Treat Early or Wait and Monitor? A Qualitative Analysis of Provider Hepatitis C Virus Treatment Decision-Making in the Context of HIV Coinfection

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Abstract

Liver disease is a leading cause of death among patients with HIV coinfecting with hepatitis C (HCV); yet, studies show that less than 10% receive HCV treatment, in part because of limited treatment response, high treatment toxicity, and psychosocial barriers to treatment readiness. Using a process model framework, we sought to explore the factors and processes by which providers make HCV treatment decisions for HIV-coinfecting patients. We conducted 22 semistructured interviews with primary care providers and support staff at three HIV clinics in Los Angeles, California, in which rates of HCV treatment uptake varied from 10% to 38%. Providers agreed that stable HIV disease, favorable genotype, and significant signs of liver disease progression are all signs of need for treatment. However, two divergent treatment approaches emerged for genotype 1 and 4 patients with minimal disease, and in definitions of patient readiness. Providers with lower treatment rates preferred to delay treatment in hopes of better future treatment options, and were more conservative in requiring complete mental health screens and treatment and abstinence from substance use. Conversely, providers with higher treatment rates viewed all patients as needing treatment as soon as possible, and defined readiness more leniently, with some willing to treat even in the context of untreated depression and drug use, so long as ability to adhere well was demonstrated. Regardless of whether an aggressive or cautious approach to treatment is used, development of effective programs for promoting patient treatment readiness is critical to ensuring greater treatment uptake.

Introduction

NEARLY 30% OF HIV-POSITIVE AMERICANS are coinfecting with hepatitis C (HCV),¹ and with HIV antiretroviral therapy (ART) extending the life of people living with HIV, end-stage liver disease is now a leading cause of death in this population.^{2,3} Studies show that a majority of coinfecting patients have at least moderate liver inflammation or other signs of disease progression,^{4,5} however, several studies published over the past 5 years have shown that less than one third of HIV coinfecting patients in the United States are deemed eligible for HCV treatment, and under 10% actually receive treatment.^{6–12} Despite the apparent discord between the need for more aggressive HCV clinical management and the low treatment rates that are generally observed, few studies have examined the treatment decision-making of providers of HIV-coinfecting patients.

The relatively low efficacy and high toxicity of HCV treatment undoubtedly contribute to the low treatment uptake. Rates of sustained viral response (SVR) or a “cure” have improved with the advent of pegylated-interferon (PEG-IFN) in combination with ribavirin (RBV), but still remain limited with rates ranging from 27%–45% among HIV coinfecting patients^{13–16}; rates are even lower among genotype 1 patients at 17%–38%, who represent the vast majority of the patients in the United States. New treatment agents (e.g., protease and polymerase inhibitors) that may improve treatment efficacy are at various stages of development and testing, but are not expected to be available for routine practice for at least a few years and interferon will remain a component of treatment.¹⁷ HCV treatment is considered highly burdensome with flu-like symptoms (nausea, diarrhea, weight loss), fatigue associated with hematologic abnormalities (anemia, neutropenia), and neuropsychiatric symptoms (depression, irritability) being

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highly prevalent,¹⁸ and dropout rates as high as 40%–50% in community samples of coinfecting patients.^{14,19,20} Conversely, proponents of HCV treatment can argue that PEG-IFN/RBV, unlike ART, has a limited duration and at least a chance of a cure.

Although HCV treatment guidelines for HIV coinfecting patients have been published,²¹ there remains a lack of consensus and variable expert opinion with regard to several key factors. Stage of disease with regard to both HIV and HCV is thought to play a leading role in influencing provider decisions about whether to recommend HCV treatment. Patients with genotype 2 or 3 are typically thought to be good treatment candidates as long as the liver disease is not too advanced because of the high treatment success rate among these patients.^{13–16} Among genotype 1 and 4 patients, HCV treatment has generally been recommended for patients with at least moderate signs of fibrosis and inflammation of the liver; however, some recommend that coinfecting patients with minimal or no fibrosis should also be considered for treatment.²² Late stage, decompensated liver disease and advanced immunosuppression (i.e., low CD4 count) are common reasons for coinfecting patients being excluded from HCV treatment,⁷ and HCV treatment has been shown to be more successful among HIV patients with higher CD4 counts and milder liver disease.^{23–25} This suggests the need to closely monitor patients and to initiate treatment prior to both HCV and HIV disease becoming too advanced. Nonetheless, studies of coinfecting patients reveal high rates (55%–84%) of advanced liver disease upon onset of HCV treatment.²⁶

Provider perception of a patient's readiness to tolerate and adhere to treatment also plays a major role in treatment decision making. Poor clinic attendance and nonadherence to ART are seen as proxies for readiness to adhere to HCV treatment and as justification to defer treatment.^{7,27} Substance abuse and mental illness each account for 20%–30% of coinfecting patients being deemed ineligible for treatment, as clinicians are concerned that the side effects of HCV treatment may lead to psychiatric deterioration, relapse into substance abuse, poor adherence, and treatment discontinuation.^{6–8,27,28} Psychiatric and substance abuse patients have been excluded from most clinical trials, but the little data available show mixed results; some studies find that such patients do equally as well in terms of ability to complete and respond to treatment,^{29–31} while others suggest that patients with active substance abuse and psychiatric problems are less likely to respond and more likely to drop out of treatment.^{32,33}

Characteristics of the provider and clinic organization can also influence HCV treatment decisions. Unlike HCV mono-infected patients, who are typically treated by liver specialists (e.g., hepatologist or gastroenterologist) with extensive experience with HCV treatment, HIV coinfecting patients are most often treated by HIV primary care providers (with relatively limited experience with PEG-IFN/RBV) because liver specialists are unavailable. Aside from medical discipline and amount of experience with HCV treatment, other provider characteristics that may influence treatment decisions include provider attitudes towards the efficacy, burden level, and urgency of HCV treatment. Organizational factors include the availability of a liver specialist either as the primary HCV care provider or as a consultant, the use of specialty subclinics devoted specifically to HCV care, clinic policies or guidelines

for determining HCV treatment candidates, and access to mental health and substance abuse specialists.

