The simplified HCV integrated management model in methadone clinics in Ukraine

Study protocol

Sponsored by:

The Western-Eastern European Partnership Initiative on HIV, Viral Hepatitis and TB

Principal Investigator:

Myroslava Filippovych, MPH

Ukrainian Institute on Public Health Policy

Running title: Evaluation of SHIM in OAT clinics in Ukraine

Version 1.4

01-Apr-25

Contents

List of acronyms

Ab	Antibody
APRI	AST to platelet ration index
ART	Antiretroviral therapy
CHC	Chronic Hepatitis C infection
DAA	Direct-acting antiviral agent
DCV	Daclatasvir
ECHO	Extension for Community Healthcare Outcomes
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
PWID	People Who Inject Drugs
Lab	Laboratory
MOH	Ministry of Health
MSM	Men who have sex with men
OAT	Opioid agonist therapy
PWID	People who inject drugs
PLWH	People living with HIV
PCR	Polymerase chain reaction
RBV	Ribavirin
RNA	Ribonucleic acid
SHIM	simplified HCV care and treatment model
SOC	Standard of care
SOF	Sofosbuvir
SVR12	Sustained viral response at week 12
VEL	Velpatasvir
VL	Viral load
WHO	World health organization

Protocol Team Roster

<table>
<tr><td colspan="2">The simplified HCV integrated management model in methadone clinics in Ukraine</td></tr>
<tr><td><u>Principal Investigator</u>
Myroslava Filippovych
MPH
Ukrainian Institute on Public Health Policy
Email: filippovych@uiphp.org.ua</td><td><u>Co-Investigator qualitative part</u>
TBD</td></tr>
<tr><td><u>Co-Investigator</u>
Frederick L. Altice
Professor
Yale University School of Medicine
Email: frederick.altice@yale.edu</td><td><u>Co-Investigator</u>
Patrizia Carrieri
Professor
French National Institute of Health and Medical research (INSERM)
Email: patrizia.carrieri@inserm.fr</td></tr>
<tr><td><u>Co-Investigator</u>
Iryna Ivanchuk
OAT, Hepatitis, STI Sector Lead
Email: i.ivanchuk@phc.org.ua</td><td><u>Co-Investigator</u></td></tr>
</table>

Summary

About 12,000 patients receive opioid agonist treatment in Ukraine, 83% of them are HCV-infected. Considering the rapidly increasing availability of DAA medications in Ukraine, this group can be efficiently covered with treatment using a simplified integrated HCV care model. The goal of the proposed project is to adapt and evaluate the effectiveness of a simplified HCV care and treatment model (SHIM) integrated into OAT clinics in Ukraine, using hybrid type 2 implementation science approach. SHIM implementation will be strengthened by Project ECHO (Extension for Community Healthcare Outcomes), a collaborative telehealth learning intervention, supporting and empowering clinicians to develop knowledge and self-efficacy about HCV care, which has not traditionally been integral to their scope of practice. As an implementation study, our project will generate much needed process data and clinical evidence for rapid scale-up of integrated HCV treatment in Ukraine and other countries of the region.

The Stage 1 aims are:

1) To develop SHIM and demonstrate its feasibility. We will develop the SHIM manual, train clinicians and conduct a pilot test with 20 OAT patients with HCV infection at an OAT clinic.

2) Using a multi-level implementation science framework, to examine the client, clinician and organizational factors that contribute to SHIM adoption and clinical outcomes.

If the pilot demonstrates feasibility and continuation is approved, the Stage 2 aim is:

3) To evaluate the effectiveness of SHIM in improving the HCV treatment cascade outcomes using a cluster-randomized three-arm trial design in 480 HCV-infected patients at 12 OAT clinics (4 clinics per arm) randomized to standard of care (N=160) versus SHIM with (N=160) or without (N=160) ECHO facilitation.

The primary outcomes of both pilot and main study phases are based on the HCV treatment cascade: (a) Completing the pretreatment evaluation; (b) Initiating and completing the full DAA course; (c) Achieving SVR12. Secondary outcomes will include treatment motivation, adherence, quality of life, treatment satisfaction. Although not sufficiently powered, we will measure re-infection rates among those achieving SVR.

Stage 1 is focused on feasibility and does not include hypothesis testing. In Stage 2 trial, we will test two main hypotheses (1) SHIM clinics will have better adoption and penetration of HCV care elements, that will ultimately result in improved patient-level outcomes like HCV cure compared to standard of care; (2) Compared to No-ECHO, ECHO-facilitated sites will have improved HCV cascade outcomes.

The results of the model evaluation, if proven effective, will allow us to advocate for its scale-up to other non-specialized settings in Ukraine and internationally and contribute to HCV elimination.

1 Scientific Rationale

It is estimated that about 70 million people are infected with HCV globally [1], and the majority are not aware of their infection. HCV infection can persist undetected for many years before manifesting as chronic liver disease, cirrhosis, or liver cancer. HCV remains one of the leading infectious disease-related causes of death. Due to the recent advances in HCV treatment with direct acting antivirals (DAAs), more than 95% of treated patients can achieve sustained viral response (SVR). It can reverse the effects of early stage fibrosis and slow the progression of cirrhosis into decompensation or hepatocellular carcinoma [2, 3]. This reduces liver-related mortality by 20-fold and all-cause mortality by 4-fold [4].

Based on expert consensus in 2015, it was estimated that 3.7% (0.9-6.7%) of the population of Ukraine was infected with HCV and are viremic (RNA positive) viraemic [5]. By 2017, it is estimated that there were 1 368 300 individuals infected, majority with genotype 1 [6]. Of those infected, only 83,000 were registered in medical care, and about 35,000 are fully diagnosed and are on the waiting list at regional health authorities.

Availability of HCV treatment in Ukraine is growing. The Ministry of Health (MoH) procured ~40,000 DAA courses from 2019-2020 state budget. These medications were distributed to the facilities, and as of 12.2021 there were ~10,000 courses left. Additionally, ~7,500 courses will be procured from 2021 funds and delivered in 2022.

In addition, some regional governments and donor-funded projects are also procuring medications. These medications are distributed to specialized infectious disease hospitals, which diagnose and register patients and manage the waiting lists. Besides these programs (providing medications at no charge), some DAA medications recently became available for purchase through pharmacies. This indicates that in the next few years, the immediate treatment need (the waiting list) will be fully covered and **more intensive case detection and treatment enrollment efforts will be needed to continue the progress toward elimination.**

It is well known that people who inject drugs (PWID) have high burden of HCV [7] and due to multiple individual and structural barriers suffer from suboptimal access to accessing life-saving treatments. Enrollment into opioid agonist treatment (OAT), especially in integrated settings, is proven to improve health of opioid users through reducing drug use and increasing access to medical care [8-10]. Integration of OAT with HIV and TB care is well studied, including in Ukraine [10-12].

The scientific premise for integrating OAT and HCV services is strong. Recently injecting PWID and OAT patients have sufficient level of adherence and high rates of SVR [13-15]. Availability and effectiveness of new pangenotypic DAA formulations makes the notion of 'special populations' no longer pertinent. Several OAT-HCV care integration models have been evaluated in the DAA era with promising results [16-18], but no studies were conducted in low and middle-income countries.

There are around 17,000 patients currently receiving OAT in Ukraine, up to 83% of them are HCV-infected [19]. Due to stigmatization from medical providers and low awareness of recent guidelines, majority are not included in the DAA waiting lists, and due to low income cannot afford medications from pharmacies. The growing availability of DAA medications and ongoing healthcare reform context in Ukraine presents **a unique and time-sensitive opportunity to build and evaluate a simplified integrated HCV care model at OAT clinics, which can serve at least 9,000 patients in short-term.** Globally, the number of patients on OAT is increasing, and majority are treated at specialized addition treatment facilities [20]. A large number of these patients can benefit from integrated HCV services using a model we are proposing.

In our stage 1 project, we have developed and piloted a simplified HCV integrated management (SHIM) algorithm for OAT clinics. The uptake of HCV treatment and virologic outcomes using the SHIM algorithm in the pilot sample was high and consistent with reports of successful treatment outcomes among PWID

2 Goal and Aims

The goal of the proposed research is to evaluate feasibility and effectiveness of a simplified HCV care and treatment model integrated into OAT programs in Ukraine. **The simplified HCV integrated model (SHIM), if shown effective, would be relevant for other non-specialty healthcare facilities globally.** SHIM implementation will be strengthened by Project ECHO (Extension for Community Healthcare Outcomes), a collaborative telehealth learning process, supporting and empowering OAT clinicians to develop knowledge and self-efficacy about HCV care, which has not traditionally been considered integral to their scope of practice.

The specific aims are:

1) To develop SHIM and demonstrate its feasibility. We will develop the SHIM manual, train clinicians and conduct a pilot test with 20 OAT patients with HCV infection at an OAT clinic.

3) Using a multi-level implementation science framework, to examine the client, clinician and organizational factors that contribute to SHIM adoption and clinical outcomes.

2) To evaluate the effectiveness of SHIM in improving the HCV treatment cascade outcomes using a cluster-randomized three-arm trial design in 480 HCV-infected patients at 12 OAT clinics (4 clinics per arm) randomized to standard of care (N=160) versus SHIM with (N=160) or without (N=160) ECHO facilitation.

