40	IDU	59	<1	Heroin	No	No	No	Nonresponder, wk 12
807	18 (M)	No	1a	2,500,000	217	IDU	27	1-6	Methamphetamine	Unknown	No	No	Nonresponder, wk 12
1402	19 (M)	No	1a	495,358	205	IDU	23	1-6	Methadone	No	No	No	Nonresponder, wk 12
1806	22 (M)	No	1	973,871	197	IDU	47	<1	Heroin	Unknown	No	No	Nonresponder, wk 12
2304	31 (M)	No	1a	16,346	78	IDU	30	1-6	Methadone	Yes	No	No	Nonresponder, wk 12
2405	43 (M)	Yes	1a	1,908,378	309	IDU	32	<1	Methamphetamine	Yes	NA	No	Nonresponder, wk 12
2602	44 (M)	Yes	1a	1,789,623	127	IDU	25	1-6	Methamphetamine	No	NA	No	Nonresponder, wk 12
116	36 (M)	Yes	1a	1782	123	Other	19	6-12	NA	No	No	Yes	Viral breakthrough, wk 24
811	50 (M)	Yes	3a	664,815	245	Other	35	Never	NA	No	No	Yes	Relapse, wk 36
1006	40 (F)	No	3a	50,278	308	IDU	44	<1	Heroin	Yes	No	No	Relapse, wk 36
653	60 (M)	No	1	284,868	135	IDU	25	6-12	NA	No	No	Yes	Relapse, wk 36
666	36 (M)	Yes	1a	16,360	118	IDU	36	6-12	NA	No	Yes	Yes	Relapse, wk 36
630	41 (M)	Yes	1a	.	.	Other	42	1-6	Methamphetamine	Yes	No	Yes	Relapse, wk 48
131	26 (M)	No	1	3,012,625	186	IDU	18	<1	Methamphetamine	No	NA	Yes	Relapse, wk 36
2406	54 (M)	Yes	2c	2,116,535	125	Other	27	Never	NA	No	No	Yes	Relapse, wk 36
2605	41 (M)	No	1a	3,106,444	69	IDU	68	<1	Methamphetamine	Yes	No	Yes	Relapse, wk 36

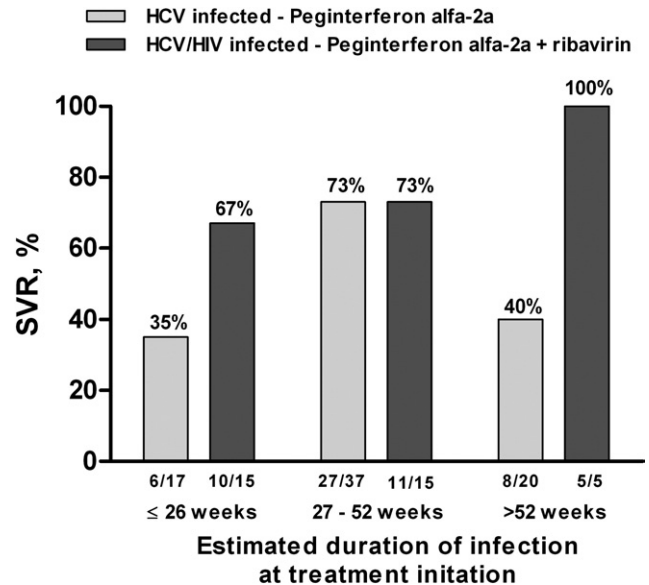
RVR, rapid virologic response.



Supplementary Figure 1. Adherence to PEG-IFN by the number of total PEG-IFN alfa-2a injections received in HCV (n = 74) and HCV/HIV infected (n = 35) participants.



Supplementary Figure 2. Impact of baseline HCV-RNA level on SVR rates stratified by HCV RNA (<400,000 vs ≥400,000 IU/mL) in (A) HCV mono-infected participants adherent to therapy (n = 48; with genotype available) and (B) HCV/HIV co-infected participants adherent to therapy (n = 29; with genotype available). BL, baseline; vL, viral load.



Supplementary Figure 3. Impact of estimated duration of infection (≤26 wk, 27–52 wk, and >52 wk) on SVR in HCV (n = 74) and HCV/HIV co-infected (n = 35) participants.