Published in final edited form as:

J Clin Gastroenterol. 2015 ; 49(5): e41–e50. doi:10.1097/MCG.0000000000000151.

Adherence during Antiviral Treatment Regimens for Chronic Hepatitis C: A Qualitative Study of Patient-Reported Facilitators and Barriers

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Abstract

Goals—To understand patients' perceptions of factors which facilitate and hinder adherence in order to inform adherence-enhancing interventions.

Background—Adherence to antiviral therapy for hepatitis C viral infection is critical to achieving a sustained virological response (SVR). However, persistence with and adherence to antiviral regimens can pose challenges for patients that interfere with SVR.

Study—A qualitative analysis of 21 semi-structured patient interviews using open-ended questions and specific follow-up probes was conducted. Interviews were audio-recorded, transcribed, and content-analyzed iteratively to determine frequent and salient themes.

Results—Three broad themes emerged: 1) missing doses and dose-timing errors; 2) facilitators of adherence; and 3) barriers to adherence. Open-ended questioning revealed few dose-timing deviations, but more specific probes uncovered several more occurrences of delays in dosing. Facilitators of adherence fell into two broad categories: (a) patient knowledge and motivation and (b) practical behavioral strategies and routines. Facilitators were noted *post hoc* to be consistent with the Information-Motivation-Behavioral Skills Model of Adherence. Barriers to adherence involved changes in daily routine, being preoccupied with family or work responsibilities, and sleeping through dosing times. A few patients reported skipping doses due to side effects. Patients with previous HCV treatment experience may have fewer dose-timing errors. Finally, a high level of anxiety amongst some patients was discovered regarding dosing errors. Emotional and informational support from clinical and research staff was key to assuaging patient fears.

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Declaration of Personal Interests: None.

Conclusions—This qualitative study improves our understanding of patients' perspectives regarding adhering to hepatitis C treatment and can lead to the development of adherence-enhancing interventions.

INTRODUCTION

Adherence to antiviral treatment regimens for chronic hepatitis C viral (HCV) infection is imperative to successful eradication of the virus (1). Previous research has shown that patients may discontinue HCV treatment prematurely due to patient-driven issues such as noncompliance, lost to follow-up, patient preference, or the inability to tolerate uncomfortable, but not life-threatening treatment side effects (2). Patient-driven treatment discontinuations is often referred to as "nonpersistence" in the broader adherence literature, and refers to the patient's ability to stay on the treatment for the fully prescribed regimen (3, 4). In contrast, "medication adherence" refers to the patients' ability to conform to the regimen's timing, dosage, and dosing frequency prescribed by the doctor (3, 4). Patients undergoing HCV treatment can have issues with both medication persistence (i.e., persisting on the full course of antiviral therapy) and medication adherence, (i.e., taking all of the medications exactly as prescribed without missed doses). Previous research, including that conducted by our group, demonstrates that HCV patients can have difficulty taking their medications as prescribed, nonadherence worsens over the course of treatment, and is linked to lower virological response and sustained virological response (SVR) (1, 2, 5, 6). Notably, patients have a more difficult time dosing oral antiviral medications, such as ribavirin (RBV), compared to dosing once a week self-injection of pegylated interferon (PegIFN). This observation will be of great clinical importance as many countries begin to phase out the use of PegIFN antiviral regimens in the coming years, which may improve persistence on HCV treatment. However, adherence to dosing of oral medications may still be a clinically important issue to understand from the perspective of the patient, so clinicians know what questions to ask and how to discuss adherence-enhancing tactics with their patients.

While previous quantitative studies describe the pattern and prevalence of medication nonadherence during HCV treatment (2, 5, 6), exactly how and why patients do or do not take their HCV medications as prescribed remains unclear. Although previous adherence research with medication regimens for other patient populations has been cited, there may be more dissimilarities than commonalities among these regimens and populations (7, 8). Thus, caution needs to be applied when generalizing other adherence findings to the HCV patient population and regimen, until more systemic research is conducted in this rather unprecedented patient population. Understanding the unique patient perceptions and experiences of what factors facilitate or sabotage adherence to HCV treatment will improve our understanding of these nuances, and inform clinical practice and interventions to help patients optimize treatment outcomes. In particular, understanding patients' nonadherence to taking oral medications will become increasingly salient in the years to come.

Qualitative methods using in-depth, open-ended patient interviews or focus groups are particularly useful to study under-developed research areas, and have recently been applied to the field of HCV, although not specifically to study patient adherence to HCV treatment

(9–12). In this study, we applied qualitative research methods, which can either generate hypotheses to test in larger quantitative studies or inform intervention development and practice, (13) to understand patients' perceptions of the most salient facilitators and barriers to adhering to antiviral treatment regimens for HCV. These data were obtained from a larger parent study, a needs assessment of patient experiences during HCV treatment to inform interventions to optimize adherence and persistence with antiviral HCV regimens.