3 Study Design and Research Methods

3.1 Study conditions

3.1.1 Standard of care (SOC)

As of today, HCV diagnostics and treatment is available through the network of specialized infectious diseases clinics. Other clinics (primary care, secondary level or clinics with other specialization) may prescribe and in some cases perform HCV screening, and in case of positive test result provide referrals to the specialized infectious diseases clinics or departments (hepatology centers). Upon admission, physicians are prescribing diagnostic tests to confirm the diagnosis, determine fibrosis stage, and detect possible contraindications. Based on the diagnosis and availability of medications, a treatment regimen is prescribed. Despite the fact that current MoH policy is permitting the use of international clinical guidelines, such as WHO or EASL, in routine practice the number and choice of diagnostic tests and treatment regimens is left to physician's discretion. In most cases, patients are required to have blood biochemistry (liver enzymes), quantitative HCV RNA, genotyping, liver ultrasound, FibroScan, kidney function tests. The cost of diagnostic tests is fully paid by the patients. The choice of treatment regimens usually includes the generic SOF formulations procured by the MoH or regional programs (see Rationale), or other DAA generics that recently became available for purchase at pharmacies. Hepatology center physicians are also prescribing follow-up tests (HCV RNA) to monitor treatment effectiveness.

In this study, the OAT clinics in the SOC arm will be informed of availability of medications at the hepatology centers and instructed to refer patients for screening (to primary care or other clinics, or harm reduction programs) and treatment (to hepatology centers).

3.1.2 Simplified HCV integrated model (SHIM)

SHIM will be based on the latest research evidence informing 5 steps to quality HCV treatment in non-specialized care settings [21] and recently approved National Standard on Hepatitis C in adults [22]. The provisional algorithm is presented in Appendix.

(1) diagnosis

Majority of the OAT programs in Ukraine already have reasonably high rates of HCV screening (~80% according to our preliminary data), therefore we will enroll patients who have a documented anti-HCV antibody test result. Patients without a documented test result will be referred to receive HCV screening on-site or at a local harm reduction program where it is provided at no cost.

We will evaluate and compare the HCV treatment cascade outcomes starting from HCV diagnosis (HCV RNA test). Where available, a qualitative HCV RNA assay with a lower limit of detection of ≤1,000 IU/ml will be used to minimize the costs.

(2) pretreatment evaluation

SHIM will include the minimum of laboratory tests recommended by the guideline [21], including complete blood count, metabolic panel (creatinine), hepatic function panel, fibrosis score, hepatitis B test. The blood samples, where possible, will be collected at the OAT clinics. APRI or FIB-4 indices will be calculated to determine fibrosis score. Additional ultrasound assessment may be prescribed if APRI or FIB-4 indicate severe fibrosis.

(3) simple, once-daily, pan-genotypic HCV treatment regimens

According to the prospective SHIM algorithm, certain conditions (e.g. decreased kidney function, cirrhosis) will trigger a referral to the hepatology center for specialist treatment. In other cases, the OAT physicians will be trained to prescribe the available DAA medications and provide adherence counseling. Given that the OAT patients show up at the clinics daily or on a regular basis, treatment will start as soon as the pre-treatment evaluation is complete. **Given the implementation science premise of this proposal, we will not control which regimens are prescribed by physicians.** On the individual level, the frequency of dispensing may vary depending on the patient's OAT clinic visit schedule, but should not be more frequent than once a week. HIV co-infection (present in almost half of the OAT patients) will be considered an indication for referral to an HIV clinic, but not the hepatology center. HCV treatment in HIV/HCV co-infected patients will be managed by the OAT physician in consultation with the HIV specialist.

(4) on-treatment monitoring

The minimized number of clinical assessments will be performed at 4, 8, 12 weeks of treatment. This will include adherence assessment and counseling, side effect assessment, and drug interaction assessment.

(5) posttreatment monitoring

HCV RNA PCR to confirm SVR will be performed 12 weeks following completion of therapy. If SVR is not achieved, the patient will be referred to a specialist for re-treatment. Annual HCV RNA testing will be recommended to evaluate for re-infection and liver function tests to monitor other liver conditions.

3.1.3 Project ECHO

In this study, for ECHO intervention we will use Zoom videoconferencing that can be accessed on PCs, tablets and smartphones. Participation is linked to continuous medical education (CME), which is required every 2 years for OAT doctors. ECHO meets all of the recommended criteria for CME effectiveness. After a 1-day in-person, comprehensive training session, each bi-weekly / monthly multimedia ECHO session will include a brief didactic training by a national HCV expert (or potential guest speakers from related disciplines like gastroenterology, infectious diseases), followed by a series of cases presented by OAT doctors from their clinics. The ECHO coordinator will seek cases before each session for the specialist to review. "Interactive techniques" emerge from intensive patient-case discussion, where OAT clinicians discuss treatment options and challenges with experts. "Multiple and repeated exposures" to important clinical information is central to ECHO, which focuses repeatedly on evidence-based practices. All video sessions will be recorded and archived for review by providers and participation is monitored centrally through the ECHO hub. If semi-urgent questions arise in between sessions, tele-consults can be sent to the expert and addressed within 24 hours. Tele-consults can then be presented as cases at the next ECHO session. Feedback from prior cases are often discussed briefly to learn about a patient response.

3.2 Provision of DAA medications and laboratory tests

To enable on-site medication prescription and dispensing, we will work with the MoH through an established working group to re-route the required number of treatment courses procured by the MoH or regional programs to the OAT clinics.

Due to the centralized procurement (see Rationale), all regions have approximately same ratio of available formulations (with SOF+DAC comprising about 65% in the 2019 procurement). We will ensure that OAT clinics have at least one pan-genotypic regimen available (SOF+DAC or SOF/VEL). **Given the implementation science premise of this proposal, we will not control which regimens are prescribed by physicians.** Available pangenotypic DAA regimens are expected to have comparable effectiveness in our study population [16, 23]. Given that, and assuming even prevalence of genotypes and complicating conditions (e.g. cirrhosis) across the regions, we may safely assume that overall treatment effectiveness will not differ a priori, and the observed differences will result from the study interventions.

Medications will be provided to patients at no cost.

Currently, the diagnostic tests for HCV are provided at a wide range of public and private clinics and laboratories, however these assessments have to be paid for by patients. The average total cost for pre-treatment assessment is about $100, including the complete blood count, metabolic panel, hepatic function panel, fibrosis staging, INR, but not including elastography. Given the implementation science nature of the proposed research, focusing on real-life outcomes, the costs of laboratory testing will NOT be covered by the project.

For those participants who complete HCV RNA PCR to confirm SVR, HCV RNA PCR for re-infection assessment (12 month after treatment completion) will be recommended. Cost of re-infection assessment will be reimbursed by the project.

3.3 Research methods for Aim 1

1) To develop SHIM and demonstrate its feasibility. We will finalize SHIM, train the clinicians and conduct a pilot-test in 10 OAT patients with HCV infection.

We will establish a technical working group on viral hepatitis elimination to finalize SHIM and oversee the study progress. The group will review the latest consensus documents [24], guidelines

(WHO, EASL, AASLD), and the National Standard [22] and produce a localized manual for simplified HCV integrated management model in non-specialty health care institutions.

A systematic training on SHIM for OAT physicians participating in the study will be conducted by the sub-group experts and will cover all parts of the SHIM manual.

Training on research procedures for interviewers and clinical data collectors will occur simultaneously with the intervention training. All research procedures, including participant recruitment (with informed consent), assessment, clinical data collection, etc) will be presented using the Standard Operating Procedures.

Under close supervision of the national experts, we will pilot the manual on a small sample of patients (N=20) at a large OAT site in Lviv. Considering the timeline, the pilot phase will assess HCV care continuum stages up to SVR12. The pilot participants will also undergo all research-related procedures developed for the main phase trial (see the Aim 3 section).

3.4 Research methods for Aim 2

3) Using a multi-level implementation science framework, to examine the client, clinician and organizational factors that contribute to SHIM adoption and clinical outcomes.

3.4.1 Approach

For this Aim we use a conceptual framework that serves as a comprehensive heuristic model that may identify different multi-level characteristics that may influence SHIM integration into OAT, including: 1) Client-level factors that may help identify how different subgroups of clients respond to the intervention arms; 2) Provider-level factors that emphasize factors related to the characteristics of the staff, their attitudes toward SHIM and OAT clients with HCV, and fidelity of implementation of SHIM and ECHO; 3) Organizational-level factors that emphasize organizational characteristics of the clinic site (e.g., budget, caseload, size) and more broadly clinical staff attitudes toward change and uptake of SHIM activities. Community-level factors that include local regulations, stigma/discrimination, policing, drug-related policies, institutional response towards incorporating new strategies like SHIM will be assessed based on and controlled for by geographic region. To examine the influence of multi-level factors on implementation of intervention, we will employ a mixed methods approach collecting quantitative and qualitative data to evaluate the influence of client-level, provider-level, organizational, community-level and structural factors that impede or facilitate the implementation of SHIM and effectiveness of study arm interventions. Quantitative data on *changes* in the multi-level factors (client, provider, organization, and community) over time and how they influence the effectiveness of SHIM integration on HCV care cascade (e.g., diagnosis, DAA treatment and retention, SVR) will be compared and contrasted to key themes that emerge from the qualitative data. By merging these data, we may more accurately interpret study findings if one of the intervention arms fails to meet the hypotheses and together these data will inform dissemination strategies to scale-up SHIM more broadly across Ukraine and regionally, where healthcare delivery structures are similar.

3.4.2 Qualitative Assessments

The qualitative data will help us identify the real-world contexts and different organizational, community and structural factors that promote or impede the successful SHIM integration into OAT clinics, which would otherwise be unobserved.

We will conduct two rounds of qualitative assessments during the pilot phase and two rounds in the main phase. The first round will be conducted at the beginning of patient enrolment and the second round at the end of patient follow-up, at the pilot site and each of the 12 sites of the main phase. Each assessment round will include a focus group with randomly selected 6-8 patients and

semi-structured in-depth interviews with clinical staff involved in SHIM implementation, including 1 physician, 1 nurse, and the Chief Administrator. In-depth interviews will also be conducted with participants who haven't started HCV treatment at any stage after receiving positive PCR test for HCV. For the first round of patient focus groups, we will randomly select patients with a positive anti-HCV test result. For the second round, we will select patients who have completed treatment (including testing for SVR12) and several patients (if there are any) who have dropped out of treatment or not completed SVR12 testing. In-depth interviews will also be conducted with participants who have dropped out of treatment or not completed SVR12 testing and was not participating in focus groups. The focus groups and in-depth interviews will be conducted according to the guides that will be modified from the guides that we developed for integrating OAT into primary care [25].

