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Treatment of Chronic Hepatitis C in Patients Receiving Opioid Agonist Therapy: A Review of Best Practice

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Abstract

Injection drug use is the most common route of transmission of the hepatitis C virus and high rates of hepatitis C infection have been observed among individuals on opioid agonist therapy (OAT). Though people who inject drugs (PWID) carry the highest burden of hepatitis C, few have initiated treatment. In this article we present a comprehensive review of the evidence on the efficacy of HCV medications, drug-drug interactions with OAT, and barriers to and models of care for hepatitis C treatment in patients on opioid agonist therapy. Cohort studies and subsets of large clinical trials have demonstrated comparable efficacy for individuals who are on opioid agonist therapy compared to those who are not. These findings have been validated in a recent phase III clinical trial examining treatment efficacy, adherence, and reinfection exclusively among individuals on opioid agonist therapy. Yet, significant barriers including HCV screening, linkage to care, HCV-related knowledge, perceptions of poor candidacy, concerns about adherence, and unsubstantiated beliefs about re-infection remain. Because many persons on OAT continue to inject and use drugs, we propose that a strategy of treatment and cure-as-prevention is imperative in this population to curb the hepatitis C epidemic in the US.

Keywords

Hepatitis C Virus; Opioid Agonist Therapy; Drug-Drug Interactions; Direct Acting Antivirals; Best Practice

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Disclosures

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Introduction

Mortality from hepatitis C virus (HCV) infection has increased over the past 15 years and HCV now exceeds HIV as a cause of death in the United States¹. Up to 4 million people in the United States (US) are thought to be infected with HCV^{2,3} and the true prevalence is likely to be even higher⁴. The risk of morbidity and mortality related to HCV infection is markedly decreased in patients who achieve a cure with antiviral therapy^{5,6}. Injection drug use is the most common route of transmission of HCV, particularly amongst younger people where the incidence of HCV is on the rise^{2,7}. The prevalence of HCV in the US amongst persons who inject drugs (PWIDs), both former and current PWID, is 70–77% resulting in a population of approximately 1.5 million PWIDs with HCV in the US alone⁸. Between 2007 and 2012, reports of new HCV infection increased 50% nationally and seventeen US states reported a 200% increase⁹. At least 70% of those infections are related to injection drug use among older adolescents and young adults. Globally, approximately 10 million PWIDs are thought to be infected with HCV⁸.

Opioid treatment programs (OTPs), such as methadone maintenance programs, provide opioid agonist therapy (OAT) to more than 300,000 opioid-dependent patients in the US¹⁰. Buprenorphine is also widely prescribed for OAT, primarily outside of OTPs and in the outpatient medical setting. More than twice as many people are prescribed buprenorphine than methadone nationwide^{11,12} and 9.3 million buprenorphine prescriptions were filled in the United States in 2012 alone¹³. Approximately 70% of patients on OAT are HCV antibody positive^{14–16}, and many continue to use and inject drugs while in drug treatment^{17,18}.

Though PWIDs carry the highest burden of HCV disease, few initiate treatment. HCV providers often exclude PWIDs due to perception of poor candidacy and disappointing treatment outcomes, concerns about treatment adherence, or unsubstantiated beliefs about re-infection^{19–22}. Patient barriers include limited HCV knowledge, competing life priorities due to other comorbidities or to drug use, low perceived vulnerability from a disease without early symptoms, and fears of HCV treatment side effects^{23,24}. PWIDs also cite stigma and discomfort encountered in the healthcare setting, leading to poor self-efficacy and inability to navigate the healthcare system^{19,25}. Furthermore, the majority of US states and health insurance companies have recently required varying durations of abstinence ranging from 1–12 months in order to approve prior authorization for directacting antiviral (DAA) HCV medications²⁶.

Multiple models suggest that even a moderate increase in HCV treatment uptake and cure in PWIDs will reduce overall HCV prevalence, with potential HCV disease eradication^{27–29}. Treatment guidelines do not exclude PWIDs from HCV treatment and, in fact, guidelines from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) recommend that HCV therapy must be considered for each individual, whether they are current users of illicit drugs or are on OAT^{4,30}. Furthermore, HCV treatment outcomes are no different in people who use drugs compared to people who do not use drugs^{31,32}. With the advent of highly effective, all oral treatments for HCV infection we review the current evidence-based approaches to the treatment of

HCV in PWID (both current and former) who are taking OAT, a population that is already engaged in medical care and may be readily available to initiate HCV treatment.

Efficacy of HCV treatment in patients on OAT

Prior to 2011 HCV was treated with a 24- or 48-week course of pegylated IFN (PegIFN) and ribavirin (RBV). In 2011 two HCV NS3/4A protease inhibitors, telaprevir and boceprevir, were approved for the treatment of HCV genotype (GT) 1 in combination with PegIFN/RBV after studies showed they improved sustained virologic response (SVR) rates in patients with HCV GT1 compared with PegIFN/RBV alone^{33,34}. Clinical registration trials of these new DAA therapies have generally excluded or minimized entry of patients who are either active PWIDs or on OAT. However, cohort studies have shown that similar results can be achieved in these patient populations when compared with clinical trial results, which we will outline below and are summarized in Table 1.

PegIFN/RBV

In large clinical trials of PegIFN/RBV, patients infected with HCV GT1 achieved an SVR rate of around 42–46%, while approximately 76–82% of patients with HCV GT2/3 achieved SVR^{35,36}. Studies of PegIFN/RBV in patients receiving OAT have demonstrated SVR rates of 36–45% in GT1 and 57–88% in GT2/3, demonstrating that SVR rates are broadly comparable with clinical trials^{16,37–45}. A number of studies have directly compared the efficacy of PegIFN/RBV in patients who are receiving OAT compared with those not on OAT and have also shown similar SVR rates between the two populations^{37,46,47}.