MATERIALS AND METHODS

Participants and Setting

Eligible participants were adults 18 years of age or older, diagnosed with HCV genotypes 1, 2, or 3, and either undergoing or within 4 weeks of completing antiviral therapy, at a large tertiary care medical center in the US. We purposively enrolled patients who were in the early and late phases of various treatment regimens to capture the wide spectrum of heterogeneous experiences that occur across the span of HCV treatment. Participants were recruited from two settings: (1) an outpatient liver clinic where patients engaged in standard of care biotherapy with PegIFN+RBV therapy; or (2) a clinical research center at the hospital where patients were participants in Phase II pharmaceutical trials to evaluate combining direct acting antivirals (DAAs) with PegIFN+RBV which were not FDA-approved at the time of data collection in 2011. Patients on standard PegIFN+RBV dosed a total of 5–6 RBV pills twice a day and injected weekly PegIFN. The clinical trial participants were involved in trials of triple or quadruple therapy which included PegIFN, 5–6 RBV pills dosed twice a day, and a once a day dosed DAA (e.g., NS3 or NS5 protease inhibitors, polymerase inhibitors, and protease inhibitor boosters). Therefore, all regimens required dosing 6–8 pills twice a day plus weekly interferon injections. The only difference between regimens was the dosing of an additional DAA once a day among patients in the clinical trials. All dosing regimens had a 12-hour dosing window; none required dosing every 8 hours. Only one regimen required one patient to dose an experimental pill with food. Therefore, in most ways the regimens were very similar preventing comparison of differences in pill burden. Thirty consecutive patients were screened for eligibility. Nine patients were not enrolled in the study: 3 did not meet inclusion criteria, 2 declined to participate, and 4 were missed in clinic. The final sample of 21 patients participated in individual, single-session, semi-structured interviews from January through May 2011. This study was approved by the UNC Biomedical IRB. All patients gave written informed consent and were compensated $20 for their participation.

Study Design and Interview Guide Development

At routine medical or research visits, hepatologists introduced the study to potential participants and interested patients were recruited for the study by the coordinator.

The overarching goal of the interviews was to gather qualitative information about patient experiences with 1) undergoing antiviral treatment, including treatment-related side effects, and psychological and behavioral coping with such side effects, and 2) medication adherence, by specifically querying about facilitators and barriers. Based on clinical experience, including knowledge of common treatment-related side effects and a review of

the HCV treatment and broader adherence literatures, two investigators (D.M.E., C.E.G.) developed the interview guide (Table 1). Each interview, conducted by one of two interviewers (J.E.B., D.M.E.) lasted about 45 minutes (range 30–90). Initial open-ended questions were followed by closed-ended prompts to first allow unanticipated themes to arise and then to obtain information about all topics hypothesized to be possibly relevant. During the data collection period, study interviewers revised the interview guide to probe more about dose-timing deviations based on initial interviews.

Data Collection

Interviews were audio-recorded and transcribed by an external transcriptionist. One author (J.E.B.) reviewed all 21 transcriptions for accuracy. At the end of each interview, participants completed a brief 15-item self-administered demographic survey. We obtained sociodemographic and clinical data such as HCV genotype and evidence of cirrhosis from electronic medical records.

Data Analysis

Data were analyzed using a thematic content approach to identify themes relevant to the study aims and the relationship among those themes (14). Two coders (D.M.E. and J.E.B. who also conducted the study interviews) independently reviewed all transcripts, recording preliminary themes based on the major topical headings specified in the interview guide. Each also incorporated additional themes pertinent to the study aims that emerged from the interview data. Participants' utterances regarding adherence were generally elicited during sections 6 and 7 of the Interview Guide (Table 1) during which the interviewee specifically inquired about the process of taking HCV medications; however some utterances related to adherence were captured during other sections of the interview. After independently reviewing all transcripts, they compared each theme and their associated representative texts and came to consensus to develop a codebook with definitions and representative text. The two coders then trained a third coder (J.V.) who reviewed all transcripts independently and marked appropriate text relating to the themes in the codebook using ATLAS.ti 6.2 qualitative analysis software, refining the codebook when necessary. The two initial coders (D.M.E and J.E.B) jointly reviewed the revised themes and coded text for accuracy and further refined the codebook based on review and discussion of coded text, and, with a fourth coder (CAG), finalized the coding in ATLAS.ti. Key themes were extracted and representative quotes were selected from the final coded data and codebook. We linked each utterance to gender, history of depression, cirrhosis status, treatment experience, and whether a participant was undergoing treatment via standard of care (SC) or engaged in a clinical trial (CT) to determine any group differences. Descriptive statistics were analyzed in SPSS v20 (Chicago, IL).

RESULTS

Three broad themes emerged from the final analysis: 1) Missing Doses and Dose-Timing Errors; 2) Facilitators of Adherence; and 3) Barriers to Adherence.

Patient Characteristics

Baseline patient demographic and clinical characteristics are shown in Table 2. The age of participants ranged from 33 to 64 (mean=51; SD=8.84). The majority of patients (n=16, 76%) were infected with genotype 1, followed by genotype 3 (n=3, 14%), and genotype 2 (n=1, 5%) and genotype 4 (n=1, 5%). Evidence of cirrhosis based on biopsy, fibrosure test or physician documentation was documented in 9 cases (43%). Nineteen patients were currently undergoing antiviral therapy and two were four weeks post-treatment at the time of the interview. We purposively sampled from all weeks during treatment to obtain a wide perspective, such that time on treatment ranged from 4 to 40 weeks (mean=17; SD=11.6). Eleven patients (52%) were receiving standard of care (SC) dual PegIFN/RBV therapy, while 10 Clinical Trial (CT) patients (48%) were participating in clinical trial protocols, all of which included PegIFN/RBV in combination with another direct-acting antiviral(s).

