Outpatient directly observed therapy for hepatitis C among people who use drugs: a systematic review and meta-analysis

Cara L McDermott1,2,*, Catherine M Lockhart3 and Beth Devine4

1 Cambia Palliative Care Center of Excellence, School of Medicine, University of Washington, Seattle, WA, USA
2 Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA
3 Biologics and Biosimilars Collective Intelligence Consortium, Alexandria, VA, USA
4 CHOICE Institute, School of Pharmacy, University of Washington, Seattle, WA, USA

Abstract

Objective: We conducted a meta-analysis of randomised studies that assessed the effectiveness of directly observed hepatitis C medication therapy delivered in outpatient clinics compared to treatment as usual.

Methods: We completed a systematic literature review up to the end of August 2017, including online databases, study abstracts and references of pertinent articles. We assessed the results of randomised studies using the Cochrane Collaboration risk of bias assessment tool, and observational studies using the ROBINS-I tool. From each study, we extracted the number of patients who did or did not attain sustained virological response (SVR). We utilised a DerSimonian and Laird random effects model for our meta-analysis. This study is registered with PROSPERO (CRD42014012957).

Results: We included six studies with 407 patients in our systematic review; four of those studies (215 patients) used randomisation and were included in our meta-analysis. Overall effect estimates showed that compared to treatment as usual, directly observed therapy demonstrated significantly higher odds of SVR attainment (odds ratio 2.01, 95% confidence interval 1.13–3.59).

Conclusion: Among people who use drugs, directly observed therapy may lead to higher odds of attaining SVR. Further research on the best ways to use directly observed therapy to administer HCV therapy to people who use drugs is warranted.

Keywords: Hepatitis C, treatment, meta-analysis, review

Introduction

Hepatitis C virus (HCV) represents a considerable morbidity and cost burden, contributing to approximately 400,000 deaths annually worldwide [1], and estimated yearly costs of at least US$6.5 billion in the United States [2]. Given the advent of all-oral direct-acting antiviral agents (DAAs) to treat HCV, with lower toxicity and no injections such as those required with interferon-based regimens, it is possible to reduce mortality associated with HCV [3] and to extend therapy to people who may have previously been reticent to undergo treatment [4]. The goal of HCV therapy is attainment of sustained virological response (SVR), defined as undetectable RNA levels in the blood 12 weeks after treatment completion. Patients who attain SVR are considered cured, thus avoiding HCV-related mortality and morbidity [5].

A significant reduction in HCV incidence and prevalence will require treatment for people who use drugs (PWUD), as injection drug use comprises the most common mode of HCV transmission [6]. The mean burden of HCV among PWUD is estimated to be approximately 60%, with HCV prevalence varying between 25% and 90% depending on local prevalence patterns [7]. In addition to the therapy recipient of HCV, that person can then no longer transmit HCV, thus preventing HCV transmission to other PWUD [8]. HCV treatment among PWUD can be cost-effective [9], since treatment can negate HCV-related sequelae such as cirrhosis and hepatocellular carcinoma, which HCV-infected PWUD are likely to develop in mid to late adulthood [10].

PWUD may not receive treatment as a result of clinician concerns about compliance with the treatment regimen, and the possibility of HCV re-infection following a course of antiHCV treatment [11,12]. Effectively treating PWUD for HCV requires both a significant increase in treatment availability, for example by incorporating treatment into methadone maintenance therapy, and uptake by patients who may be distrustful of healthcare systems or unable to adhere to regimens due to unmet social needs [4,13]. Additionally, it is important to note that the treatment-as-prevention strategy is successful in lower-HCV prevalence areas compared to those with higher HCV prevalence [14], and thus care models may need to be adapted to local populations. Clearly, creative models of treatment delivery are needed to reach PWUD who are infected with HCV.

Directly observed therapy (DOT) is a care delivery model that was first established for treatment of tuberculosis [15] and was then adapted to deliver treatment to people infected with HIV [16]. DOT has been shown to deliver effective HCV treatment in prisons, primary care clinics, hepatology clinics, drug treatment facilities and multidisciplinary health centres [17–20]. Prior reviews have assessed ways to deliver HCV treatment to PWUD, looking at predictors of treatment completion or HCV treatment delivery mechanisms [21,22]. Given the potential of DOT to deliver treatment among PWUD [9], we conducted a systematic review and summarised existing literature on DOT used in outpatient programmes and SVR attainment in HCV-infected PWUD using meta-analytic techniques. We report our results to augment the available data to inform treatment strategies.