In this report, we document findings from semistructured, qualitative interviews conducted with 11 HCV primary care providers and 11 support staff at 3 HIV clinics in Los Angeles, California. The goals of the study were to explore the factors and processes by which providers make HCV treatment decisions, and the barriers to HCV treatment uptake, among HCV treatment-naïve HIV patients with chronic HCV infection.

Methods

Study design

We used a process model framework³⁴ and case study evaluations with semistructured interviews to explore the HCV treatment decision making of providers. This approach assumes that decisions involve considerable uncertainty, as providers may be uncertain about how to define the decisional problem, the outcomes of decisional options and their probabilities, or alternative decisional choices. We would expect providers to deal with this uncertainty by attempting to simplify the process by emphasizing some aspects of the problem more than others, to differ in which factors influence their decisions, and to use heuristics and guidelines to structure the decision making process. The interviews explored factors that influence the provider's decision to recommend or defer HCV treatment for HIV coinfecting patients.

Setting

The study was conducted at three HIV clinics in Los Angeles, California. As listed in Table 1, the sites differ on a number of characteristics including the number of HIV patients and HIV/HCV co-infected patients, involvement of a liver specialist, and HCV treatment rates.

Each of the sites instituted efforts to increase access to HCV treatment approximately 5 years ago. Although sites A and B reside within a hospital or larger medical center, the HIV coinfecting patients at each of the three sites receive their HCV care at the HIV clinic. Providers from outside the HIV clinic are involved in HCV care only at site B, where a liver specialist attends clinic to provide HCV treatment; this is the only site where a liver specialist is involved.

The system of providing HCV care varies at each of the three sites. At site A, HIV and HCV primary care are largely provided by nurse practitioners (NPs) who are supervised by two infectious diseases (ID) attending physicians. The physicians often play an active role in consultations with patients, and treatment decisions are made jointly between the physicians and the NPs. Support staff includes nurses, case managers, and mental health providers (psychiatrist and psychology fellows). This site differs from the other two sites in two key ways: it does not serve as a repository of referrals for HCV care from other clinics; and its HCV specific clinic session is only for patients who are on HCV treatment, not patients being evaluated for treatment candidacy.

Site B is one clinic located within a hospital that is part of a larger system of care centers. This clinic provides HCV care to its patients as well as HIV coinfecting patients referred from one other Los Angeles clinic within the associated care system. HIV primary care is provided by four ID physicians at this site. These physicians refer their HCV coinfecting patients

TABLE 1. SITE CHARACTERISTICS

	Site A	Site B	Site C
Number of HIV patients	1000	400	1700
Patients: % female	25%	5%	15%
Patients: % ethnic/racial minority	85%	72%	75%
Number (%) HIV/HCV coinfecting patients	150	100 ^a	650 ^a
Number of HCV-treated coinfecting patients	15 (10%)	30 (30%)	250 (38%)
Liver specialist involved in HCV care	No	Yes	No
Number of HCV primary care providers	5	6	2

^aIncludes HIV co-infected patients referred from other clinics. HCV, hepatitis C virus.

to one of the hospital's gastroenterologists who comes to the clinic to conduct a biweekly HCV care clinic session for HIV coinfecting patients. Some of the physicians refer only patients whom they believe are good treatment candidates, while others refer all their coinfecting patients for an evaluation. The gastroenterologist conducts this clinic session in tandem with one of the clinic's physician's assistants (PA); these two providers evaluate patients and make treatment decisions jointly, with added consultation from the ID physicians when warranted. Once a patient starts HCV treatment, they are followed biweekly by the PA to monitor progress and side effects, and more intermittently by the gastroenterologist. Support staff at the clinic includes other PAs and a psychiatrist.

Site C is part of a large system of HIV clinics operated in Los Angeles County by a single private organization. This site is the base of HCV care for all of the organization's other clinics in the county; hence, these other clinics refer their HCV coinfecting patients to site C for HCV evaluation and treatment. The clinic director reports that most of the referring providers refer all of their HCV patients for evaluation at the time that HCV is detected; however, some providers do not refer until they perceive the patient to have some indications for HCV treatment. The clinic has three primary care providers, of whom two (one ID physician and one NP) provide HCV primary care during a once-a-week clinic session devoted specifically to manage HCV. Support staff includes a pharmacist who regularly meets with patients on treatment to monitor side effects, nurses, case managers, and a social worker who provides mental health counseling; patients with serious mental illness are referred out for psychiatric consultation and treatment.

