Patient-centred models of hepatitis C treatment for people who inject drugs: a multicentre, pragmatic randomised trial

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Summary

Background To achieve WHO targets for the elimination of hepatitis C virus (HCV) as a public threat, an increased uptake of HCV treatment among people who inject drugs (PWID) is urgently needed. Optimal HCV co-located treatment models for PWID have not yet been identified. We aimed to compare two patient-centred models of HCV care in PWID with active drug use.

Methods We did a pragmatic randomised controlled trial at eight US cities in eight opioid treatment programmes and 15 community health centres. PWID actively injecting within 90 days of study entry were randomly assigned (1:1) to either patient navigation or modified directly observed therapy (mDOT) using computer-generated variable block sizes of 2–6 stratified by city, clinical settings, and cirrhosis status. The randomisation code was concealed, in a centralised REDCap database platform, from all investigators and research staff except for an authorised data manager at the data coordinating centre. All participants received a fixed-dose combination tablet (sofosbuvir 400 mg plus velpatasvir 100 mg) orally once daily for 12 weeks. The primary outcome was sustained virological response (SVR; determined by chart review between 70 days and 365 days after end of treatment and if unavailable, by study blood draws), and secondary outcomes were treatment initiation, adherence (measured by electronic blister packs), and treatment completion. Analyses were conducted within the modified intention-to-treat (mITT; all who initiated treatment), intention-to-treat (all who were randomised), and per-protocol populations. This trial is registered with ClinicalTrials.gov, NCT02824640.

Findings Between Sept 15, 2016, and Aug 14, 2018, 1891 individuals were screened and 1136 were excluded (213 declined to participate and 923 did not meet the eligibility criteria). We randomly assigned 755 participants to patient navigation (n=379) or mDOT (n=376). In the mITT sample of participants who were randomised and initiated treatment (n=623), 226 (74% [95% CI 69–79]) of 306 participants in the mDOT group and 236 (76% [69–79]) of 317 in the patient navigation group had an SVR, with no significant difference between the groups (adjusted odds ratio [AOR] 0·97 [95% CI 0·66–1·42]; p=0·35). In the ITT sample (n=755), 226 (60% [95% CI 55–65]) of 376 participants in the mDOT group and 236 (62% [57–67]) of 379 in the patient navigation group had an SVR (AOR 0·92 [0·68–1·25]; p=0·61) and in the per-protocol sample (n=501), 226 (91% [87–94]) of 248 participants in the mDOT group and 235 (93% [89–96]) of 253 in the patient navigation group had an SVR (AOR 0·79 [0·41–1·55]; p=0·44). 306 (81%) of 376 participants in the mDOT group and 317 (84%) of 379 participants in the patient navigation group initiated treatment (AOR 0·86 [0·58–1·26]; p=0·44) and, among those, 251 (82%) participants in the mDOT group and 264 (83%) participants in the patient navigation group completed treatment (AOR 0·90 [0·58–1·39]; p=0·63). Mean daily adherence was higher in the mDOT group (78% [95% CI 75–81]) versus the patient navigation group (73% [70–77]), with a difference of 4·7% ([1·9–7·4]; p=0·0010). 421 serious adverse events were reported (217 in the mDOT group and 204 in the patient navigation group), with the most common being hospital admission (176 in the mDOT group *vs* 161 in the patient navigation group).

Interpretation In this trial of active PWID, both models resulted in high SVR. Although adherence was significantly higher in the mDOT group versus the patient navigation group, there was no significant difference in SVR between the groups. Increases in adherence and treatment completion were associated with an increased likelihood of SVR. These results suggest that active PWID can reach high SVRs in diverse settings with either mDOT or patient navigation support.

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Introduction

Globally, 58 million individuals have chronic hepatitis C virus (HCV) infection,[1] including 3 million people in the USA, where HCV is a leading infectious cause of death.[2] People who inject drugs (PWID) are disproportionally affected by HCV,[3] especially in the USA, where incidence

Research in context

Evidence before this study

Clinical trials have reported high hepatitis C virus (HCV) cure rates among people who inject drugs (PWID), although most of these trials have excluded people with ongoing drug use, who are at highest risk for transmission. Co-located care models at opioid treatment programmes (OTPs) and community health centres (CHCs) are effective approaches to HCV treatment. In this study, we evaluated two patient-centered models of HCV care—modified directly observed therapy (mDOT) and patient navigation—provided at OTPs and CHCs to PWID.

Added value of this study

In this pragmatic, randomised controlled trial of 755 PWID actively injecting within 90 days of study entry, sustained virological response (SVR) was not significantly different between the mDOT group and the patient navigation group. Although treatment adherence was 5% higher in the mDOT group compared with the patient navigation group, this did not translate into a clinically significant difference in SVR. Treatment initiation and completion were high (>80%) in both treatment groups. Despite suboptimal adherence of 74%, SVR was achieved by a high proportion of participants (92%) in the per-protocol analysis. Increases in adherence and treatment duration were associated with an increased likelihood of SVR. Our HERO study has unique strengths: a strict definition of recent injection drug use; participants from eight diverse cities throughout the USA; community treatment settings were used, specifically OTPs and CHCs; and both national and local stakeholders were involved in study implementation.

Implications of all the available evidence

Our results show that active PWID can reach high SVR in diverse settings with either mDOT or patient navigation support. The HERO study suggests the need to remove restrictive HCV treatment access policies for PWID with recent or ongoing injection drug use. The unrestricted and broad adoption of these models will accelerate progress toward HCV elimination in the USA and globally.

tripled between 2009 and 2018 due to the opioid crisis.[4] Worldwide, guidelines recommend prioritising PWID for HCV treatment given the potential to substantially reduce transmission and prevalence.[5] HCV can now be cured in more than 95% of people using direct-acting antivirals (DAAs). Multiple countries are aiming to eliminate HCV as a public health threat by 2030 with broader access to treatment.[6] Enhanced access for PWID is essential to reach the WHO elimination target; however, barriers to access remain. Access to DAAs for active PWID is often restricted because of concerns about adherence and reinfection,[7] despite AASLD–IDSA HCV guidelines stipulating that all people with HCV should be treated with DAAs, except for those with short life expectancies and in pregnancy. Therefore, only a minority of PWID in the USA and globally have been treated for HCV,[8,9] and only 3% have been cured, threatening the prospect of HCV elimination.[10]

Clinical trials have shown high rates of sustained virological response (SVR)—ie, cure of HCV infection—among PWID, although most trials have excluded people with active drug use, who are at highest risk for transmission.[9,11] Studies of PWID are limited by small sample sizes, single sites, and heterogeneous definitions of drug use. To our knowledge, few randomised clinical trials done in active PWID have defined injection drug use as recently as within 90 days. Although most HCV treatment occurs within specialty settings, co-located care models at opioid treatment programmes (OTPs) and community health centres (CHCs) are effective in promoting treatment initiation, adherence, completion, and SVR.[12,13] However, PWID might require additional support to promote optimal treatment initiation, adherence, and cure. The Patient-Centered Outcomes Research Institute (PCORI) funds comparative effectiveness trials of models of care that are evidence-based or already used in clinical practice.[14] Two intensive interventions used at OTPs and CHCs include modified directly observed therapy (mDOT) and patient navigation;[15,16] however, the effectiveness of these models has not been directly compared in active PWID.

This Hepatitis C Real Option (HERO) study, a large, multicentre, pragmatic, randomised controlled trial, evaluated two patient-centred models of HCV care (mDOT and patient navigation) provided at OTPs and CHCs to people with injection drug use within 90 days before study enrolment.[17] The goal of HERO was to test the effectiveness of both interventions in reaching SVR (primary outcome), and to assess treatment initiation, completion, and adherence (secondary outcomes). We hypothesised that patient navigation would be associated with greater treatment initiation but that mDOT would be associated with higher SVR, adherence, and treatment completion.

Methods

Study design and participants

The HERO study was conducted at eight OTPs and 15 CHCs in eight US cities: New York City (NY), Providence (RI), Albuquerque (NM), San Francisco (CA), Boston (MA), Baltimore, Seattle (WA), and Morgantown (WV).[18]

Of the 15 CHC sites, 11 offered buprenorphine on site. Of eight sites that provided methadone, seven offered buprenorphine on site and six offered buprenorphine by directly observed therapy.

Potential participants were identified through chart reviews of existing patients at the clinics, community-based

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For more on the **AASLD–IDSA HCV guidelines** see https://www.hcvguidelines.org/evaluate/testing-and-linkage

outreach (discussing the HERO study at community-based organisations), and medical provider referrals. Participants were screened to see if they met basic eligibility criteria and were asked if they were currently seeing a health-care provider. If the individuals had a health-care provider, a release of information to view clinical records was obtained, data to assess eligibility were extracted, and study eligibility was documented on the electronic case report forms. If the individuals did not have a health-care provider, they were referred to one at the CHC or OTP (if also interested in opioid agonist treatment) before obtaining a release of information for clinical records. After chart review to assess study eligibility, a research staff member met with the potential participant to confirm eligibility; discuss study procedures, including randomisation to the mDOT or patient navigation interventions; clarify risks and benefits of participation; and obtain written informed consent. Eligible participants were enrolled within 1 month of screening. If enrolment did not occur within 1 month, eligibility was reassessed.