Taking Doses “As Soon As”: Missing Doses and Dose-Timing Deviations

When participants were asked in an open-ended manner to describe the process of taking their medications, only a few (n=3) reported missing any doses. However, when probed further about dose-timing errors or reasons for delaying medication-taking, 11 out of 21 participants subsequently described deviations in the timing of their doses, i.e., taking them later than intended, missing them, or doubling up on doses once they realized they had missed a previous dose. The following interchange exemplifies how information about dose timing was elicited after the participant initially seemed to be adherent:

Interviewer: *So, talk to me a little bit about the process of taking both your medicines, the shot and then the pills.*

Participant: *It hasn’t been any problem for me. I give my own shots and that’s a piece of cake.*

Interviewer: *What day or nights have you done it?*

Participant: *I think it’s every Thursday night.*

Interviewer: *So, you took a shot last night?*

Participant: *No, I couldn’t do it - - you know, so I’ll do it tonight. If I don’t do it Thursday night I do it Friday night.*

Most deviations in dose timing involved participants taking their doses later than they intended, but as soon as possible once they remembered or gained access to their medications. One woman said that she might miss it if she got busy, but *“as soon as I came home, I’d take it. I’ve never been one to miss doses of anything.”* Similarly, participants reported taking medications “as soon as” they came home after being out to dinner or “as soon as” they woke up after falling asleep prematurely. Some participants generally did not express concern about taking their oral medications a few hours later because the dosing requirement gave a 12-hour window. One woman said, *“So, my medication is like one day I may take it at 9:30; one day I may take it at noon and so, you know, there’s a lot of leeway*

around that, the time I took it;" another participant said that missing a dose "*wasn't the end of the world*." No perceptible group differences in dose-timing errors occurred between SC and CT patients, with both mentioning missing or accidentally delaying doses. However, a perceptible difference was found for patients who were previously naïve or experienced with HCV treatment. Of 15 patients previously naïve to treatment, 9 (60%) mentioned dose-timing errors, while only 2 out of 6 (33%) treatment experienced patients mentioned dose-timing errors. This suggests that prior experience with HCV treatment may be associated with fewer dose-timing errors and greater adherence.

Facilitators of Medication Adherence

Patients provided many insights into factors that aided them in taking their medications as prescribed. These factors generally fell into two broad categories: those having an impact on their motivation or commitment to adhere and behavioral strategies to aid in remembering to take medications.

Sources of Motivation—Participants discussed different phenomena they used to motivate themselves to take their medications. These phenomena included knowledge or information, committing to an external source (e.g., HCV provider/research coordinator or research trial), and cognitive (internal locus of control, optimistic thinking) and emotional factors (e.g., fear/anxiety). Knowledge or information that antiviral treatment could cure them of hepatitis C was a necessary and strong motivator for over half of the participants. They used many statements to reflect that simply having information and knowing that treatment was effective helped them to take their medications. Several examples include: *"I know I need to take them," "Knowing I'm getting better," "Just to know that this is the procedure to get well," "Just knowing that I need to take 'em. And, you know, that if I don't that it's not gonna work."*

Eleven participants described forms of 'social motivation' by talking about making a commitment and wishing to comply with an external source, as a strong motivator of adherence. Several CT participants described committing to a clinical trial as motivation; one man said *"I was talking about being in the study too 'cause it keeps you focused and this is something you've committed to"* another man indicated, "*This trial means a lot, you know. I don't want to jeopardize the trial in any way."* Six patients, both SC and CT, described a commitment to their medical providers' advice (i.e., doctor, nurse practitioner, or research study coordinator); as one woman said, *"Hey, you want to get well you better listen to the doctor."* Another participant reported adhering to treatment because he did not want to *"mess up this opportunity"*. One man described in detail how trust in his provider and commitment to the Alcoholics Anonymous (AA) program motivated him during HCV treatment:

> "That's what [doctors] do for a living, you know. If I didn't trust the doctor when this crap started… I know where to go get some valiums, OK? You can go get what you want if you've got some cash money. And I want a couple blues. And I'm in this A.A. program. They said 'don't do that.' They said 'don't be your own doctor. You tried that shit all your life and it didn't work.' So I don't do that at all. And I don't try to con the doctor out of it either, you know?"

