Hepatitis C virus treatment rates and outcomes in HIV/hepatitis C virus co-infected individuals at an urban HIV clinic

Melanie C.M. Murray[a], Rolando Barrios[c], Wendy Zhang[c], Mark Hull[a,c,d], Valentina Montessori[a,c], Robert S. Hogg[c,d] and Julio S.G. Montaner[b,c]

Objectives **The factors associated with hepatitis C virus (HCV) treatment uptake and responses were assessed among HCV/HIV co-infected individuals referred for HCV therapy at an urban HIV clinic.**

Methods **Retrospective review of HIV/HCV patients enrolled in the HCV treatment program at the John Ruedy Immunodeficiency Clinic in Vancouver. The factors associated with treatment uptake were assessed using multivariate analysis.**

Results **A total of 134 HCV/HIV co-infected individuals were recalled for assessment for HCV therapy. Overall 64 (48%) initiated treatment, and of those treated 49 (76.6%) attained end treatment response, whereas 35 (57.8%) achieved sustained virological response (SVR). When evaluated by genotype, 53% (17/32) of those with genotype 1, and 65% (20/31) of those with genotype 2 or 3 infections attained SVR. In treated individuals, alanine aminotransferase dropped significantly after treatment ($P<0.001$). During treatment, CD4 counts dropped significantly ($P<0.001$) in all patients. The counts recovered to baseline in patients who achieved SVR, but remained lower in patients who failed the therapy ($P=0.015$). On multivariate analysis, history of injection drug use (odds ratio: 3.48; 95% confidence interval: 1.37–8.79; $P=0.009$) and low hemoglobin levels (odds ratio: 4.23; 95% confidence interval: 1.36–13.10; $P=0.013$) were associated with those who did not enter the treatment.**

Conclusion **Only half of treatment-eligible co-infected patients referred for the therapy initiated treatment. Of those referred for the therapy, history of injection drug use was associated with lower rates of treatment uptake. Treated HIV/HCV co-infected individuals benefitted from both decreased alanine aminotransferase (independent of SVR), and rates of SVR similar to those described in HCV monoinfected patients. *Eur J Gastroenterol Hepatol* 23:45–50 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

European Journal of Gastroenterology & Hepatology 2011, **23**:45–50

Keywords: co-infection, hepatitis C virus, HIV, interferon, ribavirin, treatment

[a]Division of Infectious Disease, [b]Division of AIDS, Department of Medicine, University of British Columbia, [c]British Columbia Centre for Excellence in HIV/AIDS, Providence Health Care and [d]Faculty of Health Sciences, Simon Fraser University, Vancouver, Canada

Correspondence to Dr Melanie C.M. Murray, MD, PhD, 452D, Heather Pavilion East, VGH 2733 Heather Street, Vancouver, BC Canada V5Z 3J5
Tel: +1 604 505 8322; fax: +1 604 806 9044;
e-mail: Drmel.murray@gmail.com

Received 21 July 2010 **Accepted** 26 October 2010

Introduction

Hepatitis C virus (HCV) infection is a leading cause of morbidity and mortality in HIV co-infected patients [1–3]. It is estimated that 74–86% of individuals infected with HCV will progress to chronic disease [4,5]. Further, evidence indicates that approximately one-third of individuals infected with HCV will progress to cirrhosis and end-stage liver disease within 20–30 years [6,7], and that those with HIV/HCV co-infection, more frequently, have more severe and quicker progression of their HCV disease [8–10]. Unfortunately, few HIV/HCV co-infected patients ever receive HCV treatment [11,12]. When providers are questioned, reasons for patients not receiving HCV therapy are varied, and include decompensated liver disease, comorbid illness, ongoing substance use issues, and psychiatric illness, and provider bias and patient choice [10,13,14]. Patient described factors that act as treatment barriers in HCV/HIV co-infected individuals include fear and vicarious experiences, whereas facilitating factors include patient–provider relationships, gaining sober time, and facing treatment head-on [15].

Earlier studies have generally shown discouragingly low rates of HCV treatment uptake in HCV/HIV co-infected populations. HCV treatment uptake as low as 1.1 and 3.4% in all HCV infected and HCV/HIV co-infected patients, respectively, has been reported [12,16], whereas treatment uptake as high as 10.4% has been shown in HCV/HIV co-infected patients screened and referred for therapy [12].

