## Title

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# Clinicians' Views of Hepatitis C Virus Treatment Candidacy With Direct-Acting Antiviral Regimens for People Who Inject Drugs

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## Abstract

**Background:** Direct-acting antivirals (DAAs) are curative in most persons with chronic hepatitis C virus (HCV) infection. However, high cost and concerns about adherence and reinfection may present continued barriers to treatment, particularly for people who inject drugs (PWID).

**Objective:** To understand changes in assessments of treatment candidacy, given advances in treatment.

**Methods:** Clinicians attending the Liver Meeting® in 2014 who reported prescribing HCV treatment in the past three years were invited to complete a survey regarding HCV treatment decisions. Participants assessed their likelihood to treat HCV in PWID in association with time of abstinence from injection drug use and what impacts their decision to provide treatment using interferon and DAAs.

**Results:** 108 clinicians completed the survey; 10% were willing to treat an active PWID (last injection within 30 days) using interferon-containing regimens, and 15% with all-oral regimens. For each increasing time interval of injection abstinence, there was an increase in the odds of a clinician reporting willingness to treat with DAAs (Odds Ratio (OR) 2.57, 95% CI 2.18, 3.03) and with interferon-based treatment (OR 2.22 (95% CI 1.90, 2.61), Reinfection and medication cost were cited as most important concerns when determining candidacy.

**Conclusions:** A cure is now the norm in HCV treatment, and there is an increasing need to address the barriers to treating PWID, the population with the highest burden of infection. Understanding treatment candidacy assessments is essential to improving uptake. This study provides insight into how clinicians view treatment candidacy in this era of DAAs and can help identify supportive treatment environments and concurrent programs.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

**Keywords**

Hepatitis C treatment; people who inject drugs (PWID); injection drug use; direct-acting antiviral hepatitis treatment candidacy; providers; hepatitis C cure; abstinence

Direct-acting antiviral (DAA), all-oral medications for treatment of the hepatitis C virus (HCV) are curative for the vast majority of people with chronic infection (Aghemo & De Francesco, 2013, Hagan, Wolpe, & Schinazi, 2013). Despite their effectiveness, and the high cost of HCV-related morbidity and mortality (Kowdley et al., 2013; Lawitz et al., 2013; Myles, Mugford, Zhao, Krahn, & Wang, 2011), it is not clear if clinicians have adapted their eligibility criteria given how medications are evolving. This study sought to understand how the availability of DAAs for HCV treatment impacts clinician's decision to treat people who inject drugs (PWID), and to identify barriers to treatment for PWID.

## Background

PWID have the highest prevalence of HCV in the United States, yet have extremely limited HCV treatment access (Mehta et al., 2008). Interferon-based treatment was suboptimal due to low efficacy and severe side effects, forcing clinicians and patients to carefully weigh the risks and benefits of treatment (Mehta et al., 2008; Morrill, Shrestha, & Grant, 2005; Strathdee et al., 2005). The recent advances in HCV treatment point to a need to examine what influences a provider's willingness to treat. Understanding who gets treatment and under what conditions, can inform clinicians about changing eligibility criteria, provide information about ancillary support programs needed to improve treatment uptake, and plan for the future burden of HCV-related morbidity and mortality for those untreated. The purpose of this study was to (Aghemo & De Francesco, 2013) identify changes in the proportion of PWID considered eligible to receive HCV treatment by physicians; and (Hagan et al., 2013) identify physicians' views of what are barriers to treatment in this population.

## Research methods

This cross-sectional study enrolled clinicians (MDs, Physician Assistants, Nurse Practitioners) who reported prescribing a HCV treatment medication in the past 3 years attended the Liver Meeting® in 2014. The investigator and research assistants invited attendees to participate in a 15-minute survey developed and pre-tested with focus groups of HCV treatment-experienced clinicians.

