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Hepatitis C patients' self-reported adherence to treatment with pegylated interferon and ribavirin

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SUMMARY

Background
Prior research on adherence to hepatitis C treatment has documented rates of dose reductions and early treatment discontinuation, but little is known about patients' dose-taking adherence.

Aims
To assess the prevalence of missed doses of pegylated interferon and ribavirin and examine the correlates of dose-taking adherence in clinic settings.

Methods
One hundred and eighty patients on treatment for hepatitis C (23% co-infected with HIV) completed a cross-sectional survey at the site of their hepatitis C care.

Results
Seven per cent of patients reported missing at least one injection of pegylated interferon in the last 4 weeks and 21% reported missing at least one dose of ribavirin in the last 7 days. Dose-taking adherence was not associated with HCV viral load.

Conclusions
Self-reported dose non-adherence to hepatitis C treatment occurs frequently. Further studies of dose non-adherence (assessed by method other than self-report) and its relationship to HCV virological outcome are warranted.

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INTRODUCTION

The combination of pegylated interferon and ribavirin (PEG-IFN/RBV) is the standard of care treatment for HCV for both mono- and HIV-co-infected patients. The side effects of HCV treatment (e.g. anaemia, neutropenia, depression, flu-like symptoms) often result in dose reductions (30–40% of patients) and early treatment discontinuation.[1–3] While the 80/80/80 rule (continued prescription of at least 80% of IFN doses and 80% of RBV doses for at least 80% of the planned treatment duration) is widely referred to as the gold standard of HCV treatment adherence,[2] this standard refers to dose reductions and premature discontinuation of treatment only, not to patient dose-taking adherence.

Rates of treatment uptake are low,[4] particularly among HIV-co-infected patients (~5–10%);[5, 6] this is not only because of limited treatment efficacy, but also because of anticipated difficulties with adherence as a result of common treatment toxicities. Rates of HCV virological response have been found to be lower in HIV-co-infected patients (27–40%)[7–9] than in HCV mono-infected patients (54–56%).[1, 10] These findings may in part be as a result of the fact that lower doses of RBV were generally used in the main co-infection trials compared with the mono-infection trials.[11, 12] There is evidence that suboptimal dosing and dose reductions in HCV therapy, particularly of RBV, are associated with lower rates of HCV virological response.[2, 3] These observations suggest that missed doses of PEG-IFN and RBV are also likely to impact HCV virological response negatively.

To date, only two published studies have reported on patient dose-taking adherence to HCV therapy.[13, 14] In an observational clinic cohort of HIV-co-infected patients, Fumaz *et al.*[13] found that over 98% of patients self-reported taking all doses of PEG-IFN/RBV in the prior 2 weeks at weeks 12, 24 and 48. In a clinical trial sample of HCV mono-infected subjects, Smith *et al.*[14] found that at least 95% of subjects self-reported taking all doses of PEG-IFN in the prior 4 weeks at weeks 4, 12, 24, 36 and 48. They found that the per cent of patients who self-reported taking all doses of RBV in the prior 4 days decreased over time (91% at 4 weeks, 85% at 12 weeks, 83% at 24 weeks, 76% at 36 weeks, 75% at 48 weeks). Self-report measures have been found to overestimate adherence compared to objective measures such as electronic monitoring.[15, 16] Studies of HIV antiretroviral adherence have demonstrated mean adherence rates ranging from 80% to 95% when measured by self-report, and rates as low as 55–65% when measured by electronic monitoring.[15–17] Consistent with these findings, Smith *et al.*[14] found lower rates of adherence to PEG-IFN/RBV as measured by a Medication Event Monitoring System (MEMS) compared with self-report in their clinical trial sample.

To gain a greater understanding of the prevalence of missed doses of PEG-IFN/RBV, and correlates of non-adherence, we conducted a cross-sectional survey of dose-taking adherence to PEG-IFN/RBV among mono- and HIV-co-infected patients currently on PEG-IFN/RBV for at least 4 weeks. All patients who had completed at least 4 weeks of HCV treatment were eligible to complete the survey.

MATERIALS AND METHODS

Participants were recruited from seven clinical settings, three in Los Angeles and four in New York City. All study procedures were approved by the respective Institutional Review Board at each site of data collection. Written informed consent was waived at all sites given that it was an anonymous survey in which no personal health identifiers were collected.