Barriers to successful treatment of HCV do not end with treatment initiation. Patients who do start HCV therapy often experience side-effects resulting in diminished adherence to treatment regimens. It is estimated that 10–20% of patients being treated for HCV discontinue therapy secondary to side-effects, whereas a further 20–30% will require dose modification, with resultant decrease in sustained virological response (SVR) [17].

0954-691X © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/MEG.0b013e328341ef54

The aim of this study was to examine the uptake and outcomes of HCV treatment between HCV/HIV co-infected individuals attending an urban multidisciplinary primary and specialty care clinic, located in Vancouver, British Columbia, Canada. Starting in 2002, we actively recalled HIV/HCV co-infected individuals registered in the clinic who had no known contraindications to HCV treatment. We assessed the factors associated with treatment uptake and response among returning patients who were deemed eligible for HCV therapy.

Materials and methods

Study setting

The John Ruedy Immunodeficiency clinic, at St Paul's Hospital, Vancouver, Canada, is a multidisciplinary University affiliated primary and specialty care clinic for HIV-infected patients. The clinic offers primary care and specialty consultation services, antiretroviral therapy distribution, and monitoring for HIV infected patients, and a specialty clinic for individuals with HCV co-infection. As per Canadian healthcare standards, all medical care, and medication costs for treatment of HIV, were offered free of charge. Patient cost of HCV treatment is deductible-based according to income. Those on social assistance received all treatment free of charge.

Study population

Patients included in this study were HCV/HIV co-infected, aged 19 years or more, and were assessed for HCV therapy by a physician specializing in HCV treatment between January 1, 2002 and May 31, 2008. Participants considered to be eligible for HCV treatment were referred for additional counseling for treatment with pegylated interferon and ribavirin. On the basis of contemporary guidelines [18], individuals who had decompensated liver disease, or serious comorbidities, were not offered treatment.

The design and scope of this study was approved by the University of British Columbia Ethics Committee.

Treatment and follow-up

Baseline testing was done to rule out other causes of liver disease (e.g. Wilson's disease, hemachromatosis, α-1 antitrypsin, and autoimmune hepatitis). A liver biopsy was offered to all patients to examine for evidence of chronic inflammation and cirrhosis. Lack of liver biopsy did not preclude access to HCV treatment if other parameters of inflammation (e.g. liver enzymes) were present.

HCV treatment followed published British Columbia guidelines [18]. Briefly, individuals with HCV genotype 1 were treated for 48 weeks (there were no patients with subtypes 4, 5, and 6) and those with HCV genotype 2 or 3 were treated for 24 weeks. From 2007 onward, individuals with genotype 2 or 3 infection occasionally received longer courses based on treatment response [19]. Treatment included pegylated interferon and ribavirin (weight-based after 2005) as per the American Association for the Study of Liver Diseases guidelines [20]. Follow-up appointments with hematology panel, and liver enzyme assessment occurred every 2 weeks for the first 2 months, then at monthly intervals. CD4 counts were drawn for assessment at baseline, end of treatment, and at 6 months post-treatment. Genotype 1 patients had blood drawn for HCV viral load at 12 weeks to examine for early virologic response (EVR), whereas all had blood drawn at the end of treatment to evaluate the end of treatment response (ETR), and at 6 months post-therapy to evaluate SVR as a surrogate of HCV eradication. Any patient withdrawing from treatment was counted as having a detectable HCV viral load at each of the endpoints (EVR, ETR, and SVR) after which they discontinued the therapy.

Analyses

The primary outcome of this study was to determine the proportion of treatment-eligible patients referred for treatment counseling who underwent treatment for their HCV infection with pegylated interferon and ribavirin. Secondary outcomes focused on proportion completing treatment, EVR, ETR, and SVR. Analyses included descriptive summaries of patient demographic and clinical variables at baseline and post-treatment (if applicable). Bivariate analysis was done using Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables to compare patients who underwent treatment with those who did not. Sociodemographic and clinical characteristics which were significant ($P < 0.05$) in the bivariate analysis were entered into a multivariate logistic model to determine factors associated with starting treatment. The Wilcoxon signed rank sum test was used to compare baseline alanine aminotransferase (ALT) with post-treatment ALT (last available) for those who are undergoing treatment.