Direct-Acting Antivirals

Post-hoc analyses of Phase II/III clinic trials—In the SPRINT-1, SPRINT-2, and RESPOND-2 trials of boceprevir, 20 patients on methadone received PegIFN/RBV plus boceprevir and four received PegIFN/RBV plus placebo. In the boceprevir group, SVR rates were 50% in the 20 patients on methadone versus 63% in the 1528 patients not on methadone. In the placebo group, SVR rates were 25% in the four patients on methadone versus 37% in the 543 patients not on methadone⁴⁸. Given the limited number of patients involved it is difficult to draw conclusions from this data but SVR rates were broadly comparable.⁴⁹

Of all the patients treated with fixed dose sofosbuvir/ledipasvir in the three Phase 3 ION trials, 70 received opioid replacement therapy (40 on methadone, 30 on buprenorphine +/- naloxone). In retrospective analyses, mean SVR rate in patients not on OAT was 96.8% (1822/1882) and mean SVR rate for patients on OAT was 94.3% (66/70). The overall cure rates were similar⁵⁰.

Six patients on OAT (5 methadone/1 naltrexone) were enrolled in the Phase 3 ALLY-2 trial, which studied the combination of daclatasvir and sofosbuvir in HIV/HCV co-infected patients. All 6 patients on OAT achieved SVR with 12 weeks of combination therapy and there were no AEs related to OAT, nor dose adjustments in OAT.

Data from the ASTRAL-1, -2, and -3 trials, demonstrated that sofosbuvir/velpatasvir was well tolerated among patients on OAT. SVR was achieved by 49/51 (96%) of patients on OAT and 966/984 (98%) not on OAT with similar adherence and adverse event profiles in both groups⁵¹.

Phase II/III Clinical Trials—Data from a Phase II, multicenter, open-label, single-arm study in HCV GT 1-infected patients on methadone or buprenorphine +/- naloxone who received 12 weeks of co-formulated ombitasvir/paritaprevir/ritonavir and dasabuvir plus weight-based RBV has been published. This study enrolled 38 treatment-naïve or PegIFN/RBV treatment-experienced non-cirrhotic patients with HCV GT1 infection who were on stable OAT with methadone (n=19) or buprenorphine ± naloxone (n=19). SVR was achieved by 97% (37/38) of patients⁵² which was similar to non-OAT patients treated with the same regimen in the Phase II trial⁵³. No changes to the dose of methadone or buprenorphine were required during the study in any patient⁵².

The Phase III *C-EDGE CO-STAR* trial evaluated the efficacy and safety of the investigational once-daily tablet elbasvir/grazoprevir in patients with HCV GTs 1, 4 or 6 infection who were receiving OAT, the majority of whom were also currently using drugs. Ninety-four percent (189/201) of patients treated with elbasvir/grazoprevir for 12 weeks achieved cure, similar to cure rates in other large trials of elbasvir/grazoprevir in patients not on OAT. The use of non-prescribed illicit drugs, such as cocaine, amphetamines, marijuana, and other opiates was observed in 59.2% of patients at baseline and remained steady throughout the trial; however, adherence to treatment was high and 97% of patients took at least 95% of their study medication over the 12 weeks of therapy. There were no AEs related to OAT, and no dose adjustments to OAT while on HCV treatment were required⁵⁴.

Real-World Clinical Data—There are many recent unpublished data (abstracts presented) that have evaluated the efficacy of DAAs in persons on OAT in both prospective clinical trials and retrospective cohort studies. The PREVAIL study was one of the first clinical trials to evaluate various models of care for DAA treatment onsite at a methadone clinic¹⁷. Persons were randomized to either individual onsite treatment, weekly group treatment, or directly observed therapy (DOT). SVR rates were high in all groups, with a trend towards better outcomes in the more supportive models of care [SVR rates: 90% (46/51) for individual, 98% (50/51) for DOT, 96% (46/48) for group, p=0.76]. All patients were on OAT, and nearly half were also currently using drugs (49.3% (74/150) had a positive urine toxicology screen at baseline). Urine toxicology results were not associated with SVR rates (p=0.99). In multiple retrospective real-world cohorts studies, SVR rates for patients on OAT have been high, ranging from 95%–100%^{55–58}. In all of these studies patients were treated for HCV onsite at the OTP, and in many cases, the clinicians used this unique setting to offer DOT. Another study treated patients for HCV onsite at a community-based primary care clinic. SVR rates were high for patients on OAT, and cure rates were similar to patients not on OAT [SVR rates: 97% (35/36) for patients on OAT, 95% (41/43), p=0.99]. The majority (56%) of patients on OAT were also currently using drugs⁵⁹.

Addressing barriers to HCV treatment in patients on OAT—Although SVR rates have been comparable for patients on OAT versus non-drug users, a low proportion of

PWIDs ever initiate HCV treatment^{14,16}. In one study comparing current opioid users to those without opioid dependence, 8.8% of patients with opioid use disorder initiated treatment compared with 18% of those without an opioid use disorder⁶⁰. In general, studies show that linkage to HCV care and evaluation for PWIDs is poor, and that less than 10% of PWIDs who are evaluated for their HCV infection ever initiate antiviral therapy^{23,32}. Furthermore, only 60–70% of patients at OTPs are offered screening for HCV^{41,61}. Between 2003 and 2011 there was no significant change in the proportion of OTPs offering HCV screening, though the proportion of for-profit OTPs offering screening fell while the proportion of nonprofit OTPs offering screening increased⁶¹. Factors associated with HCV screening for patients in substance abuse treatment were: provision of primary care at the OTP center (OR 3.18; 1.99–5.38); a hospital-affiliated setting (OR 2.56, 1.5–4.37); and a nonprofit/public setting (OR 1.79; 1.08–3.03)⁶². Based on recommendations from the US Preventive Services Task Force, the Centers for Medicare & Medicaid Services covers a single HCV test for patients at high risk of infection (history of illicit injection drug use or blood transfusion prior to 1992) and for adults born from 1945 through 1965 who do not fall into the high-risk category. Annual testing for individuals who continue to inject drugs after a negative HCV test is also covered⁶³. Given the nearly universal history of injection drug use at OTPs, HCV screening rates should reach nearly 100% in these setting, especially given the fact that the majority of patients accessing OTPs have insurance.

