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Evidence-Based Interventions to Enhance Assessment, Treatment, and Adherence in the Chronic Hepatitis C Care Continuum

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Abstract

Background—With the explosion of newly available, direct acting antiviral (DAA) Hepatitis C virus (HCV) treatments that demonstrate 95% sustained virologic response (SVR) rates, evidence-based strategies are urgently needed to achieve real-world effectiveness in challenging patient populations. While HIV is incurable, lessons from over 30 years of experience overcoming obstacles to the HIV treatment cascade could be applied to the HCV context.

Methods—Using Institute of Medicine guidelines, we conducted a systematic review of published interventions from PubMed, Medline, GoogleScholar, EmBASE, and PsychInfo bibliographic databases and citation indices. Abstracts were first screened by three independent reviewers and studies were included if they involved original research, described a specific intervention, were published in English in a peer-reviewed journal between 2001 and 2014, and had full text available.

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JPM and FLA conceived of and designed the study, with input from YM, RM, JKL, and AHL. JPM, YM, and RM conducted the literature review and collaboratively selected and organized manuscripts for inclusion. JPM, YM, and RM drafted the manuscript with subsequent input from JKL, AHL, and FLA. All authors have seen and approved of the final version for publication.

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Results—Evidence-based interventions to enhance HCV assessment, treatment, and adherence generally fell into one of 4 categories, including those involving: 1) Diagnosis or case-finding; 2) Linkage to HCV care; 3) Pre-therapeutic evaluation or treatment initiation; or 4) Treatment adherence. While most available eligible studies described interventions using non-contemporary interferon-based HCV treatments, future research will need to address how these interventions apply to the context of well-tolerated, simple, oral treatment regimens. In some cases, we explored how HIV-specific interventions might be modified to fit the HCV spectrum of care engagement.

Conclusions—Evidence-based interventions should be strategically incorporated into HCV treatment implementation efforts to most effectively deliver treatment and maximize treatment outcomes.

Keywords

Hepatitis C; interventions; implementation; care continuum

Background

A variety of new therapeutic options have recently emerged to meet the treatment needs of people living with chronic Hepatitis C virus (HCV) infection (Pawlotsky, 2014). The goal of treatment is cure, defined as sustained virologic response (SVR), to avert major complications of HCV, including cirrhosis, hepatocellular carcinoma, and death. Chronic HCV treatment is transformed with new direct acting antivirals (DAAs) that can cure >95% of infections with short-course, simple and well-tolerated regimens. From a public health perspective, HCV prevalence can be reduced if available treatment is not only expanded, but targeted to those most likely to transmit the virus (Martin et al., 2014; Martin, Vickerman, Goldberg, & Hickman, 2015; Martin et al., 2013; Rolls et al., 2013). It is therefore imperative to examine effective strategies to improve treatment outcomes along the entire chronic HCV care continuum from diagnosis through “cure” and have evidence to treat patients deemed by providers as being “challenging.”

To translate the promise of clinical trial efficacy into real-world effectiveness, however, well-executed action plans, appropriate resource allocation (Mondelli MU), and comprehensive public health policies (Dalgard & Mauss, 2014) are urgently needed (Department of Health and Human Services, 2014). Evidence-based interventions are critical tools to effectively engage individuals with chronic HCV in care and treatment, since many have underlying comorbid psychiatric and substance use disorders, HIV, and social instabilities (like homelessness and incarceration) that complicate care delivery (Hellard, Sacks-Davis, & Gold, 2009). Among people who inject drugs (PWIDs), the HCV seroprevalence is 60%–80% globally, and drug injection is the major driving force behind the HCV pandemic (Nelson et al., 2011). With adequate support, however, PWIDs can overcome social and structural barriers to achieve parity with other people with HCV in terms of treatment success (Robaey et al., 2006; Soriano & Gallego, 2013; D. L. Sylvestre, 2005; M. Zeremski et al., 2013). A scale-up of antiviral treatment options requires a parallel expansion of evidence-based interventions, like medication-assisted therapies with methadone, buprenorphine (e.g. both better classified as opioid agonist treatments; OAT)

and high-coverage needle and syringe exchange programs (NSP), that support effective treatment dissemination and reduce HCV incidence (Martin et al., 2013).

The so-called “continuum of care” (E. M. Gardner, McLees, Steiner, Del Rio, & Burman, 2011) provides a useful framework to discuss strategies for intervention. In order to ultimately achieve SVR, individuals must: 1) first be tested for, diagnosed with, and made aware of their HCV infection; 2) then engage with a healthcare provider with treatment knowledge and capacity; 3) then be evaluated for and 4) initiate treatment; 5) adhere to and complete treatment; and 6) prevent re-infection. Recent estimates suggest that nearly half of people with HCV remain undiagnosed or unaware of their HCV infection and less than 10% with chronic HCV effectively achieve SVR (Irving et al., 2006; Mondelli MU; Yehia, Schranz, Umscheid, & Lo Re, 2014). Clinical pathways are frequently neither linear nor continuous, so interventions must often target one or more steps along the care continuum (Robaey et al., 2013).

While we are just beginning to understand and shape the chronic HCV care continuum, the HIV treatment community has been grappling for decades with care engagement issues (Lazarus et al., 2014). Although HIV, unlike HCV, is currently incurable and requires lifelong commitment to daily medications, the two chronic viral infections are similar in terms of epidemiology, routes of transmission, and associated stigma, and many people live with both HIV and HCV. Moreover, both HIV and HCV disparately affect individuals marginalized from systems of care, by virtue of their race/ethnicity, socioeconomic status, health illiteracy, substance use, and interactions with the criminal justice system. As such, where there is a paucity of data on HCV-related interventions, we extrapolate from the HIV literature (Kamarulzaman & Altice, 2015; Meyer, Althoff, & Altice, 2013). In doing so, we address the call to apply lessons learned from the HIV epidemic to identify specific interventions that have high likelihood to facilitate the chronic HCV care continuum (Lazarus et al., 2014). Whereas models of care have previously been reviewed (Bruggmann & Litwin, 2013), we focus instead on specific evidence-based intervention strategies. The purpose of this systematic review was to identify and synthesize data on evidence-based interventions that strategically target one or more steps along a chronic HCV care continuum (Figure 1).