Many participants talked about their personal motivations to adhere which seemed to involve both their belief systems (cognitions, schemas, self-statements) as well as emotional states (e.g., anxiety) that appeared to be catalysts related to adherence. They described actively shoring up internal sources of personal motivation, through a sense of internal locus of control to help them adhere to treatment although the mechanisms for this varied by individual. Notably, patients without cirrhosis (7 out of 12; 58%) had a higher proportion of utterances implying an internal sense of control compared to patients with cirrhosis (2 out of 9; 22%). Other participants described a heightened sense of commitment to treatment driven by anxiety, as one man said of his treatment, *"I'm kind of uptight about it."* Other participants said *"I'm really persistent when I get myself in that frame of mind to start treatment…. I'm like a rabid dog when it comes to taking the treatment when I get myself ready for it"*, and *"You just "rah" all the way through it. Try to get yourself psyched."* Sometimes, however, the internal locus of control and sense of responsibility led to heightened anxiety levels, particularly if a participant missed his/her medication: *"Because getting off schedule really, when I get off schedule 'cause I have one time, I got very scared and in order for my disease to go away I have to really stay on schedule and do as I'm told."* One patient summed up motivation as being a dually stemming from anxiety and external locus of control*: "When I get off schedule cause I have one time, I got very scared and in order for my disease to go away, I have to really stay on schedule and do as I'm told."*

Several participants described using helpful cognitive self-statements to motivate themselves for treatment; the language they used in such messages seemed almost aphoristic. Examples of such sayings include *"If you're going to take them, take them right;" "I've got to take it. I've got to take it;" "Let's go get it done;" "I made a decision I'm going to do this and I'm going to do this"; "If you want to get better, you've got to take it;"* and *"Why bother doing this if I'm not gonna do it?"*

Other participants said that future-oriented thinking and contemplating the positive consequences of curative treatment was motivating. One man said he was motivated by *"Knowing that I want to be better. Knowing that I want this stuff away from me. I feel like I've got a lot more to live for, you know."* Another described reassuring himself that treatment would be worthwhile when his disease was cured:

> "As soon as I'm off this stuff, you know, whenever the treatment runs out and we're done, then these effects are going to go away. And then if all goes well then the virus is gone. And that's going to, in the long run after a while, make you feel even better. So, that's what you've got to focus on, you know, is you might suffer now but you're gonna feel a lot better later."

With the exception of social motivation related to an external commitment to a clinical trial, no other differences between SC and CT participants were noted. Patients without cirrhosis made more utterances reflecting an internal locus of control (i.e., I can control life events through my own behaviors/actions) compared to cirrhotic patients. SC and CT patients both perceived a similar sense of anxiety regarding missed or delayed doses, and both expressed a sense of external commitment to HCV treatment personnel: the treating nurse practitioner for SC patients and the "doctor" and study research coordinator for CT participants.

Behavioral Strategies—Participants listed a wide range of specific behavioral strategies they used to help them remember or manage taking their medications, which did not differ between SC and CT patients. Some individuals devised ways to organize their routine or lifestyle to incorporate dosing into their daily activities, some described very specific tools or cues used to remember doses, and others talked about strategies they developed preemptively to manage taking their medications in the event of a deviation from their normal routine, such as travel away from home.

The most frequently mentioned behavioral facilitators were the use of routinized schedules, mentioned by all but two participants. Many such routines hinged on mealtime since the oral medications were often paired with food to increase absorption or counteract nausea. As one participant described, *"I'll take my trial drug after breakfast before work. I'll take three Ribavirin at the same time and I take all my other medications at the same time too every morning. Like I said, that way I won't forget any. Then I'll take three more Ribavirin after lunch, after I've had lunch. And then the Peg, I take it on Friday evenings about 8:00, about an hour or two before bed."* Participants also said they contoured their dosing routine around when they expected their side effects to be worst. One man took his pills just before bed: *"They say if the side effects are gonna be there, they're gonna be the first so you want to sleep through the first, the worst part of it."* Several said they scheduled their injection for Friday evening so that side effects would happen over the weekend rather than during the week; as one man said, *"I have picked Friday nights to do them cause that way I know that I'm gonna be feeling the worst over the next day or two after I take the shot. So, the weekends are usually a little freer for me to lay around and be like 'ehh,' you know, 'I'm just not feeling well.' If you need to get something done during the week, then you're going to be able to get something done."*

Three participants spoke of key elements or rituals that were personally important to self-administering the medication. One CT patient described in detail all the steps of her ritual: *"I would wake up at 6:00, get my spoon of peanut butter and then I'd get all my medications together right there and separate them out, take my pills and I'd take my shot and then I'd drink my water."* A SC patient said that it was important to take his shot alone: *"It was just one of those things. I didn't mind taking the shots or people knowing I was taking the shots. I just didn't want somebody watching me take the shots. I don't know."* Another said she always sat down in a *"certain spot"* to do her injection.

A few participants said they had to plan ahead and make adjustments to find a schedule that worked best for their lifestyle. As one woman said, *"For me I've just had to juggle to decide what's best for me. It seemed like if I took really early, mid-day, I was feelin' punk. But if I waited, I didn't feel punk until it was just about time for bed and I could sleep through it."* Some described a collaborative relationship with their provider and spoke of being given flexibility from the provider in dosing to select a routine that worked best for them. One participant described, *"You can tweak around with your timing as long as the doctor knows you're doing it and possibly how many pills you're taking in the morning versus how many pills you're taking at night or maybe even, you know, there's a possibility you can take them all at once."*

Four participants described specific strategies they used to reduce the unpleasantness of treatment or its side effects. One woman described in detail several pieces of her routine designed to make taking the shot more tolerable: *"And then the injection I take on Friday night at 6:00 and I take it at about 15 minutes before I inject it and let it warm up a little bit. And I usually count to seven slow so it won't go in too fast. 'Cause I think if you push it fast, it burns. And then I like to do mine slow. Then I sit there and rub it…"* Another participant said he took Tylenol about an hour before the injection. Another said he would try to distract himself from the injection's unpleasant side effects by working, reading a book, or watching television. Still another described eating something sweet *("…one or two Skittles, you know, a piece of chocolate, whatever…"*) to counteract the bitter-tasting pills.

