


Key Populations: Identification and Management of HCV in People Who Inject Drugs

Prevalence of HCV Among People Who Inject Drugs

Injection drug use (IDU) is the most common risk factor for HCV infection in the United States and Europe, with an HCV seroprevalence of 10% to 70% depending on geographic location and duration of IDU exposure ([Hagan, 2008](#)); ([Amon, 2008](#)); ([Nelson, 2011](#)). In this section, the term people who inject drugs (PWID) includes individuals who are actively using drugs and those who have previously used injection drugs.

The first few years after an individual begins to inject drugs constitute a high-risk period during which the rate of HCV infection can exceed 40% ([Maher, 2006](#)). According to the National Survey on Drug Use and Health, heroin use has increased across the US among men and women, most age groups, and all income levels ([Jones, 2015](#)). IDU accounts for the majority of new HCV infections (approximately 70%) and is the driving force in the perpetuation of the epidemic. Given these facts and the absence of a vaccine against HCV, testing and linkage to care combined with antiviral treatment have the potential to decrease HCV incidence and prevalence ([Martin, 2013](#)); ([NAS, 2017](#)).

Recommendations for Screening and Treatment of HCV Infection in People Who Inject Drugs (PWID)

RECOMMENDED	RATING 
Annual HCV testing is recommended for PWID with no prior testing, or past negative testing and subsequent injection drug use. Depending on the level of risk, more frequent testing may be indicated.	IIa, C
Substance use disorder treatment programs and needle/syringe exchange programs should offer routine, opt-out HCV-antibody testing with reflexive or immediate confirmatory HCV-RNA testing and linkage to care for those who are infected.	IIa, C
PWID should be counseled about measures to reduce the risk of HCV transmission to others.	I, C
PWID should be offered linkage to harm reduction services including intranasal naloxone, needle/syringe service programs, medications for opioid use disorder, and other substance use disorder treatment programs.	I, B
Active or recent drug use or a concern for reinfection is not a contraindication to HCV treatment.	IIa, B

HCV Testing Among PWID

All individuals who currently inject drugs or have previously used injection drugs should be tested for HCV infection. Data are limited regarding the optimal interval for repeat testing among individuals actively using drugs. An HCV-antibody test is recommended and if the result is positive, current infection should be confirmed by immediate HCV-RNA testing (see [HCV Testing and Linkage to Care](#)). This can be accomplished using phlebotomy for a combined reflex test performed by a laboratory, which is appropriate for clinical settings. In certain community settings, a point-of-care antibody test with an immediate blood draw or dried blood spot collection for a confirmatory HCV-RNA test may be implemented.

Among persons at risk for HCV reinfection after previous spontaneous or treatment-related viral clearance, HCV-RNA testing is recommended because an HCV-antibody test is expected to remain positive. Among persons with a negative HCV-antibody test who are at high risk for a new HCV infection due to current IDU, testing for HCV RNA or follow-up testing for HCV antibody is recommended if HCV exposure may have occurred within the past 6 months.

Integration of HCV testing services into substance use disorder treatment programs, needle/syringe service programs, and acute detoxification programs provide an opportunity for routine screening in this key population ([Harris, 2010](#)); ([Aronson, 2017](#)).

Linkage to HCV Care and Treatment Adherence

Treatment of HCV-infected PWID should ideally be delivered in a multidisciplinary care setting with services to reduce reinfection risk and manage the common social and psychiatric comorbidities in this population.

Regardless of the treatment setting, recent and active IDU are not absolute contraindications to HCV therapy. There is strong evidence from various settings in which PWID have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit HCV therapy access in this patient population ([Aspinall, 2013](#)); ([Hellard, 2014](#)); ([Grebely, 2011](#)); ([Dore, 2016](#)). Modeling studies illustrate the high return on the modest investment of addressing this often-ignored segment of the HCV-infected population ([Martin, 2013b](#)); ([Fraser, 2018b](#)); ([Zelenev, 2018](#)). Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned because they create barriers to treatment, add unnecessary cost and effort, miss an opportunity to decrease HCV transmission, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Instead, scaling up HCV treatment in PWID is necessary to positively impact the HCV epidemic in the US and globally.