All analyses were conducted using SAS version 9.1.3 (SAS, Cary, North Carolina, USA). All significance tests are two-sided and P values of less than 0.05 were considered statistically significant.

Results

A total of 134 recalled HCV/HIV co-infected individuals presented for HCV therapy counseling and assessment. Sixty-four (48%) individuals initiated HCV treatment with ribavirin and pegylated interferon, whereas 70 (52%) did not. Of those opting for HCV treatment, demographic factors including age, sex, ethnicity, number of years of known infection with HCV, and highly active antiretroviral therapy (HAART) were not associated with opting in or out of HCV treatment. Laboratory factors not affecting HCV treatment uptake included platelet count, creatinine (though both patients with a creatinine higher than 150 went untreated), baseline CD4 count, and plasma

Table 1 Bivariate analysis of factors associated with treatment uptake in hepatitis C virus/HIV co-infected patients (*N*=134)

Variable	Treatment not started (*N*=70)	Treatment started (*N*=64)	*P* value
Age (years)			
Median (IQR)	45 (40–51)	44 (39–50)	0.532
Sex, *n* (%)			
Female	13 (65.00)	7 (35.00)	0.216
Male	57 (50.00)	57 (50.00)	
Ethnicity, *n* (%)			
Aboriginal/first nations	6 (50.00)	6 (50.00)	0.912
Nonaboriginal	62 (51.67)	58 (48.33)	
Missing=2			
Risk of IDU, *n* (%)			
No	10 (27.03)	27 (72.97)	<0.001
Yes	51 (60.71)	33 (39.29)	
Missing=13			
Risk of MSM, *n* (%)			
No	40 (58.82)	28 (41.18)	0.008
Yes	13 (32.50)	27 (67.50)	
Missing=26			
HCV (years from diagnosis)			
Median (IQR)	10 (6–14)	11 (5–19)	0.753
Missing=32			
HCV genotype, *n* (%)			
1	46 (58.23)	33 (41.77)	0.096
2,3	24 (43.64)	31 (56.36)	
Baseline CD4 (cells/mm^3)			
Median (IQR)	370 (260–460)	400 (270–510)	0.599
Missing=6			
Baseline PVL (copies/ml)			
Median (IQR)	45 (45–10 400)	45 (45–647)	0.536
Missing=4			
Liver biopsy, *n* (%)			
Not done or missing	23 (48.94)	24 (51.06)	0.574
Performed	47 (54.02)	40 (45.98)	
Liver biopsy: IK score, *n* (%)			
0–8	19 (63.33)	11 (36.67)	0.630
9 or more	16 (57.14)	12 (42.86)	
No IK score=29			
On HAART, *n* (%)			
No	28 (60.87)	18 (39.13)	0.148
Yes	42 (47.73)	46 (52.27)	
ALT (U/l), *n* (%)			
Low (<82.5 U/l)	23 (74.19)	8 (25.81)	0.003
High (≥ 82.5 U/l)	44 (44.00)	56 (56.00)	
Missing=3			
Hemoglobin (g/l), *n* (%)			
Low[a]	21 (77.78)	6 (22.22)	0.003
Normal[b]	48 (45.28)	58 (54.72)	
Missing=1			
Neutrophil count ($\times 10^9$/l), *n* (%)			
<1.5	11 (73.33)	4 (26.67)	0.078
≥ 1.5	58 (49.15)	60 (50.85)	
Missing=1			
Platelet count ($\times 10^9$/l), *n* (%)			
<70	2 (40.00)	3 (60.00)	0.673
≥ 70	66 (51.97)	61 (48.03)	
Missing=2			
Creatinine (μmol/l), *n* (%)			
<150	65 (50.39)	64 (49.61)	0.496
≥ 150	2 (100.00)	0 (0.00)	
Missing=3			
Lab tests, *n* (%)			
Hemoglobin, ANC, Plt, Cr			
>1 abnormality	8 (88.89)	1 (11.11)	0.018
≤ 1 abnormalities	58 (47.93)	63 (52.07)	

ALT, alanine aminotransferase; ANC, absolute neutrophil count; Cr, creatinine; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; IDU, intravenous drug user; IK, Ishak–Knodell score, scored out of total of 24; IQR, interquartile range; MSM, men who have sex with men; Plt, platelets; PVL, plasma viral load.
[a]Female <120 g/l, male <135 g/l.
[b]Female ≥ 120 g/l, male ≥ 135 g/l.