Participants employed other behavioral strategies to assist them in the task of remembering to take their medications. For example, one woman said she left her pill box out in her office as a cue to remember to take her pills at work, and another described a system he had developed of moving the pill bottle from one side of a drawer to another to remember whether he had taken them. Seven participants discussed using pill boxes to help them remember. Two participants wrote themselves notes; as one described, *"Yeah, and if you want to do something, write notes. Write notes. I've been doing that for a long time anyway, you know, cause I'm a type A and I have 15 things going and two jobs and 15 other things to do. And if I don't make notes, it doesn't get done, you know."* One man relied on his wife to remind him to take his pills; as he put it: *"She's 'take your pills. Take your pills.'"* Another said he set an alarm on his phone as a cue to dose.

Specific strategies that helped participants who experienced a change in routine, like being away from home unpredictably, were described. For example, one participant kept medication doses in both his and his wife's car.

Soliciting emotional and informational support from the doctors, nurse practitioner or research coordinators was another behavioral coping strategy employed when patients missed or had a delay in dosing. SC participants described their relationship with the treating nurse practitioner while the CT patients relied on the study coordinators for emotional and tangible support. One CT participant related that she was reassured by the study coordinator that if she does experience a deviation in dosing, she should *"just call [the coordinator] and she'll put me back on track."* One SC participant described: :

> "I had just fallen asleep. And then I had called (nurse practitioner) on Monday and she said it was OK, go ahead and take it Monday."

Another CT participant related, *"Yesterday I had to call [my coordinator] and ask her, yesterday was a very heavy day. And like I said, I normally eat my lunch and then take my three Ribavirin after lunch. I couldn't remember if I took the Ribavirin or not. So, I called her and I said 'Look, I've got about 15 left.' She said 'Look. Just don't take anything till you get here and we'll just go from there.'"*

Another SC participant indicated, *"I had just fallen asleep. And then I had called (nurse practitioner) on Monday and she said it was OK, go ahead and take it Monday."*

Communication with providers and coordinators was vital, not only for the provision of informational support about safe dosing, but also for the provision of emotional support to alleviate anxiety when they did not dose properly. The level of fear and need for emotional support is eloquently exemplified by the following utterance: "*One day I didn't take mine and I was scared to death. And I called (nurse practitioner) and I told her and she said don't worry about it, just take it within 24 hours of that time that I missed. And that scared me to death… I mean it could make you have a nervous breakdown or stress level go up."* Thus, the patient-provider relationship provided multiple mechanisms by which improvements in patient adherence could be obtained: (a) as a social motivator that provided an external commitment to adhere; (b) by providing practical informational support in what "to do"; and (c) by alleviating patients' anxiety about missing doses through emotional support.

Barriers to Antiviral Treatment Adherence

Study participants reported many different barriers to taking their medicines as prescribed and these barriers did not differ significantly between SC and CT participants. They generally talked about factors that contributed both to skipping doses altogether and to taking doses late, without distinguishing between the two; therefore, we present data on barriers to both types together. Most of the barriers described were logistical and led participants to miss or delay medication unintentionally. A few participants, however also discussed how side effects, most often nausea, led them to intentionally avoid taking medication (RBV tablets).

The most frequently described barrier to taking medications was getting busy or having a change in one's daily routine (N=9). One man reported that taking a phone call distracted him from taking a dose: *"I got busy! Phone calls…. The phone is ringing a lot."* Another participant found that his daily responsibilities taking care of his children sometimes led him to take doses later than scheduled: *"Just, you know, life gets in the way. So, you know, getting the kids ready for school or getting the kids ready for bed. Just familial type stuff can get in the way of taking the medication."* Both work and leisure activities were listed as other examples of how getting busy can lead to missed or delayed doses. One woman reported: *"When you get too busy or you're out having fun or if you're having fun, yeah, and time catches up with you;"* another man described, *"I get involved in work and then a couple hours pass on by. So I've got to stop and take my meds."*

Participants also described that getting busy affected their adherence indirectly by altering their eating schedule (N=6). One man described, *"I remember one time I didn't eat till like, like I missed breakfast. I was trying to get a bunch of stuff done. And I kept putting off breakfast and I didn't eat. And then before I realized it, it was like 3:00 and then I figured 'well, I'll make sure I take it at 10:00'."* Some participants reported particular problems adhering to a medication schedule because they do not eat at the same times every day; as one described, *"One of my problems is I don't eat every day at the same time. If I ate every day at the same time then it would be easy to remember."* Another man said that poor access to food sometimes kept him from taking a dose.