Each of the eight research sites formed a Local Stakeholder Advisory Board, which consisted of a site principal investigator, a site project director, patients, local advocacy organisations, and local representatives from OTPs and CHCs. During the course of the study, the Local Stakeholder Advisory Board met on a quarterly basis to discuss study implementation, recruitment, retention, intervention delivery, dissemination, and sustainability. A National Stakeholder Advisory Board was also created, consisting of a principal investigator, the site principal investigators, a local representative of each site, and representatives from governmental organisations (eg, professional policy, educational, advocacy, and patient organisations) and industry. The National Stakeholder Advisory Board met on a quarterly basis to review study progress, outcomes, and dissemination, as well as plan national and global implementation efforts.

Eligibility criteria were the following: age 18–70 years; current HCV infection (viraemia) and an HCV viral load test from any time within the past 12 months; aspartate aminotransferase, alanine aminotransferase, and platelets measured at 12 months or less before study enrolment; self-reported active substance injection within 90 days of screening; no previous DAA treatment; willingness to receive sofosbuvir–velpatasvir; willingness to be randomly assigned to patient navigation or mDOT; if receiving methadone maintenance, willingness to attend the OTP at least five times per week; able to provide written informed consent; and English or Spanish fluency. Participants were ineligible if they were pregnant, breastfeeding, or diagnosed with hepatocellular carcinoma.

The study was approved by the institutional review board of each institution (Prisma Health, Johns Hopkins, Harvard Medical School, Albert Einstein College of Medicine, University of California San Francisco, University of New Mexico Health Sciences Center, University of Rhode Island, University of Washington, and West Virginia University). All participants provided written informed consent. All clinical investigations were done according to the principles of the Declaration of Helsinki.

Randomisation and masking

Participants were randomly assigned 1:1 to receive patient navigation or mDOT using computer-generated stratified variable block sizes of 2–6. Randomisation was stratified by three factors: city, OTP versus CHC, and stage of liver disease (cirrhosis or Fibrosis-4 score of more than 3·25 *vs* no cirrhosis), which was ascertained by medical chart review. The stratified randomisation allocations were created and kept confidential by the HERO study data coordinating centre at the University of New Mexico. When an eligible participant was available at a site, the site retrieved their site-specific allocations through the REDCap data management platform. The allocation sequence was concealed for investigators and study personnel except for the REDCap programmer and statistician from the study data coordinating centre. Storage and distribution of random allocation codes were done in a centralised manner. The statistician from the statistical and data coordinating centre generated the codes for all sites and types of clinics, and these codes were embedded into the REDCap data management system so that the identification of a treatment assignment was ready and immediate, without needing to contact the coordinating centre when treatment assignment was requested through the REDCap electronic request form by research staff at sites.

We ensured the sample sizes of participants who initiated the HCV treatment between the patient navigation and mDOT groups were balanced. Additional details of the study design have been published previously.[17]

Procedures

Participants were required to be evaluated and initiate treatment within 12 weeks of enrolment. All participants received the oral fixed-dose combination tablet of sofosbuvir (400 mg) with velpatasvir (100 mg) once daily for 12 weeks. All medications were contributed by Gilead Sciences and packaged in electronic blister packs (Information Mediary Corporation, Ottawa, ON, Canada) with an integrated sensor that recorded the time and date when each dose was removed.

Participants completed surveys of sociodemographic factors, drug and alcohol use (modified version of the Addiction Severity Index, which included only sections on drug and alcohol use questionnaire items), injecting behaviours (Behavioral Risk Assessment questionnaire), substance use treatment, depression (Patient Health Questionnaire-9), anxiety (General Anxiety Disorder-7),

quality of life (EQ-5D), and stigma and shame (shame and HCV-related stigma scale; appendix 1) at the baseline visit. Research visits occurred at weeks 4, 8, and 12, and every 12 weeks after up to week 168 (the detailed schedule along with assessments made at each visit are shown in appendix 2).

Participants answered surveys administered by research assistants who either recorded the responses directly into the REDCap database or onto a paper form, and the information was then entered into the REDCap database after the research visit was finished. HCV RNA was tested by Quest Diagnostics using COBAS TaqMan real-time RT-PCR assay (Roche Diagnostics; Basel, Switzerland) at baseline, week 24, and every 12 weeks through to week 168, for a total of 12 visits after week 24. Biospecimens of plasma from the 12 visits after week 24 will be analysed for evidence of reinfection and viral resistance, and these results will be presented in future manuscripts. Urine specimens were tested with multi-drug screen dip cards (ABMC; Kinderhook, NY, USA) for amphetamine, methamphetamine, benzodiazepine, cocaine, delta-9-tetrahydrocannabinol or cannabis, opiate, and oxycodone at baseline and during follow-up visits (appendix 2). Participants were compensated US$20 for each of 17 research visits and an additional $5 for returning each of the 12 blister packs. Participants were compensated up to $400 for completing all research visits and returning all blister packs.

mDOT was delivered at both OTP and CHC settings and considered a modified version of DOT because not all doses were directly observed. For participants at OTPs, observation of DAA treatment occurred at daily visits at the time that methadone or buprenorphine was administered. These participants received observed treatment for 5 days or more per week and take-home doses for self-administration on the other days. Participants who were taking buprenorphine in the OTPs followed the same pick-up schedules as those who were taking methadone. Participants at CHCs received a 1-week blister pack supply of medication and used a smartphone application (emocha Mobile Health from emocha Health; Baltimore, MD, USA) to video-record medication consumption. The emocha application was selected on the basis of stakeholder experience with the application in a tuberculosis treatment setting. Daily videos were securely uploaded for review by research staff.

The patient navigation model (ie, the Check Hep C programme) was developed by the New York City Department of Health and Mental Hygiene (Long Island City, NY, USA). Patient navigators were trained by the New York City Department of Health and Mental Hygiene and followed a protocol.[16] Consistent with a pragmatic trial, the patient navigators were a heterogeneous group in terms of previous relationships with the clinic, formal education, and community health worker status; only a few patient navigators had history of injecting drugs or were living with HCV. Patient navigators had four roles: coordinate HCV treatment, offer health education and promotion, assist participants to overcome personal and structural barriers, and provide psychosocial and adherence support.

See Online for appendix 1

The goal of the Check Hep C programme was for patient navigators to link HCV-infected individuals to medical care and support, complete HCV medical evaluation, reach SVR, and maintain liver health after treatment. Patient navigators attended three required trainings: Hepatitis C Basics Training; Check Hep C Program Start Up Training; and Motivational Interviewing and Health Care Access for Drug Users. Additionally, patient navigators attended monthly patient navigator programme management and technical assistance meetings. Patient navigation assessment was conducted within 2 weeks of enrolment in the Check Hep C programme and the purpose of the assessment was to learn about the patient and their readiness to engage in HCV medical care and treatment, and identify and develop plans to overcome barriers. The patient navigator indicated whether the patient required low intensity (eg, minimum of four patient navigator encounters and could attend visits independently) or high intensity services (eg, more than four patient navigator encounters and multiple reminders and accompaniment). The patient navigator provided each patient with a minimum of four encounters, which consisted of enrolment, assessment and referrals in the 12 weeks before treatment initiation (eg, harm reduction and substance use treatment services), treatment readiness, treatment adherence check-in in the 12 weeks after treatment initiation (ie, 3 days after the start of treatment and weekly as needed), and check-in in the 12 weeks after treatment completion. Encounters occurred more frequently if needed and occurred in-person or by telephone call or text message. The patient navigator used the existing Health Promotion Guides to educate, assess, counsel, and develop goals and plans with the patients. Module I (Hep C Basics) was completed on enrolment, Module II (Getting Ready for Hep C Care) during the patient navigator assessment phase, Module III (Getting Ready for Treatment) right before starting treatment, and Module IV (After Treatment) immediately after treatment. Participants in the patient navigator group received 2 weeks of blister packed medication at a time. The Check Hep C–Patient Navigation Program Protocol is shown in appendix 3.

See Online for appendix 2

See Online for appendix 3

Outcomes

The primary endpoint was SVR, defined as HCV RNA below the limit of quantitation (≤15 IU/mL) for 12 weeks or longer after treatment completion. The time window for determination of SVR was 70–365 days after the end of treatment. SVR was determined on the basis of HCV viraemia collected from clinical chart review or, if unavailable, by study blood draws. Cases with undetermined SVR were considered unsuccessful.