Another barrier to treatment lies in the fact that significant gaps in HCV knowledge have been identified among high-risk populations, including PWIDs. This lack of knowledge and misinformation hinders the ability of HCV positive persons to appropriately interpret their disease and lessens their interest in care, potentially contributing to the persistently low uptake of HCV treatment in this population⁶⁴. Therefore, patient education on HCV is critical to the success of implementing HCV screening and treatment at OTPs⁶⁵. Studies have shown that improved HCV knowledge leads to an increase interest in HCV care, as well as adherence to an HCV specialty clinic appointment (64% adherence for patients who received education vs. 39% adherence for patients without education, $P < 0.0001$)⁶⁶. Furthermore, education on HCV infection, treatment, side effects, and coping strategies was shown to improve SVR rates in patients on OAT infected with HCV GT1/4 who received pegylated interferon alfa-2a and ribavirin therapy (SVR 76% vs. 55% of patients without the education program, $P = 0.038$)⁶⁷. Recommendations for the management of HCV in PWIDs include pre-therapeutic education on HCV transmission, risk factors for progression of fibrosis, HCV treatment regimens and side effects, reinfection, and harm reduction strategies⁶⁸.

Failure to complete the evaluation process once linked to care, and physician-perceived patient risk factors as contraindications to therapy (such as drug use) have been amongst the most common reasons patients are not considered for HCV treatment^{69–71}. Historically, liver biopsy has often been the greatest barrier to completing the evaluation process for HCV treatment due to fear, payer complications, lack of transportation, and subspecialist reluctance to perform a liver biopsy on patients undergoing OAT^{15,16}. It is vital that the extent and progression of liver fibrosis and cirrhosis is monitored and managed as the population of patients on OAT is aging and higher rates of cirrhosis can be expected, Guidelines published by AASLD and the IDSA support the noninvasive evaluation of liver

fibrosis. Liver biopsies are now rare, which should further reduce the barrier to pretreatment staging among PWIDs and patients on OAT. Transient elastography or panels of fibrosis biomarkers (APRI score, FIB-4, or fibrosure) are well established for the assessment of liver fibrosis and should be used to increase the number of patients who can complete an assessment for treatment^{30,68}, and patients should be specifically educated regarding the fact that biopsies are unnecessary for treatment initiation. Fears that patients on OAT or active PWIDs may have low adherence to HCV therapy may also result in low HCV treatment rates. However, studies in the IFN era showed similar adherence in patients with and without a history of drug use^{42,47,72}. In one study of 71 patients maintained on methadone and treated with PegIFN/RBV, intermittent drug users were similarly adherent to those strictly abstinent from illicit drugs⁷³. In the era of DAAs, one study of 61 methadone maintained patients on sofosbuvir-based regimens showed that mean weekly adherence by electronic monitors was 88% and mean adherence by visual analog scale (VAS) was 95%. SVR rates were similar to registration trials with sofosbuvir-based regimens⁷⁴. Finally, the CO-EDGE C-STAR Phase 3 trial of fixed-dose once daily grazoprevir/elbasvir enrolled only patients on OAT, of whom nearly 60% continued illicit drug use while on HCV treatment. All participants within that trial achieved over 80% adherence and 96.5% achieved over 95% adherence⁷⁵.

Furthermore, current drug use is not a contraindication for HCV treatment⁷⁶. In a meta-analysis of 36 studies of people who use drugs treated for HCV with PegIFN/RBV, 13 studies reported the number of patients who were current drug users and found that current drug use was not associated with treatment failure ($P=0.76$)³⁸. In one study of PegIFN/RBV, persons with frequent drug use ($N=9$) had a decreased SVR (22%) when compared with occasional drug use ($N=10$, 80%, $P=0.12$), though this was not significant due to the very low number of patients. This was mainly due to a higher rate of discontinuation in patients with frequent drug use (56%) than in those who did not use drugs or had occasional drug use (29%)⁴⁰. Discontinuations will likely be less, even for people with current drug use, in the era of DAAs where side effects are tremendously reduced and adherence to therapy is easier given once daily regimens. In the recent Phase III trial of grazoprevir/elbasvir coformulation, current illicit drug use during HCV treatment was common (59%), and the proportion of people who had positive urine drug screens remained consistent during the 12 weeks of therapy. The SVR rate was the same for people who had positive urine drug screens compared to those with consistently negative urine drug screens (95.5% and 95.4%, respectively)¹⁸.

Another perceived barrier to treating former or active PWIDs is the fear of HCV reinfection after successful treatment if a patient returns to or continues active drug use. A thorough review focusing on reinfection in the era of interferon found that, though approximately half of patients return to active drug use following successful HCV treatment, reinfection rates amongst patients were low (1–5%); this may be due to the development of partial protective immunity as well as use of harm reduction measures⁷⁷. In the recent Phase III trial of grazoprevir/elbasvir in patients on OAT, there were six probable reinfections out of the 301 patients following treatment completion (4.6 reinfections per 100 person-years). Half of these patients (3/6) had spontaneous clearance of their reinfection. A study conducted in Norway specifically evaluated patients that continued to inject drugs after DAA treatment

completion; reinfections rates were 4.9/100pyrs. Long-term follow-up studies are needed in order to improve our understanding of the impact of re-infection in the era of DAAs. Even when considering a consistent rate of re-infection, models suggest that HCV treatment among people who are actively injecting drugs can still substantially reduce the prevalence of HCV²⁸. Though we may initially see reinfection rates increase after treatment among PWID (due to the rise in the number of people susceptible to infection), studies suggest that even a moderate scale-up of treatment among PWID will eventually reduce the pool of the infected, leading to a decrease in transmission and overall HCV prevalence^{78,79}. Therefore, if we are to achieve HCV elimination, we must actively treat people who use drugs and expect to see some occurrence of reinfections. Patient care following successful treatment for HCV should take into account the possibility of a return to drug use and take measures to limit the risk of reinfection such as education around harm reduction, referral to syringe exchange services, and co-treatment of drug using partners and friends. Patients with continued risk factors should be screened with HCV RNA testing on an annual basis, and if reinfection occurs patients should be tested for the possibility of a new HCV genotype and baseline resistance. The limited risk of reinfection should not exclude PWIDs from receiving treatment for HCV⁶⁸, especially since reducing transmission and overall prevalence of HCV requires specific attention to the treatment of people who are actively injecting drugs.