HIV-1-RNA levels (Table 1). Treatment uptake was not associated with having undergone liver biopsy, or the presence of mild versus moderate-to-severe liver disease as based on the Ishak–Knoddell score for liver biopsies available in 87 (65%) patients [21]. In bivariate analysis, significant factors promoting treatment uptake were being a man who has sex with men (MSM) ($P = 0.008$), and not using intravenous drugs ($P < 0.001$), (Table 1), having a higher baseline ALT ($P = 0.003$) and a normal hemoglobin ($P = 0.003$), (Table 1). There was a trend toward those with genotype 2 or 3 being treated more frequently than genotype 1 ($P = 0.096$) (Table 1). No patients with two or more baseline laboratory abnormalities (of creatinine, hemoglobin, platelets, and neutrophil count) underwent treatment ($P = 0.018$) (Table 1). In multivariate analysis intravenous drug use (IDU) (odds ratio: 3.48; 95% confidence interval: 1.37–8.79; $P = 0.009$) and having low hemoglobin levels (odds ratio: 4.232; 95% confidence interval: 1.36–13.10; $P = 0.013$) were predictors of not entering treatment (Table 2).

Table 2 Multivariate analysis of factors not associated with treatment uptake in hepatitis C virus/HIV co-infected patients (*N*=134)

Variable	Adjusted OR (95% CI)	*P* value
Risk of IDU[a]		
Yes vs. no	3.48 (1.37–8.79)	0.009
Hemoglobin (g/l)		
Low[b] vs. normal[c]	4.23 (1.36–13.20)	0.013

CI, confidence interval; IDU, intravenous drug user; OR, odds ratio.
[a]Male intravenous drug user.
[b]Female <120 g/l, male <135 g/l.
[c]Female ≥ 120 g/l, male ≥ 135 g/l.

Table 3 Descriptive characteristics of treated individuals stratified by outcome[a]

Variable	SVR-no (*N*=27)	SVR-yes (*N*=37)
Age (years)		
Median (IQR)	45 (39–52)	43 (39–49)
Sex, *n* (%)		
Female	3 (42.86)	4 (57.14)
Male	24 (42.11)	31 (57.89)
Ethnicity, *n* (%)		
Aboriginal/first nations	3 (50.00)	3 (50.00)
Nonaboriginal	24 (41.38)	34 (58.62)
Risk of IDU, *n* (%)		
No	12 (44.44)	15 (53.57)
Yes	14 (42.42)	19 (57.58)
Missing=4		
Risk of MSM, *n* (%)		
No	12 (46.43)	16 (55.56)
Yes	11 (48.48)	16 (51.52)
Missing=9		
HCV (years), *n* (%)		
Median (IQR)	11.0 (7.0–20.0)	10.0 (4.0–18.0)
Missing=8		
Genotype, *n* (%)		
1	15 (46.48)	17 (53.12)
2,3	11 (35.48)	20 (64.52)
Mixed infection (genotypes 1, 2)	1 (100.00)	0 (0)

HCV, hepatitis C virus; IDU, intravenous drug user; IQR, interquartile range; MSM, men who have sex with men; SVR, sustained virological response.
[a]No comparisons reached significance.