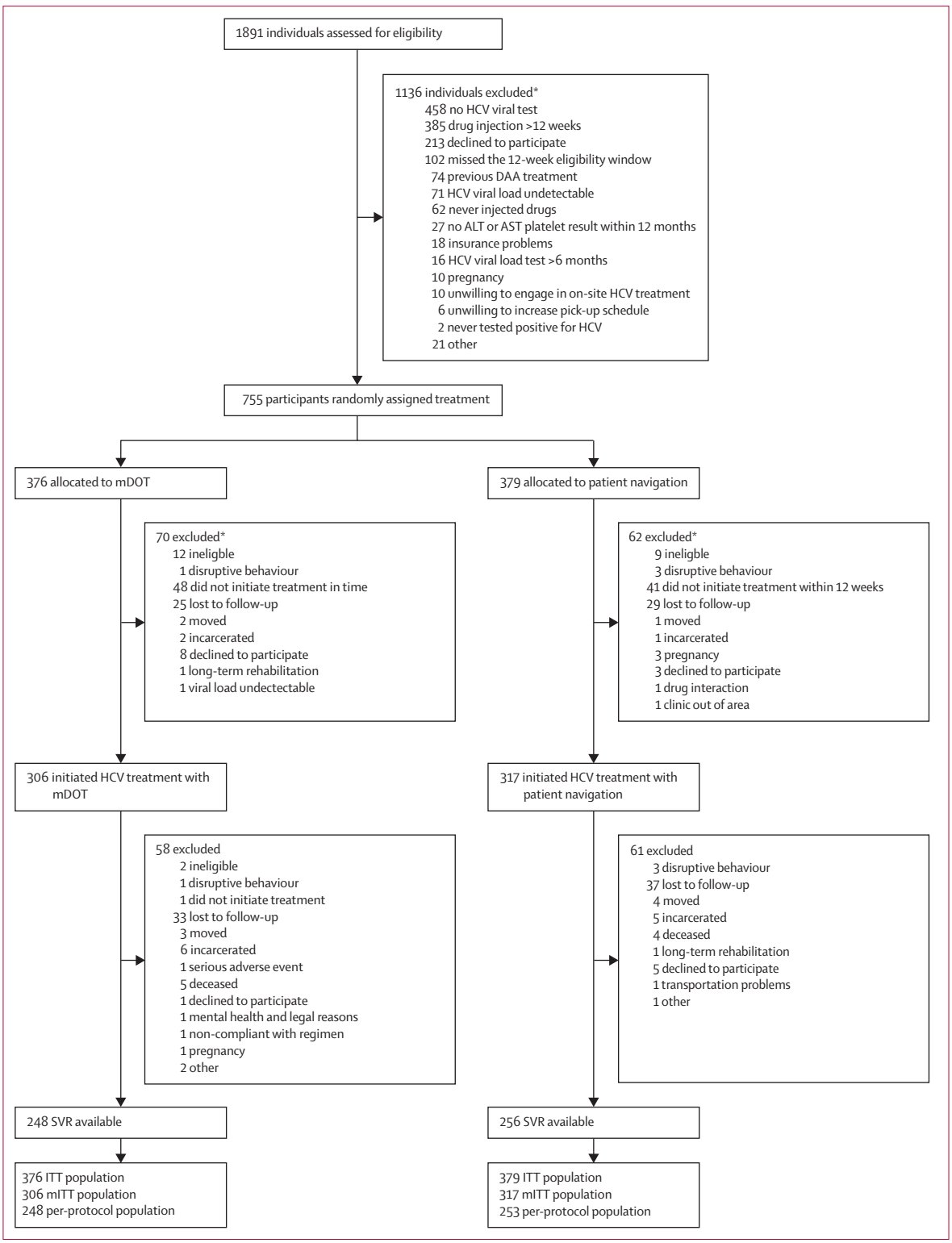


Figure 1: **Trial profile**

ALT=alanine aminotransferase. AST=aspartate aminotransferase. DAA=direct-acting antivirals. HCV=hepatitis C virus. ITT=intention-to-treat. mDOT=modified directly observed therapy. mITT=modified intention-to-treat. SVR=sustained virological response. *For some participants, more than one reason for exclusion from the study was provided.

Secondary outcomes were treatment initiation, treatment adherence, treatment completion, reinfection, and drug resistance. Data on the reinfection and drug resistance outcomes were not been available at the time of the present analysis. However, we will address these outcomes in subsequent manuscripts. Treatment

	ITT sample*			mITT sample*			p value†
	Total (n=755)	mDOT (n=376)	Patient navigation (n=379)	Total (n=623)	mDOT (n=306)	Patient navigation (n=317)	
Demographic characteristics							
Gender							
Total	n=754	n=376	n=378	n=623	n=306	n=317	
Female	218 (29%)	109 (29%)	109 (29%)	172 (28%)	81 (27%)	91 (29%)	0·871
Male	528 (70%)	262 (70%)	266 (70%)	445 (71%)	222 (73%)	223 (70%)	..
Transgender or gender non-conforming	8 (1%)	5 (1%)	3 (1%)	6 (1%)	3 (1%)	3 (1%)	..
Age, years							
Mean (SD)	43·2 (11·5)	43·5 (11·5)	42·9 (11·6)	43·4 (11·4)	43·6 (11·5)	43·1 (11·4)	0·552
Median (IQR)	41·8 (34·0–52·3)	42·3 (34·4–53·0)	41·6 (33·7–51·0)	42·0 (34·2–52·5)	42·3 (34·4–53·7)	41·5 (34·1–51·0)	..
Race							
Total	n=730	n=362	n=368	n=601	n=293	n=308	
White or Caucasian	476 (65%)	226 (62%)	250 (68%)	397 (66%)	188 (64%)	209 (68%)	0·0022
Black or African American	103 (14%)	66 (18%)	37 (10%)	82 (14%)	54 (18%)	28 (9%)	..
Other	151 (20%)	70 (19%)	81 (22%)	122 (20%)	51 (17%)	71 (23%)	..
Latino or Hispanic ethnicity							
Total	n=755	n=376	n=379	n=623	n=306	n=317	
Yes	163 (22%)	79 (21%)	84 (22%)	136 (22%)	62 (20%)	74 (23%)	0·353
No	592 (78%)	297 (79%)	295 (78%)	487 (78%)	244 (80%)	243 (77%)	..
Marital or cohabitation status							
Total	n=738	n=369	n=369	n=622	n=305	n=317	
Single, separated, divorced, or widowed	640 (87%)	321 (87%)	319 (86%)	543 (87%)	268 (88%)	275 (87%)	0·625
Married or living together	90 (12%)	46 (13%)	44 (12%)	72 (12%)	35 (12%)	37 (12%)	..
Other	8 (1%)	2 (1%)	6 (12%)	7 (1%)	2 (1%)	5 (2%)	..
Education							
Total	n=738	n=369	n=369	n=622	n=305	n=317	
Less than high school	171 (23%)	92 (25%)	79 (21%)	143 (23%)	75 (25%)	68 (22%)	0·591
High school diploma or Graduate Equivalency Degree	295 (40%)	148 (40%)	147 (40%)	245 (39%)	120 (39%)	125 (39%)	..
College or higher	272 (37%)	129 (35%)	143 (39%)	234 (38%)	110 (36%)	124 (39%)	..
Living situation‡							
Total	n=738	n=369	n=369	n=622	n=305	n=317	
Shelter	58 (8%)	30 (8%)	28 (8%)	47 (8%)	24 (8%)	23 (7%)	0·916
Street or outdoors	58 (8%)	27 (7%)	31 (8%)	42 (7%)	23 (8%)	19 (6%)	..
Someone else's apartment, room, or house	193 (26%)	93 (25%)	100 (27%)	159 (26%)	75 (25%)	84 (27%)	..
Institution	55 (8%)	24 (7%)	31 (8%)	48 (8%)	21 (7%)	27 (9%)	..
Own or rented apartment, room, or house	339 (46%)	177 (48%)	162 (44%)	299 (48%)	149 (49%)	150 (47%)	..
Other	35 (5%)	18 (5%)	17 (5%)	27 (4%)	13 (4%)	14 (4%)	..
Availability of transportation							
Total	n=738	n=370	n=368	n=621	n=305	n=316	
Yes	302 (41%)	149 (40%)	153 (42%)	261 (42%)	126 (41%)	135 (43%)	0·966
Maybe, if I can get a ride	50 (7%)	28 (8%)	22 (6%)	40 (6%)	21 (7%)	19 (6%)	..
Maybe, if public transportation is available	375 (51%)	187 (51%)	188 (51%)	312 (50%)	154 (51%)	158 (50%)	..
No	11 (2%)	6 (2%)	5 (1%)	8 (1%)	4 (1%)	4 (1%)	..
Employed with a regular job or informal work§							
Total	n=737	n=368	n=369	n=621	n=304	n=317	
Yes	257 (35%)	135 (37%)	122 (33%)	220 (35%)	115 (38%)	105 (33%)	0·220
No	480 (65%)	233 (63%)	247 (67%)	401 (65%)	189 (62%)	212 (67%)	..