The focus groups and in-depth interviews **with clients** will elicit feedback on barriers to HCV treatment at the specialized clinics, interactions with clinicians and police, peer norms about HCV, relevance of SHIM (or a theoretical decentralized HCV care model at the SOC sites) and how it could influence their engagement and retention in HCV care, adherence to health recommendations. Interviews with clinicians will elicit their feedback on their perceptions about the relevance of SHIM and ECHO, and perceptions of organizational climate and organizational factors that may facilitate or impede their ability to deliver HCV care. Interviews with clinic administrators will assess their perceptions of organizational factors that may facilitate or impede SHIM integration and ECHO. At the end of follow-up, the patient focus groups will assess whether the HCV treatment became more accessible, what barriers remain, whether any norms and perceptions have changed.

The interviews **with clinicians and administrators** will assess the actual experience with SHIM, their perception of SHIM sustainability, uptake of HCV diagnosis, treatment and post-treatment monitoring, medication adherence, training and technical assistance using ECHO, as well as their observations about how the integration is proceeding. For the SOC arm, the specific questions about ECHO will be rephrased to ask about theoretical clinical mentoring support.

In all study cities in the main phase, we will additionally recruit for both rounds of in-depth interviews **two infectious disease physicians from the hepatology centers**. These interviews are aimed to collect information on the existing models of HCV care, attitudes toward PWID and OAT patients and existing barriers and facilitators to HCV diagnosis and treatment. We will also elicit their feedback on the relevance of SHIM, potential weaknesses and strengths of decentralized integrated HCV care provision.

All individual interviews and focus groups will be conducted by trained study staff, at a location identified to assure adequate privacy and confidentiality. Participants will be provided with a separate reimbursement for participation in the individual interview. The interviews will last about one hour, and the focus group up to two hours. The interviews/ focus groups will be digitally recorded and transcribed verbatim for qualitative data analyses by a professional transcription service. 10% of the transcript will be checked by the Co-Investigator responsible for the qualitative component to ensure accurate transcription. All identifying information will be removed from the transcripts, and only the research team and the transcribers will have access to the audio interview data. Audio recordings of interviews will be destroyed after the analyses are complete.

3.4.3 Quantitative Assessment of Organizational Factors

During the main phase of the project, OAT site staff and administrators (average N=3 per site) will complete a survey at baseline and the end of follow-up phase. Provider-level Factors will include provider characteristics (e.g., socio-demographics, education and work experience) and their attitudes toward SHIM (or a theoretical integrated HCV care model at the SOC sites) and their

level of self-efficacy implementing SHIM. Attitudes and stigma towards drug users with and without HIV and HCV will be assessed using feeling thermometers operationalized as stereotypical beliefs, attribution beliefs, expectations with regard to rehabilitation chances and social distance [26], and previously used to compare attitudes over time as clinicians gain more contact and experience [27]. For Organizational Factors, clinic administrators will be asked to complete brief surveys on organizational characteristics (number, type, and turnover of staff, types of services provided, hours spent on clinical and administrative tasks, budget). Routine organizational assessments to gauge the progress of implementation and identify areas for future growth are conducted initially by improvement coaches with transfer of implementation to the country team. To understand the organizational changes, we will also have clinic staff and administrators complete several brief validated scales twice annually using REDCap: Organizational Capacity Inventory (e.g., perceived organizational climate, norms, trust and communication) and Organizational Readiness to Change Scale [28] and Organizational Functioning Scale [28]. These brief organizational measures include standardized scales for Social Dominance Orientation [29], which assesses the differences in how staff perceive themselves as "superior" to their patients and often observed in addiction treatment (α>0.90); Resistance Towards Change [30], which assesses how staff respond to innovation within an organization (α>0.90). Discrimination toward OAT patients with HCV by staff will be measured using feeling thermometers [31], which assesses the extent to which staff members believe that individuals should be treated differently for their mental illness (a weakness) and related activities (α>0.85; including subscales) [32], that assesses staff attitudes toward mental illness; as well as additional attitudes that we have created that include information, motivation and necessary skills needed for integration of SHIM into OAT settings and towards provision of HCV services. A review of policies and procedures (and changes) will be used to assess Community-level Factors, including types of services available, geographic proximity of treatment and prevention services, and perceived barriers from patients to accessing services (e.g., hours of service, transportation) from Aim 2. Structural factors will include indicators of policing (i.e. frequency of arrests); incarceration, stigma and discrimination experienced by participants.

3.4.4 Analytic plan

Analyses will focus on exploring whether different provider-related or organizational factors influence achieving pre-specified HCV care indicators.

Qualitative data analyses will be conducted on an ongoing basis in coordination with data collection. Thematic coding will be used to analyze the data from the individual interviews based on a grounded theory approach using MAXQDA software system. The Consensual Qualitative Research Method (CQR) will be used by the study team to analyze the data. The CQR method provides a reliable, systematic, and rigorous method in conducting qualitative data analyses - recognizing the importance of context, incorporating an inductive analytic process, using a team and making decisions by consensus, using auditors, and verifying results by systematically checking against the raw data. The key elements of conducting qualitative data analyses using the CQR method include: (1) develop and code domains, (2) construct core ideas, and (3) develop categories to describe consistencies across cases (cross analysis). Key themes related to how different factors may influence the delivery of the intervention will be compared to the quantitative study results for Aim 2 and fidelity of implementation data. Themes that emerge will be put into an organizational matrix to observe changes that occur during integration and participation in ECHO activities.

Some scales may be collinear with each other, therefore principal components will be used to determine which scales should be combined and then either treated as continuous vs ordinal (e.g., high, moderate, low) variables. Bivariate analyses—specifically organizational factors by site—will be conducted to examine trends in the influence of multi-level characteristics on the

implementation and effectiveness of SHIM and ECHO implementation. Analyzing these trends will enable us to address important questions as: "How does organizational readiness to change influence uptake of the HCV care by the staff?" "Are certain subgroups of patients (e.g., younger vs. older) more likely to initiate HCV treatment?" Do changes in stigma (individual, healthcare setting) impact DAA retention or achievement of treatment goals. "Does the doctor/patient relationship influence the HCV care continuum? "Does OAT patient caseload influence the coverage of SHIM?" Since the study data collection period is 18 months, temporal trends for measures will also be quantitatively described by providing parameters of best fitting parametric models (linear, quadratic/polynomial, exponential) to analyze such questions as: "Do increases in provider confidence lead to greater improvement in HCV cascade indicators?"

In the second part of the analysis, we will examine the role of barriers and facilitators measured using the multi-level framework that includes client-, provider-, organizational-, community-level variables. First, using principal component analysis (PCA), we will identify various dimensions of clinician and organizational behavior that might influence HCV care integration into OAT settings through adoption and implementation of SHIM +/- ECHO at each site, which would summarize the variability in the data. PCA, a transformation used for data reduction, will be applied to multi-level organizational variables. Each principal component represents a different weighted average of the various organizational and client level variables, and each explains a different aspect of the variation observed in patterns of the organization and staff member. Principal components are important ways to group variables that are independent of each other by design, which addresses the issue of multicollinearity [33, 34], which can undermine various modeling strategies. To test the extent to which the barriers and facilitators are associated with higher or even increasing HCV diagnosis, treatment initiation and SVR achievement, we would estimate, using a generalized linear mixed model in which the outcome would be measured at the patient level (level 1), as a dichotomous variable of having been diagnosed/treated/cured or not. Among the covariates in the model, we would include an additional parameter that would incorporate the random effects associated with each provider (level 2), and a random effect associated with each site (level 3), which would be modeled as a function of estimated barrier and facilitator principle components.

3.4.5 Power Analysis

The qualitative sub-study sample during the pilot phase will be limited to one focus group with patients and three in-depth interviews with providers.

In the main phase, we will conduct two focus groups with 6-8 patients, one in-depth interview with participant who have dropped out of treatment, or not completed SVR12 testing, or didn't start treatment, two in-depth interviews with 2-4 providers.

In order to conduct the proposed analysis, a sample size of 900 patients, provides more than sufficient power to conduct the proposed analyses. The use of principal component analysis (PCA), for parsimoniously grouping variables is a reductionist strategy to explain groupings of variables with multiple collinearity. The time-dependent analysis allows for detection of even small changes in the primary and secondary outcome, even if the primary (or secondary) outcome increases any of the study groups. Thus, as few as 200-300 participants in each group is more than sufficient to achieve sufficient power (>0.95) to detect an intervention effect, including a synergistic effect of intervention^[No ECHO] x intervention^[ECHO] and even by site type (by varying degrees of integration), over time.

3.5 Research methods for Aim 3

Aim 3: To evaluate the effectiveness of SHIM in improving the HCV treatment cascade outcomes using a cluster-randomized three-arm trial design in 480 HCV-infected patients at 12 OAT clinics

randomized to standard of care (N=160) versus SHIM with (N=160) or without (N=160) ECHO facilitation.

3.5.1 Design overview

Individual randomization of subjects within each site would likely lead to a high degree of cross-contamination between the study groups because the selected interventions are designed to sustainably change the provider knowledge and practice. Therefore, we have chosen a cluster-randomized trial design, where participating sites will be randomly assigned to one of the three implementation arms. Based on our preliminary studies suggesting region-specific differences in HCV level among OAT patients, we will stratify 12 OAT sites by 4 defined geographic regions (Center, East, South, West) at a 1:1:1:1 ratio. To achieve the desired sample size (see Sample Size section) and retain equal size in each group, we will select and match 3 clinics across the 4 regions. One clinic per triplet will be randomized to one of the three arms: Standard of Care, SHIM and SHIM+ECHO (see Study Conditions), resulting in total 4 clinics per arm. Each clinic will aim to recruit 40 patients. In case of clinic's capacity the availability of DAA medication in region, the clinic's capacity to include in treatment and monitor the course of treatment of a larger number of patients) the number of participants can be increased up to 60). All sites will follow the same patient recruitment and data collection procedures.