Methods

We performed this meta-analysis following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [23]. Our study protocol is registered with PROSPERO (registration number CRD42014012957).

Data sources

We performed a comprehensive search for eligible studies, searching the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and references of relevant articles from the start of each respective database through to the end of August 2017. We also reviewed the conference proceedings and websites
We conducted our analysis using Stata version 15 (College Station, TX, USA). For this analysis, we applied without describing them as DOT. Given the burden of HCV among PWUD and the advent of newer therapies that may decrease this burden [28], research that identifies the most effective strategies to deliver such medication to PWUD is needed. While previously conducted pre–post studies that evaluated DOT as a means to achieve SVR using older HCV medications (e.g. PEG–IFN and ribavirin) showed a positive association between DOT and SVR, with the percentage of patients attaining SVR ranging from 55% [17] to 65% [29], up to 94% [30] and 98% [18], observational studies comparing DOT to treatment as usual have had more mixed results, with patients receiving DOT having similar SVR to those receiving treatment as usual [19,27]. We conducted this meta-analysis to increase sample size available for analysis and summarise the quality of and findings of available studies.

We found a statistically significant increase in attainment of SVR among individuals receiving DOT while receiving opioid maintenance therapy and/or actively injecting drugs. While other systematic reviews and meta-analyses have evaluated treatment completion determinants among PWUD or HCV treatment delivery settings available for analysis and summarise the quality of and findings of available studies. Given the burden of HCV among PWUD and the advent of newer therapies that may decrease this burden [28], research that identifies the most effective strategies to deliver such medication to PWUD is needed. While previously conducted pre–post studies that evaluated DOT as a means to achieve SVR using older HCV medications (e.g. PEG–IFN and ribavirin) showed a positive association between DOT and SVR, with the percentage of patients attaining SVR ranging from 55% [17] to 65% [29], up to 94% [30] and 98% [18], observational studies comparing DOT to treatment as usual have had more mixed results, with patients receiving DOT having similar SVR to those receiving treatment as usual [19,27]. We conducted this meta-analysis to increase sample size available for analysis and summarise the quality of and findings of available studies.

We found a statistically significant increase in attainment of SVR among individuals receiving DOT while receiving opioid maintenance therapy and/or actively injecting drugs. While other systematic reviews and meta-analyses have evaluated treatment completion determinants among PWUD or HCV treatment delivery mechanisms for PWUD [21,22], we filled a knowledge gap by assessing the association between DOT and SVR as an outcome, focusing on randomised studies with a comparator group. In our pooled analysis, 58% of people receiving DOT and 39% of those receiving treatment as usual attained SVR. A recent prospective, observational trial found that while PWUD had a high rate of discontinuation of PEG–IFN/ribavirin therapy, those who completed treatment had SVR attainment rates similar to other cohorts [31].
Records identified through database searching (n=689)

Additional records identified through other sources (n=1)

Duplicates excluded (n=44)

Titles excluded as not pertinent to study (n=593)

Records available for title review (n=646)

Additional records identified through other sources (n=1)

Abstracts excluded as not pertinent (n=24)

Abstracts screened (n=53)

Full-text articles assessed for eligibility (n=29)

Reasons for full-text articles exclusions
- Prison setting (n=6)
- Single arm (n=8)
- Review (n=3)
- Not about HCV (n=2)
- No report on SVR as outcome (n=2)
- Update on another paper (n=2)

Studies included in systematic review (n=6)

Studies included in meta-analysis (n=4)