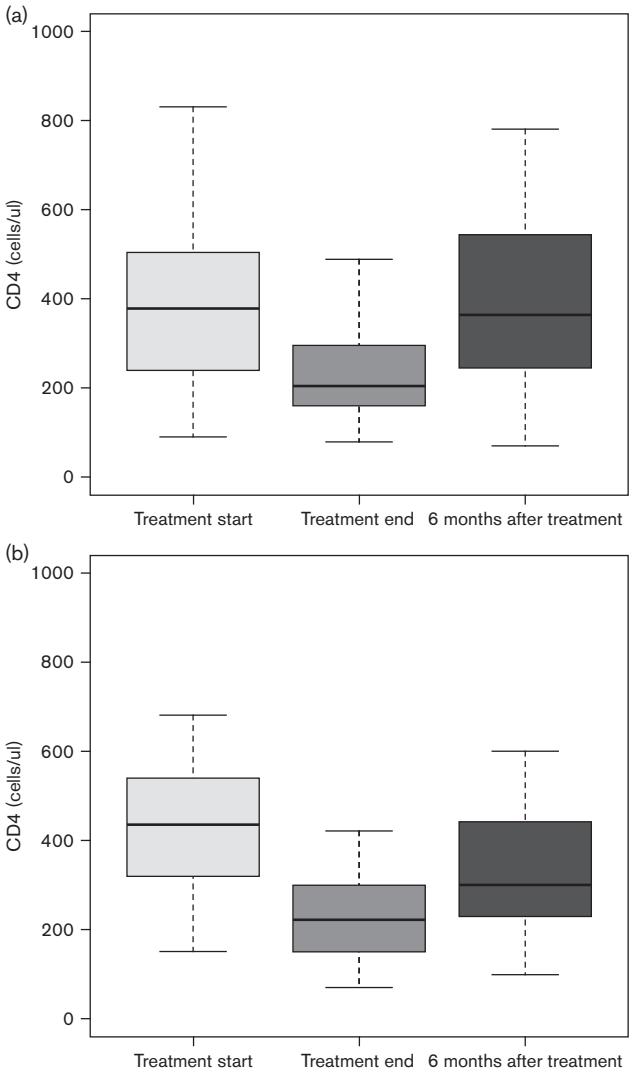
Of 64 individuals treated, 32 had genotype 1, whereas 31 were infected with genotype 2 or 3, and one had a mixed infection of genotypes 1 and 2 (included in outcomes of both genotypes). Forty-nine (76.6%) attained ETR, and 37 (57.8%) SVR. Of the 12 patients with ETR who did not achieve SVR, five had been lost to follow-up and had no viral load measurement recorded at 6 months post-treatment. The remaining seven have detectable HCV virus. Of those with genotype 1 infections, 22 (69%) attained EVR (four did not have an available viral load), 25 (76%) ETR, and 17 (53%) SVR. When treatment of genotype 2 or 3 infections was examined, 25 (78%) attained ETR and 20 (65%) SVR (Table 3).

Descriptive analyses of the baseline factors of treated individuals by SVR are shown in Table 3.

Fifty-nine of 64 treated patients had baseline and post-treatment (i.e. last available) ALT values available for comparison. A total of 56 patients showed a decrease in ALT post-treatment, with a median decrease in ALT of 55 IU/L [interquartile range (IQR) 15–99] after HCV treatment ($P < 0.001$).

Median CD4 counts at treatment initiation, treatment end, and at 6 months post-therapy were 380 cells/mm^3 (IQR 240–505), 205 cells/mm^3 (IQR 160–295), and 365 cells/mm^3 (IQR 245–545), respectively, for those attaining SVR (Fig. 1a), and were 435 cells/mm^3 (IQR 320–540), 220 cells/mm^3 (IQR 150–300) and 300 cells/mm^3 (IQR 230–440), respectively, for those failing therapy (Fig. 1b). CD4 counts fell significantly from baseline to treatment end, and recovered significantly from treatment end to 6 months post-therapy ($P < 0.001$) in all cases. When baseline CD4 counts were compared with counts taken 6 months post-therapy, however, counts had recovered in those achieving SVR ($P = 0.583$), but remained significantly lower compared with baseline in those who failed in the therapy ($P = 0.015$).

Fig. 1



(a) Median CD4 counts over time in hepatitis C virus (HCV) treated patients attaining sustained virological response (SVR). (b) Median CD4 counts over time in HCV treated patients not attaining SVR.

Discussion

As a general rule, rates of HCV treatment uptake are very low. In our cohort, patients were already engaged in care, were prescreened as treatment-eligible based on known factors about their overall health, and were actively being called back to the clinic, thereby representing the subgroup of patients most likely to obtain treatment for HCV. Despite this, only 64 of 134 (48%) HCV/HIV-1 co-infected individuals in our cohort underwent HCV treatment. A recent study from Australia showed a treatment uptake of 76% for newly identified HCV positive patients, showing that under ideal circumstances, a majority of HCV infected patients can be treated [22]. These data are encouraging that the early offering of HCV therapy in combination with a supportive treatment environment can result in good SVR's for infected patients.