Models of Care for HCV therapy in patients on OAT—As reviewed recently by Bruggmann and Litwin⁸⁰, administration of HCV therapy to patients with a history of drug use can be managed under a number of different settings, including OAT clinics, primary-care centers, or in specialty clinics. Management of therapy may also include delivery by directly observed therapy (DOT)⁷¹ or in conjunction with peer-based treatment support⁸¹. The key to successful HCV treatment in PWIDs is the availability of a multidisciplinary team including substance abuse services, psychiatric treatment and primary medical care^{68,80}. A meta-analysis of 19 studies of PWIDs treated with PegIFN/RBV considered the effect of HCV GT, HIV coinfection, and the involvement of a multidisciplinary team on SVR. In a multivariate analysis they showed that involvement of a multidisciplinary team improved SVR rates ($P < 0.0001$) independent of any other factors³⁸.

Provision of HCV screening, assessment, and therapy onsite at OTPs or in a primary care setting has many advantages. Screening of patients on OAT and people who are actively injecting drugs ensures that HCV infection is diagnosed quickly and targeted education programs can be initiated. Staff at OAT clinics are familiar with the needs of their patients, many of whom will have psychosocial needs not regularly encountered by HCV specialists at hospital-based HCV clinics. Furthermore, adherence to HCV therapy can be monitored if HCV therapies are administered with OAT in a DOT setting. Providing HCV-specific training to existing staff, teaching primary care providers how to deliver HCV treatment onsite in OTPs^{15,41}, inviting outside specialists to administer HCV care at the OTP, or facilitating regular review of OTP patients by consultant hepatologists⁸⁰ are all methods in which to provide HCV care within OTP settings. Community-based primary care clinics can also be an ideal setting in which to provide HCV evaluation and care. A US-based study used telehealth technology to train primary care staff at 21 community or prison clinics to provide interferon-based HCV treatment, and ongoing support was delivered via weekly

teleconferences with a multidisciplinary team of providers. The community/prison clinics achieved the same SVR rates as the hospital-based university HCV clinic (58%, $P=0.9$)⁸². In one study of patients receiving onsite HCV treatment at an urban primary care clinic, with support from an HCV care coordinator, there were no differences in cure rates for persons who use drugs (PWUD) (96%) compared to non-PWUDs (95%)⁵⁹. These methods could also be replicated for HCV treatment in OTP settings.

Group Treatment

Group treatment may also improve adherence and thereby SVR rates. In an OTP-based study of concurrent group treatment (CGT) with PegIFN/RBV, during weekly meetings patients discussed adherence to medication and AEs, received their PegIFN injection, and provided mutual support. More than half (15/27) of the patients had positive urine drug tests during treatment for opiates, cocaine, or both. The majority of patients (26/27) opted to continue CGT after the first 12 weeks of treatment demonstrating acceptability of this intervention⁴⁵. In the PREVAIL study persons on OAT were randomized to individual onsite treatment vs. weekly group treatment vs. or directly observed therapy (DOT). SVR rates were high in all groups, but there was a trend towards better outcomes in the more supportive models of care [SVR rates: 90% (46/51) for individual, 98% (50/51) for DOT, 96% (46/48) for group, $p=0.76$]. In the OTP setting, there exists a unique opportunity to address HCV education, lack of support, and adherence concerns by conducting groups, a modality in which many PWID are familiar.

Directly Observed Therapy

In the IFN era, DOT demonstrated promising results in several models of care among drug users and individuals on OAT. Comparable rates of SVR were seen among active drug users using PegIFN given through DOT with self-administered RBV to those seen in clinical trials of non-drug users^{83,84}. Administration of DOT by nursing and medical staff in a methadone maintenance clinic aided in addressing concurrent substance use and mental illness and facilitated access to and completion of treatment⁸⁵. Specialized outpatient drug treatment centers have also been utilized successfully to deliver DOT among methadone and buprenorphine-maintained PWID receiving PegIFN through DOT⁸⁶. Data on DOT in the era of DAAs is limited; however, in a prospective study of 61 PWID with chronic HCV treated with sofosbuvir-based regimens, pill count adherence was higher among those patients receiving DOT (77%) versus those treated in a group (70.7%) versus those treated by an individual provider (73.2%) but these differences were not statistically significant. SVR rates for the participants that received DOT was 100% (13/13); overall SVR rates were 98% (60/61)⁷⁴. Again, in the PREVAIL study persons SVR rates were high in all treatment arms, but there was a trend towards better outcomes in the more supportive models of care [SVR rates: 90% (46/51) for individual, 98% (50/51) for DOT, 96% (46/48) for group, $p=0.76$], particularly DOT. Given the unique setting of OTPs, where many patients are coming to the program multiple times a week, DOT for HCV treatment may be a viable and easy to implement treatment strategy.

Side effect management

Side effect management in the IFN era was complicated by nausea, insomnia, myalgia, irritability, and depression^{35,36}, all similar to the symptoms of opioid withdrawal; however, the concern that these side effects could trigger resumption of drug use was not shown to be true⁸⁷. Furthermore, a meta-analysis of 14 studies of PWIDs treated with PegIFN/RBV found no effect of psychiatric comorbidities on SVR ($P=0.76$)³⁸, and the prescription of prophylactic or on-treatment antidepressants showed a reduction of IFN-related depression⁸⁸. DAAs have much fewer side effects and are generally well tolerated. Though there are few Phase 3 studies specific to patients on OAT, the Phase 2 trial with Ombitasvir/paritaprevir/ritonavir and dasabuvir plus RBV in HCV GT 1-infected patients on methadone or buprenorphine showed similar AE and discontinuation rates as patient not on OAT in Phase 2 trials⁵². The most common AEs were nausea, fatigue, and headache. Similarly, of the 70 patients on OAT in the ION-3 trial of sofosbuvir/ledipasvir, treatment was safe and well-tolerated⁵⁰. In the Phase 3 trial of Elbasvir/Grazoprevir in patients on OAT using methadone or buprenorphine, AEs were the same for patients on study drug versus placebo. The most common AEs were fatigue (17%), headache (13%), nausea (10%), and diarrhea (9%)^{54,75}.