Methods

We systematically reviewed published scientific literature using Institute of Medicine guidelines (Institute of Medicine, 2011). We first searched PubMed, Medline, Google Scholar, EmBASE, and PsychInfo using key words “Hepatitis C,” “surveillance,” “testing,” “adherence,” “treatment,” and “intervention”; additional references were extracted from citation indices. Titles and abstracts were then screened by three independent authors (JPM, YM, and RM) for the following inclusion criteria: in English, full text available, original research, described an intervention with measurable outcomes, and published between 2001 and 2014 (2001 was chosen because this was the year that pegylated interferon first became available). Full texts of included abstracts were then further reviewed and critical data were extracted for analysis, using a standardized tracking sheet. Final studies were selected through an iterative process involving three authors (JPM, YM, and RM), in which the

inclusion criteria described above were applied to each manuscript and selected manuscripts were categorized by topic area. Where disagreement about classification occurred, the third reviewer broke the tie. Because the chronic HCV treatment cascade of care is rapidly evolving, there is no single definition of “linkage to care.” Some studies describe “linkage” in terms of completing a referral for specialty care, whereas others equate “linkage” with undergoing fibrosis staging or initiating treatment. To include all possible studies, we defined “linkage to care” interventions as those with the common purpose of shifting HCV-diagnosed individuals towards HCV-specific care for further evaluation and treatment. With the simplicity of treatment with newer DAAs, however, treatment may move towards primary care venues (Westergaard et al., 2014). Specific details about quantity of and reasons for exclusions are described in the Results section that follows. Beyond the HCV-specific systematic review, for each cascade step, we additionally comment on the applicability of HIV-related strategies to the HCV context, drawing from our prior published research on HIV (Meyer et al., 2013).

Results: Intervention Strategies

Diagnosis and Case-Finding

According to current U.S. clinical guidelines (American Association for the Study of Liver Diseases (AASLD) & Infectious Diseases Society of America (IDSA), 2014), routine chronic HCV screening is recommended for all individuals born between 1945 and 1965 and those with specific risk behaviors, exposures, and comorbid conditions, including injection drug use, hemodialysis, incarceration, and HIV. Though this guideline is supported by Level Ib evidence and expands on previous recommendations for risk-based testing only, uptake is limited by a lack of targeted outreach strategies and by providers’ limited incorporation of current guidelines into clinical practice. In other global settings, screening recommendations do not include the age-specific risk group (World Health Organization, 2014).

We found 13 published studies addressing HCV screening; of these 7 were excluded because no intervention was described. The remaining 6 screening-related interventions (Table 1) demonstrate high rates of uptake and case-finding when interventions target high-risk individuals in specific settings, including PWID in NSPs (Aitken, Kerger, & Crofts, 2002), patients in a primary care clinic with certified methadone prescribers (Cullen et al., 2006), patients in specialty addiction treatment clinics and prison (Craine et al., 2014; Hickman et al., 2008), patients in a mobile medical clinic (Morano et al., 2014), and individuals with co-occurring substance use and serious psychiatric disorders in community mental health programs (Slade et al., 2013). The interventions described include free counseling and testing (Aitken et al., 2002), point-of-care testing (Morano et al., 2014), streamlined screen-test-immunize-reduce risk-refer protocols (Slade et al., 2013), dried blood spot testing (Craine et al., 2014; Hickman et al., 2008), and provider education with nursing support (Cullen et al., 2006). Programs were found to be generally effective at identifying new cases of chronic HCV and cost-effective when compared to treatment-as-usual, though often they required ancillary structural support to increase testing rates.

Linkage to Care

We found 29 published studies addressing linkage to care (as broadly defined); of these 9 were excluded because no intervention was described. The 20 remaining interventions designed to link patients to care (Table 2) were distinguished based on treatment settings: addiction treatment centers providing OAT, primary care, and correctional settings. Other interventions were distinguished by whether they involved multidisciplinary teams or were peer-based models.

Interventions based in addiction treatment centers initiated HCV care at different stages of addiction treatment. One study showed that HCV care could be successfully initiated in a detoxification unit, rather than waiting the customary 6–12 months of sobriety; low rates of re-infection or relapse were observed even among those who relapsed to drug injection (Backmund, Meyer, Von Zielonka, & Eichenlaub, 2001). Other interventions introduced on-site HCV care with patients previously established in OAT programs and showed comparable rates of uptake and SVR to non-PWID populations (Alavi et al., 2013; Belfiori et al., 2009; Bonkovsky et al., 2008; Bruce et al., 2012; Alain H Litwin et al., 2009; Martinez et al., 2012). One retrospective chart review demonstrated that longer duration on OAT with methadone was independently and positively associated with HCV treatment initiation (Seidenberg, Rosemann, & Senn, 2013). Common to all of these interventions is a multidisciplinary approach that combines medical and addiction treatment with intensive social support (Dimova et al., 2013).

Primary care settings have also represented key opportunities for HCV care linkage interventions, often within clinics that have prolonged engagement with homeless, substance using populations, or PWIDs. These studies demonstrated that patients with ongoing drug use and psychiatric comorbidity-- those traditionally excluded from systems of care-- can be effectively linked to care from and sometimes treated within these settings (Bruce et al., 2012; Jack, Willott, Manners, Varnam, & Thomson, 2009; McAllister et al., 2014; Morano et al., 2014; Newman et al., 2013; Seidenberg et al., 2013). One study implemented an integrated, multidisciplinary medical group visit to integrate care (Ho et al., 2013). In primary care settings where providers lacked experience treating HCV, the Extension for Community Healthcare Outcomes model (Project ECHO) provided tele-health consultation that demonstrated equivalent SVR rates between remote tele-health sites and a specialty HCV clinic in an academic center (Arora et al., 2011). Another intervention in Canada used a public health nurse and physician partnership to link patients to care from rural and small towns (Hill, Butt, Alvarez, & Krajden, 2008).

Correctional settings are ideal for generating linkages to HCV treatment because of the high prevalence of disease and the highly structured nature of a controlled environment, though are woefully underutilized (Beckwith et al., 2015) especially due to the cost of DAAs (Nguyen et al., 2015). One intervention involving a nurse with physician support through telemedicine proved safe and effective for assessment and treatment (Lloyd et al., 2013).