Recent hepatitis C test-and-link programs have identified the use of patient navigators or care coordinators to be an important intervention in overcoming challenges to linkage to and retention in care ([Trooskin, 2015](#)); ([Coyle, 2015](#)); ([Coyle, 2016](#)); ([Ramirez, 2016](#)); ([Ford, 2017](#)); ([Coyle, 2019](#)). The Check Hep C program in New York City compared services delivered at 2 clinical care sites to 2 sites that linked patients to off-site care. Participants receiving clinical care co-located with testing services had higher odds of initiating treatment than those linked to off-site care ([Ford, 2017](#)). Ongoing assessment of efficacy and comparative effectiveness of this and additional strategies is a crucial area of future research for patients with chronic HCV. Replication and expansion of best practices and new models for linkage to HCV care will be essential to maximize the public health impact of newer HCV treatment paradigms.


HCV Treatment Among PWID

Clinical trials among PWID reporting current IDU at the start of HCV treatment and/or continued use during therapy demonstrate SVR12 rates approaching 95% ([Dore, 2016](#)); ([Grebely, 2018](#)). Moreover, high SVR rates among PWID are not limited to clinical trials but are also observed in clinical practice settings. A cohort study was conducted with 89 patients initiating HCV treatment between January 2014 and August 2015 at a primary care clinic in the Bronx, New York. Four patient groups were compared: no active drug use or medications for opioid use disorder (MOUDs); no active drug use with MOUDs; active drug use without MOUDs; and active drug use MOUDs. The study found that regardless of active drug or MOUD use, patients who received direct-acting antiviral (DAA) therapy at this urban primary care clinic achieved high HCV cure rates (SVR \geq 95%) ([Norton, 2017](#)).

Furthermore, MOUDs do not compromise HCV treatment outcomes. Similar SVR12 rates are achieved by PWID engaged in MOUD use compared to individuals not engaged with such medications in clinical trials involving various DAA regimens ([Feld, 2014](#)); ([Lalezari, 2015](#)); ([Grebely, 2016](#)); ([Zeuzem, 2015](#)); ([Dore, 2016](#)). HCV-infected patients receiving MOUDs who were treated with elbasvir/grazoprevir had high rates of adherence to antiviral treatment and SVR12 rates $>$ 89% regardless of ongoing IDU ([Dore, 2016](#)). Similarly, an SVR12 of 97.4% was reported in a clinical trial evaluating ombitasvir/paritaprevir/ritonavir plus dasabuvir and ribavirin for 12 weeks among patients receiving MOUDs ([Lalezari, 2015](#)). Further, an analysis of a clinical trial evaluating outcomes of sofosbuvir/velpatasvir treatment in patients receiving MOUDs (n=51) compared to those not receiving these medications (n=984) demonstrated that MOUD use did not

significantly reduce treatment completion, antiviral adherence, SVR12, or safety ([Grebelly, 2016](#)).

Recommendation for Testing for Reinfection in People Who Inject Drugs (PWID)

RECOMMENDED	RATING 
At least annual HCV-RNA testing is recommended for PWID with recent injection drug use after they have spontaneously cleared HCV infection or have been successfully treated.	Ila, C

Reinfection

As HCV therapy is expanded to populations of PWID with high-risk behaviors for re-exposure, acknowledgement that HCV reinfection will occur in some individuals is critical, and appropriate strategies must be in place to maximize prevention of reinfection and offer retreatment for reinfection ([Grebelly, 2017](#)). Importantly, the rate of HCV reinfection in the PWID population is lower (2.4/100 person-years) than the rate of incident HCV infection in the general population of PWID (6.1 to 27.2/100 person-years), although the rate of reinfection increases with active or ongoing IDU (6.44/100 person-years) and available data on follow-up duration are limited ([Aspinall, 2013](#)); ([Grady, 2013](#)).