Getting busy and changes in daily routine got in the way of dose-taking particularly when they involved being away from home without medicines (N=6). One participant predicted

that if she ever did miss a medication it would happen if she was away from home: *"That I got busy doing something away from the house because I don't carry them with me."* Other participants recounted delaying or missing doses due to not bringing medications with them to work, out to eat, and on a trip out of town. A specific challenge of taking medications away from home is the time-consuming nature of taking these particular medication regimens. One participant illustrated how the "ritual" required for taking hepatitis C medications is difficult to slip into an altered schedule: *"Well, I guess traveling or being, you know, not set in your home environment…. I was concerned about my medicines and, you know, someone else's schedule and then getting back to my bag of medication and to - - even though I don't like rituals, it turns into one. I just want to be able to pop one and go. But, no, you have to get them out of the packaging and do your diary and so it turns into a little ritual that you need some time to count, make sure you get it and don't just think you did it and come back later and there they are, still there. 'Whoops. I thought I took those,' which has happened; not a long length of time but I said 'I thought I'd popped them but there they are right there'."* Another man said that the large amount of medication supplies made it unlikely that he would take them with him outside of the home: *"And then if you're out or whatever, I mean you're not going to carry this big week's supply thing around, you know."*

Another salient barrier to taking medicines participants discussed was sleep. Participants reported both sleeping through morning doses and falling asleep (often watching television) before taking scheduled nighttime doses (N=7). One woman reported missing doses due to falling asleep prior to her evening dose: *"And I've only forgotten to do it maybe three times. I actually fell asleep in the evening. Woke up a couple hours later and remembered to take it. And I just this past, last week, fell asleep and got up and went to bed. I forgot to take it at all. And that's the only time that's happened so far."*

A few patients intentionally skipping doses due to side effects, most notably nausea. Another problematic side effect mentioned by one participant was short-term memory loss, which made it difficult to remember to take doses; he described using a pill counter to help keep track of his doses: *"I'd look at [the pill counter] and even if I knew I'd taken 'em 'cause this stuff will give you like short-term memory loss big-time. Big time. You go to the kitchen. 'What the hell am I doing here?' I mean that's not uncommon. You walk in the kitchen and it's like you're suddenly senile, you know?"*

Although he did not admit to missing or delaying doses, one CT participant spoke in-depth about the burden of taking HCV medications, which could represent a negative attitude as a barrier to medication adherence and persistence:

> *"You'll get tired of it. You'll get overwhelmed by it all the time. 'I just took it. I've got to do it again.' And some people, if they're ready to forget, they'll do it on purpose. I could see where, OK, 'God, I forgot. What are you going to do? Kill me?'" … "[the pills would] get stuck in my throat", "there seems to be a lot of them, a lot of pills and it gets to be a bigger and bigger job sometimes",* and *"mentally, you know, gets a little old."* Although this theme was not mentioned by

other participants, it emerged strongly from this individual and may represent others' experiences.

Additional reasons for missing doses that were probed included "feeling too good," "being overwhelmed," or "depressed" but none were endorsed. Additionally, no significant group differences were found for gender or history of depression. Notably, no major differences between SC and CT participants, except where indicated above, were identified, suggesting that the dose-timing errors, facilitators and barriers identified here were ubiquitous across different patient characteristics and various antiviral regimens.

DISCUSSION

Adherence to HCV treatment plays a critical role in achieving a sustained virological response and when optimized may substantially improve health outcomes at the individual and public health level. The current study expands upon the handful of quantitative HCV adherence studies that exist, by capturing qualitatively, patients' experiences with these treatment regimens, a perspective overlooked in the HCV adherence literature until now. Several of our findings are consistent with previous adherence studies conducted in other medical or treatment populations, such as HIV (15). Other findings, however, were new, perhaps unique to HCV treatment, and are worthy of further exploration, as described below. Additionally, while we did not apply a theory-guided approach during interview guide development, we recognized *post-hoc* that many of our findings, particularly factors which facilitate adherence, fit exceptionally well within an *a priori* conceptual model known as the Information-Motivation-Behavior Skills (IMB) Model of Adherence (16) that may serve as a useful framework for HCV adherence researchers, as well as clinicians preparing their patients for treatment and supporting adherence efforts during treatment.

The IMB model of adherence is based upon an analysis and integration of social and health psychology theories and supported by twenty years of research (16), with various health behaviors, most commonly HIV antiretroviral adherence. The IMB model posits that three fundamental determinants drive adherent behavior: 1) information/knowledge; 2) personal and social motivation; and 3) behavioral skills(16). Accordingly, patients who are well-informed about treatment, have internal and external motivations to adhere, and possess effective behavioral skills will be more likely to adhere to treatment.

Consistent with the IMB model and previous studies in HIV, HCV patients in the current study described knowledge and information about the important role of medication adherence, as being critical to adherence. Patients also described both social and personal motivators as key to adherence. Social motivators came in the form of an external commitment to a research trial, having a strong rapport built with the research coordinator/medical provider, or simply feeling grateful and "having the opportunity to undergo treatment." These findings are consistent with the IMB model and a growing body of work demonstrating that the patient-provider relationship and patients' perception of provider support are critical to medication adherence (16–19). For HCV patients, the provider-patient relationship seems to be a critical mediator or mechanism of treatment engagement, including adherence (18, 20). In the current study, we found that through various