Participants were asked to assess their willingness to provide HCV treatment to patients with a history of injection drug use (IDU) using different regimens, and different times of abstinence (time since last IDU). Clinicians were also asked to assess the importance of traditional barriers to HCV treatment using a five-point Likert scale (1 = not important, 5 = very important). The study protocol and procedures were approved by the University of California San Francisco Institutional Review Board.

## Data analysis

Data were coded and imported into Stata/SE Version 13 (StataCorp, 2013) for analysis. Frequencies for categorical variables and medians, means and standard deviations for continuous variables were generated. Differences between provider's willingness to treat with interferon-containing regimens compared to all-oral regimens depending on time since last injection were calculated using ordinal logistic regression. Willingness to provide treatment using either medication type in association with time of abstinence was calculated using ordinal logistic regression. The Bonferroni method was applied to compare differences in willingness to treat between the time points of abstinence from IDU. Bootstrapped *t*-tests with 1,000 repetitions to provide bias-corrected nonparametric confidence intervals for drawing statistical conclusions given the nonnormal distributions examined the differences in the mean Likert scale rating between barriers to treatment given each the medication regimen (Efron, 2000; Erceg-Hurn & Mirosevich, 2008; Wehrens, Putter, & Buy-dens, 2000).

## Results

Of 108 participants, 64% were male, 46% practiced in North America, Europe or Australia (Table 1). Most (47%) were in hepatology; 24% were in gastroenterology, 19% were in infectious diseases. All respondents reported experience prescribing interferon. Half (48–51%) reported experience using boceprivir or telaprivir triple therapy, and 33% had prescribed sofosbuvir or simeprivir. The median proportion of HCV-infected patients in the total patient load was 30% (interquartile range [IQR]: 11, 60).

Just over half (55%) of participants reported willingness to treat a patient with an interferon-based regimen if they were abstinent for ≥12 months. One quarter (25%) were willing to treat a patient who were abstinent from IDU for ≥12 months even if engaged in non-IDU, and 20% indicated that they would not treat a patient with any history of IDU in the last 6 to 12 months. One-third reported willingness to treat HCV infection if the patient has not been abstinent within the past 6 months, and 10% reported willingness to treat a patient who was currently injecting. Compared to recent injection use (in the previous 30 days), the odds of a clinician reporting willingness to treat with an interferon-based treatment increased with abstinence time: 1–6 months, OR 3.92; 6–12 months—OR13.98; and ≥12 months, OR 24.28. Bonferroni post-hoc contrast analyses showed significant differences between times of abstinence: last use 6–12 months vs. 1–6 months, and ≥12 months compared to 1–6 months. There was no significant difference between clinician's willingness to treat if last use was 6–12 months ago or more than 12 months ago (Table 2). For each category of time since last injection, the odds of willingness to treat increased with longer duration of abstinence (2.2 higher odds for interferon-based treatments and 2.57 higher odds for all oral treatment).

When asked the same questions about all-oral regimens, half (52%) of respondents reported willingness to treat a patient whose was abstinent for 6 or more months, one-third (35%) reported willingness to treat a patient who had not been abstinent in the last 1–6 months, and 15% were willing to treat an active PWID. Compared to recent injection use (in the previous

30 days) the odds of a clinician reporting willingness to treat with DAAs increased with abstinence time: 1–6 months, OR 4.80; 6–12 months, OR 17.10; and ≥12 months, OR 17.46 (Table 2). Post-hoc analyses showed significant differences between most of time points, but showed no significant difference between clinician's willingness to treat if last use was 6–12 months ago or more than 12 months ago.

IDU and non-IDU were "important or very important" considerations in determining treatment candidacy, regardless of treatment type (Table 3). For interferon-containing regimens, clinicians said adherence, IDU and pre-existing mental illness were most important when considering treatment. For all-oral DAA regimens, adherence, reinfection and medication cost were scored as the most important considerations, with reinfection and cost significantly more important for all-oral DAA medications compared to interferon-containing medications. Clinicians reported less concern about side effects and contraindications when prescribing all-oral regimens for PWID. IDU and non-IDU were rated 'important or very important' for both medication regimens (IDU mean 4.10 for interferon-based treatment and 3.91 for all-oral treatment; non-IDU mean 3.73 vs. 3.60 (Table 3).