Peer-driven interventions are well-accepted and efficient ways to facilitate linkage to care (Norman et al., 2008). Peer-driven interventions have demonstrated high uptake of HCV treatment and SVR rates among PWIDs (Grebely, Genoway, et al., 2007; D. L. Sylvestre &

Clements, 2007). Concurrent group treatment is highly influenced by peer-driven interventions, in which HCV treatment is delivered in a peer group that is provider-led (M. R. Stein et al., 2012). Despite these promising peer-based interventions, data is generally limited and primarily descriptive with few randomized or controlled studies measuring or reporting the impact of peer-driven interventions (Crawford & Bath, 2013), except for the case of HIV. Systematic evaluations of the impact of HCV peer programs are still needed, including how they affect uptake and treatment outcomes, and how different models of peer involvement may suit various settings (Roose, Cockerham-Colas, Soloway, Batchelder, & Litwin, 2014).

As HCV treatment options expand, treatment providers will likely also need to expand to accommodate new healthcare consumers. Although highly complex HCV patients may continue to require care by infectious disease and hepatology specialists, when treatment options no longer require significant clinical support and infrastructure, which appears to be the case with the newer DAA treatments, some HCV patients can be successfully treated in primary care settings. In this rapidly evolving landscape of clinical care, it is unclear how the “linkage to care” interventions described here will apply to less-specialized care settings. This is especially salient in rural settings where specialty services are largely unavailable (Westergaard et al., 2014).

Pre-therapeutic Evaluation/Treatment Initiation

HCV treatment is often deferred or not recommended for active PWIDs (Hepworth, Bain, & van Driel, 2013). Providers often unjustifiably defer HCV treatment for PWIDs because of concerns about treatment adherence, neuropsychiatric tolerability (Hepworth et al., 2013), or risk of re-infection, especially in the setting of ongoing drug injection (Soriano & Gallego, 2013), but often treatment is deferred because of perpetuated stigma against PWIDs (Meyer et al., 2013; Westergaard, Ambrose, Mehta, & Kirk, 2012). One study showed that 51% of patients diagnosed in a primary care setting were never referred for specialist care (Irving et al., 2006). In reality, PWIDs are those who might benefit most from HCV treatment, especially since they have the highest risk of transmission to others, and can achieve SVR if adequately supported through the treatment initiation process.

Several innovative healthcare delivery models facilitated treatment initiation among persons with psychiatric or substance use disorders. Effective models of care at the patient, peer, and provider level combine behavioral and therapeutic approaches as part of integrated care (Bruce et al., 2012). When PWIDs are surveyed to assess HCV treatment knowledge and barriers to treatment initiation (Mehta et al., 2008), interest in (M. D. Stein, Maksad, & Clarke, 2001; Strathdee et al., 2005), and willingness to receive treatment (Marija Zeremski et al., 2014), treatment-naïve patients were consistently more willing to enter into a treatment program if they perceived themselves at-risk for cirrhosis or liver cancer (Strathdee et al., 2005), were younger, or had more knowledge about HCV (Marija Zremski et al., 2014). Based on these findings, evidence-based interventions can be implemented to initiate the treatment process, particularly among PWIDs, but may not be as necessary in the current treatment era where DAAs are better-tolerated, more effective and have shorter treatment durations.

A preliminary search revealed 15 studies related to HCV treatment initiation and 7 met all inclusion criteria; the remainder involved descriptive studies, reviews, or no specific intervention was described (Table 3). Interventions varied in terms of strategic levels and settings. In a VA-based randomized controlled trial, patient self-management workshops were compared with information provision only, and major outcomes of interest were HCV knowledge, depressive symptoms, energy, and health-related quality of life (Groessl et al., 2013). Despite improvements in personal factors related to HCV, no difference was noted between the two arms in treatment initiation. Peer-driven interventions, such as the Organization to Achieve Solutions in Substance Abuse (OASIS) program based at a California community clinic, combined a biopsychosocial (Educate-Motivate-Facilitate) peer-driven approach with buprenorphine maintenance therapy to improve treatment engagement (Diana L. Sylvestre & Zweben, 2007). Of the 352 HCV-infected patients at a NSP receiving OASIS care, 53 (15%) initiated HCV treatment (Diana L. Sylvestre & Zweben, 2007). Using the same OASIS model, a Vancouver-based study found that among 204 PWIDs evaluated and attending the support group, 57 (28%) initiated treatment (Grebely et al., 2010). Another intervention involved a decentralized, visiting hepatitis service that delivered monthly clinics at 30 different prisons and provided effective assessment and treatment for patients who might be difficult to treat in community settings (Boonwaat, Haber, Levy, & Lloyd, 2010).

While these interventions focused on individual or peer support to help PWIDs navigate the pre-treatment process, other initiatives rely on providers, pharmacists (Marino et al., 2009), or care coordination. One randomized controlled trial delivered a behavioral intervention, consisting of motivational interviewing, education, and case management services, and evaluated receipt of onsite initial Hepatitis A and B vaccination, and HCV clinic visit attendance among patients in a MMT program (Masson et al., 2013). The intervention group was 4-times more likely than those receiving usual treatment to attend a HCV clinic visit (i.e. complete a referral) within 6 months. Another multi-site randomized controlled trial among persons previously deferred from HCV treatment due to a substance use disorder or psychiatric condition, involved integrated care with a hepatologist and psychologist conducting a behavioral intervention (Evon et al., 2011). Compared to individuals receiving usual care, those in the intervention group were 2.4-times more likely to initiate treatment within 9 months of enrollment.

Interferon-based regimens have traditionally been associated with long courses, debilitating side effects, and reduced efficacy among individuals with more advanced liver disease or less favorable genotypes. Except for those meeting highest priority for treatment because of advanced fibrosis or extra-hepatic manifestations of HCV, the pre-treatment process often requires multiple measurements of HCV RNA and fibrosis assessment (with either liver biopsy or non-invasive measures) (American Association for the Study of Liver Diseases (AASLD) & Infectious Diseases Society of America (IDSA), 2014). As more tolerable treatment regimens become available, the benefits and cost-effectiveness of an extensive pre-treatment evaluation are unknown.