Sample

In the summer of 2008, we conducted semistructured interviews with primary care providers, nurses, mental health providers, case managers, and clinic administrators at each site. Although primary care providers are likely the primary decision-makers with regard to whether or not HCV treatment is recommended to patients, we chose to interview these added stakeholders as well, as they observe and play a role in the environment in which key decisions occur. At each site, we attempted to interview all of the primary care providers, up to two of each type of support staff (e.g., nurse, case manager, mental health provider), and the clinic administrator (although at each of the sites, the clinic director or administrator was also a primary care provider). A total of 22

interviews were conducted. Nine providers and support staff were interviewed at site A (4 primary care providers, 2 nurses, 2 case managers, and 1 mental health post-doctoral fellow), 7 at site B (5 primary care providers and 2 PAs), and 7 were interviewed at site C (2 primary care providers, 2 nurses, 2 case managers, and 1 social worker). Among the 11 primary care providers, the length of experience in HIV coinfecting patients with PEG-IFN/RBV ranged from 3 to 5 years, and having provided HCV treatment to a range of 2 to 200 HIV coinfecting patients.

Semistructured interviews

The interviews were organized into the following sections: background information on training and experience providing HCV care; personal attitudes with regard to liver biopsies and HCV treatment; clinic procedures/protocols for determining liver disease stage and providing treatment with PEG-IFN/RBV; factors influencing HCV treatment decisions; and perceptions of patient decision making and adherence to HCV treatment. The primary goal was to understand the factors that influence provider decisions to recommend or defer HCV treatment. We examined (1) who makes the decision and whether multiple providers are involved in the decision-making process, (2) what physical, mental, behavioral, and sociodemographic characteristics of patients are considered, (3) the role of support staff such as nurses, case managers, and mental health providers in treatment decisions, and (4) whether organizational policies and/or barriers affect decision making.

Structured interview guides were constructed to ensure that all key questions were asked and to permit provider comparisons within and across clinics. Open-ended questions preceded closed-ended questions to avoid biasing responses, to elicit unanticipated leads for further exploration, and to highlight areas of greatest significance to the respondents. Standard probes, such as verification and compare and contrast questions, were used to more fully elucidate specific content areas. All interviews were conducted by Drs. Wagner and Chan-Osilla, digital recorded, and transcribed verbatim. Written informed consent was obtained from all respondents, and all were remunerated \$50 for the interview, except at one site where institutional regulations did not allow any payment.

Qualitative data analysis

Transcripts were reviewed to identify key themes, as we looked for text that involved processes, actions, assumptions,

and consequences, repetitions across informants, and shifts in content with regard to the decision making process. After separately examining portions of the transcripts, we reached consensus about which themes to examine in detail. We constructed a framework of major factors and components influencing decision making, and developed a codebook using standard procedures and text management software (e.g., Atlas/ti) to mark instances where each theme occurred in the interviews. For each theme, we examined the range, central tendency, and distribution, which allowed us to discover decision criteria, patterns and generalities related to the decision-making process within and across provider groups.

Results

HCV treatment protocol and procedures

Each respondent was asked to describe the procedures or protocol used at the clinic to treat coinfecting patients with PEG-IFN/RBV. At all three clinics, standard doses of PEG-IFN are used (mostly peginterferon alfa-2a with a dose of 180 µg per week), along with weight-based doses of RBV (doses ranging from 800 to 1400 mg/d). There was a consensus among all providers that maintaining high, maximum doses of both PEG-IFN and RBV were important for virologic response; accordingly, aggressive side effect management with common use of erythropoietin and recombinant granulocyte colony-stimulating factor (G-CSF) to manage anemia and neutropenia, respectively, were reported at each site. Occasional use of prophylactic antidepressants for patients with past histories of depression (not current) was reported by providers at two sites in an attempt to prevent treatment induced depression.

There was some variation within and across sites with regard to the duration of treatment and rules used for stopping treatment. For genotype 1 patients, who represent the vast majority of patients at these clinics, all providers reported a treatment duration of at least 48 weeks, but providers at two of the sites reported extending treatment to 72 weeks or longer. Providers at one site reported extending treatment for African American patients, given the lower treatment response rates found in this subgroup of patients³⁵; treatment was always extended to at least 36 weeks after the point at which an undetectable HCV viral load was achieved. The other site reported extending treatment for those on their second or third course of IFN treatment, and with advanced disease, risk of liver decompensation, or a fatty liver. For genotype 2 and 3 patients, providers at two sites reported considering a treatment duration of less than 48 weeks, while the other site reported maintaining 48 weeks as the treatment duration. Finally, providers at one site reported that they had recently started to consider early virologic response (undetectable HCV viral load by Week 4 of treatment) as an indication for shortening treatment, even among genotype 1 patients, and especially if tolerance of treatment side effects was a problem for the patient.

Studies consistently show that if a patient does not achieve virologic response by week 12, there is virtually no chance of achieving a sustained virologic response,^{13,14} which has led many providers to discontinue treatment at week 12 in the absence of a 2-log drop in HCV viral load. None of the providers indicated strict adherence to this criteria for stopping

treatment at week 12, but at each clinic there were providers who reported using this rule in their decision making. Several indicated that even if there was not a 2-log drop in viral load, they would consider continuing treatment if there was some response. At two of the sites there were providers who preferred to treat for at least 24 weeks before possibly discontinuing treatment.

Factors that influence treatment decision making

The three participating sites reported substantially different treatment rates, ranging from 10% at site A to 38% at site C (Table 1). The lower treatment rate at site A is likely in part due to the two organizational factors that differentiate it from sites B and C as described in the site descriptions. With patients from other clinics referred to sites B and C for HCV care, it is likely that at least some of these patients are referred because they are appropriate for HCV treatment, therefore increasing the proportion of the patient pool that warrants treatment initiation. Also, at sites B and C the coinfecting patients (regardless of whether they are on HCV treatment or not) receive care during the HCV subclinic sessions where providers can focus solely on the patient's HCV care management; whereas at site A, patients who are not on HCV treatment are intermingled among other HIV patients and HCV is one of many problems that are discussed by the primary care providers.