In our study, IDU and low hemoglobin were predictors in multivariate analysis of not entering HCV treatment. The majority of individuals in this study infected with HCV who were not IDU were MSM. When compared with IDU, MSMs may be more likely to be offered treatment because of physician perception of ability to adhere to treatment regimens. Alternatively, socioeconomic factors such as education may make MSMs more likely to accept treatment. With regard to the decreased HCV treatment uptake among those with low hemoglobin, we suspect that this acts as a surrogate for overall poorer health and nutrition [23]. This is supported by the fact that of nine patients with two or more baseline laboratory abnormalities, only one received treatment, whereas neither of the patients with creatinine more than 150 (above which

there is an indication not to treat the patient) were treated, quite possibly because of concern over treatment toxicity.

Of those who underwent treatment, EVR was 68.8% (genotype 1 only), ETR was 76.6%, and SVR was 57.8% overall. A recent Cochrane review of 14 studies in HCV/HIV co-infected patients reported SVR for genotype 1 or 4 to be 27%, whereas SVR for genotype 2 or 3 was 56% [24]. Interestingly, our results for genotype 2 or 3 infection in this population approximated the values expected, however, our outcomes in genotype 1 infection were much better and approximated results seen in studies of HCV monoinfection [25,26]. The reasons for our more favorable outcomes for genotype 1 are not clear but may reflect the intensive degree of multidisciplinary care offered at the John Ruedy Immunodeficiency clinic, and improved adherence to treatment as a result.

Despite only 37 of 64 patients attaining eradication, almost all have experienced a decrease in ALT post-treatment regardless of whether virus was detectable at the end of the study. Considering that HIV/HCV co-infected individuals are more likely to progress to cirrhosis [8–10], a decrease in ALT (a marker of inflammation in the liver), is likely to provide benefit to the patient. In addition, other studies have shown post-treatment decreases in fibrosis scores [27], and HAART-related toxicity [28], both of which are likely to represent the product of reduced inflammation. Our study is limited by measuring only one ALT in the 6 months post-treatment, further study regarding long-term affect on ALT is needed.

CD4 counts fell significantly in all treated patients, and recovered after treatment cessation as seen earlier [29]. In patients achieving SVR, CD4 counts recovered to baseline by 6 months post-treatment. Despite similar rates of HIV treatment, however, CD4 counts of patients who failed in the therapy remained significantly lower than baseline 6 months after HCV treatment. It has been reported earlier that HCV/HIV co-infected patients experience slower CD4 cell recovery after the initiation of HAART, and if not treated, increased CD4 cell decline when compared with HIV monoinfected patients [30]. This is reflected in our findings, and may be a product of increased immune activation from active HCV infection. More study is needed to fully elucidate the effect of HCV treatment outcomes on long-term CD4 cell counts.

Study conclusions were limited by the fact that no individuals with genotypes 4, 5, or 6 were treated in this study and as such no conclusions could be made in relation to these genotypes. Treatment uptake was calculated as a proportion of those who presented for HCV counseling and assessment, and thus only considers a small proportion of those infected with HCV. Study numbers, and in particular, the number of individuals undergoing the treatment, were small enough that only descriptive analysis could be carried out on the treatment group. Further study would ideally include a greater number of patients so as to allow for multivariate analysis of the treatment group. Finally, study conclusions were limited by the fact that adherence to and doses of medications were not recorded sufficiently to comment on the effect of missed doses or dose adjustments on SVR. This is important, because individuals capable of taking at least 80% of ribavirin, and interferon doses for at least 80% of the prescribed treatment duration have significantly better rates of SVR over less adherent patients (the '80/80/80 rule') [31]. We are, thus, only able to speak of treated patients in general terms.