(Table 1 continues on next page)

	ITT sample*			mITT sample*			p value†
	Total (n=755)	mDOT (n=376)	Patient navigation (n=379)	Total (n=623)	mDOT (n=306)	Patient navigation (n=317)	
(Continued from previous page)							
Clinical characteristics							
Clinical setting							
Total	n=755	n=376	n=379	n=623	n=306	n=317	
OTP	312 (41%)	153 (41%)	159 (42%)	273 (44%)	132 (43%)	141 (45%)	0·736
CHC	443 (59%)	223 (59%)	220 (58%)	350 (56%)	174 (57%)	176 (56%)	..
Any medication for opioid use disorder in the past 3 months							
Buprenorphine							
Total	n=715	n=358	n=357	n=620	n=305	n=315	
Yes	119 (17%)	67 (19%)	52 (15%)	96 (16%)	52 (17%)	44 (14%)	0·289
No	596 (83%)	291 (81%)	305 (85%)	524 (85%)	253 (83%)	271 (86%)	..
Methadone							
Total	n=715	n=358	n=357	n=620	n=305	n=315	
Yes	399 (56%)	194 (54%)	205 (57%)	358 (58%)	169 (55%)	189 (60%)	0·247
No	316 (44%)	164 (46%)	152 (43%)	262 (42%)	136 (45%)	126 (40%)	..
Depression PHQ-9 severity							
Total	n=715	n=358	n=357	n=620	n=305	n=315	
Mild (<10)	358 (50%)	176 (49%)	182 (51%)	319 (52%)	154 (51%)	165 (52%)	0·824
Moderate (10–14)	186 (26%)	94 (26%)	92 (26%)	159 (26%)	78 (26%)	81 (26%)	..
Moderately severe or severe (>14)	171 (24%)	88 (25%)	83 (23%)	142 (23%)	73 (24%)	69 (22%)	..
Anxiety GAD-7 severity							
Total	n=713	n=357	n=356	n=618	n=304	n=314	
Mild (<10)	434 (61%)	211 (59%)	223 (63%)	381 (62%)	179 (59%)	202 (64%)	0·379
Moderate (10–14)	144 (20%)	76 (21%)	68 (19%)	123 (20%)	65 (21%)	58 (19%)	..
Moderately severe or severe (>14)	135 (19%)	70 (20%)	65 (18%)	114 (18%)	60 (20%)	54 (17%)	..
HCV genotype							
Total	n=713	n=250	n=264	n=456	n=220	n=236	
Type 1	368 (72%)	185 (74%)	183 (69%)	327 (72%)	164 (75%)	163 (69%)	0·596
Type 2	45 (9%)	22 (9%)	23 (9%)	41 (9%)	19 (9%)	22 (9%)	..
Type 3	94 (18%)	39 (16%)	55 (21%)	81 (18%)	33 (15%)	48 (20%)	..
Type 4	4 (1%)	2 (1%)	2 (1%)	4 (1 %)	2 (1%)	2 (1%)	..
Mixed	3 (1%)	2 (1%)	1 (<1%)	3 (1%)	2 (1%)	1 (<1%)	..
HIV infection (positive)							
Total	n=523	n=256	n=267	n=442	n=212	n=230	
Yes	102 (20%)	52 (20%)	50 (19%)	85 (19%)	42 (20%)	43 (19%)	0·810
No	421 (81%)	204 (80%)	217 (81%)	357 (81%)	170 (80%)	187 (81%)	..
Cirrhosis (positive)							
Total	n=755	n=376	n=379	n=623	n=306	n=317	
Yes	51 (7%)	25 (7%)	26 (7%)	39 (6%)	18 (6%)	21 (7%)	0·702
No	704 (93%)	351 (93%)	353 (93%)	584 (94%)	288 (94%)	296 (93%)	..
Alcohol misuse¶							
Total	n=706	n=353	n=353	n=613	n=302	n=311	
Yes	229 (32%)	112 (32%)	117 (33%)	190 (31%)	90 (30%)	100 (32%)	0·529
No	477 (68%)	241 (68%)	236 (67%)	423 (69%)	212 (70%)	211 (68%)	..
Injection characteristics							
Last drug injection (within 3 months of screening)							
Total	n=754	n=376	n=378	n=623	n=306	n=317	
0–4 weeks	572 (76%)	281 (75%)	291 (77%)	471 (76%)	229 (75%)	242 (76%)	0·746
5–8 weeks	115 (15%)	61 (16%)	54 (14%)	99 (16%)	52 (17%)	47 (15%)	..
9–12 weeks	67 (9%)	34 (9%)	33 (9%)	53 (9%)	25 (8%)	28 (9%)	..

(Table 1 continues on next page)

	ITT sample*			mITT sample*			p value†
	Total (n=755)	mDOT (n=376)	Patient navigation (n=379)	Total (n=623)	mDOT (n=306)	Patient navigation (n=317)	
(Continued from previous page)							
Drug injection reported within 3 months of baseline‖							
Total	n=716	n=358	n=358	n=621	n=305	n=316	
Yes	683 (95%)	340 (95%)	343 (96%)	592 (95%)	291 (95%)	301 (95%)	0·926
No	33 (5%)	18 (5%)	15 (4%)	29 (5%)	14 (5%)	15 (5%)	..
Number of days injected drugs in the past 3 months**							
Mean (SD)	34·5 (31·9)	34·1 (31·4)	35·0 (32·4)	33·3 (31·1)	32·7 (30·1)	33·8 (32·0)	0·963
Median (IQR)	25·0 (5·0–60·0)	25·0 (6·0–60·0)	27·5 (5·0–60·0)	25·0 (5·0–60·0)	25·0 (6·0–60·0)	22·5 (5·0–60·0)	..
Times injecting drugs a day**††							
Mean (SD)	3·1 (3·0)	2·9 (2·5)	3·3 (3·4)	3·0 (2·9)	2·9 (2·4)	3·2 (3·4)	0·311
Median (IQR)	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–4·0)	2·0 (1·0–3·0)	2·0 (1·0–3·0)	2·0 (1·0–4·0)	..
Total	n=680	n=340	n=340	n=590	n=291	n=299	
≤2 times per day	355 (52%)	182 (54%)	173 (51%)	316 (54%)	162 (56%)	154 (52%)	..
>2 times per day	325 (48%)	158 (47%)	167 (49%)	274 (46%)	129 (44%)	145 (49%)	..
Urine drug screen results at baseline visit‡‡							
Any drug§§							
Total	n=682	n=338	n=344	n=596	n=292	n=304	
Yes	655 (96%)	326 (96%)	329 (96%)	571 (96%)	281 (96%)	290 (95%)	0·610
No	27 (4%)	12 (4%)	15 (4%)	25 (4%)	11 (4%)	14 (5%)	..
Amphetamine							
Total	n=682	n=338	n=344	n=596	n=292	n=304	
Yes	193 (28%)	97 (29%)	96 (28%)	163 (27%)	84 (29%)	79 (26%)	0·447
No	489 (72%)	241 (71%)	248 (72%)	433 (73%)	208 (71%)	225 (74%)	..
Methamphetamine							
Total	n=230	n=338	n=344	n=596	n=292	n=304	
Yes	218 (32%)	106 (31%)	112 (33%)	186 (31%)	91 (31%)	95 (31·3%)	0·982
No	464 (68%)	232 (69%)	232 (67%)	410 (69%)	201 (69%)	209 (69%)	..
Benzodiazepine							
Total	n=682	n=338	n=344	n=596	n=292	n=304	
Yes	358 (53%)	175 (52%)	183 (53%)	318 (53%)	155 (53%)	163 (54%)	0·896
No	324 (48%)	163 (48%)	161 (47%)	278 (47%)	137 (47%)	141 (46%)	..
Cocaine							
Total	n=681	n=338	n=343	n=595	n=292	n=303	
Yes	287 (42%)	148 (44%)	139 (41%)	251 (42%)	128 (44%)	123 (41%)	0·424
No	394 (58%)	190 (56%)	204 (60%)	344 (58%)	164 (56%)	180 (59%)	..
Delta-9-tetrahydrocannabinol or cannabis							
Total	n=682	n=338	n=344	n=596	n=292	n=304	
Yes	337 (49%)	168 (50%)	169 (49%)	294 (49%)	144 (49%)	150 (49%)	0·995
No	345 (51%)	170 (50%)	175 (51%)	302 (51%)	148 (51%)	154 (51%)	..

(Table 1 continues on next page)

initiation was declared when participants took one or more doses after being randomly assigned to treatment. Electronic blister pack data were used to estimate daily adherence, calculated as a binary measure that indicated whether one or more doses was taken per day. Weekly adherence was then computed in terms of percentages (ie, the number of adherent days out of 7 days for each participant). Treatment completion was declared if there were 84 days or more between treatment initiation and completion. All subgroup analyses were prespecified in the HERO statistical analysis plan.