Treatment Adherence Facilitation

Once patients are successfully diagnosed, linked to care, and initiated on treatment, adherence to therapy needs to be optimized. High levels of adherence to interferon-based regimens directly correlate with early virologic response (EVR) and SVR (Lo Re et al., 2011; McHutchison et al., 2002). Developed for statistical analyses in cohort studies, the “80/80/(80) rule” defines optimal adherence as having taken at least 80% of prescribed doses at least 80% of the time. The 80/80 adherence rule, though not formally validated, has since been applied in numerous other adherence studies for HCV. It is unclear what level of adherence is optimal to achieve SVR with non-interferon-based regimens that are more potent and (perhaps) durable, but with potentially lower barriers to developing genotypic resistance. Furthermore, it is not yet known whether adherence to DAAs is problematic enough to warrant targeted intervention, since DAA-based regimens also comprise lower pill burdens and shorter treatment courses. In clinical trials to date, DAA treatment adherence and completion rates have been extremely high, but it remains to be seen how this will play out in real-world clinical practice- issues that may be addressed by currently ongoing cohort studies (e.g., HCV-TARGET and TRIO).

We identified 33 published studies relating to HCV treatment adherence interventions; of these 16 were excluded because they did not describe a specific intervention. The remaining 17 interventional studies are detailed further in Table 4. While some of the adherence-promoting interventions described here did define optimal adherence using the 80/80 rule (Alam, Stainbrook, Cecil, & Kistler, 2010; Carrion et al., 2013), others defined adherence by attendance at study visits (Ho et al., 2013) or treatment completion (Bertino et al., 2010; Bonkovsky et al., 2008). The latter concept technically refers not to adherence, but treatment persistence, which is a closely related construct that is the continuation of prescribed treatment over time (Bae, Guyer, Grimm, & Altice, 2011). Adherence was most often measured by self-report, though some additionally measured pill counts (A. H. Litwin, Berg, Li, Hidalgo, & Arnsten, 2011), pharmacy claims (Ho et al., 2013; Hussein et al., 2010), or used medication event monitoring system (MEMS) caps (Bruce et al., 2012).

Recognizing the extraordinary daily pill burden otherwise associated with ribavirin-containing regimens, one intervention involved delivering a higher-dose formulation of ribavirin known as RibaPak (Alam et al., 2010). Compared to those receiving standard ribavirin, those receiving the intervention had significantly higher rates of adherence, measured compositely by treatment completion, pill counts, and self-report, but clinical impact (in terms of SVR) was not reported (Alam et al., 2010). Other studies of patients on standard-dose ribavirin have attempted to proactively intervene on side effects like anemia, depression, and fatigue that often impede adherence, but interventions achieved minimal impact in clinical trials (Bertino et al., 2010; Morasco et al., 2010; Zucker, 2010).

Similar to the implementation of directly administered antiretroviral therapy or directly observed therapy (DOT) for HIV (Berg, Litwin, Li, Heo, & Arnsten, 2011; Binford, Kahana, & Altice, 2012), a number of interventions involved the provision of HCV treatment as DOT (Flanigan, Taylor, & Mitty, 2005). By using a modified DOT approach (mDOT) to observe only the morning dose of ribavirin or weekly injections of interferon, HCV treatment was successfully delivered in OAT programs (Bonkovsky et al., 2008; Bruce et

al., 2012; A. H. Litwin et al., 2011), prison settings (Saiz de la Hoya et al., 2014), and multidisciplinary health clinics (Grebely, Raffa, et al., 2007). Effects of DOT, compared to self-administered therapy, were consistently modest and likely related to small, highly selective samples of motivated patients in the available studies. Another study provided ribavirin as once-daily DOT, demonstrating extremely high rates of SVR among patients stably maintained on opioid substitution therapy (Waizmann & Ackermann, 2010).

A number of studies described multidisciplinary support programs to promote treatment adherence, retention, and completion. These programs may involve collaborations between physicians specializing in internal medicine, addiction, and hepatology (Carrion et al., 2013; Curcio et al., 2010; Ho et al., 2013), and between physicians and nursing support staff (Larrey et al., 2011), with a focus on multidisciplinary psychoeducation (Hussein et al., 2010; Reimer et al., 2013). Many of these studies were non-randomized or were subject to selection bias; other limitations are detailed further in Table 4.

Applying Lessons Learned from the HIV Care Continuum

Unlike in the case of chronic HCV, universal screening for HIV is currently recommended, regardless of risk profile. To maximize effectiveness of screening, interventions target sites where high-risk individuals, such as PWIDs, congregate. Opt-out and onsite rapid testing strategies facilitate targeted testing at substance abuse treatment centers (Metsch et al., 2012), emergency departments (Kelen et al., 1999), and prisons or jails (de Voux et al., 2012; Kavasery, Maru, Cornman-Homonoff, et al., 2009; Kavasery, Maru, Sylla, et al., 2009). Opt-out testing alleviates the burden of consent and removes potential structural barriers to diagnosis- a strategy that could also be applied to HCV screening (Jones et al., 2014).

Unlike in HIV, HCV diagnostic technology has mostly been limited to 2-stage enzyme immunoassay (EIA) and nucleic acid testing. Rapid point-of-care screening tests for HCV antibodies were FDA-approved in 2010, allowing screening to be expanded to non-clinical settings (Stockman, 2014), but implementation strategies have not yet been rigorously evaluated or published, with the exception of one preference study (Morano et al., 2014).

Drawing from the HIV literature, an interventional strategy for linking diagnosed individuals to care involves strengths-based intensive case management (Althoff et al., 2012; L. I. Gardner et al., 2005). Intensive case management can be particularly helpful for PWIDs, who often have many unmet needs and require assistance obtaining housing, medical insurance, and treatment for comorbid psychiatric and substance use disorders to successfully initiate and remain in care. Intensive case management services are a core component of Ryan White-funded Early Intervention Services for people with HIV, but many HCV treatment programs also anecdotally incorporate case management services into patient care, despite limited existing data on effectiveness at improving HCV treatment uptake or outcomes.

The HIV epidemic has required a scale-up of multimodal approaches to adherence promotion since optimal adherence is frequently defined as 95% and treatment is life-long. With support, PWIDs can adhere to antiretroviral therapy (ART) and successfully achieve

viral suppression (Malta et al., 2010; Werb et al., 2010). Though self-management tools like pillboxes or alarms are effective in some HIV populations, they are often insufficient strategies for PWIDs (Altice et al., 2010; Thompson et al., 2012), who may require additional supportive interventions, like those described here.