In conclusion, our study showed that even in the setting in which patients are prescreened for suitability for HCV treatment before being recalled to clinic, and treatment is affordable to the patient, treatment uptake is still only approximately 50%. Of those treated, genotype 2 or 3 outcomes approximated those of other studies in similar populations of HIV/HCV co-infected individuals, whereas genotype 1 outcomes were better. In addition, ALT (a marker of inflammation) post-treatment was diminished almost universally in those who underwent treatment for their HCV disease suggesting treatment benefit, independent of SVR. These results suggest that further efforts are needed to optimize the uptake of HCV treatment among HIV infected patients.

Acknowledgements

R.B., R.S.H., M.H., V.M., and M.C.M.M. conceived and designed the study. W.Z. did all of the statistics, whereas W.Z., M.C.M.M., R.B. interpreted the data. M.C.M.M. drafted the manuscript. R.B., W.Z., M.H., V.M., R.S.H., and J.S.G.M. critically revised the manuscript for content. All authors saw and approved the final study. They are grateful to all of the study nurses and clinical staff at the John Ruedy Immunodeficiency clinic, at St Paul's Hospital, Vancouver, Canada for all of their hard work in helping patients through their treatment. There is no declaration of funding.

Conflicts of interest: none declared.

References

1 Weis N, Lindhardt BO, Kronborg G, Hansen AB, Laursen AL, Christensen PB, *et al.* Impact of hepatitis C virus coinfection on response to highly active antiretroviral therapy and outcome in HIV-infected individuals: a nationwide cohort study. *Clin Infect Dis* 2006; **42**:1481–1487.

2 Smit C, Van den Berg C, Geskus R, Berkhout B, Coutinho R, Prins M. Risk of hepatitis-related mortality increased among hepatitis C virus/HIV-coinfected drug users compared with drug users infected only with hepatitis C virus: a 20-year prospective study. *J Acquir Immune Defic Syndr* 2008; **47**:221–225.

3 Anderson KB, Guest JL, Rimland D. Hepatitis C virus coinfection increases mortality in HIV-infected patients in the highly active antiretroviral therapy era: data from the HIV Atlanta VA Cohort Study. *Clin Infect Dis* 2004; **39**:1507–1513.

4 Alter MJ, Kruszon-Moran D, Nainan OV, McQuillan GM, Gao F, Moyer LA, *et al.* The prevalence of hepatitis C virus infection in the United States, 1988 through 1994. *N Engl J Med* 1999; **341**:556–562.

5 Conry-Cantilena C, Van Raden M, Gibble J, Melpolder J, Shakil AO, Viladomiu L, *et al.* Routes of infection, viremia, and liver disease in blood donors found to have hepatitis C virus infection. *N Engl J Med* 1996; **334**:1691–1696.

6 Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet* 1997; **349**:825–832.

7 Poynard T, Ratziu V, Benhamou Y, Opolon P, Cacoub P, Bedossa P. Natural history of HCV infection. *Baillieres Best Pract Res Clin Gastroenterol* 2000; **14**:211–228.

8 De Ledinghen V, Barreiro P, Foucher J, Labarga P, Castera L, Vispo ME, *et al.* Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. *J Viral Hepat* 2008; **15**:427–433.

9 Martinez-Sierra C, Arizcorreta A, Diaz F, Roldan R, Martin-Herrera L, Perez-Guzman E, *et al.* Progression of chronic hepatitis C to liver fibrosis and cirrhosis in patients coinfected with hepatitis C virus and human immunodeficiency virus. *Clin Infect Dis* 2003; **36**:491–498.

10 Markowitz JS, Gutterman EM, Hodes D, Klaskala W. Factors associated with the initiation of alpha-interferon treatment in Medicaid patients diagnosed with hepatitis C. *J Viral Hepat* 2005; **12**:176–185.

11 Mehta SH, Genberg BL, Astemborski J, Kavasery R, Kirk GD, Vlahov D, *et al.* Limited uptake of hepatitis C treatment among injection drug users. *J Community Health* 2008; **33**:126–133.

12 Mehta SH, Lucas GM, Mirel LB, Torbenson M, Higgins Y, Moore RD, *et al.* Limited effectiveness of antiviral treatment for hepatitis C in an urban HIV clinic. *AIDS* 2006; **20**:2361–2369.

13 Khokhar OS, Lewis JH. Reasons why patients infected with chronic hepatitis C virus choose to defer treatment: do they alter their decision with time? *Dig Dis Sci* 2007; **52**:1168–1176.