These organizational differences notwithstanding, provider approaches to treatment decision-making may also be a significant contributor to the differences in treatment uptake. Our interviews with providers and staff at each of the three sites clearly indicated that this decision process is almost solely in the hands of the primary care providers, and so the following analysis centers on the interviews with the primary care providers. The support staff play an informative role in the decision process, which will be described later. The factors that influence provider treatment decision making, as elucidated in these interviews, can be broken into three main components: biologic (HIV and HCV diseases), psychosocial (motivation, adherence, mental health and substance use), and provider or organizational.

Biologic factors

When speaking of the process by which decisions are made regarding the appropriateness of HCV treatment for an individual patient, providers focused first on biological disease factors. With this study focusing on HIV coinfecting patients, providers spoke of a dual emphasis on HIV and HCV diseases.

Stability of HIV disease. There is little difference between the sites with regard to the role of HIV disease in HCV treatment decisions, as all providers spoke of the need for a patient's HIV disease to be stable prior to initiation of HCV treatment. Considerations in determining stability of HIV included HIV viral load, CD4 count, HIV antiretroviral regimen, and opportunistic infections. Providers at Site B said that CD4 counts must be above 200, as declared by one provider, "I do not make an exception on that rule." Providers at the other two clinics spoke of wanting CD4 count to be in the 300s, although there was not a rigid threshold. All providers also spoke of a need for very low HIV viral levels, and one

provider at site C reported that viral load must be undetectable if the patient's CD4 is not in the 300s.

There is no good reason at this time that they should have detectable (HIV) viral loads. There are fabulous drugs out there. I probably can count on my fingers, maybe three or four people who have detectable viral loads at this point. There are no good reasons for that. That is something I don't accept. (C1)

For patients with low CD4 (<350), the patient needed to be on ART for at least several weeks and responding to it well in terms of tolerance, adherence and clinical response. In addition, providers spoke of needing to switch antiretrovirals for a patient whose ART regimen included zidovudine (AZT) or didanosine (DDI), which have been shown to have interaction effects with RBV.²¹ The patient needs to be stable on the new regimen with the replacement antiretrovirals prior to initiating HCV treatment. Finally, all acute HIV opportunistic infections and other medical conditions (e.g., anemia, neutropenia, hypothyroid) need to be effectively treated and in remission prior to initiating HCV treatment.

HCV disease stage. Once a patient's HIV disease is stable, providers then shift their focus to the patient's HCV and liver disease. A series of laboratory tests and procedures are used to determine the patient's stage of liver disease and the appropriateness for HCV treatment. Standard practice at each of the clinics is an assessment of physical symptoms that may be suggestive of liver disease and a routine laboratory work-up that includes HCV viral load, genotype, liver function tests (LFTs), and a panel of others tests including alpha fetoprotein, platelet counts, albumin, and others. Although these tests have a low level of precision in evaluating liver disease stage, they are able to provide some indications of the presence of disease progression. If the labs show elevated liver enzymes or signs of liver inflammation, ultrasounds and computed tomography (CT) scans were performed to further evaluate the condition of the liver at each site.

Liver biopsies have been the gold standard for evaluating stage of liver disease and fibrosis, but have been used very sparingly at the study sites (ranging from none to five or six biopsies performed over the past 2 years) unless treatment was being provided as part of a research study in which biopsies were required. All providers spoke of informing treatment candidates that they could have a biopsy done, but that it was not needed for treatment to be provided, and patients typically opted out of having the procedure. Barriers such as low insurance rates for covering the cost (site C) and low institutional capacity for performing the biopsies (site A) also contributed to the low utilization of the procedure. Reasons that biopsies were viewed as not being essential included the rationale that disease progression is much more rapid in HIV patients and thus treatment needs to be initiated earlier, few co-infected patients have no signs of disease, and the potential inaccuracy of biopsies.³⁶ Furthermore, at each site, biopsies were only considered when treatment was a possible option for the patient; this meant that the patient was both an appropriate candidate for treatment based on other criteria, and was at least willing to consider treatment. This latter condition includes patients who are "on the fence" about treatment and could benefit from seeing evidence from the biopsy about the state of their liver before making a decision.

I cannot think of anyone who's gotten a liver biopsy who was not interested in treatment. People will say, "Well, if I don't want treatment, why do I want to subject myself to an invasive procedure?" In honesty, it probably comes the other way also. It's like if you're not ready (for treatment), then what are we going to do with that information (from a biopsy)? What would we do different (with regard to treatment) with the information from a liver biopsy? But I have said to patients, "If you knew that you had progressive disease, would that change your mind about treatment? And, if so, then that liver biopsy would actually be worthwhile getting." But I haven't had anybody take me up on that. (A2)

There were noted differences across the sites with regard to the role of HCV disease stage in determining appropriateness of HCV treatment initiation. The providers were unanimous in seeing no need for a biopsy if the patient had a genotype of 2 or 3, as these patients were generally seen as appropriate for treatment given the high rate of treatment success with these patients. In contrast, the providers differed considerably in how they approach genotype 1 and 4 patients. Several providers at sites A and B spoke of a preference for deferring treatment if signs of disease were minimal; these providers perceived LFTs and liver biopsies as being useful for assessing stage of disease and clarifying the need for treatment.