Statistical analysis

We planned to recruit 300 participants in each group. Assuming an 80% SVR rate in the patient navigation group, a minimum difference of 9% between groups could be detected (ie, 89% *vs* 80%, odds ratio [OR] 2·1), with more than 80% power at a two-sided significance level of 0·05 in a multivariable logistic regression model

	ITT sample*			mITT sample*			p value†
	Total (n=755)	mDOT (n=376)	Patient navigation (n=379)	Total (n=623)	mDOT (n=306)	Patient navigation (n=317)	
(Continued from previous page)							
Opiate							
Total	n=682	n=338	n=344	n=596	n=292	n=304	
Yes	350 (51%)	180 (53%)	170 (49%)	302 (51%)	157 (54%)	145 (48%)	0·138
No	332 (49%)	158 (47%)	174 (51%)	294 (49%)	135 (46%)	159 (52%)	..
Oxycodone							
Total	n=682	n=338	n=344	n=596	n=292	n=304	
Yes	182 (27%)	94 (28%)	88 (26%)	157 (26%)	81 (28%)	76 (25%)	0·448
No	500 (73%)	244 (72%)	256 (74%)	439 (74%)	211 (72%)	228 (75%)	..

CHC=community health centre. GAD-7=General Anxiety Disorder-7 scale. ITT=intention-to-treat. mITT=modified intention-to-treat. mDOT=modified directly observed therapy. OTP=opioid treatment programme. PHQ-9=Patient Health Questionnaire-9. *Extent of missing observations varies across the characteristics. Underlying reasons for missing information were mostly unknown. †p values are based on the χ^2 test, Fisher's exact test, the Student's *t*-test, or the Wilcoxon test, comparing mDOT and patient navigation groups among the mITT sample. ‡Participants were asked: "In the last 3 months, where have you been living most of the time?" Answers included: shelter; street or outdoors; someone else's apartment, room, or house; institution (institution, halfway house, residential treatment facility or programme); own or rented apartment, house, or room; other (dormitory or college residence, other, refused, don't know). §Participants were asked: "In the last 3 months, what were your sources of income?" Employed was defined as including (a) a regular job and (b) informal work. ¶Based on the Alcohol Use Disorders Identification Test score: yes (alcohol misuse *vs* no). Cutoffs are different for male and female participants. ||Percentages were calculated on the basis of the Behavioral Risk Assessment administered at baseline visit. **Participants were asked: "In the past 3 months, on how many days did you inject anything, including prescribed medications not intended to be injected?" ††Participants were asked: "How many times a day did you usually inject on the days you injected?" ‡‡Percentages were calculated on the basis of the conducted urine drug screen at baseline visit. §§Positive for any drug toxicology (including cannabis, barbituates, buprenorphine, and methadone).

Table 1: **Baseline characteristics of HERO participants among ITT and mITT samples**

in which adjusting variables explain 10% of variation in the predictor variable.

Statistical analyses were conducted using three analytic samples: the primary modified intention-to-treat (mITT) sample, which included participants who were randomly assigned and initiated treatment; the intention-to-treat (ITT) sample, which included all participants who were randomised; and the per-protocol sample, which included participants who were randomly assigned, initiated treatment, complied with the assigned model of care without crossover, and had a determined SVR status. Analyses of SVR and completion were conducted using the mITT, ITT, and per-protocol populations, analyses of initiation were based on the ITT population, and adherence was assessed in the mITT and per-protocol samples.

Comparisons of baseline characteristics between participants in the mDOT and patient navigation groups were made using the χ^2 test, Fisher's exact test, the Student's *t*-test, or the Wilcoxon test. Comparisons of cascade of HCV treatment care outcomes between participants in the mDOT and patient navigation groups were made using χ^2 tests. We computed exact 95% CIs for estimated proportions. In models testing a main effect of the two groups on the study outcomes, we included randomisation stratification variables as covariates for analysis of the ITT: site, setting (OTP or CHC), and stage of liver disease (cirrhosis *vs* no cirrhosis). For analysis of the mITT and per-protocol samples that no longer reflected a randomised pool of participants, race was included as an additional covariate because its distribution was significantly different between the two groups (two-sided $p<0·01$). To test differences in proportions of SVR, initiation, and completion between treatment groups, we applied multivariable logistic regression: logit=arm + covariates.

To test difference in longitudinal weekly adherence between treatment groups, we applied the mixed-effects linear models with a first-order autoregressive covariance structure. All the other effects were considered fixed in the form of: adherence=arm + week + arm × week + covariates in which the scale of the week variable was considered discrete (as opposed to continuous) throughout all analyses.

For the models to identify factors associated with outcomes, we included only study group and sites as common covariates: logit=factor + arm + site, for the binary outcomes and adherence=factor + week + factor × week + arm + site, for the longitudinal weekly adherence levels.

To test heterogeneity of intervention effect across patient subgroups defined by factor levels, we tested significance of intervention by subgroups interaction effects, including sites in the statistical models:

logit=factor + arm + factor × arm + site, for the binary outcomes and adherence=arm + subgroup + week + arm × factor + arm × week + site, for longitudinal weekly adherence.

We provided estimates, 95% CI, and two-sided p values. All analyses were performed using SAS version 9.4. This trial is registered with ClinicalTrials.gov, NCT02824640.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Of the 1891 patients screened between Sept 15, 2016, and Aug 14, 2018, 755 participants were randomly assigned to patient navigation (n=379) or mDOT (n=376; figure 1). The demographic and baseline clinical characteristics of the ITT and mITT samples are presented in table 1, and these details for the per-protocol samples are provided in appendix 3 (pp 20–24). Of 755 participants, 312 (41%) were enrolled in an OTP and 443 (59%) were enrolled in a CHC. Participants had a mean age of 43·2 years (SD 11·5), and the majority were male (528 [70%]), White (476 [65%]), unemployed (480 [65%]), and had HCV genotype 1 infection (368 [72%]). Except for one participant with missing information, all participants had injected substances within 90 days and 572 (76%) participants had injected within 4 weeks.

The median time to treatment initiation from baseline was not significantly different between the two groups: 18 (IQR 10–33) days in the mDOT group versus 19 (11–34) days in the patient navigation group. In the mITT sample (n=623), 462 (74% [95% CI 71–78]) participants had SVR, and there was no significant difference between the two treatment groups (adjusted odds ratio [AOR] 0·97 [0·66–1·42]; p=0·35); table 2). Among the 623 participants who initiated treatment, 119 (19%) were considered to have not reached SVR owing to study termination before SVR assessment: 58 participants in the mDOT group and 61 participants in the patient navigation group, including nine deaths (figure 1).

In the ITT sample (n=755), 462 (61% [95% CI 58–65]) participants had SVR, and, in the per-protocol population (n=501), 461 (92% [89–94]) participants had SVR. There were no significant differences in SVR between the two treatment groups in the ITT sample or the per-protocol sample (table 2). The median time to SVR from end of treatment was not significantly different between the two treatment groups: 91 (IQR 84–119) days in the mDOT group and 91 (84–120) days in the patient navigation group in the mITT population (p=0·68).

Analyses of treatment initiation (based on the ITT population) showed that, among all participants (n=755), 623 (83% [95% CI 80–85]) participants initiated treatment, and there was no significant difference between the mDOT group and patient navigation group (figure 2, table 2).

In the mITT sample, mean daily adherence was 74% (95% CI 73–76). Adherence was higher in the mDOT group (78% [95% CI 75–81]) than in the patient navigation group (73% [70–77]; p=0·0010; figure 3). Participants receiving mDOT had significantly greater adherence in the OTP setting (p=0·0001; figure 3) but not in the CHC setting (p=0·33; figure 3).

Among 623 participants who initiated treatment (mITT sample), 515 (83% [95% CI 80–86]) completed treatment, with no significant difference between treatment groups (AOR 0·90 [0·58–1·39]; p=0·63; table 2). Mean treatment length was 83·5 (SD 28·6) days, with no significant difference between the two treatment groups (81·6 [23·7] days for mDOT *vs* 85·3 [32·5] days for patient navigation; p=0·15).

SVR was significantly associated with adherence, treatment duration, and completion in the mITT sample.