14 Grebely J, Genoway KA, Raffa JD, Dhadwal G, Rajan T, Showler G, *et al.* Barriers associated with the treatment of hepatitis C virus infection among illicit drug users. *Drug Alcohol Depend* 2008; **93**:141–147.

15 Bova C, Ogawa LF, Sullivan-Bolyai S. Hepatitis C treatment experiences and decision making among patients living with HIV infection. *J Assoc Nurses AIDS Care* 2010; **21**:63–74.

16 Grebely J, Raffa JD, Lai C, Krajden M, Kerr T, Fischer B, *et al.* Low uptake of treatment for hepatitis C virus infection in a large community-based study of inner city residents. *J Viral Hepat* 2009; **16**:352–358.

17 Manns MP, Wedemeyer H, Cornberg M. Treating viral hepatitis C: efficacy, side effects, and complications. *Gut* 2006; **55**:1350–1359.

18 BC Health Services. Clinical Management of Chronic Hepatitis C. 2004. [cited; November 4, 2010, Available from: *http://www.bcguidelines.ca/gpac/pdf/hepatitis_c.pdf*].

19 Soriano V, Puoti M, Sulkowski M, Cargnel A, Benhamou Y, Peters M, *et al.* Care of patients coinfected with HIV and hepatitis C virus: 2007 updated recommendations from the HCV-HIV International Panel. *AIDS* 2007; **21**:1073–1089.

20 Strader DB, Wright T, Thomas DL, Seeff LB. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; **39**:1147–1171.

21 Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, *et al.* Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. *Hepatology* 1981; **1**:431–435.

22 Grebely J, Petoumenos K, Matthews GV, Haber P, Marks P, Lloyd AR, *et al.* Factors associated with uptake of treatment for recent hepatitis C virus infection in a predominantly injecting drug user cohort: the ATAHC Study. *Drug Alcohol Depend* 2010; **107**:244–249.

23 Dong X, Mendes de Leon C, Artz A, Tang Y, Shah R, Evans D. A population-based study of hemoglobin, race, and mortality in elderly persons. *J Gerontol A Biol Sci Med Sci* 2008; **63**:873–878.

24 Iorio A, Marchesini E, Awad T, Gluud LL. Antiviral treatment for chronic hepatitis C in patients with human immunodeficiency virus. *Cochrane Database Syst Rev* 2010; CD004888.

25 McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, *et al.* Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. *N Engl J Med* 2009; **361**:580–593.

26 Moreno A, Barcena R, Garcia-Garzon S, Muriel A, Quereda C, Moreno L, *et al.* HCV clearance and treatment outcome in genotype 1 HCV-monoinfected, HIV-coinfected and liver transplanted patients on peg-IFN-alpha-2b/ribavirin. *J Hepatol* 2005; **43**:783–790.

27 Lissen E, Clumeck N, Sola R, Mendes-Correa M, Montaner J, Nelson M, *et al.* Histological response to pegIFNalpha-2a (40KD) plus ribavirin in HIV-hepatitis C virus co-infection. *AIDS* 2006; **20**:2175–2181.

28 Cooper C. De'Liver'-ing HIV/hepatitis C virus-coinfected patients from antiretroviral hepatotoxicity. *J Infect Dis* 2007; **196**:656.

29 Soriano V, Bravo R, Samaniego JG, Gonzalez J, Odriozola PM, Arroyo E, *et al.* CD4+ T-lymphocytopenia in HIV-infected patients receiving interferon therapy for chronic hepatitis C. HIV-Hepatitis Spanish Study Group. *AIDS* 1994; **8**:1621–1622.

30 Potter M, Odueyungbo A, Yang H, Saeed S, Klein MB. Impact of hepatitis C viral replication on CD4+ T-lymphocyte progression in HIV-HCV coinfection before and after antiretroviral therapy. *AIDS* 2010; **24**:1857–1865.

31 McHutchison JG, Manns M, Patel K, Poynard T, Lindsay KL, Trepo C, *et al.* Adherence to combination therapy enhances sustained response in genotype-1-infected patients with chronic hepatitis C. *Gastroenterology* 2002; **123**:1061–1069.