Pharmacokinetics between DAAs and OAT

Many DAAs have the potential to interact with methadone and buprenorphine through the metabolism, inhibition, and induction of the cytochrome P450 3A enzyme⁸⁹. Consequently, specific drug combinations have been noted to alter opioid drug levels. Despite common metabolic pathways, studies to date have shown no significant signs and symptoms of opioid withdrawal or toxicity that would preclude concurrent administration (Table 2)⁹⁰.

Patients on OAT or people who actively use drugs may also be receiving other medications for comorbid conditions such as HIV coinfection or depression. Careful attention must be given to both prescribed and non-prescribed drugs including antiretrovirals for HIV, antidepressants, antihypertensives, sedatives, statins, acid-reducers, erectile dysfunction medications, anticonvulsants, and herbal remedies (especially St John's Wort and milk thistle). Interactions between these drugs and DAAs have been reviewed recently by Mauss and Klinker⁴⁶.

Liver transplant in patients on OAT—Once a patient with HCV related cirrhosis develops decompensation (ascites, variceal bleeding, hepatic encephalopathy) and/or hepatocellular carcinoma, liver transplantation should be considered. Experience of liver transplant in patients receiving OAT is extremely limited; however, liver transplant is a therapeutic option for patients with a history of drug use and OAT is not a contraindication for transplant⁶⁸. Two case reports have demonstrated the procedure can be successful in this population^{72,91}. Of the eight patients in these cases, all were former drug users (no active IDU for at least 5 years) and two received OAT^{72,91}. Graft survival, patient survival, and rejection rates were similar in former IDUs compared with non-IDUs⁷², and of the two patients treated for HCV, one patient achieved SVR and remained infection free four years post-transplant^{72,91}. While intraoperative anesthesia and post-operative analgesia can present

a challenge in patients on OAT, collaboration with pain specialists can help remove this as a barrier to care⁹¹.

HCV Prevention and Elimination—With the advent of new curative therapy, HCV elimination may be possible; however, this can only be achieved by focusing on HCV prevention and treatment among PWIDs, the key drivers of the HCV epidemic. Prevention of HCV requires appropriate screening among high-risk populations such as PWIDs, implementation of syringe exchange and opioid treatment programs, as well as an aggressive approach to HCV treatment as prevention. HCV testing to increase awareness of one's HCV status is crucial in order to educate persons about harm reduction measures, such as engaging in safer sex and reducing household sharing of razors and toothbrushes, as well as the abolition of sharing any drug paraphernalia (including needles, cookers, cotton, water, pipes, and nasal devices). One study in Australia estimated that syringe exchange programs directly averted 50% (97,000) of new HCV infections during 2000–2009 (14). Furthermore, participation in methadone maintenance has been shown to significantly lower the rate of risky injecting and sexual behavior among PWIDs. In one study, the estimated cumulative incidence of HCV per 100 PWIDs per year before MMT participation was 36.48 (25.84 – 47.11), compared to 13.84 (95% CI: 6.17 – 21.51) after MMT participation, potentially averting 22.64 (19.67 – 25.6) new HCV infections per 100 PWIDs/year⁹². There is much evidence to support the combination of both these harm reduction approaches, and modeling studies have shown that, in a setting where HCV prevalence is 40%, scaling up opioid substitution therapy and needle exchange coverage can reduce HCV prevalence over 10 years by up to a third⁹³. Making these programs available to the highly growing population of young PWIDs is of particular importance since this population has been shown to be a key driver of new infections in the US. HCV cure-as-prevention will also be an important component to HCV prevention and eradication. Given the new highly effective and easy-to-use HCV regimens, reducing the prevalence of disease through aggressive treatment stands to reduce rates of new infections. This is particularly important for populations with high prevalence and incidence such as PWIDs. For a PWID population that starts with an HCV prevalence of 65%, minimal scale-up of treatment to 98 per 1,000 PWIDs annually could significantly reduce the HCV prevalence by 75% within 15 years⁷⁹. Because the near-majority of patients on OAT continue to use and inject drugs^{17,94,95}, HCV care and treatment in OTPs where PWID are already engaged in medical care is crucial to HCV elimination efforts. Reducing the incidence and prevalence of HCV with potential for elimination is possible, but a strategy of seek, test, treat, and cure, particularly among PWIDs, must be adopted. Scale-up to 22, 54, or 98 per 1,000 PWID annually could reduce prevalence by three-quarters within 15 years.

Summary

The majority of new HCV infections in the USA are transmitted via injection drug use and the prevalence of HCV in current and former PWID is high. The incidence of new infections is particularly high amongst young PWID⁹⁶. However, data on HCV treatment in the era of DAAs are limited for patients on OAT and for active PWID, and more research is needed regarding the optimal models of care for increasing diagnosis, treatment uptake, adherence

and completion, and rates of SVR. Young suburban and rural PWIDs, a growing population, must have access to syringe exchange and OAT to prevent acquisition and transmission of HCV, and novel approaches are needed to engage them in HCV care and treatment.

Though new DAA medications promise high HCV cure rates, few PWIDs initiate treatment, even when they are engaged in OAT.^{14,16} Despite a number of barriers to HCV treatment for this population, both real and perceived, HCV can be successfully cured in patients on OAT and active PWIDs, and data suggest that similar cure rates are achieved by patients on OAT compared to those not on OAT in the era of DAAs. Measures should be taken to improve the uptake and success of treatment in this population.