We're not necessarily promoting treatment to patients who have normal LFTs. Not because there's great data behind that, but just because it's a toxic treatment and we don't always get a great result; in fact, more often than not we don't (get a good treatment response). (A1)

Some patients have a low chance of getting a good result (treatment response), and if they have no indication of chronic liver disease, then they are better off waiting, and we wouldn't do a biopsy on those. Patients who have an indication that they may, may have some cirrhosis—some abnormality in ultrasound, a liver that feels firm upon examination, any indication they might have fibrosis—even though they have a minimum chance or a relatively lower chance of getting a good response, those patients can benefit significantly, depending on their stage from a biopsy. They can benefit significantly from giving the interferon and ribavirin a shot. So those patients we would biopsy to determine stage of disease. (B3)

Conversely, providers at site C and some at site B view all patients as treatment candidates with regard to liver disease stage as long as the liver is not decompensated. (Decompensated liver was a contraindication to treatment for providers at all three clinics).

I really look at it very much from an infectious disease perspective. It's an organism in the body that doesn't belong there; it needs to get out of the body. If somebody is a candidate, has a good ability to do treatment, I will go ahead and treat, because I don't want them to be sicker and then treat them later on. That's because it's two issues. It's the HIV and the Hep C. We know that HIV progresses faster; we know that Hep C progresses faster. Both of these are having a negative effect on each other. There is no reason to not treat them. (C1)

Providers at Site C put little credence into the value of LFTs and biopsies. Although one provider added the caveat that if more effective and less toxic treatments were available, disease stage would be more relevant and biopsies may be viewed as more important. Also, site C often uses the Fibrosis test (profile of biochemical markers) to elicit information about disease progression and fibrosis.

Psychosocial factors

Once it is determined that the patient's HIV disease is stable and their liver disease stage is appropriate for treatment, then the provider's focus shifts to the patient's psychosocial readiness for treatment. Specifically, each provider spoke of the importance of the patient's motivation and commitment to undergo treatment, and demonstration of being ready to adhere well. Mental health and substance abuse were also considered by all providers, but with different conditions for being appropriate for treatment.

Motivation. While the biologic appropriateness of the patient may be the first thing that a provider assesses, if the patient is not interested in starting treatment, then treatment is not even a possibility. Providers spoke of the need for patients to understand the importance of treatment for their long-term health, and to be willing and motivated to adjust their lifestyle if necessary. Only a few providers spoke of trying to persuade resistant or ambivalent patients about the importance of treatment and these providers tended to be those who reported higher treatment rates and a greater sense of urgency towards treatment initiation. One provider at site C was particularly outspoken about her philosophy of trying to treat every patient and to treat as soon as the patient is willing. This provider spends considerable time educating the patient and emphasizing the importance of treatment until it starts to sink in.

I tell them, "A year and we're talking (viral) eradication. This is a very important concept and so I really want you to understand. I'm not talking of lifelong therapy. I'm trying to shoot for eradication. We're getting it out of the body. So whatever it takes." (C1)

Adherence. All providers spoke of the patient being ready to adhere well to treatment as a critical factor in determining whether treatment would be recommended. Most providers used clinic attendance, and adherence to ART (if applicable) as key indicators of whether the patient was ready to adhere to PEG-IFN/RBV.

Generally substance abuse, nonadherence with clinic, signs of nonadherence with other medications, like HIV medications or other medications, then we would feel that they might not be ready for treatment. If we feel that they will be able to adhere, and they're willing to try to go through the side effects-not everybody gets the side effects-then we feel that they will be able to do well with treatment. (A3)

They need to come frequently. If they can't, then that is another thing I guess that I always look at too, is if they can't make frequent visits, then I don't think I would start therapy, because they wouldn't be monitored adequately. I tell them right up front. (C2)

Mental health. Providers at each clinic reported some level of screening of depression and psychiatric problems, and needing clearance from mental health providers before starting a patient on HCV treatment. However, there was variation in the definition of who was required to have such a clearance. At the site with the lowest treatment uptake (site A), one provider said that all patients who are potential treatment candidates are required to have a mental health screening and clearance, while another provider at that clinic

indicated that such a clearance was needed if the patient had current psychiatric problems. At Site B, patients with any history of depression or mental illness, past or current, were required to have a mental health clearance. Finally, the site with the highest treatment uptake (site C) required a mental health consultation and clearance only for patients with current serious psychiatric problems such as suicidality or severe depression, schizophrenia, and bipolar depression.

Patients with current mental health problems were required not only to be cleared for HCV treatment by a mental health provider, but also had to receive mental health treatment for the problem such that the condition was stable or in remission, and to receive ongoing follow-up and monitoring from the mental health provider. An exception to this was at Site C where the lead provider views moderate depression as less problematic, and the decision of whether to postpone HCV treatment until the depression is treated is left up to the patient after a thorough discussion about the options and risks.

Depression is so common; it's in 60% of the patients. Depression is not something that's going to stop me treating them. I just need to know how they understand their depression. I will analyze what they think, what they understand, how they know that this is going to make their depression worse. If they are depressed, I will ask them, "Do you need an antidepressant? Do you think that this will get worse?" The other thing I think is that they're in control; I'm not. I ask them to decide everything. "Do you think that your depression is at a point where, if it gets worse, will you be able to handle it? Because it takes three weeks or whatever for it to be effective, do you want me to start now or do you want to start later? Do you want to tell me when?" They're very involved in that decision. (C1)

Substance use. Each provider reported some criteria related to substance use, but as with mental health, providers at the clinics with higher treatment rates described greater leniency regarding reports of some substance use, and there were differences with regard to alcohol versus illicit drug use. At Sites A and B, some providers said absolutely no drinking or use of drugs was allowed for as long as 6 months before treatment could be initiated.