3.5.2 Site eligibility and selection

To participate in the study, each OAT site will need to meet the following criteria: (a) at least 100 patients receiving OAT; and (b) regional administrator approval for the site to receive the DAA medications and its clinicians to participate. Before the start of the first year of the main phase of the project there were 202 OAT sites in Ukraine, with 34 having over 100 patients (12, 10, 7, 5 sites in Center, East, South, West, respectively) and 21 have over 150 patients. OAT sites are minimally staffed with 1 narcologist and two nurses; the number of counselors and case managers may vary. After we define the three sites from each region, we will randomize them into one of the three study arms.

3.5.3 Participant eligibility and recruitment

To be enrolled into this study, the participants will have to match the following criteria: (a) currently receiving treatment at the selected OAT site (this also implies that the patient is (i) 18 years of age or older, (ii) meets ICD-10 criteria for opioid dependence, (iii) residing within the study catchment area); (b) not planning to move to another region in the upcoming 6 months; (c) ability to provide informed consent; (d) having a positive HCV antibody test documented in the medical chart; (e) no history of HCV treatment in the past by self-report; (f) not being pregnant and not planning pregnancy in the next 3 months; (g) absence of active TB; (h) interest in study participation.

Participants will be recruited using the following systematic random sampling procedure, adapted from our previous studies. At the first step, the OAT site staff will prepare a de-personalized list of all patients with their patient IDs (without names to maintain confidentiality), OAT admission dates, dates of most recent HCV screening test documented in their medical chart, and test result. At the second step, the study data manager will filter out patients without positive HCV test result, and apply a random number generator to sort potentially eligible patients in random order, which will form a Screening Log. At the third step, the clinical staff responsible for recruitment will contact the patients in the order of appearance in the Screening Log for eligibility screening. During the eligibility screening, the clinical staff will assess patients' cognitive ability, ask patients about their plans to stay in the same city for the next 6 months, and about their prior history of HCV treatment. The results of the screening procedures will be documented in the Screening Log. Additionally, during eligibility screening, patients are screened for TB symptoms (night sweats,

cough for more than 2 weeks, unusual weight loss, fever). Patients who present any of these symptoms are referred for TB diagnosis. In case of TB diagnosis, patients are referred for TB treatment and HCV treatment is postponed. Those who are Patients meeting all criteria will be referred to the interviewer to finish the remaining enrollment procedures, which include informed consent, completion of locator information. Reasons for declining study participation will be documented.

Eligibility screening and recruitment will stop once the target sample size is reached. If the required number of participants is not recruited when the end of the patient list is reached, the sites will be instructed to encourage patients without a documented HCV test result to undergo screening. Majority of the OAT clinics are able to provide anti-HCV testing on-site or by referral to harm reduction programs, which routinely provide this testing to PWID at no charge. Patients who test positive will be added to the Screening Log and will be screened for other eligibility criteria.

Diagnosis confirmation will be done using HCV RNA PCR test (qualitative or quantitative). Each site will decide on the most convenient option for test provision – optimally with blood sample collection on-site. In case diagnosis is not confirmed, the patients will be excluded from the study. Baseline survey will be administered after diagnosis confirmation, for patients with a positive test.

3.5.4 Primary Endpoints

Primary outcomes are based on the HCV treatment cascade:

P1. Completing pretreatment evaluation (completing all clinical and laboratory assessment prescribed by the physician according to the SHIM algorithm);
P2. Initiating DAA treatment (taking the first dose of DAA medication prescribed by the physician);
P3. Achieving SVR12 (having an undetectable HCV RNA PCR result at 12 weeks after treatment completion).

3.5.5 Secondary Endpoints

Secondary outcomes will include the interim cascade steps:

S1a. Testing for HCV RNA;
S1b. Assessment of fibrosis staging;
S1c. Completion of DAA treatment (receiving the last prescribed medication supply);
S1d. Testing for HCV RNA at 12 weeks after treatment completion;

Factors that affect treatment effectiveness:

S2a. DAA treatment motivation (summary score measured by the investigator-developed questionnaire at baseline);
S2b. DAA treatment adherence (defined as percentage of doses taken using two measures: visual analog scale administered at treatment completion, and pill counts at each dispensing visit);
S2c. Treatment satisfaction (measured by investigator-developed questionnaire at treatment completion);

Treatment outcomes:

S3a. Quality of Life (measured by SF-12 questionnaires at all four interviews);
S3b. Re-infection (measured at 12 months after treatment completion among those achieving SVR).

3.5.6 Data collection

Given the primary and secondary outcomes of interest, data collection for Aim 1 will include three main sources: clinical chart review data and quantitative survey of patients.

De-identified medical chart review data extracted by authorized clinic staff will inform outcomes P1-P3, S1a-d and S3b. We will use the electronic Simple Treatment Monitoring Application (STMA)

developed and used in our previous [35] and ongoing projects to collect detailed data on all relevant assessments and treatments, including HCV diagnostic tests, pre-treatment assessments, DAA treatment prescription, on-treatment and post-treatment monitoring, OAT admission and discharge, OAT medication prescription. The database will also collect information on important clinical covariates, including HIV, TB and HBV co-infection, mental health screening and its results, prescription of ART and other medications and side effects. STMA data will be collected on a monthly basis from all sites.

It is expected that physicians at the SHIM sites will comprehensively manage HCV care, and the medical charts and STMA will contain all up-to-date diagnostics and treatment information. However, all SOC sites' patients and possibly some SHIM patients will receive HCV services elsewhere, and their HCV-related clinical data will not be available at the OAT clinic. To ensure completeness of the key outcome data for all participants, we will use an external clinical data verification procedure, similar to one used in our ongoing IMPACT project. In order to avoid intervention contamination, this procedure is conducted by research staff, and not by OAT clinic personnel. At the end of each quarterly clinical data collection cycle, the data manager will generate the HCV treatment cascade report in STMA. For each patient who will not have information about any of the three primary clinical endpoints (HCV diagnosis, treatment initiation, post-treatment HCV RNA PCR) in the report, the interviewers will conduct a brief follow-up by phone. If the patient will report receiving this service, the interviewer will ask about when and where the service was received. At the second stage, the interviewers will contact the respective healthcare facilities to verify the receipt of the services and results (for assessments). This procedure will be enabled by a separate third-party disclosure agreement signed by the patient.

For the secondary outcomes S2b-c, we will collect data using a **paper-based adherence form** administered by clinical personnel during patient visits at treatment initiation, medication pick-up at 4 and 8 weeks, and treatment completion at 12 weeks after initiation. The baseline form will assess self-efficacy and anticipated barriers to treatment adherence for the whole treatment period. The follow-up forms will assess treatment satisfaction, past 30-day and 7-day adherence using visual analog scale [36], side effects, reasons for non-adherence, and reasons for treatment discontinuation (if occurred). At treatment completion, the form will additionally assess the readiness and anticipated barriers to SVR check at 12 weeks after.

For the secondary outcomes S2a and S3a and relevant co-variates, we will collect data using a **patient survey**. The survey will be conducted for the pilot patients and all 3 arms of the main phase at baseline, treatment completion (or 12 weeks after initiation if not completed or 16 weeks after the baseline if not started) and 12 weeks after treatment completion (or 24 weeks after treatment initiation if not completed, or 28 weeks after the baseline if not initiated treatment).

The baseline survey will be administered after confirmation of the diagnosis using HCV RNA test. Patients who will test negative for HCV RNA will be excluded from the following study procedures.

All patient surveys will be collected by an independent interviewer, using study ID via UIPHP REDCap server with clerical checking and patient safeguards described in detail in the human subjects section.

The surveys will include demographics, geospatial assessment, depression (PHQ-9), substance use, alcohol use disorders (AUDIT-C), HIV comorbidity and treatment history, Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV) [37], trust in physician scale [38, 39], HIV risk behaviors, family and social support [40], drug use and mental illness stigma [41], and socio-demographic information.

The baseline survey will additionally assess knowledge about HCV, history of HCV diagnosis and treatment, barriers and facilitators to diagnosis and treatment experienced previously. The post-treatment surveys will assess anticipated and experienced barriers and facilitators to post-treatment monitoring. The forms will be completed by clinical personnel at medication pickup visits, and then transferred to research staff for data entry into REDCap. The forms will contain the study ID and will not contain any personally identifiable information.

The schedule of assessments is presented in the adjacent table.

	Enrollment	Tx init.	Tx init. + 4 weeks	Tx init. + 8 weeks	Tx compl.	Tx compl. + 12 weeks
Screening and consent	X					
Diagnosis confirmation and lab testing	X					
Survey	X				X	X
Medication dispensing		X	X	X		
Adherence form		X	X	X	X	
SVR confirmation						X
Qualitative assessment	X					X

3.5.7 Retention in the study

Given our intent-to-treat approach to outcome evaluation, discharge from the OAT program, non-completion of clinical assessment, non-initiation or non-completion of treatment will not result in withdrawal from the study. Collection of clinical data at OAT clinics does not require patient's presence, and this will not be affected by retention.

To ensure sufficient retention in follow-up assessments, we will use several strategies used in our studies of PWIDs in Ukraine where retention in all cases exceeds 83% at 12 months, including: 1) providing compensation time for travel time and assessment costs; 2) detailed locator information, including contact information of a chosen contact person, usually a relative or a social worker; 3) maintaining regular contact through visits to OAT clinics.