**Table 1. Studies identified in systematic review and characteristics of each study population**

| Author [ref] | Country | Year | Study type | Outpatient setting | Genotypes | DOT Treatment | TAU | Outcome | Number enrolled DOT | TAU |
|--------------|---------|------|------------|-------------------|-----------|---------------|-----|---------|-------------------|-----|
| Bonkovsky [40] | USA     | 2008 | Randomised open-label | Six study sites; methadone clinics and outpatient clinics within each site | 1–3 | Self-administered RBV, provider-administered weekly PEG-IFN | Self-administered RBV, first PEG-IFN injection provider-administered then self-administered PEG-IFN | SVR | 24 | 24 |
| Bruce [41] | USA     | 2012 | RCT | One site with a methadone clinic and a hepatology clinic | 1–4 | Provider administered weekly PEG-IFN with RBV in MEMS container | Self-administered PEG-IFN and RBV in MEMS containers | SVR | 12 | 9 |
| Hilsden [42] | Canada  | 2013 | Randomised open-label | Two urban outpatient health clinics | 1–3 | Self-administered RBV, provider-administered weekly PEG-IFN | Self-administered RBV, provider-administered weekly PEG-IFN after a delay in treatment initiation | SVR | 48 | 18 |
| Litwin [43] | USA     | 2010 | RCT | Nine outpatient methadone clinics | Not reported | Directly observed RBV, provider-administered weekly PEG-IFN | Self-administered RBV, provider-administered weekly PEG-IFN | SVR | 40 | 40 |
| Cioe [19] | USA     | 2013 | Retrospective cohort | Two hospital outpatient clinics; primary care and hepatology | Not reported | Self-administered RBV, provider-administered weekly PEG-IFN | Self-administered PEG-IFN and RBV | SVR | 97 | 58 |
| Nosotti [27] | Italy   | 2014 | Prospective cohort | One outpatient drug treatment clinic | Not reported | Directly observed RBV, provider-administered weekly PEG-IFN | Self-administered RBV and PEG-IFN | SVR | 21 | 16 |

DOT: directly observed therapy; MEMS: medication event monitoring system; PEG-IFN: pegylated interferon; RBV: ribavirin; RCT: randomised controlled trial; SVR: sustained virological response; TAU: treatment as usual.

**Figure 1.** PRISMA flow diagram detailing inclusion and exclusion criteria for studies [23]
DOT in conjunction with other services can help connect PWUD with treatment while meeting social and medical needs. One study randomised pharmacies in Scotland to screen for HCV among people receiving outpatient methadone therapy, then allowed pharmacists to prescribe ledipasvir/sofosbuvir to facilitate HCV treatment [32]. Another study used community health workers to observe HCV therapy among patients, varying the medications received while all subjects received DOT. Patients receiving sofosbuvir plus PEG-IFN and ribavirin achieved 100% SVR while 68% of patients receiving sofosbuvir plus ribavirin attained SVR [33]. As all study subjects received DOT simultaneously without a comparison to those not receiving DOT, this study was not included in our analysis.

While the dominant paradigm has been to deliver HCV treatment to PWUD in the setting of methadone clinics, furthering the reach of HCV treatment, such as using pharmacists and innovative health models, reaches more PWUD. Treatment among PWUD with newer agents may be cost-effective, but this depends on the number of PWUD who are reached with treatment [34]. A recent systematic review showed that community-based HCV treatment, when compared to treatment received in a tertiary care centre such as a hospital, is effective with respect to treatment uptake and SVR achievement [35]. As DAA receipt is most effective in PWUDs when liver fibrosis has not progressed [36], delivering care in this population in a timely fashion following diagnosis may help decrease HCV-related complications.

Our study has multiple strengths, including a focus on randomised studies with a comparator group, interventions delivered in outpatient settings rather than closed settings such as prisons, and assessing the relationship between DOT and SVR. We also note several limitations to our study. As few studies met our inclusion criteria, we were unable to control for confounding using meta-regression techniques. Accordingly, the studies that included the smallest number of participants were assigned less weight in the meta-analysis. All studies included herein involved PEG-IFN/ribavirin, which has a more significant side-effect profile and disutility associated with injection when compared to the newer, oral agents. Future evaluations that include only oral agents delivered by DOT may find even greater increased odds of achieving SVR, and should be the focus of future research in PWUD.