Data suggest that reinfection is rare in drug users who clear HCV with therapy even if they continue to inject drugs provided steps are taken to minimize the risk. Studies of HCV reinfection in PWID have demonstrated rates of reinfection post SVR ranging from 1 to 5/100 person-years in patients who have ever injected drugs, increasing to 3 to 33/100 person-years in patients with continued injecting risk behavior ([Midgard, 2016b](#)); ([Marco, 2013](#)); ([Grebelly, 2010](#)); ([Grebelly, 2012](#)); ([Bate, 2010](#)); ([Currie, 2008](#)); ([Dalgard, 2002](#)); ([Grady, 2012](#)). Relapse into drug use has been associated with HCV reinfection after cure ([Midgard, 2016b](#)) while interventions that reduce drug use, such as utilization of MOUDs and mental health services, have been associated with reduced HCV reinfection risk ([Islam, 2017](#)). These services should be made available to PWID.

PWID found to be HCV reinfected should be retreated. Retreatment of a new reinfection should be as detailed in the [Initial Treatment](#) section. Increasing the HCV treatment rate among the PWID population would reduce numbers of new HCV and liver-related disease cases ([Jiang, 2017](#)). In a study that evaluated reinfection and injecting risk behavior following DAA therapy, participants on MOUDs for ≥ 3 months had a reinfection rate of 2.3/100 person-years, with a persistent reinfection rate of 1.6/100 person-years due to spontaneous HCV clearance in several instances. A reinfection rate of 4.2/100 person-years was found among those who reported IDU ([Dore, 2017](#)).

Harm Reduction

Harm reduction is a way of preventing disease and promoting health that “meets people where they are” and provides the tools and information they need to keep themselves and those around them well ([Logan, 2010](#)). Harm reduction places drug use within the larger sociopolitical spheres of poverty, criminalization, and mental health. Accepting that not everyone is ready or able to curtail or stop high-risk behavior, harm reduction focuses on promoting a spectrum of scientifically proven, practical strategies for reducing the negative consequences of drug use and other high-risk behaviors. Harm reduction strategies include but are not limited to condom distribution; access to sterile injection equipment; utilization of MOUDs (such as methadone, buprenorphine and naltrexone); safe injection spaces; and overdose education and naloxone distribution. Heroin overdose deaths in the US increased 286% from 2002 to 2013 ([Jones, 2015](#)). Broad implementation of harm reduction strategies has the potential to significantly impact the HCV epidemic.

Medications for Opioid Use Disorder

Methadone, buprenorphine, and naltrexone are FDA-approved treatments for opioid use disorder with evidence from randomized controlled trials and real-world cohorts to support their effectiveness in reducing opioid use, improving mortality, decreasing criminal activity, and improving social functioning and retention in care ([Volkow, 2014](#)); ([Kampman 2015](#)); ([Tasillo, 2017](#)). Methadone is a long-acting opioid agonist that has the longest history in clinical use and is proven to reduce illicit drug use and improve social functioning ([Mattick, 2009](#)). Although methadone is effective, concern about diversion leads to methadone maintenance being highly regulated in the US, typically requiring daily visits to a dedicated dispensing clinic ([Mattick, 2014](#)). Buprenorphine-naloxone is a partial opioid agonist that also relieves withdrawal, and quells opioid craving. Multiple randomized trials support its effectiveness in reducing drug use and improving retention in care ([Tasillo, 2017](#)); ([Volkow, 2017](#)); ([Kampman, 2015](#)); ([Volkow, 2014](#)); ([Mattick, 2014](#)); ([Moore, 2012](#)); ([Weiss, 2011](#)); ([Comer, 2010](#)); ([Jones, 2010](#)); ([Ling, 2010](#)); ([Lucas, 2010](#)); ([Mattick, 2009](#)); ([Kakko, 2007](#)); ([Fischer, 2006](#)); ([Jones, 2005](#)); ([Fudala, 2003](#)); ([Kakko, 2003](#)); ([Johnson, 2000](#)); ([Ling, 1998](#)); ([O'Connor, 1998](#)); ([Ling, 1996](#)); ([Johnson, 1995](#)). Buprenorphine-naloxone's major benefits include that it is a partial agonist which limits its overdose risk; coformulation with naloxone provides a deterrent from injecting; and it can be successfully prescribed in routine primary care settings ([Korthuis, 2017](#)); ([LaBelle, 2016](#)); ([Fudala, 2003](#)). Prescribing buprenorphine-naloxone requires 8 hours of training and registration with the US Drug Enforcement Agency and receiving a waiver from the Substance Abuse Mental Health Services Administration, which limits the number of providers ([Stein, 2015](#)). Naltrexone is an opioid antagonist that prevents the euphoric and respiratory effects of opioids, reducing cravings ([SAMHSA, 2019](#)). Naltrexone has low diversion potential and requires no special licensing for prescribers ([Rudd, 2016](#)). Further, it is available as a monthly injection. Naltrexone precipitates opioid withdrawal, however, and is therefore only initiated in opioid-abstinent patients.