With me it's a hard and fast rule (no drugs and alcohol for 6 months). I tell them, 'If I test you (urine sample) and I find it's positive, then I'm going to recommend that you stop treatment. (B5)

So what I tell the patients is this, especially with alcohol, where there's evidence for this: I say that the alcohol can make the virus proliferate faster and makes the disease progress faster, and it's only adding one other factor to make the disease worse, and patients who drink are not going to respond to the drugs, and that's actually established. So I say, "You can't drink, and you've got to be committed to that, and one way to be committed is not to drink for six months. And then I'm confident that you're committed." And so I say, "You know, I just don't feel you're ready for that. You're not going to be able to follow through. It's kind of complicated, and you're not there yet." And they actually agree with me. They'll say, "Yeah, doc, give me 6 months, I'll get myself in shape." (B2)

Yet even the provider quoted above said that if a patient told him that he had an "occasional" drink, he would treat the patient as long as the patient did not have a history of alco-

holism. At each site there were providers who said they encouraged patients not to drink and use drugs but would still provide treatment if the patient only had a few social drinks or used some marijuana. A number of providers singled out marijuana as an exception, and would allow it to be used, but not other types of drugs. Some providers at each of the sites referred to substance use as a gray area in determining a patient's readiness for treatment and they made these decisions on an individual case basis.

In regards to alcohol and substance use, my own perspective is that we don't want to be punitive. A person who has a glass of beer a week is a person that could still be treated. The person who is engaging in the sporadic marijuana for appetite is different than the person who's using crack cocaine under bridges and alleys, so to speak. But most of these factors, you know, there's a little bit of a gray scale here rather than absolute black and white situation, and clearly judgment is applied. (B1)

While providers at sites A and B did not allow active illicit drug use (other than marijuana), at site C the providers were willing to provide HCV treatment to patients who were actively using drugs such as cocaine and crystal methamphetamine, so long as they believed the patient was sufficiently motivated and adherent. This viewpoint was influenced by observations of patients who regularly used drugs, yet were still able to adhere well to ART.

I have had very good success. I have a couple or maybe one person who uses cocaine, maybe one or two other people who use something else. I think it's Ecstasy or something like that. But most of them are crystal meth users. And they can be very compliant. I have this patient who uses crystal meth regularly every week, but he is fabulous with taking his HIV meds. (C1) I think if they're actually able—if they're interested enough to be there, and they understand the treatment is 48 weeks, and they're willing to start it knowing the side effects and everything, even if they are using, I would not deny them treatment. (C2)

One of these providers at site C spoke of an emphasis on being nonjudgmental with patients about their substance use and that this enables patients to be candid about their use. This in turn results in mutual trust and respect and often the patient taking on a sense of responsibility in terms of their treatment behavior and assessing the impact of their drug use.

I'm very nonjudgmental and very clear about this. "Are you taking them now? I need to know this." They're very honest. They're very open. I have had them say it very nicely, "I want to tell you that I'm going to be doing crystal for these three days. So whatever regimen we have to do, we have to make it work around this so it doesn't coincide with my crystal taking." (C1)

The one person that I'm planning to treat now, he's down to one can of beer a week. I have to trust him. That's what he tells me. I talk a lot about this. "I need to trust what you're telling me because everything that I design, everything that I do will be based on what you tell me. If I can trust you, I can make sure that I can fix things for you. If I can't trust you, there's no point in you doing this." (C1)

Provider characteristics

As providers consider a patient's HIV and HCV disease factors, and psychosocial readiness for treatment, this deliberation and decision making process is influenced by the

provider's overall view of HCV treatment and in particular the degree of urgency needed in initiating treatment. Among the providers in this study, those at site C have the most urgent view of treatment, and they spoke emphatically of the sense of obligation to treat all patients as soon as a minimal level of criteria was achieved.

I did general ID in the hospital and the reason I got into this was because I saw so many people dying of Hep C—not HIV but Hep C. I didn't know anything about Hep C at that time. I started referring them out and I had the most difficult experience with people that I referred out. They would come back three months later, huffing and puffing. I think I even told you about this guy too, white as a ghost, hemoglobin of 5. You can't see these patients three months later. That's not possible in co-infected patients. That's when I thought, "Okay, I need to do this. Because this is a 32-year-old guy who should not be dead, who should not be dying." That's the background in the way I approach it now. I do not want to be the judge of whether I will offer you treatment. I'm not God. So I don't want to play that I will offer you treatment, I will not offer you treatment. The philosophy I have is that I offer everyone treatment, because that's their right. (C1)

Another provider, at site B, who advocates for aggressive, urgent care, spoke of how his clinic has evolved over the 5 years of its existence, and that through their experience in treating patients that many thought were "risky", and observing the success of treatment, that the clinic providers have grown in confidence and willingness to treat more aggressively.