mechanisms of social support, the patient-provider/coordinator relationship served multiple purposes: it motivated patients; provided tangible informational support in the event of missed doses; and helped patients manage dosing-related anxiety after “messing up.” Interestingly the importance of the patient-provider relationship to adherence may have trumped the importance of family support, as evidenced by more references to the importance of the patient-provider relationship than to family relationships. Also consistent with the IMB model, participants in this study described experiences they had shoring up their personal motivation to adhere, such as developing an internal sense of determination and resolve, using helpful, cheerleading-like self-statements, and future-oriented optimistic thoughts about the long-term positive consequences they associated with being cured. These were all important cognitive motivators patients believed fueled their adherence and persistence. No major differences were found in types of motivators for patients treated in SC or CTs or those with and without cirrhosis. An exception to this was that patients without cirrhosis, compared to those with cirrhosis, made more utterances reflecting motivation from an internal locus of control (i.e., the belief that their behaviors/actions controlled events in their lives). Finally, behavioral skills were essential to facilitating adherence such as documented in studies of HIV adherence (15, 21). The most common behaviors were establishing weekly dosing routines, which were even described as “ritualistic.” The routine sometimes occurred after some trial and error to configure dosing around anticipated side effects, occupational and family duties, meal time, and sleep habits. Patients also described ways in minimize the impact of side effects and reduce the unpleasantness of the medication dosing experience (e.g., how to carefully administer the injection or counteract the bitterness of pills with candy or chocolate). Taken together, these findings provide strong support for the three main determinants/facilitators of the IMB model (information, motivation, behavioral skills) and offer a useful conceptual framework in which to study, and potentially intervene upon, HCV treatment adherence.

With regard to barriers to adherence, patients cited numerous hindrances that have been reported elsewhere, such as in the HIV adherence literature: changes in routine, being too busy, sleeping through dosing times, as well as short-term memory issues, pill burden, competing work and family responsibilities (15). Only a few patients described purposefully skipping doses due to side effects, which may be more common in other treatment populations (22). Patients did not endorse missing doses due to feeling good, feeling depressed or overwhelmed, however, many indicated that treatment was overwhelming and interfered with their daily lives. Finally, pairing medication-taking with meal time had its advantages and disadvantages: meals were a good environmental cue to prompt medication taking as long as the patients always ate meals on schedule. However, if they became too busy to eat, then medication-taking was also delayed.

Two other themes that emerged are noteworthy because they provide highly useful information that clinicians can use to facilitate communication about adherence with their patients: (a) delays in dosing and (b) adherence-related anxiety. First, participants did not consider delays in dosing to be the same as “missed doses,” highlighting the need to be cognizant of how adherence is queried in the clinical setting. Patients did not endorse missing doses when asked in a routine manner (e.g., “Did you miss any doses?”), but when

probed further about *delays in dosing*, patients then acknowledged times when dosing occurred a few to several hours later than they originally intended, and this applied to patients treated in clinical trials and in standard of care. Patients who had previously undergone HCV treatment demonstrated fewer dose-timing errors (33%) than patients on their first course of treatment (60%), suggesting that patients with prior experience with HCV treatment may have fewer dose-timing errors and greater medication adherence during a subsequent course of treatment. We noted a few instances where patients "doubled up" on their oral medications when they forgot the earlier dose. Delayed dosing may not be as critical when there is a 12-hour or 24-hour window to dose; however, when a routine is not implemented and patients take their medications at any time point during the day, there is more room for forgetting to take them. Also, if oral regimens in the future require stricter dosing windows, such delays may have an impact on adherence, drug efficacy, development of mutant viral strains, and treatment success (22–24) Clinically, this finding highlights the importance of patient-provider communication style, suggesting that subtle differences in questioning style may elicit dramatically different patient self-reports (22). Querying about differences between intended and actual dosing times, such as, "You've told me that you try to take your medications at 8a.m. and 6p.m. What gets in the way of taking them right at 8 or 6 where you might find that you take them several hours later?" may elicit more useful information about delayed dosing that can be used to coach patients about behavioral skills. Use of "implementation intentions" can help patients determine exactly when, where and how to dose medications as prescribed in an environmentally-cued, ritualistic manner (25). Finally, patients described a "trial and error" period in the first few weeks of treatment as they attempted to develop a dosing routine. Clinicians may consider recommending a "trial and error" period *prior* to starting HCV treatment using fake medicines (e.g., jellybeans) so that patients can work through these logistical issues before starting the real regimen, thereby reducing dose-timing errors early in treatment that could impede achieving rapid virological response.

A second somewhat unexpected theme was the level of anxiety and fear both SC and CT patients reported regarding adherence to the HCV regimen. "Adherence-related anxiety" is not a well-described phenomenon in the adherence literature and warrants consideration. First, adherence-related anxiety is not described as a specific determinant of adherent behaviors in the IMB model, although theoretically, it could be categorized as a moderator such as general mental health (16). It is possible that the adherence-related anxiety taps into pre-existing anxiety but it will be important to make this distinction. Second, it may be that adherence-related anxiety is somewhat unique to HCV treatment due to a variety of factors but including: a) the tremendous perseverance it takes to become eligible and start HCV treatment; b) the perceived benefit of HCV treatment (i.e., "cure"); and c) the relatively intense but time-limited regimen. Third, consistent with the Yerkes-Dodson theory, it may be that a moderate level of anxiety is optimal for best adherence performance (26). When anxiety is too low, individuals may be complacent; when too high, it may interfere with performance. Thus, one aspect of helping patients' achieve optimal adherence may involve helping them to maintain a moderate level of anxiety that keeps them vigilant and on-task, but not overly fearful.