Universal HCV screening should be implemented at OAT programs, substance abuse clinics, and primary care clinics that treat patients with substance abuse disorders. HCV patient education can help to improve patients' understanding of the risk of HCV to their health, dispel myths about HCV medications, and encourage harm reduction in order to reduce risk of transmission. IFN-free and RBV-free regimens carry a lower burden of adverse events, and can be dosed as once-daily regimens. Such regimens are more amenable to prescription and monitoring by non-specialists than PegIFN/RBV-based regimens, which allows the opportunity to treat PWIDs within their primary care medical homes, and where they receive OAT. Providing care to patients via multidisciplinary teams of physicians, nurses, psychiatrists, and addiction counselors trained in HCV care, and with the close support of HCV providers, results in the best treatment outcomes and has been established at a number of OAT clinics and primary care centers treating some of the most underserved patients in the US, Canada, Europe, and Australia. Successful implementation of new HCV therapy for a population that carries one of the highest burdens of infection should be a goal of all healthcare providers involved in the treatment of HCV and/or drug addiction. It is only through aggressive treatment of PWIDs that we will reduce the morbidity and mortality of this disease, with the potential for elimination.

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HCV Care Recommendations for Patients Receiving Opioid Replacement Therapy

Screening and Prevention: Mandatory HCV antibody screening of all patients accessing opioid treatment programs and yearly screening of patients who currently use drugs.

- Onsite HCV RNA testing to confirm chronic HCV is best; reflex testing where possible
- If confirmation with an HCV viral load cannot be performed, HCV-antibody positive patients should be referred to a clinic where HCV RNA measurement can be done.
 - Case managers, patient navigators, or peer escorts may facilitate adherence to follow-up visits.
- All HCV-antibody negative patients should be counseled to prevent future HCV infection. Patients should be advised not to share syringe, cooker, cotton, and rinse water.
- Patients should be referred to harm reduction/syringe exchange programs if necessary
- Clinical registries should be created to ensure that case management is provided for patients with HCV who are not currently engaging in care.

Education: Provide patient education on HCV transmission, risk factors for progression of fibrosis, HCV medication, adherence, reinfection, and harm reduction strategies to HCV-positive patients on OAT and/or who actively use drugs.

- All medical staff and substance use counselors should receive basic HCV-related education.
- HCV-related literature should be available to patients on-site

Make regular HCV support groups available on-site

- Ideally, support groups should be co-facilitated by staff members (medical or non-medical) and patients.
- On-site HCV peer programs for patients who co-facilitate support groups should be considered.

Provide education on substance use disorders and provide community based drug treatment resources to HCV specialists such as hepatology and Infectious Diseases physicians.

- Efforts must be undertaken to reduce the shame and stigma of substance use, opiate agonist treatment, and HCV, all of which are barriers to engaging HCV-infected patients in care.

Staging: Primary care and drug treatment providers *not* providing on-site HCV treatment must still have a basic understanding of HCV evaluation and management in order to help facilitate appropriate off-site care

- Liver biopsies are not necessary to stage liver disease. Patients should be made aware of this.
- Use non-invasive staging methods such as APRI or FIB-4 (readily available with basic labs including AST, ALT, and platelets) to determine advanced fibrosis and cirrhosis to increase the completion of disease assessment in patients on OAT and people who are currently using drugs.
- An attempt should be made to engage all patients with HCV in care, however if APRI score is >2 or FIB-4 >3.25 patients need to be educated about the possibility of cirrhosis and a more active process must be in place to get these patients into treatment.

Linkage to HCV Treatment: Provide care and treatment via multidisciplinary teams including HCV providers (practitioners with expertise in HCV treatment which may include hepatology, gastroenterology, infectious diseases, and/or trained primary care providers), addiction specialists and addiction counselors, psychiatric services and social support (including peer support groups if available).

- Use telemedicine to more readily facilitate these team efforts.
- Establish working relationship with HCV providers and communicate with HCV providers in real-time if issues arise (e.g. side effects or insurance problems that may lead to loss of access to medications)

Linkage to HCV provider will be key for off-site treatment

- Establish working relationship with HCV provider that understands patient population
- Use case management and peers to support linkage
- Peer accompaniment to appointments can be beneficial

Encourage patients who are currently using drugs to start substance use treatment as HCV treatment in conjunction with addiction treatment improves the rates of treatment completion.

- Do not withhold HCV treatment from patients who defer substance use treatment.
- Patients who are currently using drugs can be successfully treated for HCV and should be considered for treatment on a case-by-case basis. Motivation and engagement should help decide about treatment readiness, not patterns of drug use.

Onsite HCV Treatment: Consider establishing on-site treatment at OTP or primary care clinics with OAT.

- Evaluate HCV infection and treatment options by following an established protocol based on the latest established HCV guidelines. Use hcvguidelines.org as a resource.
- All DAAs can be used in patients on OAT without dose alterations and there are data to support the efficacy and safety of these regimens in this specific population.
- Consider all medications taken by each patient to assess drug-drug interactions with DAAs.
- For those with cirrhosis, HCC screening every 6 months with ultrasound and refer to gastroenterology for upper endoscopy to screen for varices.
- Establish a community of HCV providers to discuss issues as they arise e.g. side effect management, drug-drug interactions, etc.
- Refer to HCV specialists for treating complicated cases (e.g. autoimmune hepatitis; decompensated cirrhosis; any case that provider is not comfortable with).

Train non-medical staff at OTPs to administer HCV therapy in DOT at methadone pick-up window and monitor patients for side effects.

- Substance abuse counselors should know the HCV status of each patient and be able to provide basic HCV-related case management, and know what services are available onsite.
- Substance abuse counselors should be able to identify lapse or relapse to drug and/or alcohol use and provide support; help with adherence to HCV visits and medications; and be aware of emerging psychiatric conditions while patients are on HCV therapy

Table 1
Published clinical studies evaluating HCV treatment outcomes among patients on OAT.