3.5.8 Analytic plan

All analyses will be according to the principle of intent-to-treat, i.e., analysis of site and individuals within the site as randomized. The primary individual-level outcomes are achieving three elements of the HCV treatment cascade (diagnosed, treated, achieving SVR). We have powered the study based on a comparison of the proportions among the three groups (see below). The denominator for all cascade indicators is the number of OAT patients who are screened positive for HCV and are enrolled in the study. The numerators, the number who completed the pre-treatment evaluation, started DAA treatment and achieved SVR, will be obtained from the electronic clinical data collection system. Data will be assessed for missingness. A repeated measures likelihood based mixed model with missing at random (MAR) assumptions will be used for the analysis of the primary outcome to compare the three allocations, adjusted for the stratification variables (geographic region) plus age and gender. We will also adjust for covariates that are predictive of missingness to be consistent with the MAR assumption. Sensitivity analyses as described below will be done to assess this assumption, which is a reasonable starting point given missing data is expected to be low. Results will be displayed as point estimates with corresponding 95% confidence limits. The primary (and secondary) outcomes will be tested at the 5% (2-sided) significance level.

Hypotheses

1) OAT facilities implementing the simplified integrated model will have adoption and penetration of HCV care elements, that will ultimately result in improved patient-level outcomes like HCV cure compared to standard of care (SOC);

2) Compared to No ECHO, clinicians at ECHO-facilitated sites will have improved HCV care cascade outcomes.

Aim 3's analysis will involve three distinct strategies. First, we will examine the time difference in HCV cascade elements (% diagnosed, % treated, % achieving SVR), with sub-analyses for geographic area and OAT dropout +/- ECHO vs SOC setting. To do this, we will use a generalized mixed linear model (with a logit link), where group will vary by either study arm or by geographical area. Our dependent variables will include: 1) a binary indicator for whether an individual patient achieved the desired HCV diagnosis/treatment coverage cut-off (e.g. diagnosis coverage>80%), as previously used to measure comprehensive and holistic integrated primary care for PWID receiving buprenorphine [42]. The same approach will then be used for secondary individual outcomes (treatment motivation and adherence, treatment satisfaction, quality of life), which we have done previously when integrating addiction treatment into specialty services in the US [43] and Ukraine [12]. 2) treating the primary and secondary indicators as a continuous variables. Any changes in national guidelines that might influence HCV treatment availability would not be scored until after at least 1 year after publication in order to allow for uptake changes by clinicians. Our covariates will include time trends, client-level variables including demographic characteristics, fibrosis stage, treatment motivation and adherence, addiction severity and mental health measures, as well as organizational and provider level measures (from Aim 2).

In addition, we have planned to test for a linear trend among the intervention levels for the proposed outcomes, testing that SHIM+ECHO > SHIM with No ECHO > SOC. We also plan to test the treatment effects using similar methods for OAT dropout strata separately. In addition to direct effects, mediation and moderation regression will be conducted as described by Donaldson. Testing will be conducted at a Bonferroni corrected type I error level of 0.025 to control for multiple testing. Secondary and process outcomes will similarly be tested. These measures and their subscales will be compared as pre/post and over time using one-way ANOVA/Duncan test, with general linear models to identify differences in treatment effect stratified by the geographic region (cluster). Mean scores will be normalized, with comparisons between the three groups, with the referent being SOC. To address multiple testing, we will use the Benjamini-Hochberg method of controlling the false discovery rate. We do not expect missing data to be a concern since most of the data on primary outcomes will be derived from clinical source documentation; for the survey data, we expect that we will collect more than 90% of the data at the 24-week time point. We will, however, explore all patterns of missing data and compare those with and without data to determine whether the data may be MAR or not MAR (i.e. eliminate the missing completely at random assumption). We will conduct sensitivity analyses using an appropriate missing data method, such as multiple imputation.

3.5.9 Power Analysis

We will need a sample size of 133 per group (total sample size of 399), to have 90% power at a 5% level of significance to detect a standardized effect size of 0.20 for a null hypothesis of no difference between the proportions in the three groups versus an alternative of at least one difference at the 24-week time point. Additionally, we will have 94% power with a 2.5% type I error rate (Bonferonni corrected) to detect a standardized effect size of 0.32 within each geographic strata. Conservatively, we expect a 10% loss of information at the 24-week time point. Therefore, we have inflated the sample size by 10% and will recruit a total of 480 patients for the Aim 3 outcomes.

3.6 Premature Study Discontinuation

Participants may voluntarily withdraw from the study for any reason at any time. Site Coordinators may, with the approval of the PI, withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, or IRB terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records. If a participant chooses to withdraw, data collected from this participant will be deleted and will not be used for analysis. In all other cases, participant information will be used for analysis.

3.7 Research Quality Assessment

We will employ several strategies used in our effectiveness trials to ensure fidelity and monitor "intervention drift" among providers delivering SHIM including: 1) *Training of providers:* We will provide a clinical competency training on HCV management followed by a knowledge assessment before starting twice-monthly ECHO; 2) *Clinic Site visits*: After creating a site matrix (number of OAT patients, clinicians, administrators, other services provided, hours, proximity of nearest psychiatric clinic, etc), our Project Coordinator will schedule site visits baseline and every 6 months to meet with clinicians and administrators at each site to discuss challenges and their experiences in delivering SHIM and assess quality and fidelity of implementing the intervention. We will use methods used in our Ukraine integration pilot study where we assessed organizational factors based on what's working, not working and goals for improvement [44]; 3) *Technical Assistance*: Clinic providers will be able to access technical assistance bi-weekly from ECHO and from our experts in between sessions using tele-consult, which will be monitored and assessed; 4) *Regular review of process measure data*: Rapid collection of process measures via our electronic data management system with real-time input will allow us to monitor implementation of the intervention and assess many primary, secondary and process outcomes.

4 Safety Monitoring and Adverse Event Reporting

4.1 Safety Monitoring

Close cooperation between the Investigators, clinical and research teams will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner. The team will have regularly scheduled conference calls during the period of study implementation, and additional ad hoc calls will be convened if required.

The study site Coordinators are responsible for continuous close monitoring and management of AEs. Sites are required to follow the detailed SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol and for alerting the Principal Investigator if unexpected concerns arise.

A sub-group of the Protocol Team, including the Principal Investigator, Clinical Consultant, and Co-Investigators will serve as Study Monitoring Committee (SMC). The SMC provides support to site clinicians regarding individual participant clinical management (toxicity management, clinical holds of study drug, study drug re-challenge, permanent discontinuations, etc.). The Site Coordinators will prepare routine study conduct and safety reports for the SMC, which will meet by conference call approximately monthly and will review safety data during a closed meeting. More frequent or ad hoc reviews of safety reports may be conducted by the SMC as needed. A recommendation to stop the trial may be made by the SMC at any such time that the team agrees an unacceptable type and/or frequency of AEs has been observed. If at any time a decision is made

to discontinue the study product in all participants, the PI will notify the Site Coordinators and the responsible IRB expeditiously.

4.2 Adverse Event (AE) Reporting

Adverse events (AE) are defined as any untoward medical occurrence experienced by participants during the study, and may or may not have a causal relationship with the treatment. Information regarding all AEs regardless of seriousness or severity will be recorded in the participant's source files. Grade 3 and higher adverse events and all creatinine AEs will be recorded on study forms. All SAEs must be reported on AE Log form. All AEs that result in a clinical hold or permanent discontinuation of study product are reported on AE Log form regardless of grade. Grade 3 and higher clinical AEs will be referred to a study clinician at the time of the visit.

All critical laboratory values will be reported as applicable per site SOPs. Participants who are not present at the study site at the time a laboratory AE requiring retesting or follow-up is identified will be followed as deemed clinically appropriate. With appropriate permission of the participant, and whenever possible, records from non-study medical providers related to untoward medical occurrences will be requested and required data elements will be recorded on study forms and/or in the participant's medical chart. All AEs regardless of severity will be followed clinically, until the AE resolves or stabilizes as per the appropriate toxicity algorithm. AEs will be assessed for all participants, regardless if they continue DAA or not, after enrollment through the final study visit.

4.3 Serious Adverse Events

Serious adverse events (SAEs) will be defined per CFR 312.32 guidelines, as AEs occurring at any dose that:

- Result in death;
- Are life-threatening adverse events;
- Require inpatient hospitalization or prolongation of existing hospitalization;
- Result in persistent or significant disability/incapacity; or
- Are congenital anomalies/birth defects.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes listed above.

Note: All SAEs must be reported on the AE Log.

4.3.1 Grading System

All AEs will be graded using the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009) and the DAIDS Addendum 2 - Male Genital Grading Table, which are available at http://rsc.tech-res.com/safetyandpharmacovigilance/. Grade 1 creatinine toxicity will be determined by either the DAIDS AE Grading Table OR Grade 1 as defined by creatinine > 1.5x the participant's baseline serum creatinine, whichever is higher."

4.3.2 Assessment of Relationship to Study Agent

The relationship of all AEs to DAA will be assessed per the package insert and investigator's brochure for DAA, and clinical judgment of the investigator. The relationship categories that will

be used for this study are related and not related, as defined in the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010) which is available at http://rsc.tech-res.com/safetyandpharmacovigilance/.

4.4 Reporting Requirements for this Study

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 (or latest version) of the DAIDS EAE manual, will be used for this study. The study agents for the purposes of SAE reporting are part of a fixed dose combination tablet: sofosbuvir/daclatasvir or sofosbuvir/velpatasvir.

The SAE reporting period for this study is per the DAIDS EAE manual and continues from enrollment of a trial participant to the end of trial follow-up for that participant. All reportable SAEs occurring during the study reporting period will be reported to the principal investigator in an expedited manner, within three reporting days of site awareness of the events (see definition in Appendix D of the DAIDS EAE Manual).

Reporting requirements for the local IRB will also be followed.

4.5 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result. For example, participants could be perceived as being HIV-infected or at high risk for HIV infection and be treated unfairly or have problems being accepted by their families and/or communities. Social harms that are judged by the PI/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to its individual requirements.