Discussion

This is, to our knowledge, the first systematic review of evidence-based intervention strategies to address the chronic HCV care continuum. While the HCV field is rapidly evolving to accommodate new diagnostic technologies and treatment options, there are a number of promising interventions, described here, that maximize dissemination and uptake. At each step along the continuum of care (Kamarulzaman & Altice, 2015), from diagnosis to “cure”, there is the opportunity to intervene (Figure 1). Many of the interventions described here simultaneously target multiple steps, for example integration of healthcare delivery services (Sylla, Bruce, Kamarulzaman, & Altice, 2007), and it was often difficult to attribute an intervention to a particular step because terms were inconsistently defined. A major challenge for future research and clinical guidance on the HCV cascade of care is to identify clear and consistent definitions for “linkage to care,” “pre-treatment evaluation,” and “treatment adherence.” Although study findings must be interpreted with caution in regards to generalizability, small sample sizes, and (for many) lack of a control group, interventions generally have demonstrated clinical and cost-effectiveness. It is unclear how these interventions will need to be adapted to interferon-free regimens with DAAs, but PWIDs will likely continue to require intervention and support to effectively navigate complex systems of care.

We have learned over 30 years from the HIV pandemic that treatment for underlying substance use disorders is key to promoting adherence in PWIDs, allowing them to achieve parity with non-drug users in terms of clinical outcomes (Malta, Strathdee, Magnanini, & Bastos, 2008; Roux et al., 2009). Evidence-based treatment for substance use disorders involves combinations of behavioral interventions and medication-assisted therapies (e.g. OAT) that have been described elsewhere for people with HIV (Altice et al., 2010; Bruce & Altice, 2007). This strategy could be easily translated to HCV, since so many interventions described here already target clients at addiction treatment centers, but the specific and direct effect of addiction treatment on HCV clinical outcomes has been minimally explored (Dimova et al., 2013).

Future research must also identify strategies for retaining people with HCV in care after successful treatment completion, for continued surveillance for hepatocellular carcinoma (for those with advanced liver disease at the time of HCV treatment) and reinfection. As opposed to relapse, reinfection is defined as a subsequent HCV infection after an initial infection is completely eliminated with treatment (Blackard & Sherman, 2007). Though we initially anticipated including this post-care step, our systematic review revealed a dearth of published literature on this topic. Reinfection prevention would likely assimilate the form of primary HCV prevention interventions, including a combination of medication-assisted and behavioral treatment for substance use disorders, NSPs, harm reduction injecting techniques, and psychosocial education (Hagan, Pouget, & Des Jarlais, 2011). As in the “treatment as

prevention” paradigm that prevails in HIV, successful treatment of HCV in PWIDs could potentially eliminate transmission of HCV to others (Martin et al., 2013). The implications of reinfection, as opposed to primary infection, may be particularly challenging for patients in terms of psychological impact and restricted options for future re-treatment. Fortunately, a recent systematic review suggests low reinfection rates among PWIDs after completing treatment for HCV, ranging from 0.76–4.7 per 100 person-years (Grady, Schinkel, Thomas, & Dalgard, 2013). The low reinfection rate among PWIDs is in part, attributable to partially-conferred protective immunity from previous infection (Grebely et al., 2012), but may also reflect that PWIDs who successfully complete HCV treatment are self-selected and at lower risk of repeated HCV exposure.

Despite every attempt to be comprehensive and systematic, this literature review is not without limitations. Beyond the expected publication bias, our search was limited to manuscripts in English that may limit applicability to other global contexts where interventions are limited by different economic, social, political, or structural issues. We expect, however, that the evidence-based approaches described here could be easily adapted across cultures. Whereas continuum of care steps were inconsistently defined or overlapped, we necessarily imposed a categorization of interventions into specific steps. The interventions were categorized by several co-authors working collaboratively and, though still somewhat subjective, allowed for the overall inclusion of key published interventions in the final review.

Conclusion

In this systematic review, we described a variety of specific interventions designed to propel the HCV cascade of care and maximize dissemination of effective treatments. EBIs should be strategically incorporated into HCV treatment implementation efforts to most effectively deliver treatment and maximize treatment outcomes.

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Highlights

- Intervention scale-up is needed to support dissemination of new HCV treatments.
- We reviewed interventions that address the HCV care continuum.
- Interventions primarily applied to interferon-based treatment regimens.
- We explore applying HIV-related interventions to the Hepatitis C care continuum.

Figure 1. Overview of the Continuum of Care for Chronic Hepatitis C Virus with Targeted Interventions

HCV=Hepatitis C Virus; SVR=sustained virologic response

Table 1

Intervention Strategies for Diagnosis and Case Finding

1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major findings	Limitations
Aitken	2002	357 PWID	Melbourne, Australia NSP	Free HCV counseling and testing	Pilot	feasibility; new diagnosis; change in risk behavior	28/47 tested newly HCV +; risk behaviors decreased; HCV knowledge increased with counseling	Small N; limited generalizability; non-randomized
Craine	2014	5 prisons	UK	Dried blood spot testing for HCV	Stepped-wedge cluster RCT	HCV testing rate	Insufficient evidence of effect of intervention on outcome (in ITT or as-treated analysis)	Missing data; Intervention timing did not occur as planned in study design
Cullen	2006	196 patients in 26 general practices with certified methadone prescribers	Ireland	Educational sessions for certified methadone providers about new HCV guidelines with support from nursing liaison × 6 months vs. care as usual	Cluster RCT	% patients on MMT screened for HCV; %HCV+ patients referred out for treatment	49% screened for HCV (intervention) vs. 27% in control group, p=0.02; no difference between the 2 groups in terms of referral to hepatology for treatment	Generalizability; selection bias (main outcome determined by chart review); stratified by practice characteristics
Hickman	2007	1034 patients in 22 specialist drug clinics and 6 prisons	England and Wales	Dried blood spot testing for HCV	Cluster RCT	% individuals tested for HCV 6 months before vs. 6 months after intervention	Mean 14.5% difference between intervention and control sites in proportion patients tested for HCV; 13/14 intervention sites with positive effect	Heterogeneity of treatment effect; generalizability issues given intervention sites
Morano	2014	1345 patients on a mobile medical clinic	New Haven, CT	HCV screening using standard phlebotomy vs point-of-care testing	Preference trial	Acceptance of HCV testing; preference of standard phlebotomy vs point-of-care testing	438 clients accepted HCV testing, 47.7% preferred point-of-care test and more likely to link to HCV care than those receiving standard phlebotomy.	Not randomized; possible sampling bias; generalizability (testing provided free of charge)
Slade	2013	236 patients with co-occurring substance use and serious psychiatric disorders	Baltimore community mental health programs	Screen, Test, Immunize, Reduce Risk, Refer (STIRR)	RCT	Self-reported receipt of HBV/HCV/HIV testing and HAB/HBV vaccination in 6-months post-randomization; total	STIRR services cost \$399 more per client vs. TAU but resulted in higher proportions receiving appropriate testing and vaccination	Main outcomes self-reported; did not calculate anticipated costs/ cost-savings; selection issue since