Treatment setting	Treatment	Overall SVR	GT1 SVR	GT2 or 3 SVR	Reference
Direct Acting Antivirals					
Phase III, randomized, placebo-controlled, double-blind trial of treatment-naïve patients with HCV GT 1,4,6 who were at least 80% adherent to visits for OAT. Immediate-treatment group (ITG) received 12 weeks; deferred-treatment group (DTG) received placebo for 12 weeks, 4-week wash-out, then open-label treatment for 12 weeks.	elbasvir/grazoprevir (n=301)	ITG: 91.5% DTG: 89.5%	ITG: 93.5% (GT1): 91.7% (GT4): 60% DTG: 90.6% (GT1): 100% (GT4): 50%	NA	Dore et al. 2016 ⁵⁴
Phase II trial HCV GT 1 patients on chronic methadone (n = 19) or buprenorphine (n = 19)	ombitasvir/paritaprevir/ritonavir and dasabuvir + weight-based RBV (n=37)	97.4%	97.4%	NA	Lalezari et al. 2015 ⁵²
Retrospective cohort study of patients treated in a community-based primary care clinic.	SOF/PegIFN/RBV (n=18) SOF/RBV (n= 4) SOF/SIM (n= 22) SOF/LDV (n= 23)	96% OAT/Drug Use: 95% OAT/No Drug Use: 100% No OAT/Drug Use: 90% No OAT/No Drug Use: 95%	95% n=84	G2: 100% G3: 100% G4: 100%	Norton et al. 2017 ⁵⁹
Pegylated Interferon/ Ribavirin					
Meta-analysis of 36 studies; studies must include at least 10 people who use drugs treated for HCV	PegIFN/RBV (n=2866)	55.5%	45% (GT1/4)	70%	Dimova et al. 2013 ³⁸
Retrospective review of patient charts from an office-based OAT program run by a GP practice in Zurich, Switzerland. HCV medication was administered in the GP practice. Specialized care was available from hepatologists and psychiatrists within 3 days of referral.	PegIFN/RBV (n=35)	71%	74%	76% (GT3)	Seidenberg et al. 2013 ⁴⁴
Two US OAT clinics with a co-located hepatitis clinic. Internist-addiction medicine specialist was the primary care provider for most patients, and provided HCV care under the supervision of a hepatologist	PegIFN/RB (n=24)	54%	44%	66% (GT2) 100% (GT3)	Martinez et al. 2012 ¹⁶

Treatment setting	Treatment	Overall SVR	GT1 SVR	GT2 or 3 SVR	Reference
Retrospective cohort study of a concurrent group treatment program at an OTP in New York offering comprehensive, integrated substance abuse treatment, medical and psychiatric care	PegIFN/RBV (n=27)	42%	44%	NR	Stein et al. 2012 ⁴⁵
Non-randomized, open-label study at four tertiary hospital hepatitis clinics in Australia. Patients were all receiving OAT	PegIFN/RBV (n=53)	57%	36%	71% (non-GT1)	Sasadeusz et al. 2011 ⁴²
Patients under observed heroin maintenance therapy at German treatment centers received HCV treatment	PegIFN/RBV (n=26)	69%	42%	100% (GT2) 90% (GT3)	Schulte et al. 2010 ⁴³
Direct Acting Antivirals					
Observational UK study at a hospital-based infectious disease unit. All patients had HCV GT2/3. The study included 60 former drug users, the majority of whom were on OAT	PegIFN/RBV (n=125)	Non-drug users: 73% Former drug users: 73% (44/60) Active drug users: 40% (4/10)	NA	Non-drug users: 73% (91/125) Former drug users: 73% (44/60) Active drug users: 40% (4/10)	Alvarez-Uria et al. 2009 ³⁷
Retrospective analysis of treatment outcomes at multiple OAT clinics in New York providing onsite HCV treatment. Treatment was administered by physicians and physician assistants trained in HCV care and following a standardized procedure developed with a hepatologist	PegIFN/RBV (n=73)	45%	40% (GT1/4)	75% (GT2) 36% (GT3)	Litwin et al. 2009 ⁴¹
A multi-center, randomized, controlled, prospective study in Austria of patients with GT2/3 HCV and on stable OAT. HCV therapy administered by a multidisciplinary team at an addiction clinic	PegIFN/RBV (n=17)	88%	NA	88%	Ebner et al. 2009 ³⁹
Two Canadian clinics offering addiction services including OAT, syringe exchange, counseling and onsite consultation with infectious disease specialists. Addiction specialist performed the initial HCV medical evaluation. Nurses administered weekly PegIFN injection and monitored adherence to RBV, which was self-administered. 53% of patients were on methadone.	PegIFN/RBV (n=28) IFN/RBV (n=12)	55% (PegIFN/RBV = 61%; IFN/RBV = 42%)	44%	64%	Grebelly et al. 2007 ⁸⁴
Patients on stable OAT without illicit drug use for 6 months were prospectively matched with patients not on OAT without drug use and treated for HCV at German medical centers.	PegIFN/RBV (n=100)	OAT: 42% Non-OAT: 56% (P=0.16)	GT1/4: OAT: 38% Non-OAT: 55% (P=0.59)	OAT: 48% Non-OAT: 57% (P=0.76)	Mauss et al. 2004 ⁹⁷

ETR, End of Treatment Response; GT, Genotype; NA, not applicable; NR, not reported; SVR, sustained virologic response; OAT, opioid agonist therapy