If we went back several years ago I would've been pushing my GI doc to treat where he did not necessarily want to treat. Whereas my colleagues were more wary of treating a co-infected individual. Now that we've been doing this for the four or five years and we have accrued the surprising treatment successes, that I think my colleagues have come to be more comfortable with treating individuals and are sharing my perspective that people warrant therapy. And our GI colleague is, as well, more comfortable treating patients who he would have regarded as poor treatment candidates a few years ago. So there's been really a shift in opinion. (B1)

In contrast, there were providers at sites A and B who took a more cautious view of treatment. These providers viewed treatment as urgent for some patients with advanced disease, but for many patients with less progressed disease they believed it was best to defer treatment. The perspective of these providers puts greater weight on the burden of toxicity and limited success rate of treatment, and the ability to monitor disease and wait for better treatments to become available.

From my point of view, it's seldom an emergency decision on these patients to treat or not. And I think the fact is, the trials are looking really great—the protease inhibitors that are coming out, the anti-hep C drugs. I'm not saying don't treat the patient, but do you *have* to jump in now with that patient? Or is this patient sufficiently low risk that you could monitor and maybe wait for the next round of studies in the next 12–24 months before making that decision and having the patient go through the interferon ribavirin routine? I might feel inclined to say, "Look, if you're anxious to be treated, let's do it, okay. We will know by week 12 whether you're likely to benefit from going on or not. So we could do that. On the other hand, we are reasonably certain, based on our tests, including a biopsy, that you don't have any significant fibrosis at this point, so that if you chose to, we think at maximum 4 or 5 years, there will be a

very good or maybe a couple of good agents around that we would combine with interferon, plus or minus ribavirin. So you may want to have us watch and wait and talk about it for the next year or so." (B3)

I tell them, "You have HCV. This is long-term, it's not an emergency, but we'd like to discuss treatment with you." When we tell them about the treatment, the injectable nature of it and the side effect profile—it makes them not want to discuss it further. If biopsies were more of an option, we could avoid treating people with earlier stage liver disease, who can afford to wait for better, less toxic treatment to become available, instead of undergoing treatment now and suffering through it when it might not work, probably won't work. (A1)

Role of support staff providers

Support staff providers, such as nurses, mental health providers (social workers, psychiatrists, psychologists), and case workers also have a role in the HCV treatment decision making of primary care providers. Primary care providers typically have 10–15 minutes to spend with patients during regular clinic visits, whereas support staff can often spend quite a bit more time. This affords them the ability to develop a rapport with the patient, to hear about social and behavioral aspects of the patient's life that are troubling the patient, to provide education and support to the patient, and address issues such as side effects and adherence problems. A number of the support staff described how primary care providers seek their information and opinions about the patient's readiness for treatment with regard to mental health status, substance use, and ability to adhere. Hence, the opinions of the support staff can contribute to the decision of the primary care provider to either recommend or defer treatment.

I think we play the role of basically providing the clinical staff with the current mental status of the client, the client's behavioral focus, the client's interest in treatment, and giving background as to whether or not the client would be interested in treatment. (A8)

They ask (our opinion). And most of the time we agree. We say, "He's not ready for that. We have to first take care of this, this, and that before you can consider starting him on treatment." Once we have him in this place stable, then we could go back and address the treatment. Whatever issue it is that the patient needs to be worked on, and if I can help them, then I work with the patient. (A4)

I'm a middle person. Sometimes they're not that open with the nurse practitioner. Maybe that patient is drinking and he's not telling her. But he might tell me. And then maybe she's thinking he's ready for treatment. But then I'll go back and say, "You know what? He's not ready. They (the patients) are definitely more up to talking with me. I get that a lot of times. I didn't tell my doctor, but I just wanted to say that I'm using again." "Why didn't you tell your doctor?" "I didn't want them to be angry with me." (A4)

Discussion

HCV treatment rates reported by providers at the three participating sites ranged from 10%, which is similar to those found in the literature,^{6–12} to as high as 38%. With providers being the primary gatekeepers of treatment access, we sought to examine how the decision making process differs across the primary care providers at these three sites.

Stable HIV disease is clearly a basic tenet to HCV treatment being considered. Providers at each of the three sites preferred

CD4 counts to be in the 300s and certainly greater than 200 before treatment could be considered. This is consistent with published HCV treatment guidelines for HIV patients,²¹ and evidence that HCV treatment is more successful with higher CD4 counts,²⁵ and that HCV treatment depletes CD4 cells during the course of treatment, rendering patients vulnerable to opportunistic infections.³⁷ With a stable HIV disease, providers then shift their focus to the patient's HCV and stage of liver disease. All providers agreed that late stage, decompensated liver disease was a treatment contraindication due to the risk of serious side effects, and that the few patients with genotype 2 or 3 should be treated when at all possible given the high treatment response rates in these patients. Furthermore, there was general consensus that genotype 1 and 4 patients with significant signs of disease, fibrosis and liver inflammation should be treated.

Where these clinics and providers differed was in the treatment of genotype 1 and 4 patients who have no or minimal signs of liver disease. At sites with lower treatment rates, providers preferred to delay treatment for these patients, citing low treatment response rates, high toxicity burden, and better treatment options on the horizon, thus weighing the costs of treatment to be greater than the likely benefits. Providers at Site C (and some at Site B), who reported higher treatment rates, viewed all patients as needing treatment as soon as possible regardless of whether or not there were signs of disease; these providers cited the added risk for rapid disease progression associated with HIV,³⁸ the greater likelihood of treatment success with milder disease,³⁹ the chance of a cure, and the confidence to help patients successfully manage side effects. Provider attitudes toward liver biopsies were influenced by this decision process as providers who preferred to treat these patients saw little or no value in having a biopsy done, whereas providers who would rather defer treatment viewed biopsies as being able to confirm the stage of liver disease and treatment decision. Yet regardless of these attitudes, biopsies are not needed to provide treatment at these sites and each site reported that very few biopsies had been performed on their patients.