Several reviews have identified MOUDs as effective in reducing illicit opioid use ([Mattick, 2009](#)); ([Mattick, 2014](#)) and opioid-related death and all-cause mortality ([Deegenhardt, 2009](#)); ([Sordo, 2017](#)), and improving quality of life ([Lawrinson, 2008](#)); ([Ward, 1999](#)). Participation in methadone maintenance treatment has been shown to be protective against hepatitis C incidence among PWID, with a dose-response protective effect with increasing methadone exposure on hepatitis C incidence ([Nolan, 2014](#)).

Syringe Service Programs

Syringe service programs (SSPs) were developed to reduce the spread of bloodborne diseases among injection drug users. These programs provide PWID with sterile syringes and other equipment (cookers, filters, sterile water, alcohol swabs) to reduce the risk of bloodborne disease (eg, HIV and HCV) transmission associated with sharing injection equipment. These programs were developed in the 1980s and often include drug treatment referrals, peer education, and HIV prevention. Areas with greater syringe access through SSPs have lower rates of hepatitis C among PWID. A prospective study of PWID in New York City found a significant decline in HCV rates from 1990 to 2001, corresponding to an increase in the number of syringes distributed by SSPs during this period ([Des Jarlais, 2005](#)).

Overdose Education and Naloxone Distribution (OEND)

HCV treatment is a touchpoint with the care delivery system and should be used as an opportunity to mitigate the harms of drug use, especially overdose risk. Naloxone is a powerful opioid antagonist that reverses the respiratory depressive effects of opioids and is lifesaving to those experiencing opioid overdose ([Wermeling, 2015](#)). Expanding access to intranasal naloxone significantly decreases mortality at the community level ([Walley, 2013](#)). Many states have standing orders for intranasal naloxone, which allow providers to dispense naloxone directly to patients. When no standing order exists or when it is not feasible to provide naloxone directly, providers should offer patients a prescription for naloxone to fill at a local pharmacy. Importantly, naloxone is not an opioid and carries no overdose risk, no dependency risk, and no risk of diversion. Naloxone is safe and effective and can be prescribed with confidence by HCV providers who do not treat addictions more generally.

Benefit of Treatment to Reduce HCV Transmission

Persons cured of chronic HCV no longer transmit the virus to others. As such, successful HCV treatment benefits public health. Several health models have shown that even modest increases in successful HCV treatment among PWID can decrease prevalence and incidence ([Martin, 2013](#)); ([Durier, 2012](#)); ([Martin, 2013b](#)); ([Hellard, 2014](#)). Models developed to

estimate the impact of HCV testing and treatment on the burden of HCV at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated ([Wedemeyer, 2014](#)); ([Martin, 2015](#)). Elimination of HCV among PWID will also require scaling up harm reduction services ([Fraser, 2018](#)).