DOT in conjunction with other services can help connect PWUD with treatment while meeting social and medical needs. One study randomised pharmacies in Scotland to screen for HCV among people receiving outpatient methadone therapy, then allowed pharmacists to prescribe ledipasvir/sofosbuvir to facilitate HCV treatment [32]. Another study used community health workers to observe HCV therapy among patients, varying the medications received while all subjects received DOT. Patients receiving sofosbuvir plus PEG-IFN and ribavirin achieved 100% SVR while 68% of patients receiving sofosbuvir plus ribavirin attained SVR [33]. As all study subjects received DOT simultaneously without a comparison to those not receiving DOT, this study was not included in our analysis.

While the dominant paradigm has been to deliver HCV treatment to PWUD in the setting of methadone clinics, furthering the reach of HCV treatment, such as using pharmacists and innovative health models, reaches more PWUD. Treatment among PWUD with newer agents may be cost-effective, but this depends on the number of PWUD who are reached with treatment [34]. A recent systematic review showed that community-based HCV treatment, when compared to treatment received in a tertiary care centre such as a hospital, is effective with respect to treatment uptake and SVR achievement [35]. As DAA receipt is most effective in PWUDs when liver fibrosis has not progressed [36], delivering care in this population in a timely fashion following diagnosis may help decrease HCV-related complications.

Our study has multiple strengths, including a focus on randomised studies with a comparator group, interventions delivered in outpatient settings rather than closed settings such as prisons, and assessing the relationship between DOT and SVR. We also note several limitations to our study. As few studies met our inclusion criteria, we were unable to control for confounding using meta-regression techniques. Accordingly, the studies that included the smallest number of participants were assigned less weight in the meta-analysis. All studies included herein involved PEG-IFN/ribavirin, which has a more significant side-effect profile and disutility associated with injection when compared to the newer, oral agents. Future evaluations that include only oral agents delivered by DOT may find even greater increased odds of achieving SVR, and should be the focus of future research in PWUD.

DOT in conjunction with other services can help connect PWUD with treatment while meeting social and medical needs. One study randomised pharmacies in Scotland to screen for HCV among people receiving outpatient methadone therapy, then allowed pharmacists to prescribe ledipasvir/sofosbuvir to facilitate HCV treatment [32]. Another study used community health workers to observe HCV therapy among patients, varying the medications received while all subjects received DOT. Patients receiving sofosbuvir plus PEG-IFN and ribavirin achieved 100% SVR while 68% of patients receiving sofosbuvir plus ribavirin attained SVR [33]. As all study subjects received DOT simultaneously without a comparison to those not receiving DOT, this study was not included in our analysis.

While the dominant paradigm has been to deliver HCV treatment to PWUD in the setting of methadone clinics, furthering the reach of HCV treatment, such as using pharmacists and innovative health models, reaches more PWUD. Treatment among PWUD with newer agents may be cost-effective, but this depends on the number of PWUD who are reached with treatment [34]. A recent systematic review showed that community-based HCV treatment, when compared to treatment received in a tertiary care centre such as a hospital, is effective with respect to treatment uptake and SVR achievement [35]. As DAA receipt is most effective in PWUDs when liver fibrosis has not progressed [36], delivering care in this population in a timely fashion following diagnosis may help decrease HCV-related complications.

Our study has multiple strengths, including a focus on randomised studies with a comparator group, interventions delivered in outpatient settings rather than closed settings such as prisons, and assessing the relationship between DOT and SVR. We also note several limitations to our study. As few studies met our inclusion criteria, we were unable to control for confounding using meta-regression techniques. Accordingly, the studies that included the smallest number of participants were assigned less weight in the meta-analysis. All studies included herein involved PEG-IFN/ribavirin, which has a more significant side-effect profile and disutility associated with injection when compared to the newer, oral agents. Future evaluations that include only oral agents delivered by DOT may find even greater increased odds of achieving SVR, and should be the focus of future research in PWUD.
Treating PWUD is an essential component of any plan to eradicate HCV in the future [37], especially since prevalence of HCV is rising in some areas of the world and has only seen a small decline in other parts [1]. Care models that provide HCV treatment to PWUD must be flexible and incorporate different services to meet the needs of this population [38], as noted in a recent call for further research to include evaluation of models of care to reach PWUD and enhance treatment [39]. This study augments the available literature indicating that DOT may further facilitate treatment uptake among PWUD, and provides researchers and policymakers with additional information to inform future interventions.