Limitations of this study are the small sample size, heterogeneity of patient characteristics, and inability to statistically analyze qualitative data, though this was not the intent of this study. Also, the findings from this study may not be representative of dissimilar HCV patients or clinical settings being treated elsewhere and may not apply to other patient populations undergoing medical treatment. Conversely, findings from other adherence studies may not apply to patients undergoing HCV treatment. Patients with HCV often have to overcome significant personal, social, financial, and structural obstacles in order to embark on HCV treatment; therefore, patients who actually undergo HCV treatment such as these in standard practice and especially clinical trials may represent a relatively motivated group of individuals likely to adhere. Those that ultimately chose to undergo treatment may be markedly more motivated compared to individuals from the community who are diagnosed but not invested in treatment. Additionally, HCV treatment is intense, time-limited, and can be wrought with side effects, yet curative; thus, it represents a rather unique setting in which to study medication adherence. More systematic research is clearly warranted. Future directions for research may include large quantitative studies to confirm these findings, studies to prospectively examine whether the IMB model is a good fit to capture determinants of HCV adherence and exploration of adherence-related anxiety and whether it has a curvilinear relationship with adherence.

This qualitative study is an important first step towards understanding patient factors that should be addressed to improve HCV treatment adherence. Before adherence interventions for HCV can be developed, more research is needed to understand better the prevalence of determinants and moderators of adherence, and application of theoretical models such as the IMB will almost certainly prove useful. The data from this small study also provide clinicians with a glimpse into the needs of patients during HCV treatment and provide insight into ways in which we can improve clinical care by addressing patient knowledge, motivation, and behavioral skills.

Acknowledgments

Declaration of Funding Interests: This study was supported, in part, by National Institutes of Health: K23DK089004-02 (Evon); UL1RR025747 (Bonner); and P30-AI50410 (Golin, Grodensky).

We would like to thank the patients who participated in this study and the hepatology clinicians and research coordinators who care for them.

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TABLE 1

INTERVIEW GUIDE

	Topic Area	Specific Questions Asked	Probes
1	**Patients' General Experience with HCV Treatment**	We would like to hear from you about your experiences with undergoing HCV treatment	How do you feel about taking these medications? How do you think these medications are affecting your health? What is the hardest thing about being on this treatment? What other things has the treatment affected in your life?
2	**Side Effects/Coping**	Tell me about what kind of side effects you have been experiencing? What helps with dealing with those side effects?	Tell me about any experiences with irritability… nausea….insomnia…feeling tired…being achy? What do you do to cope with side effects? What do you think or tell yourself to help deal with side effects? How have the side effects affected your role at work, or at home?
3	**Depression/Coping**	What was your mood like before you started Hep C treatment? What has your mood been like since starting Hep C treatment? Do you think there is a direct link between the Hep C medications, and your mood? When you are feeling down/irritable/nervous, what helps you the most?	Tell me more about that… What do you think or tell yourself to help deal with your mood?
4	**Other Life Interference**	In addition to side effects, what other things have been difficult for you during treatment? What things have been good for you during treatment?	
5	**Social Support**	Tell me about the support you have had from friends, family, or other groups to which you belong? Are there other types of support that you are not getting during treatment, that you think would be helpful for you?	How has support affected you during treatment? how about … emotional support informational support tangible support affectionate/nurturing support
6	**Facilitators to Medication-Taking Adherence** **Patients Understanding of Adherence**	Tell me about the process of taking your HCV medications?	What do you do think helps you take your medications as prescribed? How important do you think it is to take your medications exactly like your doctor told you to?
7	**Barriers to Medication-Taking Adherence**	What gets in the way of you taking your medications?	Have you EVER missed taken your medications because … You felt too good You fell asleep or slept through dose time You simply forgot You had a change in your daily routine You got busy with other things You felt too sick/ill You felt depressed/overwhelmed Do you think you could benefit from talking about other ways to help take your medications

TABLE 2

PATIENT CHARACTERISTICS

Patient Characteristics	N	%
Gender		
Male	14	66.7
Female	7	33.3
Ethnicity		
Caucasian	20	95.2
African-American	1	4.8
Marital Status		
Single	5	23.8
Married or Partnered	11	52.4
Divorced	4	19.0
Widowed	1	4.8
Education Status		
< High School Diploma	4	19.0
> High School Diploma	17	81.0
Estimated Annual Household Income		
<$40,000	9	42.9
$41,000 to $60,000	2	9.5
$61,000 to $100,000	5	23.8
>$100,000	2	9.5
Refused	3	14.3
Employment Status		
Full-Time or Part-Time	12	57.1
Unemployed	4	19.0
Disabled	1	4.8
Retired	2	9.5
Homemaker	2	9.5
Insurance Status		
Private	13	61.9
Public Medicaid or Medicare	1	4.8
No Insurance/Self-Pay	3	14.3
Supplemental Hospital Support	4	19.0
Liver Disease Status		
Cirrhosis	9	43%
No Cirrhosis	12	57%
Treatment Status		
Treatment Naive	15	71%
Treatment Experienced	6	29%