Last update: November 6, 2019

Related References

- Amon JJ, Garfein RS, Ahdieh-Grant L, et al. [Prevalence of hepatitis C virus infection among injection drug users in the United States, 1994-2004](#). *Clin Infect Dis*. 2008;46(12):1852-1858.
- Aronson I, Bennett A, Marsch LA, Bania TC. [Mobile technology to increase HIV/HCV testing and overdose prevention/response among people who inject drugs](#). *Front Public Health*. 2017;5:217.
- Aspinall EJ, Corson S, Doyle JS, et al. [Treatment of hepatitis C virus infection among people who are actively injecting drugs: a systematic review and meta-analysis](#). *Clin Infect Dis*. 2013;57(Suppl 2):S80-S89.
- Bate JP, Colman AJ, Frost PJ, Shaw DR, Harley HA. [High prevalence of late relapse and reinfection in prisoners treated for chronic hepatitis C: relapse in prisoners treated for hepatitis C](#). *J Gastroenterol Hepatol*. 2010;25(7):1276-1280.
- [Centers for Disease Control and Prevention \(CDC\). 2015 sexually transmitted diseases treatment guidelines, special populations.](#); 2015. Available at: <https://www.cdc.gov/std/tg2015/specialpops.htm>. Accessed June 13, 2019.
- Comer SD, Sullivan MA, Vosburg SK, et al. [Abuse liability of intravenous buprenorphine/naloxone and buprenorphine alone in buprenorphine-maintained intravenous heroin abusers](#). *Addiction*. 2010;105(4):709-718.
- Coyle C, Viner K, Hughes E, et al. [Identification and linkage to care of HCV-infected persons in five health centers - Philadelphia, Pennsylvania, 2012-2014](#). *MMWR Morb Mortal Wkly Rep*. 2015;64(17):459-463.
- Coyle C, Kwakwa H. [Dual-routine HCV/HIV testing: seroprevalence and linkage to care in four community health centers in Philadelphia, Pennsylvania](#). *Public Health Rep*. 2016;131(Suppl 1):41-52.
- Coyle C, Moorman AC, Bartholomew T, et al. [The hepatitis C virus care continuum: linkage to hepatitis C virus care and treatment among patients at an urban health network, Philadelphia, PA](#). *Hepatology*. 2019;70(2):476-486. doi:10.1002/hep.30501.
- Currie SL, Ryan JC, Tracy D, et al. [A prospective study to examine persistent HCV reinfection in injection drug users who have previously cleared the virus](#). *Drug Alcohol Depend*. 2008;93(1-2):148-154.
- Dalgard O, Bjørø K, Hellum K, et al. [Treatment of chronic hepatitis C in injecting drug users: 5 years' follow-up](#). *Eur Addict Res*. 2002;8(1):45-49.
- Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L. [Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved](#). *Drug Alcohol Depend*. 2009;105(1-2):9-15.
- Des Jarlais D, Perlis T, Arasteh K, et al. [Reductions in hepatitis C virus and HIV infections among injecting drug users in New York City, 1990-2001](#). *AIDS*. 2005;19 Suppl 3:S20-25.
- Dore GJ, Altice F, Litwin AH, et al. [Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial](#). *Ann Intern Med*. 2016;165(9):625-634.
- Dore G, Grebely J, Altice F, et al. [Hepatitis C virus \(HCV\) reinfection and injecting risk behavior following elbasvir \(EBR\)/grazoprevir \(GZR\) treatment in participants on opiate agonist therapy \(OAT\): Co-STAR part B \[abstract 195\]](#).

Presented at the Liver Meeting 2017, October 22, 2017.

Durier N, Nguyen C, White LJ. [Treatment of hepatitis C as prevention: a modeling case study in Vietnam](#). *PLoS One*. 2012;7(4):e34548.

Feld JJ, Kowdley KV, Coakley E, et al. [Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin](#). *N Engl J Med*. 2014;370(17):1594-1603.

Fischer G, Ortner R, Rohrmeister K, et al. [Methadone versus buprenorphine in pregnant addicts: a double-blind, double-dummy comparison study](#). *Addiction*. 2006;101(2):275-281.

Ford MM, Johnson N, Desai P, Rude E, Laraque F. [From care to cure: demonstrating a model of clinical patient navigation for hepatitis C care and treatment in high-need patients](#). *Clin Infect Dis*. 2017;64(5):685-691.

Fraser H, Martin NK, Brummer-Korvenkontio H, et al. [Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe](#). *J Hepatol*. 2018;68(3):402-411.

Fraser H, Zibbell J, Hoerger T, et al. [Scaling-up HCV prevention and treatment interventions in rural United States-model projections for tackling an increasing epidemic](#). *Addiction*. 2018;113(1):173-182. doi:10.1111/add.13948.

Fudala PJ, Bridge TP, Herbert S, et al. [Office-based treatment of opiate addiction with a sublingual-tablet formulation of buprenorphine and naloxone](#). *N Engl J Med*. 2003;349(10):949-958.

Grady BPX, Vanhommerig JW, Schinkel J, et al. [Low incidence of reinfection with the hepatitis C virus following treatment in active drug users in Amsterdam](#). *Eur J of Gastroenterol Hepatol*. 2012;24(11):1302-1307.