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1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major findings	Limitations
						implementation and delivery cost	delivery cost and delivery cost	patients randomly assigned to a clinic

PWID=people who inject drugs; NSP=needle syringe exchange program; HCV=Hepatitis C virus; MMT=methadone maintenance treatment; HBV=Hepatitis B virus; HAV=Hepatitis A virus; TAU=treatment as usual; CT=Connecticut; RCT=randomized controlled trial

Table 2

Intervention Strategies for Linkage to Care

1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major findings	Limitations
Alavi	2013	387 PWID	NSW, Australia	Recruitment and referral in OST and community health centers	Prospective observational	HCV specialist assessment and treatment uptake	Assessment was undertaken in 191 (49%) and 84 (22%) commenced IFN-based treatment	May represent a group that was already engaged in health services and not generalizable to groups less engaged.
Arora	2011	407 patients with GPs	Rural and prisons, New Mexico	Video-conferencing technology (ECHO) training GPs to treat HCV	Prospective cohort	Treatment uptake and efficacy=SVR	57.5% of HCV clinic and 58% of ECHO achieved SVR	No randomization of providers or patients; potential unmeasured confounders
Backmund	2001	50 PWID in detox program	Germany	Initiation of HCV treatment in detox unit	Prospective observational	Initiation of IFN-based treatment and SVR	36% SVR	No control; small sample; selection bias
Belfiori	2009	65 PWID on OAT	Central Italy	Multidisciplinary model of HCV Care	Multi-center, prospective, observational	Initiation of IFN-based treatment and SVR	45/65 completed treatment with 37/65 with EVR and 26/65 with SVR	Non-randomized; small sample; potential for selection bias
Bonkovsky	2008	48 PWID in MMT	USA, multi-site methadone clinics	IFN as DOT or SAT, with ribavirin SAT in both arms.	Multicenter, open-label, randomized trial	Treatment completion rate	37/48 (77%) completed treatment, no sig difference between two groups	Small number of patients limited statistical power analysis for most end points.
Bruce	2012	21 HCV+ patients stably enrolled in MMT	Methadone clinic, Hepatology clinic	mDOT (a.m. RBV with methadone dose + weekly IFN) vs. SAT	Pilot RCT	Feasibility: treatment adherence (MEMS caps); Efficacy=SVR	Moving from colocation of HCV treatment and MMT services to full integration feasible but logistically challenging	Initial report (small number of patients); generalizability issues
Grebely	2007	80 PWID referred to HCV group	British Columbia, Canada	HCV support group as entry into HCV care	Prospective, Observational	Uptake of HCV treatment	18/80 initiated treatment with 67% of those attaining ETR	Selection bias of individuals with Genotypes 2/3
Hill	2008	1795 HCV+ individuals referred to specialty care	Rural and small urban centers, British Columbia, Canada	Public health nurse and physician partnership	Prospective observational	Treatment outcomes (SVR)	The overall rate of SVR was 61% (126 of 205 individuals)	No description of outcomes of the clients who received only counselling and education, rather than HCV treatment.
Ho	2013	76 PWID	Homeless clinic in San Jose, California	Multidisciplinary group medical visit	Pilot	Medication adherence and SVR rates	80% adherence rates, 55% SVR Genotype 1, 80% SVR Genotype 2/3	Small sample, pilot data
Jack	2009	353 PWID on OAT in primary care	UK	Partnership between a clinical nurse specialist employed by, and working under the supervision of, a secondary-care-based hepatitis service and drug workers and general practitioners.	Prospective observational	Feasibility, safety and efficacy of delivering HCV services including anti-viral therapy in a primary care environment.	86/174 entered care pathway, 43/174 suitable for treatment, 30/174 have been treated	No natural control group

1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major findings	Limitations
Litwin	2009	73 PWID on MMT	Bronx, NY	HCV treatment on-site in a MMT program	Retrospective chart review	EVR & SVR	37/73 treated. 86% completed treatment, 55% ETR, 45% SVR	Single institution; modest retrospective; modest sample size
Lloyd	2013	391 prison inmates	3 prisons in NSW, Australia	Nurse-led outreach program, linked to specialist supported treatment by telemedicine	Prospective observational & qualitative	Safety and effectiveness (SVR)	108/391 started treatment, 68/391 SVR	No control (treatment as usual)
Martinez	2012	157 HCV patients in MMT program	2 MMT programs in San Diego, CA	Integrated, co-located program involving internist, hepatologist, addiction specialist	Retrospective observational cohort	Referrals to hepatology center; SVR	76 adhered with referral; 17 (25%) were HIV/HCV co-infected. 13/24 evaluated attained SVR	No control group
McAllister	2014	1322 individuals in various community settings	Scotland	Dried blood spot testing as part of national testing program	Retrospective observational cohort	1 st clinic attendance with HCV specialist following testing	Of 476 with active HCV infection; 32% attended specialist clinic appointment within 12 months of testing	Sampling bias; no control group; generalizability (Scotland with specific national testing program)
Morano	2014	1345 patients on a mobile medical clinic	New Haven, CT	HCV screening using standard phlebotomy vs point-of-care testing	Preference trial	Acceptance of HCV testing; preference of standard phlebotomy vs point-of-care testing	438 clients accepted HCV testing, 47.7% preferred point-of-care test and more likely to link to HCV care than those receiving standard phlebotomy.	Not randomized; possible sampling bias; generalizability (testing provided free of charge)
Newman	2013	34 PWID	Community health center in Kingston, Ontario	Multidisciplinary treatment model	Prospective observational	Uptake and efficacy of HCV treatment	14/34 initiated treatment, 8/34 SVR	Single institution, small sample size, no control
Norman	2008	9 clients, 1 peer-worker	Community-based drug and alcohol clinic in Australia	Peer-based group intervention	Qualitative cross-sectional	Program acceptability and feasibility	Peer-based model highly accepted; multidisciplinary model highly endorsed	Small qualitative, single institution, possible selection/reporting biases
Seidenberg	2013	85 PWID on OAT	Switzerland	GP-driven addiction and HCV treatment	Retrospective Chart Review	HCV treatment and SVR	35/85 treatment started, 25/35 SVR	Not randomized
Stein	2012	42 PWID on MMT	Bronx, NY	Concurrent group treatment	Retrospective chart review	Treatment outcomes (SVR)	42 % SVR, 87% genotype 1 on DAA achieved SVR	Small sample size, no control group
Sylvestre	2007	71 PWID on MMT	Oakland, CA	Community-based clinic HCV treatment initiation	Prospective, observational	Adherence and treatment outcomes	48/71 adherent	Small, single institution; lack of control group