Social harms will be collected and reported on forms during regular visits. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SOP.

4.6 Toxicity Management

The site clinician has the discretion to hold DAA at any time if s/he feels that continued medication use would be harmful to the participant or interfere with treatment deemed clinically necessary according to the judgment of the investigator. Clinical or laboratory abnormalities that require follow up will be documented, and the research associate or clinician will contact the participant to schedule an interim visit for follow-up and/or repeat laboratory testing. All participants reporting an adverse event will be followed clinically until the occurrence resolves (returns to baseline grade, defined as grade at enrollment) or stabilizes or an effective referral to local health care providers is accomplished.

4.6.1 Discontinuation of Study Medication

Grades 1 or 2

Continue DAA treatment at the discretion of the site investigator.

Grade 3

DAA may be continued at the discretion of the site investigator if a Grade 3 toxicity is considered to be unrelated to the study medication. Study medication will be temporarily withheld if Grade 3 toxicity is considered to be related to the study medication. After a Grade 3 toxicity returns to Grade 1, the participant can be reintroduced to medication after consultation with the site investigator, and other members of the CMC. If a Grade 3 toxicity recurs and is considered to be related to study medication, DAA will be permanently discontinued.

Grade 4

For all Grade 4 laboratory-identified or clinical toxicities, DAA will be withheld unless it is determined to be not related. If a Grade 4 laboratory toxicity is not confirmed by repeat testing, it should be managed per algorithm for the new toxicity grade. Participants with Grade 4 AEs will be followed until the event resolves to baseline or stabilizes. Study drug may be restarted in the event of the resolution of a Grade 4 AE back to Grade 1, after consultation with the site investigator, and other members of the CMC. If the toxicity recurs to Grade 3 or higher after DAA is restarted and is considered to be related to DAA, the study medication will be permanently discontinued.

4.7 Concomitant Medications

With the exception of medications listed as prohibited in the paragraph below, enrolled study participants may use concomitant medications during study participation. All concomitant medications, including prescribed and over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal preparations reported within 45 days prior to confirmation of eligibility for study enrollment and throughout the course of the study will be recorded on the form designated for that purpose. Medications used for the treatment of AEs that occur during study participation will also be recorded on applicable study forms. Participants who begin taking any medication during the trial that is listed as an exclusionary medication at Screening will temporarily discontinue study drug. Study drug may be resumed if no exclusionary medication has been taken in the last 4 weeks.

Should participants report use of any of the following medications, they will be required to discontinue use of study drug: interleukin therapy, medications with significant nephrotoxic potential (including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy), and medications that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid).

5 Human Subjects

5.1 Overview

This study involves minimal risk to human subjects since all clients enrolled with be already receiving OAT and national recommendations are for all HCV positive individuals to be diagnosed and treated. Most primary data will come from clinical record-keeping, external clinical data collection procedure and participant surveys, which will be done without unique identifiers. Participants will differ solely in the site where they receive it. We will conduct a stratified cluster randomized study to compare HCV treatment cascade outcomes among OAT clients in 12 regions in Ukraine. We will use ECHO (Extension for Community Healthcare Outcomes) in HCV care to train health care providers to provide integrated care for HCV (SHIM). Of note, HCV treatment and ECHO facilitation are all evidence-based practices. Additionally, we will conduct quantitative and qualitative interviews and focus groups to assess organizational, community and structural factors that promote or impede the successful SHIM integration into OAT clinics. Quantitative and in-depth interviews will be conducted among staff, and administrators, and focus groups will be

conducted with clients. We will also quantitatively survey staff and administrators to assess organizational factors. No personal identifiers will be collected.

5.2 Description of the Population Being Studied

In this study (Aims 1 and 3) we will enroll all OAT clients within sites that agree to participation. As part of Aim 2, in addition to the study participants, we will interview and survey clients, clinicians and health center administrators from participating OAT clinics.

5.3 Storage of Data

Data from all the sites will be uploaded into a data warehouse system using REDCap. The REDcap database will be password protected and only available to research-affiliated staff at UIPHP. Only de-identified data will be made available to researchers. All information gathered from the study data sources will be stored in password-protected computers with double-password protection for opening specified files. All computers have been encrypted in accordance with stringent security policies. All essential research documentation will be stored in the double-locked research offices at UIPHP. Subject information will be stored with research study number and without any unique identifiers. The data will be stored in the manner noted above for at least three years after completion of the study.

5.4 Potential Risks

As in all research studies, there are potential risks. We go to great efforts, however, to ensure that risks are minimized.

Potential Risks Associated with HCV Diagnosis and Treatment Procedures: While HCV diagnosis and treatment is an EBP, risks may occur as part of routine clinical care. Importantly, this research is not studying new medications or diagnostic procedures. The patients will be prescribed only procedures or medications currently registered in Ukraine for diagnosis or treatment of respective clinical conditions. These procedures and medications may have certain side effects. To reduce these risks, even though all clinicians at these sites are trained in managing common complications and side effects, we will review this in great detail during the 2-day training session.

Risks Associated with Data Transfer: During the entirety of this study, patient information will be collected and transferred to UIPHP's research office using STMA encrypted datasets or REDCap data collection system WITHOUT any distinct patient identifiers. The external clinical data collection procedure involves using patients name to obtain data from other healthcare facilities, but the name is not recorded on any paper or electronic forms. There are no risks to the patients associated with this part of the study because all data will be de-identified before transfer to UIPHP. De-identification involves the removal of all identifying information, such as name, address, telephone number, date of birth and social security number. Individual locator information will be stored at the clinical research sites, and UIPHP staff will not have access to these records. Age, however, will remain on the record, as it is useful for our analysis and is not individually identifying information.

Risks Associated with Qualitative Assessments: Some clients, medical personnel and administrators from the OAT sites will participate in qualitative interviews or focus groups. Even though the participants are clients, medical professionals or administrators who will be talking about their patients, providers, or facilities, some of these topics may make some participants feel uncomfortable. Participants will be informed that they may choose not to answer all or any part of a question they are uncomfortable with during the interviews. Prior to interviewing, they will be given an information sheet and will be asked if they would like to participate. They will be given the option to take time and think about it. They may choose to withdraw from the study at any

point and decide not to come in for the interviews. During the interviews, participants may choose not to answer a question or part of a question and are free to give as little or as much information as they feel comfortable. Data from the audio-recorded interviews will be reviewed after they have been completed. No study-related unanticipated problems or adverse events are expected to occur in this part of the study. Hard copies of data collected will be stored in a locked cabinet behind double-locked doors. Electronic records of the interviews will be password-protected.

Risks Associated with Staff Surveys: Medical personnel and administrators from the participating medical centers will complete surveys. In the surveys, they may be asked questions on topics that may make them feel uncomfortable. There are minimal risks expected from completing questionnaires, such as feeling uncomfortable with certain topics. Similar to the protections of the face-to-face interviews above, if anyone feels uncomfortable, they may choose not to answer any part or all of a question. During the initial consent procedures, they will be fully informed about all parts of the questionnaires, and will be asked whether they would like to participate in the study. They may choose to withdraw from the study at any point and decide not to complete the survey but our experience has been nearly 100% acceptance since none of their individual responses will be reported and only aggregate data will be provided. No study-related unanticipated problems or adverse events are expected to occur in this part of the study. All data will be collected using REDCap and maintained on password protected computers.

Risks Associated with Patient Surveys: The surveys will be performed using an online REDCap system, either on a tablet or on a computer. There are minimal risks expected from completing questionnaires, such as feeling uncomfortable with certain topics. The patients will be told that they can refuse to answer any of the survey if they feel uncomfortable and that their responses will be kept anonymous and will in no way affect their receipt of care or treatment at the medical facility. During initial consent procedures, they will be fully informed about all parts of the study, including the questionnaires, that they will not be identified aside from the clinic where they receive their OAT, will be asked to read the informed consent form, and will be asked whether they would like to participate in the study. They may choose to withdraw from the study at any point and decide not to complete the survey. If they choose not to complete the online survey, they will be asked why (e.g., concerned about confidentiality, too busy, etc). No study-related unanticipated problems or adverse events are expected to occur in this part of the study. Electronic copies of the questionnaires will be password-protected. In no way will their responses be relayed to the clinical staff and jeopardize the relationship with their clinical providers.

Risks Associated with Loss of Confidentiality: As with all research, there is a risk that involves potential breaches of confidentiality. We intend to do everything possible to reduce this risk and this is one of the process measures we propose to measure. As part of this study, subjects who are OAT patients, medical practitioners or administrators will be interviewed in private rooms within their facilities. Potential sites for breaches of confidentiality include the recruitment process, the study interviews, or at data management systems. All information is stored in password-protected, encrypted computers with double-password protection for opening specified files. All confidential information (ICFs, study instruments, medical records, audio files, etc.) will be recorded with study participant number only and maintained in locked cabinets within offices at UIPHP and will only be available to be opened by the Data Manager, Study Coordinator, Co-Investigators or the Principal Investigator. Electronic databases will be maintained through password-protected computers and files.

5.5 Adequacy of Protection Against Risks to Subjects

Clinical Expertise in HCV: To protect against risks to patients, all providers participating in SHIM will receive expert guidance and training for treating these disorders in their clinical care settings.

Our team of HCV and Addiction Experts from Ukraine and US will provide expert guidance on screening and treating a number of comorbid conditions.

Informed Consent: All participants will sign informed consent form (ICF) allowing their de-personalized clinical data to be shared with researchers and stored in an electronic database. The same ICF will regulate the participant survey participation. For the external clinical data collection procedure, the patients will also sign a third-party disclosure agreement, required by the external healthcare facilities to share clinical data with the research staff.

Separate written informed consent forms will be used for participation in patient focus groups, staff survey, and staff in-depth interviews. Informed consent documents will be approved by the IRB at UIPHP. All participants will be reminded that their refusal to participate will in no way negatively affect their relationship with any of the participating medical centers in the future.