Table 2

Drug interactions between methadone or buprenorphine and DAAs

DAA	Methadone	Buprenorphine (/naloxone)	Symptoms of withdrawal	Treatment Recommendation	Reference
Telaprevir	<p><u>R-methadone</u></p> <p>Cmax: 0.71 (0.66–0.76) AUC: 0.71 (0.66–0.76)</p> <p><u>S-methadone</u></p> <p>Cmax: 0.65 (0.60–0.71) AUC: 0.64 (0.58–0.70)</p>	<p><u>Buprenorphine</u></p> <p>Cmax: 0.80 (0.69, 0.93) AUC: 0.96 (0.84, 1.10)</p> <p><u>Norbuprenorphine</u></p> <p>Cmax: 0.85 (0.66, 1.09) AUC: 0.91 (0.71, 1.16)</p>	No difference in symptoms between opioid alone or opioid with telaprevir as measured by SOWS	No dose adjustment	Luo et al., Van Heeswijk et al. ^{98,99}
Boceprevir	<p><u>R-methadone</u></p> <p>Cmax: 0.90 (0.71–1.13) AUC: 0.85 (0.74–0.96)</p> <p><u>S-methadone</u></p> <p>Cmax: 0.83 (0.64–1.09) AUC: 0.78 (0.66–0.93)</p>	<p><u>Buprenorphine</u></p> <p>Cmax: 1.18 (0.93–1.50) AUC: 1.19 (0.91–1.57)</p> <p><u>Norbuprenorphine</u></p> <p>Cmax: 0.54 (0.36–0.83) AUC: 0.55 (0.36–0.86)</p>	No evidence of opioid withdrawal or opioid excess, measured by SOWS	No dose adjustment	Hulskotte et al. ¹⁰⁰
Simeprevir	<p><u>R-methadone</u></p> <p>Cmax: 1.03 (0.97–1.09) AUC: 0.99 (0.91–1.09)</p> <p><u>S-methadone</u></p> <p>Cmax, AUC: unchanged, data not reported</p>	No Data	No Data		Ouwerkerk-Mahadevan et al. ¹⁰¹
Sofosbuvir	<p><u>R-Methadone</u></p> <p>Cmax: 0.99 (0.85–1.16)</p>	No Data	None as measured by DDQ, SOWS or pupil diameter	No dose adjustment	Denning et al. ¹⁰²

DAA	Methodane	Buprenorphine (naloxone)	Symptoms of withdrawal	Treatment Recommendation	Reference
	<p><u>Methadone</u></p> <p>AUC: 1.01 (0.85–1.22)</p> <p><u>S-Methadone</u></p> <p>Cmax: 0.95 (0.79–1.13)</p> <p>AUC: 0.95 (0.77–1.17)</p>	No PK Data	No difference in pooled Phase 2/3 data for CNS adverse events for patients on methadone versus not on methadone	No dose adjustment	German et al. ¹⁰³
Sofosbuvir/Ledipasvir	No PK Data	No PK Data	No difference in pupil diameter, SOWS, or DDQ score between opioid alone or opioid with HCV regimen	No dose adjustment. Monitor for increased sedation for patients on Buprenorphine given increase in Cmax, AUC	Menon et al. ¹⁰⁴
Ombitasvir/paritaprevir/ritonavir and Dasabuvir	<p><u>R-Methadone</u></p> <p>Cmax: 1.04 (0.98–1.11)</p> <p>AUC: 1.05 (0.98–1.11)</p> <p><u>S-Methadone</u></p> <p>Cmax: 0.99 (0.91–1.08)</p> <p>AUC: 0.99 (0.89–1.09)</p>	<p><u>Buprenorphine</u></p> <p>Cmax: 2.18 (1.78, 2.68)</p> <p>AUC: 2.07 (1.78, 2.40)</p> <p><u>Norbuprenorphine</u></p> <p>Cmax: 2.07 (1.42, 3.01)</p> <p>AUC: 1.84 (1.30, 2.60)</p>	No effect on opioid withdrawal or toxicity scores measured by COW and OOA	No dose adjustment	Garimella et al. ¹⁰⁵
Daclatasvir	<p><u>R-Methadone</u></p> <p>Cmax: 1.07(0.97–1.18)</p> <p>AUC: 1.08 (0.94–1.24)</p> <p><u>S-Methadone</u></p> <p>Cmax: 0.95 (0.79–1.13)</p> <p>AUC: 0.95 (0.77–1.17)</p>	<p><u>Buprenorphine</u></p> <p>Cmax: 1.30 (1.03–1.64)</p> <p>AUC: 1.37 (1.24–1.52)</p> <p><u>Norbuprenorphine</u></p> <p>Cmax: 1.65 (1.38–1.99)</p> <p>AUC: 1.62 (1.30–2.02)</p>	No symptoms or signs of toxicity	No dose adjustment	Fraser et al. ¹⁰⁶
Grazoprevir	<u>R-Methadone</u>	<u>Buprenorphine</u>			

DAA	Methodone	Buprenorphine (naloxone)	Symptoms of withdrawal	Treatment Recommendation	Reference
	<p>Cmax: 1.03 (0.96–1.11) AUC: 1.09 (1.02–1.17) <u>S</u>-Methadone Cmax: 1.15 (1.07, 1.25) AUC: 1.23 (1.12– 1.35)</p>	<p>Cmax: 0.90 (0.76–1.07) AUC: 0.98 (0.81–1.19) <u>N</u>orbuprenorphine Cmax: 1.10 (0.97–1.25) AUC: 1.13 (0.97–1.32)</p>	<p>or withdrawal in clinical trials</p>		
Elbasvir	<p><u>R</u>-Methadone Cmax: 1.07 (0.95–1.20) AUC: 1.03 (0.92–1.15) <u>S</u>-Methadone Cmax: 1.09 (0.95– 1.25) AUC: 1.09 (0.94– 1.26)</p>	<p><u>B</u>uprenorphine Cmax: 0.94 (0.82–1.08) AUC: 0.98 (0.89–1.08) <u>N</u>orbuprenorphine No Data</p>	<p>No symptoms or signs of toxicity or withdrawal in clinical trials</p>	<p>No dose adjustment</p>	<p>Marshall et al.^{107,108}</p>
Velpatasvir	<p>No PK Data</p>	<p>No PK Data</p>	<p>No symptoms or signs of toxicity or withdrawal in clinical trials</p>	<p>No dose adjustment</p>	<p>Grebely et al.^{51,109}</p>

AUC, area under the curve; COWS, SOWS, subjective opiate withdrawal scale clinical opiate withdrawal scale; DDQ, desire for drugs questionnaire; OOA, opioid overdose assessment; NA, not available; PK, pharmacokinetic