Grady BP, Schinkel J, Thomas XV, Dalgard O. [Hepatitis C virus reinfection following treatment among people who use drugs](#). *Clin Infect Dis*. 2013;57(Suppl 2):S105-S110.

Grebely J, Knight E, Ngai T, et al. [Reinfection with hepatitis C virus following sustained virological response in injection drug users: HCV reinfection following SVR in IDUs](#). *J Gastroenterol Hepatol*. 2010;25(7):1281-1284.

Grebely J, Matthews GV, Hellard M, Yeung B, et al. [Adherence to treatment for recently acquired hepatitis C virus \(HCV\) infection among injecting drug users](#). *J Hepatol*. 2011;55(1):76-85.

Grebely J, Pham ST, Matthews GV, et al. [Hepatitis C virus reinfection and superinfection among treated and untreated participants with recent infection](#). *Hepatology*. 2012;55(4):1058-1069.

Grebely J, Dore GJ, Zeuzem S, et al. [Efficacy and safety of sofosbuvir/velpatasvir in patients with chronic hepatitis C virus infection receiving opioid substitution therapy: analysis of phase 3 ASTRAL trials](#). *Clin Infect Dis*. 2016;63(11):1479-1481.

Grebely J, Hajarizadeh B, Dore GJ. [Direct-acting antiviral agents for HCV infection affecting people who inject drugs](#). *Nat Rev Gastroenterol Hepatol*. 2017;14(11):641-651.

Grebely J, Dalgard O, Conway B, et al. [Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use \(SIMPLIFY\): an open-label, single-arm, phase 4, multicentre trial](#). *Lancet Gastroenterol Hepatol*. 2018;3(3):153-161.

Hagan H, Pouget ER, Des-Jarlais DC, Lelutiu-Weinberger C. [Meta-regression of hepatitis C virus infection in relation to time since onset of illicit drug injection: the influence of time and place](#). *Am J of Epidemiol*. 2008;168(10):1099-1109.

Harris, Jr. KA, Arnsten JH, Litwin AH. [Successful integration of hepatitis C evaluation and treatment services with methadone maintenance](#). *J Addict Med*. 2010;4(1):20-26.

- Hellard M, Doyle JS, Sacks-Davis R, Thompson AJ, McBryde E. [Eradication of hepatitis C infection: the importance of targeting people who inject drugs](#). *Hepatology*. 2014;59(2):366-369.
- Islam N, Kraiden M, Shoveller J, et al. [Incidence, risk factors, and prevention of hepatitis C reinfection: a population-based cohort study](#). *Lancet Gastroenterol Hepatol*. 2017;2(3):200-210.
- Jiang Y, Nwankwo C. [Epidemiologic impact of expanding chronic hepatitis C \(CHC\) treatment in people who inject drug in the United States: a mathematical model using data from the C-EDGE CO-STAR study](#). *The Liver Meeting*. 2017.
- Johnson RE, Eissenberg T, Stitzer ML, Strain EC, Liebson IA, Bigelow GE. [A placebo controlled clinical trial of buprenorphine as a treatment for opioid dependence](#). *Drug Alcohol Depend*. 1995;40(1):17-25.
- Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. [A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence](#). *N Engl J Med*. 2000;343(18):1290-1297.
- Jones HE, Johnson RE, Jasinski DR, et al. [Buprenorphine versus methadone in the treatment of pregnant opioid-dependent patients: effects on the neonatal abstinence syndrome](#). *Drug Alcohol Depend*. 2005;79(1):1-10.
- Jones HE, Kaltenbach K, Heil SH, et al. [Neonatal abstinence syndrome after methadone or buprenorphine exposure](#). *N Engl J Med*. 2010;363(24):2320-2331.
- Kakko J, Svanborg KD, Kreek MJ, Heilig M. [1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial](#). *Lancet*. 2003;361(9358):662-668.
- Kakko J, Gronbladh L, Svanborg KD, et al. [A stepped care strategy using buprenorphine and methadone versus conventional methadone maintenance in heroin dependence: a randomized controlled trial](#). *Am J Psychiatry*. 2007;164(5):797-803.
- Kampman K, Jarvis M. [American Society of Addiction Medicine \(ASAM\) national practice guideline for the use of medications in the treatment of addiction involving opioid use](#). *J Addict Med*. 2015;9(5):358-367.
- Korthuis PT, McCarty D, Weimer M, et al. [Primary care-based models for the treatment of opioid use disorder: a scoping review](#). *Ann Intern Med*. 2017;166(4):268-278.
- LaBelle CT, Han SC, Bergeron A, Samet JH. [Office-based opioid treatment with buprenorphine \(OBOT-B\): statewide implementation of the Massachusetts collaborative care model in community health centers](#). *J Subst Abuse Treat*. 2016;(60):6-13.
- Lalezari J, Sullivan J, Varunok P, et al. [Ombitasvir/paritaprevir/r and dasabuvir plus ribavirin in HCV genotype 1-infected patients on methadone or buprenorphine](#). *J Hepatol*. 2015;63(2):364-369.
- Lawrinson P, Ali R, Buavirat A, et al. [Key findings from the WHO collaborative study on substitution therapy for opioid dependence and HIV/AIDS](#). *Addiction*. 2008;103(9):1484-1492.
- Ling W, Wesson DR, Charuvastra C, Klett CJ. [A controlled trial comparing buprenorphine and methadone maintenance in opioid dependence](#). *Arch Gen Psychiatry*. 1996;53(5):401-407.
- Ling W, Charuvastra C, Collins JF, et al. [Buprenorphine maintenance treatment of opiate dependence: a multicenter, randomized clinical trial](#). *Addiction*. 1998;93(4):475-486.
- Ling W, Casadonte P, Bigelow G, et al. [Buprenorphine implants for treatment of opioid dependence: a randomized controlled trial](#). *JAMA*. 2010;304(14):1576-1583.
- Logan DE, G. Marlatt A. [Harm reduction therapy: a practice-friendly review of research](#). *J Clin Psychol*.