Given the low uptake of treatment reported in the literature,^{6–12} and studies that report mild liver disease to be a common reason for treatment ineligibility,^{28,40} it appears that most providers in the field side with those who favor the "wait and monitor" approach for genotype 1 and 4 patients with mild disease. This approach aims to spare the patient from having to endure a toxic treatment that for most will provide no virologic benefit, so long as the patient's liver disease does not progress significantly. Providers must balance waiting for indicators of significant liver disease progression with the risk of waiting too long such that treatment is likely to be less successful or even contraindicated because the liver disease is too advanced or because CD4 count drops too low, both of which are common reasons for coinfecting patients being excluded from HCV treatment.⁷ Whether a patient is treated early in the disease stage, or not until there are at least moderate signs of disease progression, would not have significant policy implications if treatment was in fact eventually started. But the low treatment rates reported in the literature, and data showing that most coinfecting patients have at least moderate signs of fibrosis,^{4,5} highlight the role that nondisease factors play in treatment decision making.

Regardless of whether providers prefer to treat early or delay treatment depending on disease stage, they must still assess the patient's psychosocial readiness for treatment. All providers agreed on the key components of readiness, those being patient motivation and interest in treatment, demonstration of ability to adhere to treatment and clinic appointments, and a mental health status that will not impede ability to adhere and tolerate treatment. These readiness components account for a large proportion of the patients not being treated.⁶⁻¹² However, while there was general agreement on the components of readiness, there was considerable variation in how providers viewed the influence of depression and substance use in determining a patient's readiness for treatment.

Mental illness and substance use are leading causes for treatment deferment,^{6-8,27,28} and thus are prime reasons why many patients with significant liver disease continue to be untreated. Yet the empirical evidence is mixed with regard to the effects of these conditions. A number of studies have found that HCV treatment response and completion rates do not differ between patients with or without histories of psychiatric illness or substance abuse, nor between active drug users and nonusers.^{29-31,41,42} However, other studies have found that patients with past psychiatric problems are more likely to need psychiatric care during HCV treatment⁴³ and that patients who are depressed at treatment baseline are less likely to respond to treatment.⁴⁴ While all providers in the study called on mental health screens and clearance for some patients, and required that serious mental illness be stabilized by psychiatric treatment prior to initiating HCV treatment, the views on depression varied. Most providers spoke of the need to use antidepressants to stabilize current depression before starting HCV treatment, and some used antidepressants as a prophylactic for patients with past depression. However, the provider who reported the highest treatment uptake had the most lenient approach, indicating that untreated moderate depression would not prevent prescription of HCV treatment, and that it was up to the patient to decide whether or not they wanted depression treatment prior to starting HCV therapy once they were informed of the possible options and risks of not treating the depression.

There was even more variation in how the providers viewed current use of alcohol and illicit drugs. A few providers spoke of no tolerance for any alcohol and drug use for 6 months prior to the patient being considered ready for treatment, which is a common standard in the field.⁴⁵ But several experts and patient advocates have called for a more flexible approach—one that looks at the individual circumstances for each patient.^{29,46} All providers in the study spoke of strongly encouraging their patients to abstain from use of alcohol and drugs, but several conceded that there was a "gray zone" in judging this criteria and that they would allow an occasional drink or use of marijuana, but not harder drugs. Similar to evaluations of mental health, the providers at the site with the highest treatment rate were most willing to offer treatment to patients who were actively using drugs such as crystal methamphetamine, so long as the patient convinced them that they could still adhere to treatment.

In conclusion, findings from this study highlight two approaches to managing HCV treatment decisions. One views treatment initiation as more urgent and is willing to accept the risk of a more lenient definition of patient readiness for

treatment. The other takes a more cautious approach with a preference for holding off treatment until it is clear that a patient's liver disease is in need of treatment and the patient has all the signs of being ready to adhere well. There is no clear evidence indicating whether one approach is more appropriate than the other. An urgent approach to treatment results in more patients being treated and thus more patients being "cured," but also more patients who endure significant side effects that compromise mental health and quality of life without virologic benefit.

Conversely, delaying treatment can reduce unnecessary burden on a patient's quality of life, and better, less toxic treatment may become available before the patient's disease progresses to the point of definitively needing treatment; however, ultimately treatment is needed to avoid liver failure and the longer a patient waits, the lower the odds of treatment being successful with the currently available treatment. Regardless of which approach may be more appropriate, development of effective programs for promoting patient readiness for treatment are critical to ensuring that more patients receive treatment, either earlier in the disease or later, given the high mortality associated with liver disease among HIV/HCV coinfecting patients.

Finally, the examination of treatment uptake rates and the treatment decision making process cannot be fully understood without accounting for the role of the patient and their decision process for requesting, accepting or refusing treatment. Provider decisions to recommend or offer treatment is critical to providing treatment access, but whether or not a patient starts treatment is ultimately in the hands of the patient. Studies show that 10%–20% of HIV coinfecting patients choose to refuse HCV treatment.⁴⁷ In addition to analyzing the qualitative interviews of coinfecting patients who participated in this study, we will soon conduct a quantitative survey of HCV providers and their HIV coinfecting patients. The goal of these assessments is to better understand the multi-level factors that contribute to the treatment decision making of both providers and patients, and to inform the development of intervention strategies for improving HCV treatment uptake and outcomes for HIV coinfecting patients.

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