Self-report adherence measures included number of missed doses of weekly injections of PEG-IFN over the past 4 weeks, number of twice-daily oral doses of RBV that were missed over the past week and single-item visual analogue scales (VAS) of adherence to each of PEG-IFN and RBV over the course of treatment. Information related to demographics, treatment and disease characteristics, and mental health symptoms and treatment were collected. Patients were requested to grade their mood, energy and treatment side effects in the prior week on a scale from 0 to 10. Baseline and most recent HCV viral load were collected by self-report, if the patient knew this information; if not, patients were encouraged to request their health care provider to document this on the survey, which was carried out in 49% of the cases.

Analysis

For descriptive purposes, comparative analyses were used to test whether the HCV mono-infected sample differed from the HIV/HCV-co-infected sample, whether the adherent sample differed from the non-adherent sample and whether those who achieved undetectable HCV viral load differed from those who

did not. Categorical variables were examined using chi-squared tests and continuous variables were examined using *t*-tests.

RESULTS

One hundred and eighty patients completed the survey. The subjects were predominantly male (69%), non-White (57%) and on treatment for HCV for the first time (74%). The median duration of HCV treatment at the time of survey assessment was 16 weeks (range: 4–73). Forty-one subjects (23%) were co-infected with HIV, 136 subjects were HCV mono-infected (76%) and three subjects (2%) did not report their HIV status. Compared with the HCV mono-infected subjects, the HIV/HCV-co-infected subjects were more likely to be younger, non-White, on PEG-IFN alfa-2a (rather than PEG-IFN alfa-2b) and on medication for depression (Tables 1 and 2).

With regard to missed doses of PEG-IFN, only 12 subjects (7%) reported missing at least one injection in the last 4 weeks, and just nine subjects (5%) reported <80% adherence during the length of time they had been on treatment (range 10–79%). For all subjects, the mean PEG-IFN VAS = 96.5%; s.d. = 13.0. As for RBV, 21% reported missing at least 1 dose in the last 7 days (range 1–10 doses missed) and 5% reported <80% adherence during the course of treatment (range 10–79%). For all subjects, the mean RBV VAS = 94.5%; SD = 13.4. Non-adherence to IFN (<80% during treatment course) was significantly related to non-adherence to RBV (OR: 163.0; 95% CI: 22.8–1164.1; $P = 0.00$). There was no relationship between any of the adherence measures and the length of time on treatment. The sample was divided into 163 'adherent' (PEG-IFN and RBV VAS ratings ≥80%) and 12 'non-adherent' patients (either VAS rating <80%). Five patients were missing adherence data and could not be categorized. Adherent patients did not differ significantly from non-adherent patients on any of the demographic or treatment-related variables assessed. Thirteen per cent of the co-infected patients were 'non-adherent' compared to 5% of the mono-infected patients, but this difference did not quite reach statistical significance (OR: 2.8; 95% CI: 0.8–9.3; $P = 0.09$).

Seventy-eight participants (43%) were on treatment for at least 12 weeks at the time they completed the survey and reported baseline HCV viral load and follow-up HCV viral load at 12 weeks or later (mean of 28 weeks). Sixty-two of these 78 participants (79%) had achieved an undetectable HCV viral load (bDNA < 615 IU/mL or HCV RNA < 600 IU/mL) at the reported follow-up time. Those who achieved undetectable HCV viral load were more likely to have been on treatment longer (mean of 29 vs. 23 weeks; $P = 0.04$) and to report worse mood (mean of 6.0 vs. 7.3; $P = 0.03$) than those who did not achieve undetectable HCV viral load. Adherence was not associated

Table 1. Subject demographics by co-infection status

	Total (n = 180)	HCV mono-infected (n = 136)	HCV/HIV co-infected (n = 41)	Significance P	OR (95%)
Age (years), mean (s.d.)	52.2 (9.0)	53.5 (8.9)	48.1 (8.3)	**0.00**	
Gender – males, n (%)	129 (69)	89 (65)	32 (78)	0.08	0.5 (0.2–1.1)
Race/ethnicity, n (%)					
White	76 (42)	66 (49)	10 (24)	**0.04**	
Black	56 (31)	41 (30)	15 (37)		
Latino	38 (21)	23 (17)	13 (32)		
Other	9 (5)	6 (4)	2 (5)		
Past IVDU, n (%)	72 (40)	56 (42)	16 (39)	0.81	0.9 (0.4–1.9)
Past substance use treatment, n (%)	77 (43)	55 (40)	22 (54)	0.10	1.8 (0.9–3.7)
Past psychiatric treatment, n (%)	54 (30)	37 (27)	17 (41)	0.07	1.9 (0.9–4.0)
Current methadone/buprenorphine treatment, n (%)	11 (6)	10 (7)	1 (2)	0.26	0.3 (0.0–2.6)

IVDU, intravenous drug use.