	Proportion in mDOT group, n (% [95% CI]) of N	Proportion in patient navigation group, n (% [95% CI]) of N	AOR (95% CI)*	p value
SVR†				
ITT sample	226 (60% [55–65]) of 376 participants	236 (62% [57–67]) of 379 participants	0·92 (0·68–1·25)	0·61
mITT sample	226 (74% [69–79]) of 306 participants	236 (75% [69–79]) of 317 participants	0·97 (0·66–1·42)	0·35
Per-protocol sample	226 (91% [87–94]) of 248 participants	235 (93% [89–96]) of 253 participants	0·79 (0·41–1·55)	0·44
Initiation				
ITT sample	306 (81% [77–85]) of 376 participants	317 (84% [80–87) of 379 participants	0·86 (0·58–1·26)	0·44
Completion				
ITT sample	251 (67% [62–72]) of 376 participants	264 (70% [65–74]) 379 participants	0·88 (0·64–1·21)	0·44
mITT sample	251 (82% [77–86]) of 306 participants	264 (83% [79–87]) of 317 participants	0·90 (0·58–1·39)	0·63
Per-protocol sample	221 (89% [85–93]) of 248 participants	226 (89% [85–93]) of 253 participants	0·93 (0·51–1·68)	0·81

AOR=adjusted odds ratio. ITT=intention-to-treat. mDOT=modified directly observed therapy. mITT=modified intention-to-treat. SVR=sustained virological response. *Adjusted for clinic type, cirrhosis, and site for the ITT sample analysis; race (which was unbalanced) was additionally adjusted for the mITT and per-protocol analysis. Of the 119 participants whose SVR status was undetermined because of loss to follow-up, viraemia data during the 12-week treatment period was available for 61 participants. Among the 119 participants, 56 (47%) had undetectable or unquantifiable viral load: 19 at week 4, 17 at week 8, and 20 at week 12. Of the 161 participants who did not reach SVR, 11 had evidence of genotype or subtype switches between baseline and SVR measurement, which might indicate reinfection rather than unsuccessful treatment: 1a to 1b (n=2), 1a to 3 (n=3), 1b to 3 (n=1), 1b to 3a (n=1), 2 to 1a (n=1), 3 to 1a (n=1), 3a to 2 (n=1), and 3/4 to 1a (n=1). †Undetermined SVR was considered as unsuccessful SVR.

Table 2: **Comparisons of study outcome rates**

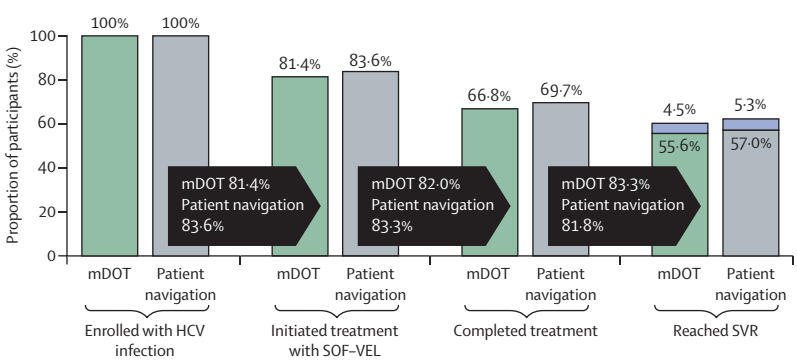
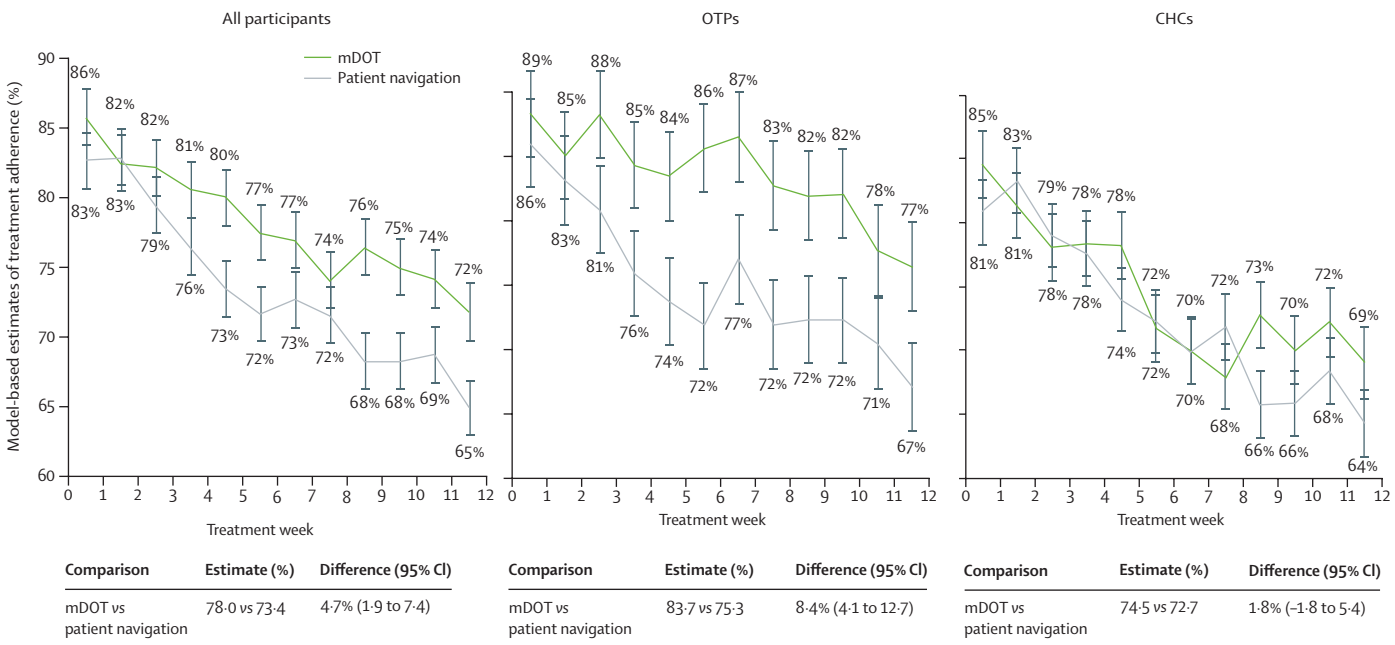


Figure 2: **Cascade of HCV treatment care**

The numbers above the bar graphs represent proportions with the number of randomised participants as the fixed denominator. The top blue bars and the numbers above them in the reached SVR column represent the SVR rate among those who did not complete treatments, whereas the other numbers and the bottom bars represent the SVR rate among treatment completers. The numbers in the black arrows represent proportions with the number of those who reached the outcome before the current outcome as the denominator. The χ^2 test p value for comparison of the proportion of participants who reached SVR in the mDOT and patient navigation groups, with the number of randomised participants as the denominator, was 0·54. HCV=hepatitis C virus. ITT=intention-to-treat. mDOT=modified directly observed therapy. SOF–VEL=sofosbuvir–velpatasvir. SVR=sustained virological response.



Comparison	Estimate (%)	Difference (95% CI)
mDOT *vs* patient navigation	78·0 *vs* 73·4	4·7% (1·9 to 7·4)

Comparison	Estimate (%)	Difference (95% CI)
mDOT *vs* patient navigation	83·7 *vs* 75·3	8·4% (4·1 to 12·7)

Comparison	Estimate (%)	Difference (95% CI)
mDOT *vs* patient navigation	74·5 *vs* 72·7	1·8% (–1·8 to 5·4)

Figure 3: **Comparisons of weekly daily-time-frame adherence between mDOT and patient navigation overall and in OTPs *vs* CHCs**
Error bars represent the standard errors. The lengths of the error bars represent the magnitudes of standard errors that were estimated on the basis of mixed-effect linear models. CHC=community health centres. mDOT=modified directly observed therapy. OTP=opioid treatment programme.

Specifically, a 10% increase in adherence was significantly associated with SVR (AOR 1·6 [95% CI 1·4–1·8]; p<0·0001). SVR was associated with treatment completion (82·5% completers *vs* 34·3% non-completers; AOR 8·4 [95% CI 5·2–13·6]; p<0·0001) and with number of days on treatment: a 10-day increase in time on treatment up to 84 days was significantly associated with SVR (1·3 [1·2–1·4]; p<0·0001).

Analyses were performed to assess factors associated with SVR, initiation, completion, and adherence. In the mITT sample, lower SVR was associated with being aged less than 40 years, receiving buprenorphine (*vs* methadone), injecting more than twice daily, injection drug use within 0–4 weeks before baseline (*vs* 5–12 weeks), and a positive baseline toxicology test for methamphetamine, cocaine, or opioids (figure 4A). Unstable housing was associated with lower treatment initiation (appendix 4 p 7), completion (appendix 4 pp 8–10), and SVR (figure 4A, appendix 4 pp 4–5). Factors associated with adherence in the mITT sample are presented in figure 4B; factors associated with adherence in the per-protocol sample are presented in appendix 4 (p 6). Factors associated with initiation and completion are presented in appendix 4 (pp 7–10). The proportion of participants with active drug use was consistent in both groups throughout the study period (appendix 4 p 11). Compared with participants receiving methadone (54 [15%] of 358 participants), a higher proportion of participants receiving buprenorphine (25 [29%] of 85 participants) did not reach an SVR because of inability to measure viral load secondary to loss to follow-up.