Acknowledgements

Previous presentation

This work was previously presented as a poster at the 2014 Society of Medical Decision Making Annual Meeting.

Research support

CMcD has received support from postdoctoral fellowship NHLBI T32 HL125195-02 and a pre-doctoral dissertation award from the PhRMA Foundation.

References

1. Hill AM, Nath S, Simmons B. The road to elimination of hepatitis C: analysis of cures versus new infections in 91 countries. J Virus Erad 2017; 3: 117–123.
2. Razavi H, Elkhoury AC, Elbasha E et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. Hepatology 2013; 57: 2164–2170.
3. Chih-Wei J, Wang X, Ayer T et al. Hepatitis C disease burden in the United States in the era of oral direct-acting antivirals. Hepatology 2016; 64: 1442–1450.
4. Grebely J, Dore GJ. Can hepatitis C virus infection be eradicated in people who inject drugs? Antiviral Res 2014; 104: 62–72.
5. Ng V, Saab S. Effects of a sustained virologic response on outcomes of patients with chronic hepatitis C. Clin Gastroenterol Hepatol 2011; 9: 923–930.
6. Metts J, Carmichael L, Kokor W, Scharffenberg R. Hepatitis C: prevalence, transmission, screening, and prevention. FP Essent 2014; 427: 11–17.
7. Rafiq SM, Banik CR, Khan S, Rashid H, Khanderkar G. Current burden of hepatitis C virus infection among injecting drug users: A mini systematic review of prevalence studies. Infect Disord Drug Targets 2014; 14: 93–100.
8. Hickman M, De Angelis D, Vickerman P, Hutchinson S, Martin NK. Hepatitis C virus treatment as prevention in people who inject drugs: testing the evidence. Curr Opin Infect Dis 2015; 28: 576–582.
9. 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: 1598–1609.
10. Smith DJ, Combellick J, Jordan AE, Hagan H. Hepatitis C virus (HCV) disease progression in people who inject drugs (PWID): a systematic review and meta-analysis. Int J Drug Policy 2015; 26: 911–921.
11. Asher AK, Portillo CJ, Cooper BA, Dawson-Rose C, Vlahov D, Page KA. Clinicians’ views of hepatitis C virus treatment candidacy with direct-acting antiviral regimens for people who inject drugs. Subst Use Misuse 2016; 51: 1218–1223.
12. Midgard H, Bjorj B, Marland A et al. Hepatitis C reinfection after sustained virological response. J Hepatology 2016; 64: 1020–1026.
13. Lima UD, Roazza I, Grebely J et al. Are interferon-free direct-acting antivirals for the treatment of HCV enough to control the epidemic among people who inject drugs? PLoS One 2015; 10: e014836.
14. 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.
15. Bayer R, Wilkinson D. Directly observed therapy for tuberculosis: history of an idea. Lancet 1995; 345: 1545–1548.
16. Woodward WC. Should directly observed therapy be considered for treatment of HIV? JAMA 1996; 276: 1956.
17. Grebely J, Genovay K, Khara M et al. Treatment uptake and outcomes among current and former injection drug users receiving directly observed therapy within a multidisciplinary group model for the treatment of hepatitis C virus infection. Int J Drug Policy 2007; 18: 437–443.
18. Weizmann M, Ackermann G. High rates of sustained virological response in hepatitis C virus–infected injection drug users receiving directly observed therapy with peginterferon alfa-2a (40KD) (PEGASYS) and once-daily ribavirin. J Subst Abuse Treat 2010; 38: 338–342.
19. Coo PA, Steen MD, Promkat K, Friedmann PD. A comparison of modified directly observed therapy to standard care for chronic hepatitis C. J Community Health 2013; 38: 679–684.
20. Sazz de la Hoya P, Portilla J, Marca A et al. Directly observed therapy for chronic hepatitis C: a randomized clinical trial in the prison setting. Gastroenterol Hepatol 2014; 37: 443–451.
21. Dimova RB, Zemerski M, Jacobson IM et al. Determinants of hepatitis C virus treatment completion and efficacy in drug users assessed by meta-analysis. Clin Infect Dis 2013; 56: 806–816.
22. Aspinall EJ, Conson 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): S50–S59.
23. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009; 151: 956–991.
24. Siemke JA, Heman MA, Reeves BC et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016; 355: i4919.
25. Berkman ND, Lohr KN, Ansari MT et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. J Clin Epidemiol 2015; 68: 1321–1324.
26. FedSimmons R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–188.
27. Nosotti L, Fagetti R, Rocchi L et al. Prevalence of HCV infection and adherence to DTT therapy in Italian and non-Italian IV drug users in Rome, Italy. Heroin Addiction and Related Clinical Problems 2014; 16: 41–44.
28. Grebely J, Robaeys G, Bruggmann P et al. Recommendations for the management of hepatitis C virus infection among people who inject drugs. Int J Drug Policy 2015; 26: 1028–1038.
29. Lindenburg CE, Lambers FA, Urbanis AT et al. Hepatitis C testing and treatment among active drug users in Amsterdam: results from the DUCH-C project. Eur J Gastroenterol Hepatoll 2011; 23: 23–31.
30. Krock AL, Stolika D, Heger B, Nygaard E. Hepatitis C treatment of opioid dependents receiving maintenance treatment: results of a Norwegian pilot study. Eur Addict Res 2007; 13: 216–221.
31. Robaeys G, Christensen S, Lucidarme D et al. Chronic hepatitis C treatment in patients with drug injection history: findings of the INTEGRATE prospective, observational study. Infect Dis Ther 2017; 6: 265–275.
32. Radley A, Tait J, Dillon JF. DOT-C. A cluster randomised feasibility trial evaluating directly observed anti-HCV therapy in a population receiving opioid substitute therapy from community pharmacy. Int J Drug Policy 2017; 47: 126–136.
33. Solomon SS, Sulowski MS, Amores P et al. Directly observed therapy of sofosbuvir/ribavirin +/- peginterferon with minimal monitoring for the treatment of chronic hepatitis C in people with a history of drug use in Chennai, India (C-DOT). J Viral Hepat 2018; 25: 37–46.
34. Bennett H, Gordon J, Jones B et al. Hepatitis C disease transmission and treatment uptake: impact on the cost-effectiveness of new direct-acting antiviral therapies. Eur J Health Econ 2017; 18: 1001.
35. Wade AJ, Veronese V, Helliard ME, Doyle JS. A systematic review of community based hepatitis C treatment. BMC Infect Dis 2016; 16: 202.
36. Couzens A, Tran VC, Doebuff-Burban S et al. Hepatitis C treatment as prevention of viral transmission and liver-related morbidity in persons who inject drugs. Hepatology 2016; 63: 1090–1101.
37. Helliard M, Doyle JS, Sacks-Davis R et al. Eradication of hepatitis C infection: the importance of targeting people who inject drugs. Hepatology 2014; 59: 366–369.
38. Bruggmann P, Litwin AH. Models of care for the management of hepatitis C virus among people who inject drugs: one size does not fit all. Clin Infect Dis 2013; 57(Suppl 2): S56–S61.
39. Grebely J, Bruneau J, Lazarus JV et al. Research priorities to achieve universal access to hepatitis C prevention, management and direct-acting antiviral treatment among people who inject drugs. Int J Drug Policy 2017; 47: 51–60.
40. Bonkovsky HL, Tice AD, Yapp RG et al. Efficacy and safety of peginterferon alfa-2a/ribavirin in methadone maintenance patients: randomized comparison of direct observed therapy and self-administration. Am J Gastroenterol 2008; 103: 2757–2765.
41. Bruce RD, Eiserman J, Azota A et al. Developing a modified directly observed therapy intervention for hepatitis C treatment in a methadone maintenance program: implications for program replication. Am J Drug Alcohol Abuse 2012; 38: 206–212.
42. Hilden RJ, Macphail G, Grebely J et al. Directly observed pegylated interferon plus self-administered ribavirin for the treatment of hepatitis C virus infection in people actively using drugs: a randomized controlled trial. Clin Infect Dis 2013; 57(Suppl 2): S90–S96.
43. Litwin AH, Li X, Moonesingh H et al. Strategies to enhance HCV assessment and adherence to therapy among people who use drugs. Suchtdiagnostik in Forschung und Praxis 2013; 15: 4 (220).