## Discussion

In this study, all-oral medications were associated with significantly higher concerns about reinfection compared to interferon-based regimens. Although the treatment threshold is lower for all-oral regimens, the barriers presented by ongoing IDU may be higher than ever given the increased concerns reported regarding reinfection, and medication cost. While current PWID remain unlikely to receive treatment, abstinence for as little as 6 months was associated with a significant increase in willingness to treat using either regimen. Engagement in substance use treatment may be an important facilitator to HCV treatment. Notably, there was no significant difference in willingness to treat when last IDU was 6–12 months compared to more than 12 months. This may be an important discussion for providers to have with patients contemplating substance use treatment. If HCV treatment were available after a relatively short time of abstinence, patients may be motivated to move from contemplation to action.

Despite the advantages of DAAs, clinicians have reservations about treating PWID. In this study, clinicians had fewer concerns about co-morbidities such as pre-existing mental illness when considering HCV treatment with all-oral DAA regimens compared to interferon-based regimens, but were significantly more concerned with adherence, reinfection, and cost. Concerns about IDU and non-IDU were high, and no different given medication regimen, confirming that drug use is an ongoing major consideration to HCV treatment. This is reflected by the overall small increase in willingness to prescribe an all oral DAA HCV treatment regimen (15%) versus an interferon based regimen (10%).

Although clinicians cited recency of IDU as a barrier to treatment, evidence in studies using interferon demonstrate that some concurrent drug use does not impact SVR, although daily use may (Hellard, Sacks-Davis, & Gold, 2009). More research is needed to examine similar outcomes using DAAs, and to examine the impact of withholding treatment. Interventions

looking at the impact of relatively short periods of engagement in substance use on HCV treatment uptake and outcomes are also needed.

It has been suggested that all-oral treatment regimens be withheld from PWID due to the high cost of treatment and concerns about reinfection (Ghany, 2015). In this study, clinicians' concerns about HCV reinfection superseded those related to costs when considering all-oral regimens compared to interferon-based regimens, though both were high. The evidence suggests that reinfection after treatment with interferon-containing regimens is rare, varying from 0.8 to 4.7 per 100 person-years (Backmund, Meyer, & Edlin, 2004; Grady et al., 2012; Grebely et al., 2010). There is some evidence that being evaluated for, or receiving HCV treatment, helps decrease IDU and other substance use, and improves the ability to value and care for oneself (Asher, Lum, & Page, 2012, Batchelder, Peyser, Nahvi, Arnsten, & Litwin, 2015). Treatment may also decrease transmission events (Hagan et al., 2013, Hagan & Schinazi, 2013, Hellard, Doyle, Sacks-Davis, Thompson, & McBryde, 2014), reducing the overall disease burden among PWID. Although the evidence suggests that concerns about reinfection should not be a reason to withhold treatment, patients may benefit from engagement in HCV preventative care post-treatment, and adding this service to existing HCV treatment programs may give clinicians the confidence necessary to treat otherwise eligible patients.

Side effects, pre-existing mental illness and clinic capacity were significantly less important considerations for treatment utilizing all-oral medications compared to interferon-containing regimens. The decreased concern about side effects may be why clinic capacity is also less of a concern to clinicians. Patients undergoing HCV therapy using all-oral medications require less monitoring than do patients on interferon-containing regimens, freeing clinic staff. The decreased concern about clinic capacity may also allow more patients to receive treatment for their HCV infection.

Although we asked whether clinicians assessed their patients for substance use, we did not ask specifically about interventions or referrals to decrease use. Given the willingness providers demonstrated to provide treatment to patient abstinent or engaged in a substance use program, more work needs to be done to engage high risk patients in substance use programs. However, overall only a small percentage of substance users are engaged in drug treatment at any given time, due to both demand and supply issues (Substance Abuse and Mental Health Services Administration, 2014). Increased access to substance use treatment programs may support increased access to HCV treatment for PWID and allay provider concerns about the risk of reinfection.