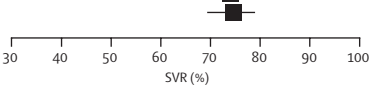
See Online for appendix 4

Analyses were also conducted to identify patient subgroups with significant heterogeneous intervention effects on study outcomes. The analysis results of intervention effects on SVR, adherence, treatment initiation, and treatment completion are presented in appendix 4 (pp 12–20). In the mITT sample, the intervention effects (AOR of mDOT *vs* patient navigation) on SVR were significantly heterogeneous across subgroups for the following characteristics: race (p=0·046); transportation (p=0·025); and any drug use at baseline (p=0·050; appendix 4 p 13). In the mITT sample, the intervention effect (difference=mDOT–patient navigation) on adherence was also significantly heterogenous between settings (p=0·034); appendix 4 p 15). Although the mDOT-versus-patient navigation effect was not significant within any of these subgroups, differences in the magnitude of the effects between the subgroups were significant.

219 participants had at least one serious adverse event (ranging from one to seven reported serious adverse events per individual), including 109 participants in the mDOT group and 110 in the patient navigation group. There were a total of 421 serious adverse events (217 in the mDOT group *vs* 204 in the patient navigation group): 35 deaths (27 in the mDOT group *vs* 18 in the patient navigation group), 17 life threatening events (six in the mDOT group *vs* 11 in the patient navigation group), 337 hospitalisations (176 in the mDOT group *vs* 161 in

A

	SVR, n/N (%)	AOR (95% CI)	p value
Race			
White	281/397 (70·8%)	0·66 (0·36 to 1·20)	0·174
Black	64/82 (78·0%)	1·17 (0·52 to 2·62)	0·704
Other (ref)	99/122 (81·1%)		
Sex			
Male	335/445 (75·3%)	1·23 (0·82 to 1·86)	0·317
Female	122/172 (70·9%)		
Age			
≥40 years	275/348 (79·0%)	1·70 (1·14 to 2·53)	0·009
<40 years	187/275 (68·0%)		
Hispanic or Latino			
Yes	113/136 (83·1%)	1·84 (0·96 to 3·52)	0·066
No	349/487 (71·7%)		
Marital status			
Married or co-habitating	56/72 (77·8%)	1·26 (0·69 to 2·31)	0·458
Other	405/550 (73·6%)		
Housing			
Stable	244/299 (81·6%)	2·28 (1·53 to 3·39)	0·000
Unstable	217/323 (67·2%)		
Transportation			
Available	194/261 (74·3%)	1·30 (0·86 to 1·98)	0·217
Maybe or no	266/360 (73·9%)		
Employment			
Employed	162/220 (73·6%)	1·20 (0·80 to 1·80)	0·379
Unemployed	298/401 (74·3%)		
Clinic type			
CHC	243/350 (69·4%)	0·72 (0·47 to 1·10)	0·126
OTP	219/273 (80·2%)		
Opioid use disorder treatment 3 months before			
Methadone	285/358 (79·6%)	2·31 (1·35 to 3·96)	0·002
Neither	129/177 (72·9%)	1·83 (1·02 to 3·28)	0·042
Buprenorphine (ref)	46/85 (54·1%)		
Depression			
PHQ–9 >14	106/142 (74·6%)	0·93 (0·60 to 1·46)	0·759
PHQ–9 ≤14	354/478 (74·1%)		
Anxiety			
GAD–7 >14	85/114 (74·6%)	0·95 (0·59 to 1·55)	0·852
GAD–7 ≤14	374/504 (74·2%)		
HCV genotype			
Type 1	250/327 (76·5%)	1·53 (0·86 to 2·71)	0·145
Type 2	30/41 (73·2%)	1·33 (0·55 to 3·22)	0·530
Type 3 (ref)	55/81 (67·9%)		
HIV infection			
Positive	66/85 (77·6%)	1·00 (0·49 to 2·02)	0·991
Negative	263/357 (73·7%)		
AUDIT-C alcohol misuse			
Yes	141/190 (74·2%)	1·14 (0·76 to 1·71)	0·537
No	313/423 (74·0%)		
Times injecting a day			
>2 times	182/274 (66·4%)	0·54 (0·37 to 0·80)	0·002
≤2 times	253/316 (80·1%)		
Last drug injection			
5–12 weeks	123/152 (80·9%)	1·93 (1·20 to 3·10)	0·007
0–4 weeks	339/471 (72·0%)		
Days injected 3 months before			
≥30 days	199/286 (69·6%)	0·69 (0·47 to 1·02)	0·060
<30 days	234/303 (77·2%)		
Urine toxicology screen for any drug			
Yes	427/571 (74·8%)	1·34 (0·56 to 3·20)	0·509
No	15/25 (60·0%)		
Urine toxicology screen for amphetamine			
Yes	125/163 (76·7%)	0·90 (0·54 to 1·51)	0·699
No	317/433 (73·2%)		
Urine toxicology screen for methamphetamine			
Yes	137/186 (73·7%)	0·57 (0·34 to 0·96)	0·035
No	305/410 (74·4%)		
Urine toxicology screen for benzodiazepine			
Yes	239/318 (75·2%)	0·86 (0·58 to 1·29)	0·472
No	203/278 (73·0%)		
Urine toxicology screen for cocaine			
Yes	178/251 (70·9%)	0·62 (0·41 to 0·93)	0·019
No	264/344 (76·7%)		
Urine toxicology screen for marijuana			
Yes	223/294 (75·9%)	0·98 (0·67 to 1·45)	0·937
No	219/302 (72·5%)		
Urine toxicology screen for opiate			
Yes	218/302 (72·2%)	0·53 (0·35 to 0·81)	0·003
No	224/294 (76·2%)		
Urine toxicology screen for oxycodone			
Yes	116/157 (73·9%)	0·76 (0·48 to 1·18)	0·223
No	326/439 (74·3%)		



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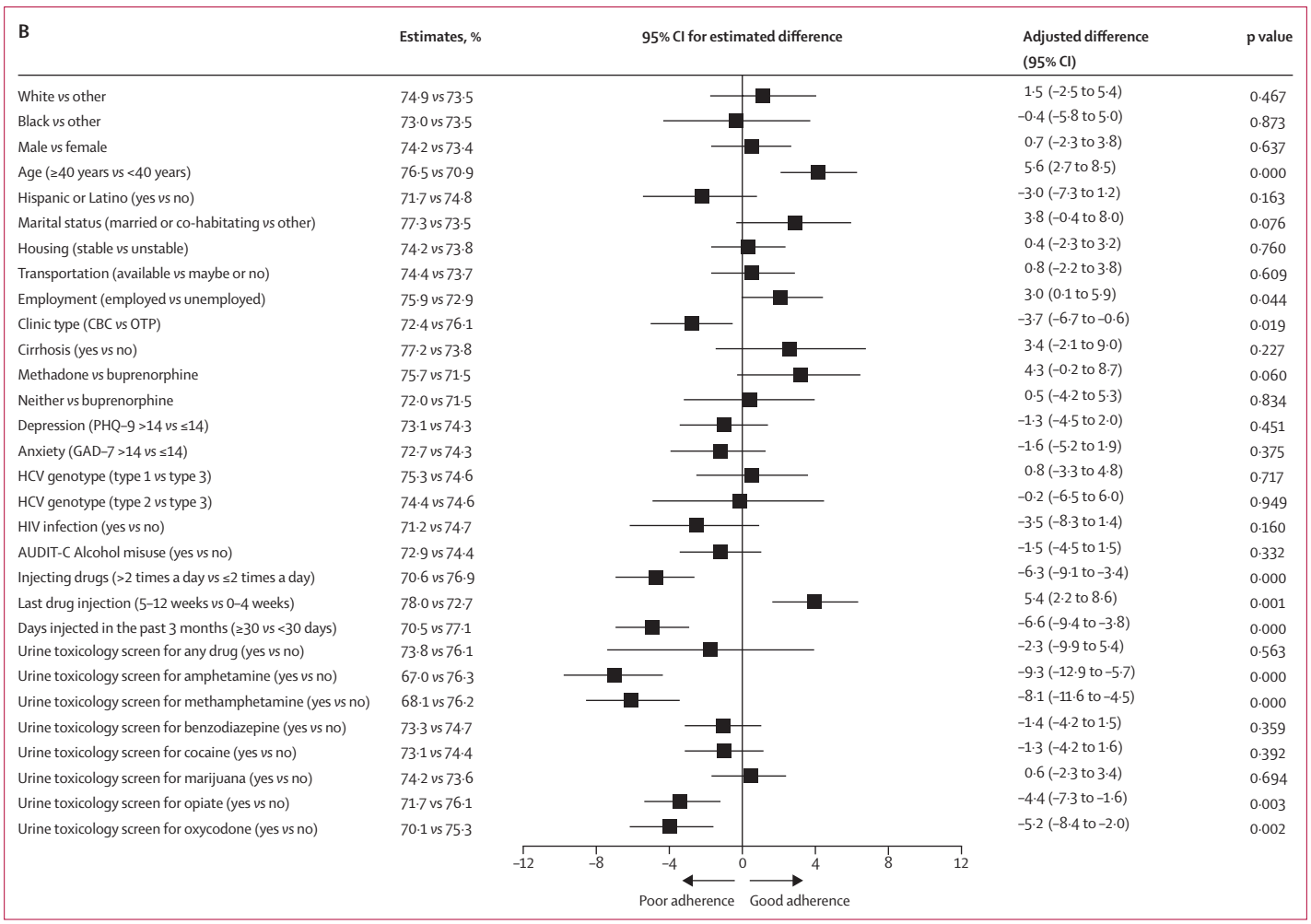