PWID=people who inject drugs; OAT=opioid agonist therapy; NSW= New South Wales; HCV= Hepatitis C Virus; IFN= interferon; GPs=general practitioners; SVR=sustained virologic response; EVR=early virologic response; DOT=directly observed therapy; SAT=self-administered therapy; MMT=methadone maintenance treatment; ETR=end of treatment response; DAA=directly acting antivirals

Table 3

Intervention Strategies for Pre-Therapeutic Evaluation and Treatment Initiation

1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major findings	Limitations
Boonwat	2010	1043 inmates in HCV clinic	Australia Prison	Decentralized, visiting hepatitis service in prisons	Retrospective, observational cohort	Selection for antiviral treatment; efficacy (SVR)	44% SVR with 100% adherence	Generalizability of model
Bruce	2012	21 HCV+ patients stably enrolled in MMT	Methadone clinic, Hepatology clinic	mDOT (a.m. RBV with methadone dose + weekly IFN) vs. SAT	Pilot RCT	Feasibility; treatment adherence (MEMS caps); Efficacy=EVR, SVR	Moving from colocation of HCV treatment and MMT services to full integration feasible but logistically challenging	Initial report (small number of patients); generalizability issues
Evon	2011	101 patients with HCV deferred from treatment because of substance abuse or mental health issues	Two outpatient hepatology practices, NC	Integrated care involving a hepatology psychologist vs. TAU	Multi-site RCT	IFN eligibility determined by hepatologist	In an ITT analysis, integrated care participants were more likely to become eligible for IFN by the end of the 9-month trial compared to participants in TAU (42 % vs. 18 %, $p = 0.009$)	Absence of treatment fidelity measures to assess intervention fidelity; generalizability
Grebely	2010	204 PWID with HCV	Vancouver, Canada	Weekly peer-support group	Retrospective observational cohort	(i) assessment for HCV infection; (ii) HCV treatment uptake; and (iii) SVR among treated individuals	Of 204 attending support group, 57 (28%) initiated treatment	No control group; generalizability
Groessl	2013	134 patients with HCV not on treatment	San Diego VA	HCV self-management program= 6 × 2-hour weekly workshop sessions vs. information-only (booklet + resource guide)	RCT	HCV knowledge, depression, energy, and HRQoL	Intervention group improved more on HCV knowledge, HCV self-efficacy, and SF-36 energy/vitality, and SF-36 physical	Study measured HRQoL and other personal factors; no difference in treatment initiation between groups

1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major findings	Limitations
Masson	2013	489 patients on MMT	MMT programs in San Francisco and NYC	On-site screening, motivational interviewing-enhanced education and counseling, on-site vaccination, and case management services vs. TAU	Unblinded RCT	Intervention adherence= attendance at HCV clinical evaluation within 6 months of referral	Intervention group participants were more likely than control group participants to receive an HCV evaluation within the 6-month case management period (65.1% vs 37.2%; OR = 4.10; 95%CI = 2.35, 7.17)	Generalizability
Sylvestre	2007	352 PWIDs with HCV	NSP	Peer-based integrated biopsychosocial model (Educate-Motivate-Facilitate)	Prospective observational cohort	Pre-treatment engagement= group attendance; HCV related knowledge	Of 352 screened, 117 were started on BUP, 87 were stable at 12 weeks, and 53 started treatment; knowledge improved above baseline for those who received a peer instructional video vs TAU	Minimal details of findings and methods are provided

Hepatitis C virus=HCV; IFN=Interferon; RBV=ribavirin; PWID=people who inject drugs; TAU=treatment as usual; VA=Veterans Affairs; HRQoL=health-related quality of life; ITT=intention to treat; NSEP=needle syringe exchange program; BUP=buprenorphine; EVR=early virologic response; SVR=sustained virologic response; MMT=methadone maintenance treatment