This study has several limitations. This was a cross-sectional survey conducted at a large conference targeted at clinicians working in liver disease. While it is unclear if nonspecialists, would make the same treatment decisions, HCV treatment is most often provided by specialists, so it may be that this sample is representative of HCV treatment clinicians. The diversity of respondents may have had an effect on responses. It is possible that some countries may have specific policies about treatment for PWID, impacting how providers answered the questions. The questions, however, were designed to examine

provider's attitudes towards treating PWID, not policies impacting their choices about who to treat.

The results show the significant concerns and reservations physicians have about treating PWID despite evidence that it is effective. Although reinfection is possible and costs of treatment are high, research demonstrates a low incidence of reinfection, and a significant financial burden of HCV-related morbidity. Overall, the annual costs associated with people living with liver disease is1.6 times that of people without liver disease, with significant increases as liver disease progresses (Primrose Healthcare, 2015). Ultimately, treatment is more cost-effective than no treatment. Despite the barriers to treatment current PWID continue to face, recent users with as little as 6 months abstinent may be able to access treatment. More work is needed to explore facilitators to treatment in this group. Although new treatments for HCV infection are promising, the population in highest need continues to face significant challenges accessing treatment. More work needs to be done to engage this population and the clinicians likely to provide this curative treatment.

## Conclusion

Healthcare costs related to HCV infection are high, and the population most impacted by the disease, PWID, do not currently have substantial access to treatment. As HCV treatment becomes easier to provide and tolerate, PWID should have increased opportunities to receive curative treatment, ultimately lowering healthcare-associated costs and transmission events. Understanding how treatment candidacy may be evolving as HCV treatment evolves is essential to decreasing HCV-related morbidity and mortality among PWID. This study provides important insight into clinician's willingness to treat PWID in an era of highly effective, all-oral antiviral treatment. The information gained from this study will help public health officials understand how to provide supportive treatment environments and concurrent programs. As HCV treatment improves, policies should address barriers to HCV treatment for PWID, paving the way for eradication of HCV.

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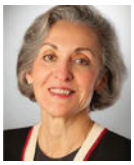
## Biographies

***Dr. Alice K. Asher*** is currently an Epidemiologist in the Division of Viral Hepatitis, Epidemiology and Surveillance Branch; this work was done as a doctoral student at the University of California San Francisco.

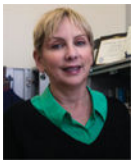


***Dr. Carmen J. Portillo*** is Professor & Chairperson of the Department of Community Health Systems at the University of California, San Francisco and conducts research on nursing workforce issues, and quality of life among people living with HIV/AIDS.

***Dr. Bruce A. Cooper*** is Senior Statistician and Associate Adjunct Professor in the School of Nursing at University of California, San Francisco, and has participated in a large body of research, particularly focused on symptom management among cancer patients.

***Dr. Carol Dawson-Rose*** is a professor of Nursing at the University of California, San Francisco, and has conducted research for over 20 years with substance users, primarily People who are living with HIV, to capture and increase our understanding of their experience of care.

***Dr. David Vlahov*** is Dean and Professor at the University of California, San Francisco School of Nursing and brings over 20 years research expertise in epidemiology, infectious diseases, substance abuse and mental health.



***Dr. Kimberly A. Page*** is the Chief of Epidemiology, Biostatistics and Preventive Medicine at the University of New Mexico Health Sciences Center (UNM HSC), and an infectious

disease epidemiologist working with populations at high risk of HIV and hepatitis C virus (HCV) infections.