Table 2. Subject treatment characteristics by co-infection status

	Total (n = 180)	HCV mono (n = 136)	HCV/HIV-co-infected (n = 41)	Significance P	OR (95%)
First HCV treatment, n (%)	129 (72)	97 (71)	32 (78)	0.47	1.4 (0.6–3.1)
Interferon alfa-2a, n (%)	144 (80)	104 (76)	40 (98)	**0.00**	**11.2 (1.5–84.6)**
HCV genotype, n (%)					
Type 1	127 (71)	96 (71)	31 (76)	0.38	
Type 2	26 (14)	18 (13)	8 (20)		
Type 3	16 (9)	14 (10)	2 (5)		
Type 4	4 (2)	4 (3)	0 (0)		
Self-injects IFN, n (%)	155 (86)	121 (89)	34 (83)	0.50	0.7 (0.3–1.9)
Ribavirin dose, n (%)					
800 mg or <	45 (25)	34 (25)	11 (27)	0.52	
1000 mg	44 (24)	36 (26)	8 (20)		
1200 mg or >	65 (36)	47 (35)	18 (44)		
Time on treatment in weeks mean (s.d.)	19.3 (13.4)	19.2 (12.8)	19.6 (15.5)	0.88	
In clinical trial, n (%)	27 (15)	22 (16)	5 (12)	0.57	0.7 (0.3–2.1)
On antidepressant, n (%)	60 (33)	35 (26)	25 (61)	**0.00**	**4.5 (2.1–9.5)**
Meds for anaemia, n (%)	67 (37)	46 (34)	21 (51)	0.53	2.0 (1.0–4.1)
Mood mean (s.d.)	6.4 (2.2)	6.5 (2.1)	6.3 (2.6)	0.74	
Energy mean (s.d.)	5.4 (2.5)	5.4 (2.5)	5.5 (2.5)	0.76	
Side effects, mean (s.d.)	4.6 (2.6)	4.8 (2.7)	4.2 (2.7)	0.26	

with HCV viral load or achievement of undetectable viral load, at follow-up.

DISCUSSION

This is one of the first studies to report on patient dose-taking adherence to PEG-IFN/RBV and to examine its relationship to demographic, medical and treatment characteristics. The findings of the study are limited by the cross-sectional design assessing patients at a large range of weeks on treatment, assessment of missed doses by self-report only, the absence of data on dose reductions, incomplete data on HCV virological response and absence of data on sustained virological response. Self-reported missed doses of RBV in the last week occurred frequently, indicating the need to address adherence barriers with patients on PEG-IFN/RBV. Using the traditional standard of 80% adherence over the course of treatment, high rates of adherence were found (95% of the sample for each PEG-IFN/RBV). The HCV adherence rates found were high in comparison to HIV treatment adherence rates reported in the literature.[15–17] Possible explanations for these higher adherence rates include the tendency of self-reports to overestimate adherence and that providers are effectively screening out patients at high risk for non-adherence; however, a number of HIV studies have shown that providers do not accurately predict whether or not a patient will adhere well to medication.[18, 19]

Psychiatric illness, in particular depression, has been found to be a risk factor for medication non-adherence in HIV-positive patients.[20] The trend for HIV-co-infected patients to be less adherent than HCV mono-infected ones may be related to the potentially higher rates of psychiatric illness (as indicated by higher rates of history of psychiatric and substance use treatment and current antidepressant medication) in the co-infected group compared with the mono-infected group. There is a need for further research to elucidate the potentially unique HCV adherence issues in HIV-co-infected patients. Larger studies may be needed to detect relationships between non-adherence and virological outcomes. Prospective studies of HCV mono-infected and HIV-co-infected patients are recommended, which include the assessment of dose reductions and missed doses (by methods in addition to self-report), to study further the determinants of non-adherence to HCV treatment and its relationship to treatment outcome. Once the salient determinants of HCV adherence are elucidated, this information can be used to develop effective interventions to support

patients during HCV treatment and increase their levels of dose-taking adherence.

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