Table 4**Intervention Strategies for Facilitation of Treatment Adherence**

1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major Findings	Limitations
Alam	2010	503 HCV-mono-infected patients prescribed IFN/RBV	33 U.S. sites	RibaPak (RBP; higher dose formulation of ribavirin) vs. 200mg tablets ribavirin	Multicenter observational prospective registry	Treatment adherence=% retained on treatment at 4, 12, 24 weeks + self-reported adherence 80%	Those on RBP had significantly higher adherence by all measures than those receiving 200mg standard RBV	Cross-over between groups; not randomized; unclear clinical impact in terms of SVR
Bertino	2010	134 with HCV genotype 1b who responded to IFN/RBV but developed anemia	Italy	Epoetin alpha (EPO) vs. weight-based RBV dose reduction	Prospective longitudinal randomized open-label study	Treatment adherence=RBV exposure (% of optimal dose); Efficacy=ETR, SVR	Group receiving EPO had 97.1% RBV exposure (vs 80.2% in comparator; 96.5% controls, p<0.001); SVR in EPO group 59.7% vs. 34.4% in comparators (p<0.01); EPO group with higher QOL scores and greater reduction in ferritinemia	Not blinded; small n in each subgroup; raises concerns about cost effectiveness of EPO since minimal clinical difference detected
Bonkovsky	2008	48 HCV patients stably enrolled in MMT	Methadone Clinics	Peginterferon alpha-2a as DOT vs. SAT	Prospective multicenter open-label randomized study	Treatment completion (ITT analysis); ETR, SVR, safety	Overall treatment completion 77%; overall SVR 44% No significant difference in prescribed treatment completion between DOT and SAT groups regardless of genotype	Small number of patients (difficulty with recruitment); possible selection bias
Bruce	2012	21 HCV+ patients stably enrolled in MMT	Methadone clinic, Hepatology clinic	mDOT (a.m. RBV with methadone dose + weekly IFN) vs. SAT	Pilot RCT	Feasibility; treatment adherence (MEMS caps); Efficacy=EVR, SVR	Moving from colocation of HCV treatment and MMT services to full integration feasible but logistically challenging	Initial report (small number of patients); generalizability issues
Carroll	2013	447 HCV patients receiving IFN/RBV	Liver unit in Spain	Multidisciplinary support program	Non-randomized controlled study	treatment adherence (>80% of each drug at least >80%)	Adherence and SVR rates higher in MSP and MSP-validation groups	Non-randomized; validation group=historical

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1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major Findings	Limitations
Hussein	2010	780 HCV patients starting on Peg IFN- α 2b/RBV and enrolled in manufacturer-sponsored program vs. 8572 controls	Program database	Be in Charge (BIC) patient support program	retrospective cohort analysis by propensity score matching-BIC enrollees vs. matched controls not in BIC	treatment adherence=# IFN injections dispensed (pharmacy claims); proportion of patients who received mean >1 injection per week	BIC subjects refilled significantly more injections than controls (6.7 more during 48 weeks) and were more likely to refill at least 12 injections in 12 weeks (72% vs. 64%, $p<0.001$)	Potential bias: intervention provided by manufacturer of PEG-IFN 2b; unmeasured potential confounders (eg GT); adherence may have been under or over-estimated
Larrey	2011	244 HCV mono-infected patients initiating IFN/RBV	Liver unit in France	standardized, systematic consultation by nurse on patient adherence and efficacy of therapy after each clinic visit vs. TAU	multicenter open-label RCT	treatment adherence= self-reported or assessed by nurse; SVR	At EOT, adherence 74% vs. 62.8% control group ($p=0.06$) but varied by treatment duration (significant benefit of intervention in those receiving 48-weeks treatment); SVR OR=2.5 (95% CI 1.3–4.6) in multivariate model	Small N (may have been underpowered), generalizability? excluded people with serious psychiatric issues; unclear how treatment adherence measured for control group
Litwin	2011	40 HCV adults initiating IFN/RBV	Methadone clinic	mDOT vs. TAU	RCT	treatment adherence= self-reported + pill count; ETR/SVR	Program appears to be feasible	Report of design and rationale only; preliminary results not provided*
Morasco	2010	39 HCV patients initiating IFN/RBV	2 VA Medical Centers	prophylactic citalopram vs. placebo	double-blind placebo-controlled RCT, block randomized by study site	depression status (by SCID); adherence=treatment completion vs. dropout; efficacy=EVR, SVR	Intervention had no effect on IFN-induced depression, changes in depressive symptoms over time, or rates of treatment completion.	low n, low power to detect differences between groups, low baseline prevalence of depression; expansive exclusion criteria

1 st Author	Year	N/characteristics	Setting	Intervention	Study design	Main outcome	Major Findings	Limitations
Ramsey	2011	29 HCV patients initiating treatment with IFN/RBV and stably enrolled in MMT	Urban hospital-based primary care clinic	8-session CBT vs. TAU	RCT	depressive symptoms (by BDI-II, LIFE); substance use; adherence=#/dose of IFN injections from medical records; SVR	Intervention had no effect on depression-related antiviral treatment failure, adherence, SVR	Small n, low power to detect differences; psychosocial interventions alone may be insufficient
Reimer	2013	189 HCV mono-infected patients on stable OAT	Germany	manualized weekly psychoeducation (PE) group sessions vs. TAU	non-randomized controlled multicenter study	adherence/retention; n=treatment completion + completion per protocol; SVR	No significant effect of PE on retention; effect of PE on SVR only when at least 5 PE sessions attended (no effect in ITT analysis)	Non-randomized; difficulty accounting for early dropouts; did not directly measure medication adherence
Saiz de la Hoya	2014	244 patients initiating IFN/RBV	Prison in Spain	DOT vs. SAT	RCT	treatment adherence=treatment completion; SVR	High rates of treatment completion in both groups; SVR 60.6% DOT vs. 65.9% SAT, $p>0.05$	Applicability may be limited to prison settings, high rates of treatment adherence in both groups
Waizmann	2010	49 patients with HCV stably enrolled in opioid substitution program	Outpatient drug treatment program in Germany	PEG-IFN + once-daily RBV + citalopram + MMT as DOT	Retrospective open-label cohort study	Treatment adherence=treatment completion; SVR, RVR, EVR	48/49 (98%) of patients achieved SVR; treatment well tolerated	No comparator group, small N
Zucker	2010	20 people with HCV on IFN/RBV	2 hepatology practices in MA	Home walking program vs. TAU	Pilot RCT	adherence=Completion of therapy; fatigue, QOL, and walking distance	Modest effect sizes	Small N, minimal effect of intervention on treatment completion

HCV=Hepatitis C Virus; IFN=interferon; RBV=ribavirin; RBP=RibaPak; SVR=sustained virologic response; EPO=erythropoietin alpha; QOL=quality of life; ETR=end of treatment response; SVR=sustained virologic response; MMT=methadone maintenance treatment; ITT=intention-to-treat; DOT=directly observed therapy; SAT=self-administered therapy; SUDs=substance use disorders; TAU=treatment as usual; GT=genotype; RCT=randomized controlled trial; EOT=end of treatment; VA=Veterans Affairs; OAT=opioid agonist therapy

* Note: Preliminary results were presented at the International Conference on Viral Hepatitis and reported elsewhere (Bruggman and Litwin (2013) Clin Inf Dis). Among 40 participants, observed a significant difference in adherence to RBV between the treatment arms (88% in enhanced DOT vs. 77% in standard DOT, $p=0.02$).