Qualitative Assessments and Staff Surveys: There are minimal risks expected from participating in interviews, such as feeling uncomfortable with certain topics being discussed. As mentioned previously, all participants for interviews will be reminded that their refusal to participate will in no way negatively affect their patient-provider or professional relationship with any of the participating agencies or clinics. If participants do feel uncomfortable about certain questions asked, subjects will be able to choose not to answer the question that makes them uncomfortable. All interviews and consultations will occur in private rooms, to ensure confidentiality. All data will be stored in secure locations. Everyone will be told that the meeting and survey data are confidential.

Recruitment: Recruitment procedures are designed to reduce the risk of confidentiality loss for participants. Patients will be recruited by regular clinical personnel using a randomly selected list of IDs. Medical and administrative personnel from the participating sites will be recruited by site coordinators. They will be reassured that their participation is voluntary and confidential.

5.6 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. The reimbursement amounts will be specified in the study informed consent forms.

5.7 Compliance with Protection of Human Subjects Regulations

All research involving human subjects will be approved by the UIPHP IRB, before recruitment starts. All research investigators and study staff are trained bi-annually in Good Clinical Practices and in Human Subjects Protection, through web-based or in-person courses. This protocol and its informed consent forms, qualitative interview (focus group) guides, as well as any subsequent modifications, will be reviewed and approved by the UIPHP IRB with respect to scientific content and compliance with applicable research and human subject regulations. The Principal Investigator agrees to adhere to the recommendations of the UIPHP IRB about the study. Investigators will make safety and progress reports to the IRB at least annually, and within three months of study termination or completion, summarizing the total number of participants enrolled, the number who completed the study, changes in the study, and unanticipated problems involving risks to human subjects.

Bibliography

1. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. The lancet Gastroenterology & hepatology. 2017;2(3):161-76. Epub 2017/04/14. doi: 10.1016/s2468-1253(16)30181-9. PubMed PMID: 28404132.
2. Poynard T, Imbert-Bismut F, Ratziu V, Chevret S, Jardel C, Moussalli J, et al. Biochemical markers of liver fibrosis in patients infected by hepatitis C virus: longitudinal validation in a randomized trial. J Viral Hepat. 2002;9(2):128-33. doi: 341 [pii].
3. Aleman S, Rahbin N, Weiland O, Davidsdottir L, Hedenstierna M, Rose N, et al. A risk for hepatocellular carcinoma persists long-term after sustained virologic response in patients with hepatitis C-associated liver cirrhosis. Clin Infect Dis. 2013;57(2):230-6. doi: cit234 [pii];10.1093/cid/cit234 [doi].
4. van der Meer AJ, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, et al. The number needed to treat to prevent mortality and cirrhosis-related complications among patients with cirrhosis and HCV genotype 1 infection. Journal of viral hepatitis. 2013. doi: 10.1111/jvh.12185 [doi].
5. Center for Disease Analysis Foundation. Public health impact of a population based approach to HBV and HCV prevention and treatment in Ukraine. Kyiv: Public Health Center of the Ministry of Health of Ukraine, 2018.
6. Yurchenko, Stepchenkova T, Karnets I, Ashworth K, Cheusova T. The results of a study on the prevalence of HIV, HCV and HBV genotypes in some regions of Ukraine. Retrovirology. 2012;9.
7. Grebely J, Larney S, Peacock A, Colledge S, Leung J, Hickman M, et al. Global, regional, and country-level estimates of hepatitis C infection among people who have recently injected drugs. Addiction. 2019;114(1):150-66. doi: 10.1111/add.14393. PubMed PMID: 30035835.
8. Mazhnaya A, Marcus R, Bojko MJ, Zelenev A, Makarenko I, Pykalo I, et al. Opioid Agonist Treatment and Improved Outcomes at Each Stage of the HIV Treatment Cascade in People Who Inject Drugs in Ukraine. Journal of acquired immune deficiency syndromes. 2018;79(3):288-95. Epub 2018/10/13. doi: 10.1097/QAI.0000000000001827. PubMed PMID: 30312275.
9. Low AJ, Mburu G, Welton NJ, May MT, Davies CF, French C, et al. Impact of Opioid Substitution Therapy on Antiretroviral Therapy Outcomes: A Systematic Review and Meta-Analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016;63(8):1094-104. doi: 10.1093/cid/ciw416. PubMed PMID: 27343545; PubMed Central PMCID: PMCPMC5036913.
10. Morozova O, Dvoryak S, Altice FL. Methadone treatment improves tuberculosis treatment among hospitalized opioid dependent patients in Ukraine. The International journal on drug policy. 2013;24(6):e91-8. doi: 10.1016/j.drugpo.2013.09.001. PubMed PMID: 24360402.
11. Sylla L, Bruce RD, Kamarulzaman A, Altice FL. Integration and co-location of HIV/AIDS, tuberculosis and drug treatment services. The International journal on drug policy. 2007;18(4):306-12. doi: 10.1016/j.drugpo.2007.03.001. PubMed PMID: 17689379; PubMed Central PMCID: PMCPMC2696234.
12. Bachireddy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL. Integration of health services improves multiple healthcare outcomes among HIV-infected people who inject drugs in Ukraine. Drug and alcohol dependence. 2014;134:106-14. doi: 10.1016/j.drugalcdep.2013.09.020. PubMed PMID: 24128379; PubMed Central PMCID: PMC3865106.
13. Macias J, Morano LE, Tellez F, Granados R, Rivero-Juarez A, Palacios R, et al. Response to direct-acting antiviral therapy among ongoing drug users and people receiving opioid substitution therapy. Journal of hepatology. 2019;71(1):45-51. Epub 2019/03/12. doi: 10.1016/j.jhep.2019.02.018. PubMed PMID: 30853642.
14. Christensen S, Buggisch P, Mauss S, Boker KHW, Schott E, Klinker H, et al. Direct-acting antiviral treatment of chronic HCV-infected patients on opioid substitution therapy: Still a concern in clinical practice? Addiction. 2018;113(5):868-82. Epub 2018/01/24. doi: 10.1111/add.14128. PubMed PMID: 29359361.
15. Mason K, Dodd Z, Guyton M, Tookey P, Lettner B, Matelski J, et al. Understanding real-world adherence in the directly acting antiviral era: A prospective evaluation of adherence among people with a history of drug use at a community-based program in Toronto, Canada. International Journal of Drug Policy. 2017;47:202-8. doi: https://doi.org/10.1016/j.drugpo.2017.05.025.
16. Litwin AH, Agyemang L, Akiyama MJ, Norton BL, Heo M, Ning Y, et al. The PREVAIL Study: intensive models of HCV care for people who inject drugs. Journal of hepatology. 2017;66(1):S72. doi: 10.1016/s0168-8278(17)30406-3.
17. Masson CL, Delucchi KL, McKnight C, Hettema J, Khalili M, Min A, et al. A randomized trial of a hepatitis care coordination model in methadone maintenance treatment. American journal of public health.