Figure 4: **Factors associated with SVR and adherence in the mITT sample**
Forest plots depicting factors associated with SVR (A) and adherence (B) in the mITT sample. mDOT=modified directly observed therapy. mITT=modified intention-to-treat. AOR=adjusted odds ratio. AUDIT=Alcohol Use Disorders Identification Test. CHC=community health centre. GAD-7=Generalised Anxiety Disorder-7 scale. HCV=hepatitis C virus. OTP=opioid treatment programme. PHQ-9=Patient Health Questionnaire-9. SVR=sustained virological response.

the patient navigation group), one disability (in the patient navigation group), two requiring an intervention to prevent impairment or damage (one in the mDOT group *vs* one in the patient navigation group), and 29 other serious important medical events (17 in the mDOT group *vs* 12 in the patient navigation group; appendix 4 p 25).

Discussion

In this multicentre, randomised clinical trial of HCV care delivery models for PWID in OTPs and CHCs, SVR was not significantly higher in the mDOT group compared with the patient navigation group, contrary to our hypothesis. Although adherence was 5% higher in the mDOT group compared with the patient navigation group, this difference was not clinically meaningful. Treatment initiation and completion were high (>80%) in both treatment groups. Despite suboptimal adherence of 74%, overall SVR was high (92%) in the per-protocol analysis. Increases in adherence and treatment duration were associated with an increased likelihood of SVR.

Although the overall SVR of 92% in the per-protocol analysis was high, the SVR of 74% in the mITT analysis was lower than other prospective HCV multisite trials of PWID, and can be attributed to high proportions of loss to follow-up (19%) compared with 0–2% in two other randomised trials.[11,12] However, loss to follow-up and SVR in HERO were similar to five observational trials of PWID that reported 14–35% loss to follow-up and an SVR of between 63% and 84%.[15,19–22] This loss to follow-up highlights the need for more aggressive follow-up interventions or shorter correlates of HCV cure, such as treatment completion, end of treatment response, or SVR at 4 weeks after end of treatment (which has a 99·7% positive predictive value for SVR12[23]). Indeed, the most recent EASL guidelines recognise that assessment of SVR

might be unnecessary in certain populations, if adherent to HCV treatment.[24] The SVR rate of 92% in the per-protocol analysis was similar to the rate of 94% reported in other multisite PWID trials.[11,12] Importantly, in the HERO study injection drug use was defined as injection drug use within 90 days of enrolment, whereas most other multisite studies had either a longer injection timeframe (6 months) or included both former PWID and non-PWID. The single-site ANCHOR study[18] enrolled HCV-infected PWID with opioid use disorder who injected within 12 weeks of enrolment and had higher SVR (82%) with lower loss to follow-up than our HERO study. SVR might have been higher in the ANCHOR study[18] because buprenorphine treatment was actively offered at the same time as HCV treatment. Although most HCV care continues to take place in specialty settings, HCV treatment in the HERO study was delivered either in the same setting as treatment for substance use disorders or in a community health centre. Taken together, these data suggest that PWID and clinicians might consider HCV treatment with either care model, based on patient preference and shared decision making, as well as ability to implement mDOT or patient navigation support. There is insufficient evidence to require mDOT models of care for PWID who are actively injecting drugs. Notably, community-based co-located treatment models versus hospital-based models of care are associated with higher treatment initiation and overall SVR.[25] Additionally, retention in buprenorphine treatment when offered in community-based models is associated with improved SVR.[18]

The overall adherence in our study was 74%, and a 10% increase in adherence was associated with 60% greater odds of SVR. Adherence was lower than other PWID studies using the same electronic blister packs (78–94%)[12,26,27] but the per-protocol SVR was 92%, which suggests that high SVR can be reached even with suboptimal adherence. In the HERO study, adherence was 8% higher with in-person mDOT delivered in OTPs than in CHCs, highlighting the importance of leveraging OTPs for HCV treatment. A meta-analysis of randomised controlled trials suggests retention with methadone is equivalent to that with buprenorphine (or buprenorphine–naloxone), with wide variation across studies.[28] However, a large trial suggested that provision of methadone was associated with better retention in treatment for opioid use disorder than buprenorphine.[29] The increased loss to follow-up for those taking buprenorphine versus methadone in the HERO study might be related to decreased retention to buprenorphine versus methadone. Differences in retention rates could have been caused by the different pharmacological properties of methadone (full agonist) and buprenorphine (partial agonist).

To our knowledge, HERO is the first study to show that drug-related behaviours were associated with decreased SVR, including recent and frequent injection and use of methamphetamines, cocaine, or opioids, and that individuals receiving methadone versus buprenorphine were more likely to reach SVR. Expanding availability of medications for opioid use disorder, integrating HCV services within opioid agonist treatment programmes, and incorporating evidence-based practices to promote retention to medications for opioid use disorder are key steps in the global response to the HCV epidemic. As with one other study,[15] we found that unstable housing had a negative effect on treatment outcomes. Interventions that ameliorate housing instability might improve the HCV cascade of care.

The HERO study had several limitations. For instance, sites were mostly urban, although three did serve participants from rural communities, and the study did not include a minimal intervention control group, as per PCORI guidelines, or an intensive group that combined mDOT and patient navigation, which might limit generalisability. The mDOT intervention might not be generalisable to methadone programmes outside of the USA with more liberal policies allowing patients who are still using drugs to attend the programme less than five times per weekly, or where methadone is prescribed by community physicians or dispensed in the community by pharmacists. Furthermore, there was inconsistent involvement of peers serving as patient navigators within the patient navigation model, and there were differences in duration of prescription of blister packs between the patient navigation and mDOT groups, which might have also affected adherence. Additionally, treatments that were unsuccessful for participants could not be differentiated from reinfections without phylogenetic analyses. Lastly, participants were monetarily compensated for completing research visits and for returning the electronic blister packs, which might have affected the generalisability of our findings. However, the HERO study has unique strengths: a strict definition of recent injection drug use; participants from eight diverse cities throughout the USA; community treatment settings were used, specifically OTPs and CHCs; and both national and local stakeholders were involved in study implementation. The use of wide inclusion and exclusion criteria (eg, participants were not required to be adherent to medications for opioid use disorder or have a minimal amount of time in OTP treatment), recruitment from diverse clinical sites (eg, opioid treatment programmes and a variety of community health centres), delivery of patient navigation by diverse providers, provision of HCV treatment by diverse clinicians (including, internal medicine, family medicine, and infectious disease physicians, as well as physician assistants and nurse practitioners) are pragmatic trial design features that might increase the generalisability of the findings.

The HERO study provides real-world evidence that PWID with active drug use can achieve high SVR, treatment initiation, and treatment completion through support from the patient navigation or mDOT models in OTPs or CHCs. The HERO study shows the need

to remove continued restrictive HCV treatment access policies for PWID with recent or ongoing injection drug use (22 states within the USA still have sobriety requirements) as well as restrictions based on provider type and stage of fibrosis.[30] The unrestricted and broad adoption of these models will accelerate progress toward HCV elimination in the USA and globally.

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AHL, PJL, LET, SHM, JIT, JF, AYK, MH, JA, PM, AK, and KP contributed to the concept and design of the study. AHL, PJL, LET, SHM, JIT, JF, AYK, MH, JA, PM, AK, KP, BLN, LA, ESS, AT, CB, KLB, SW, KW, JR, CM-K, JA, and KP contributed to the acquisition and interpretation of the data. AHL, MH, and IP-V drafted the manuscript. MH, CM-K, and JA performed the statistical analyses. AHL, PJL, LET, AK, BLN, MH, JA, PM, AYK, MDM, JWW, NJ, IP-V, KLB, KW, CM-K, VJ, AFL, OF-N, and KP provided critical revision of the manuscript for important intellectual content. AHL, PJL, LET, SHM, JIT, JF, AYK, MH, JA, PM, AK, and KP obtained the funding. AHL, PJL, LET, SHM, JTS, JF, AYK, MH, JA, PM, AK, and KP supervised the findings of this work. AHL and IP-V had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All the authors contributed to the final manuscript.
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