2010;66(2):201-214.

Lucas GM, Chaudhry A, Hsu J, et al. [Clinic-based treatment of opioid-dependent HIV-infected patients versus referral to an opioid treatment program: A randomized trial](#). *Ann Intern Med*. 2010;152(11):704-711.

Maher L, Jalaludin B, Chant KG, et al. [Incidence and risk factors for hepatitis C seroconversion in injecting drug users in Australia](#). *Addiction*. 2006;101(10):1499-1508.

Marco A, Esteban JI, Sole C, et al. [Hepatitis C virus reinfection among prisoners with sustained virological response after treatment for chronic hepatitis C](#). *J Hepatol*. 2013;59(1):45-51.

Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. [Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy](#). *Clin Infect Dis*. 2013;57(Suppl 2):S39-S45.

Martin NK, Vickerman P, Grebely J, et al. [Hepatitis C virus treatment for prevention among people who inject drugs: modeling treatment scale-up in the age of direct-acting antivirals](#). *Hepatology*. 2013;58(5):1598-1609.

Martin NK, Vickerman P, Dore GJ, Hickman M. [The hepatitis C virus epidemics in key populations \(including people who inject drugs, prisoners and MSM\): the use of direct-acting antivirals as treatment for prevention](#). *Curr Opin HIV AIDS*. 2015;10(5):374-380.

Mattick RP, Breen C, Kimber J, Davoli M. [Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence](#). *Cochrane Database Syst Rev*. 2009;(3):CD002209. doi: 10.1002/14651858.CD002209.pub2.

Mattick RP, Breen C, Kimber J, Davoli M. [Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence](#). *Cochrane Database Syst Rev*. 2014;(2):CD002207.

Midgard H, Bjørø B, Mæland A, et al. [Hepatitis C reinfection after sustained virological response](#). *J Hepatol*. 2016;64(5):1020-1026.

Moore BA, Barry DT, Sullivan LE, et al. [Counseling and directly observed medication for primary care buprenorphine maintenance: a pilot study](#). *J Addict Med*. 2012;6(3):205-211.

[National Academies of Sciences, committee on a national strategy for the elimination of hepatitis B and C, board on population health and public health practice: a national strategy for the elimination of hepatitis B and C: phase two report](#). Washington, DC: National Academies Press; 2017.

Nelson PK, Mathers BM, Cowie B, et al. [Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews](#). *Lancet*. 2011;378(9791):571-583.