## Glossary

**Direct-acting antivirals**

Medications that interfere with specific steps in the HCV replication cycle through a direct interaction with the HCV genome, polyprotein, or its polyprotein cleavage products

**Sustained viral response**

Undetectable HCV RNA using a highly sensitive assay 24 weeks following the end of HCV treatment. Used as a surrogate marker for HCV cure after completion of antiviral therapy

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**Table 1.**

Participant demographics.

| | ***N*** **= 108%** |
|---|---|
| Region of practice | |
| North America | 30 |
| Europe | 15 |
| Asia | 9 |
| Africa | 18 |
| Middle East | 14 |
| Australia | 1 |
| South America | 13 |
| Clinical licensure | |
| Medical Doctor | 76 |
| Physician's Assistant | 6 |
| Nurse Practitioner | 11 |
| Doctor of Osteopathy | 1 |
| Other | 6 |
| Practice environment | |
| Research Institution | 44 |
| Private hospital/HMO | 8 |
| Veteran's Administration | 25 |
| Private clinic | 13 |
| Community/Public Health Clinic | 10 |
| Specialty | |
| Hepatology | 48 |
| Gasteroenterology | 24 |
| Internal Medicine | 4 |
| Family/community | 1 |
| Infectious Disease | 19 |
| HIV | 3 |
| Other | 1 |
| Years in practice | |
| 0–5 | 42 |
| 6–10 | 16 |
| 11–15 | 17 |
| 16–20 | 25 |
| Proportion of patients with HCV infection | |
| 0–25% | 57 |
| 26–50% | 19 |
| 51–75% | 8 |
| 76–100% | 16 |
| Gender | |

| | ***N*** **= 108%** |
|---|---|
| Male | 64 |
| Female | 36 |

**Table 2.**

Pairwise contrasts of willingness to treat between timepoints of abstinence.

| **Interferon-based regimen** | | |
|---|---|---|
| **Last injection drug use** | **Contrast** | **95% confidence interval*** |
| 6–12 months vs. 1–6 months | 1.27 | 0.42, 2.12** |
| >12 months vs. 1–6 months | 1.83 | 0.94, 2.71** |
| >12 months vs. 6–12 months | 0.55 | −0.26, 1.36 |
| **All-oral regimen** | | |
| **Last injection drug use** | **Contrast** | **95% confidence interval*** |
| 6–12 months vs. 1–6 months | 1.27 | 0.46, 2.08** |
| >12 months vs. 1–6 months | 1.29 | 0.47, 2.11** |
| >12 months vs. 6–12 months | 0.21 | −0.77, 0.81 |

* Bonferroni-corrected

** Significant difference between time points

**Table 3.**

Importance of consideration for HCV treatment.

| | Interferon Mean[+] | All oral Mean[+] | Difference | 95% confidence interval[*] |
|---|---|---|---|---|
| Adherence | 4.53 | 4.64 | 0.11 | −0.83, 0.32 |
| Reinfection | 3.74 | 4.03 | 0.29 | 0.46, 0.55[**] |
| Cost | 3.69 | 4.44 | 0.75 | 0.47, 1.01[**] |
| Housing | 3.84 | 3.81 | −0.03 | −0.25, 0.19 |
| Neuropsychiatric effects | 4.08 | 3.17 | −0.92 | −1.18, −0.64[**] |
| Other side effects | 3.96 | 3.21 | −0.75 | −1.02, −0.52[**] |
| Pre-existing mental illness | 4.19 | 3.11 | −1.07 | −1.38, −0.81[**] |
| Clinic capacity | 3.51 | 3.24 | −0.31 | −0.05, −0.09[**] |
| Alcohol use | 4.00 | 3.84 | −0.16 | −0.37, 0.41 |
| Injection drug use | 4.10 | 3.91 | −0.17 | −0.38, 0.6 |
| Non-injection drug use | 3.73 | 3.60 | −0.13 | −0.39, 0.74 |

[+] Mean of Likert scale rating (1 = not important, 5 = very important).

[*] Bias-corrected and accelerated bootstrapped confidence interval due to highly skewed non-normal distributions.

[**] significant difference between treatment types.