Nolan S, DiasLima V, Fairbairn N, et al. [The impact of methadone maintenance therapy on hepatitis C incidence among illicit drug users](#). *Addiction*. 2014;109(12):2053-2059.

Norton BL, Fleming J, Bachhuber MA, et al. [High HCV cure rates for people who use drugs treated with direct acting antiviral therapy at an urban primary care clinic](#). Steinman M, DeLuca J, Cunningham CO, Johnson N, Laraqe F, Litwin AH, eds. *Int J Drug Policy*. 2017;47:196-201.

O'Connor PG, Oliveto AH, Shi JM, et al. [A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic](#). *Am J Med*. 1998;105(2):100-105.

Ramirez G, Cabral R, Patterson M, et al. [Early identification and linkage to care for people with chronic HBV and HCV infection: the HepTLC initiative](#). *Public Health Rep*. 2016;131(Suppl 2):5-11.

Rudd RA, Seth P, David F, Scholl L. [Increases in drug and opioid-involved overdose deaths - United States, 2010-2015](#).

MMWR Morb Mortal Wkly Rep. 2016;65(5051):1445-1452.

[Information sheet on naltrexone therapy](https://www.samhsa.gov/medication-assisted-treatment/treatment/naltrexone). 2019. Available at: <https://www.samhsa.gov/medication-assisted-treatment/treatment/naltrexone>.

Sordo L, Barrio G, Bravo MJ, et al. [Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies](#). *BMJ.* 2017;(357):j1550.

Stein BD, Gordon AJ, Dick AW, et al. [Supply of buprenorphine waived physicians: the influence of state policies](#). *J Subst Abuse Treat.* 2015;48(1):104-111.

Tasillo A, Salomon JA, Trikalinos TA, Horsburgh, Jr CR, Marks SM, Linas BP. [Cost-effectiveness of testing and treatment for latent tuberculosis infection in residents born outside the United States with and without medical comorbidities in a simulation model](#). *JAMA Intern Med.* 2017;177(12):1755-1764. doi:10.1001/jamainternmed.2017.3941.

Trooskin SB, Poceta J, Towey CM, et al. [Results from a geographically focused, community-based HCV screening, linkage-to-care and patient navigation program](#). *J Gen Intern Med.* 2015;30(7):950-957.

Volkow ND, Frieden TR, Hyde PS, Cha SS. [Medication-assisted therapies--tackling the opioid-overdose epidemic](#). *N Engl J Med.* 2014;370(22):2063-2066.

Volkow ND, Collins FS. [The role of science in addressing the opioid crisis](#). *N Engl J Med.* 2017;377(4):391-394.

Walley AY, Xuan Z, Hackman HH, et al. [Opioid overdose rates and implementation of overdose education and nasal naloxone distribution in Massachusetts: interrupted time series analysis](#). *BMJ.* 2013;346. doi:10.1136/bmj.f174.

Ward J, Hall W, Mattick RP. [Role of maintenance treatment in opioid dependence](#). *The Lancet.* 1999;353(9148):221-226.

Wedemeyer H, Duberg AS, Buti M, et al. [Strategies to manage hepatitis C virus \(HCV\) disease burden](#). *J Viral Hepat.* 2014;21(Suppl 1):60-89.

Weiss RD, Potter JS, Fiellin DA, Byrne M, et al. [Adjunctive counseling during brief and extended buprenorphine-naloxone treatment for prescription opioid dependence: a 2-phase randomized controlled trial](#). *Arch Gen Psychiatry.* 2011;68(12):1238-1246.

Wermeling DP. [Review of naloxone safety for opioid overdose: practical considerations for new technology and expanded public access](#). *Ther Adv Drug Saf.* 2015;6(1):20-31. doi:10.1177/2042098614564776.

Zelenev A, Mazhnaya A, Basu S, Altice FL. [Hepatitis C virus treatment as prevention in an extended network of people who inject drugs in the USA: a modelling study](#). *Lancet Infect Dis.* 2018;18(2):215-224. doi:10.1016/S1473-3099(17)30676-X.

Zeuzem S, Ghalib R, K. Reddy R, et al. [Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial](#). *Ann Intern Med.* 2015;163(1):1-13.