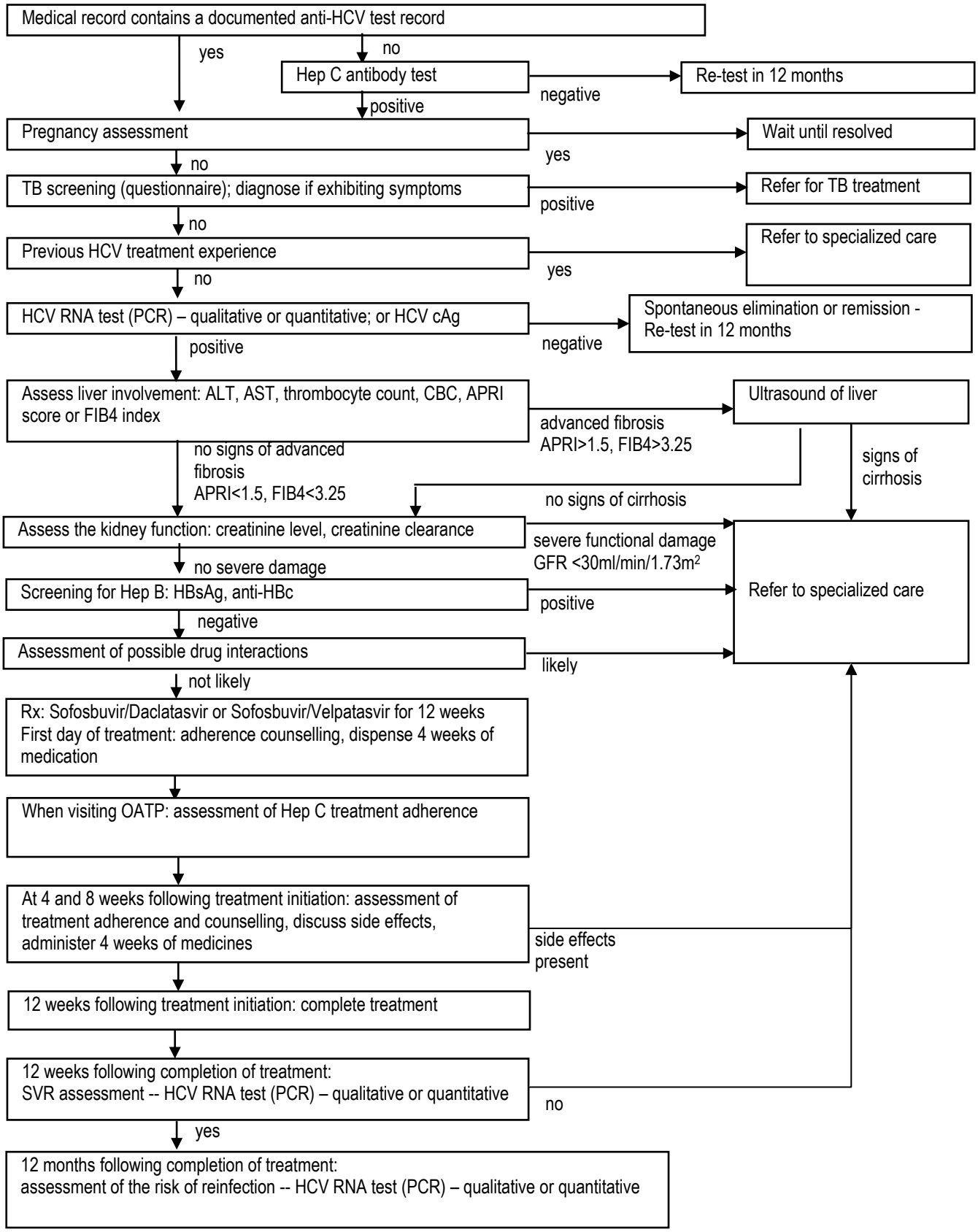
2013;103(10):e81-8. Epub 2013/08/21. doi: 10.2105/ajph.2013.301458. PubMed PMID: 23947319; PubMed Central PMCID: PMCPMC3853128.
18. Akiyama MJ, Norton BL, Arnsten JH, Agyemang L, Heo M, Litwin AH. Intensive Models of Hepatitis C Care for People Who Inject Drugs Receiving Opioid Agonist Therapy: A Randomized Controlled Trial. Annals of internal medicine. 2019;170(9):594-603. Epub 2019/04/09. doi: 10.7326/m18-1715. PubMed PMID: 30959528.
19. Dumchev K, Kornilova M, Saliuk T, Varetska O. Estimation of the Number of People Who Inject Drugs and Live with HIV And Viral Hepatitis Co-Infection in Ukraine. 7th International Symposium on Hepatitis Care in Substance Users; Sep 20. Lisbon, Portugal: Oral Abstract #360; 2018.
20. Larney S, Peacock A, Leung J, Colledge S, Hickman M, Vickerman P, et al. Global, regional, and country-level coverage of interventions to prevent and manage HIV and hepatitis C among people who inject drugs: a systematic review. The Lancet Global Health. 2017;5(12):e1208-e20. doi: 10.1016/s2214-109x(17)30373-x.
21. Kapadia SN, Marks KM. Hepatitis C Management Simplification From Test to Cure: A Framework for Primary Care Providers. Clinical Therapeutics. 2018;40(8):1234-45. doi: 10.1016/j.clinthera.2018.05.010.
22. Ministry of Health of Ukraine. Order №51 "On approval of the standards of medical care for viral hepatits C in adults" 2021 [updated 15 Jan 202101 Feb 2021]. Available from: https://moz.gov.ua/article/ministry-mandates/nakaz-moz-ukraini-vid-15012021--51-pro-zatverdzhennja-standartiv-medichnoi-dopomogi--pri-virusnomu-gepatiti-c-u-doroslih].
23. Pol S, Parlati L. Treatment of hepatitis C: the use of the new pangenotypic direct-acting antivirals in "special populations". Liver international : official journal of the International Association for the Study of the Liver. 2018;38 Suppl 1:28-33. doi: 10.1111/liv.13626. PubMed PMID: 29427485.
24. Colombo MG, Musabaev EI, Ismailov UY, Zaytsev IA, Nersesov AV, Anastasiy IA, et al. Consensus on management of hepatitis C virus infection in resource-limited Ukraine and Commonwealth of Independent States regions. World journal of gastroenterology. 2019;25(29):3897-919. doi: 10.3748/wjg.v25.i29.3897. PubMed PMID: 31413526.
25. Morozova O, Dvoriak S, Pykalo I, Altice FL. Primary healthcare-based integrated care with opioid agonist treatment: First experience from Ukraine. Drug and alcohol dependence. 2017;173:132-8. doi: 10.1016/j.drugalcdep.2016.12.025. PubMed PMID: 28242537; PubMed Central PMCID: PMCPMC5545131.
26. van 't Veer JT, Kraan HF, Drosseart SH, Modde JM. Determinants that shape public attitudes towards the mentally ill: a Dutch public study. Soc Psychiatry Psychiatr Epidemiol. 2006;41(4):310-7. doi: 10.1007/s00127-005-0015-1. PubMed PMID: 16501885.
27. van Boekel LC, Brouwers EP, van Weeghel J, Garretsen HF. Healthcare professionals' regard towards working with patients with substance use disorders: comparison of primary care, general psychiatry and specialist addiction services. Drug and alcohol dependence. 2014;134:92-8. Epub 2013/10/09. doi: 10.1016/j.drugalcdep.2013.09.012. PubMed PMID: 24099970.
28. Lehman WEK, Greener JM, Simpson DD. Assessing organizational readiness for change. Journal of Substance Abuse Treatment. 2002;22(4):197-209.
29. Sidanius J, Pratto F. Social Dominance: An Intergroup Theory of Social Hierarchy and Oppression. London, England: Cambridge University Press; 2001.
30. Oreg S. Resistance to change: developing an individual differences measure. The Journal of applied psychology. 2003;88(4):680-93. Epub 2003/08/28. PubMed PMID: 12940408.
31. Taxman FS, Young DW, Wiersema B, Rhodes A, Mitchell S. The National Criminal Justice Treatment Practices survey: multilevel survey methods and procedures. J Subst Abuse Treat. 2007;32(3):225-38. Epub 2007/03/27. doi: S0740-5472(07)00016-5 [pii] 10.1016/j.jsat.2007.01.002 [doi]. PubMed PMID: 17383548; PubMed Central PMCID: PMC2266083.
32. World Health Organization (WHO). WHO Collaborative Study on Substitution Treatment and HIV/AIDS In: Department of Mental Health and Substance Dependence, editor. Geneva, Switzerland 2006. p. See page 12: Staff attitude and satisfactions questionnaire CAS "Tough-minded about addiction". Accessed on July 29, 2013 at: http://www.who.int/substance_abuse/activities/substituion_therapy_opioid_dependence_general_protocol%20_v2.pdf.
33. Jolliffe IT. Principal Component Analysis. New York: Springer; 2002.
34. Jackson JE. A User's Guide to Principal Components. New York: Wiley; 1991.
35. Dumchev K, Dvoryak S, Chernova O, Morozova O, Altice FL. Retention in medication-assisted treatment programs in Ukraine-Identifying factors contributing to a continuing HIV epidemic. The International journal on drug policy. 2017;48:44-53. doi: 10.1016/j.drugpo.2017.05.014. PubMed PMID: 28800420; PubMed Central PMCID: PMCPMC5603251.

36. Burton MJ, Voluse AC, Patel AB, Konkle-Parker D. Measuring Adherence to Hepatitis C Direct-Acting Antiviral Medications: Using the VAS in an HCV Treatment Clinic. South Med J. 2018;111(1):45-50. doi: 10.14423/SMJ.0000000000000750. PubMed PMID: 29298369.
37. Younossi ZM, Stepanova M, Henry L. Performance and Validation of Chronic Liver Disease Questionnaire-Hepatitis C Version (CLDQ-HCV) in Clinical Trials of Patients with Chronic Hepatitis C. Value in Health. 2016;19(5):544-51. doi: https://doi.org/10.1016/j.jval.2016.02.005.
38. Anderson LA, Dedrick RF. Development ofthe trust in physician scale: A measure to assess interpersonal trust in patient-physician relationships. Psychological Reports. 1990;67:1091-100.
39. Altice FL, Mostashari F, Friedland GH. Trust and the acceptance of and adherence to antiretroviral therapy. Journal of acquired immune deficiency syndromes. 2001;28(1):47-58. Epub 2001/10/02. PubMed PMID: 11579277.
40. Sherbourne CD, Stewart AL. The MOS social support survey. Social science & medicine. 1991;32(6):705-14. doi: 10.1016/0277-9536(91)90150-b. PubMed PMID: 2035047.
41. Brown SA. Standardized measures for substance use stigma. Drug and alcohol dependence. 2011;116(1-3):137-41. Epub 2011/01/25. doi: 10.1016/j.drugalcdep.2010.12.005. PubMed PMID: 21257274.
42. Haddad MS, Zelenev A, Altice FL. Buprenorphine Maintenance Treatment Improves Comprehensive Primary Care Outcomes when Integrated into Federally-Qualified Health Centers Addiction. 2013: In Press.
43. Korthuis PT, Fiellin DA, Fu R, Lum PJ, Altice FL, Sohler N, et al. Improving adherence to HIV quality of care indicators in persons with opioid dependence: the role of buprenorphine. Journal of acquired immune deficiency syndromes. 2011;56 Suppl 1:S83-90. Epub 2011/03/01. doi: 10.1097/QAI.0b013e31820bc9a5 [doi] 00126334-201103011-00013 [pii]. PubMed PMID: 21317600.
44. Weiss L, Netherland J, Egan JE, Flanigan TP, Fiellin DA, Finkelstein R, et al. Integration of buprenorphine/naloxone treatment into HIV clinical care: lessons from the BHIVES collaborative. J Acquir Immune Defic Syndr. 2011;56 Suppl 1:S68-75. Epub 2011/03/01. doi: 10.1097/QAI.0b013e31820a8226 [doi]

00126334-201103011-00011 [pii]. PubMed PMID: 21317597.

Annex

Provisional Simplified HCV diagnosis and treatment algorithm


Medical record contains a documented anti-HCV test record
yes
no
Hep C antibody test
negative
Re-test in 12 months
positive
Pregnancy assessment
yes
Wait until resolved
no
TB screening (questionnaire); diagnose if exhibiting symptoms
positive
Refer for TB treatment
no
Previous HCV treatment experience
yes
Refer to specialized care
no
HCV RNA test (PCR) – qualitative or quantitative; or HCV cAg
negative
Spontaneous elimination or remission - Re-test in 12 months
positive
Assess liver involvement: ALT, AST, thrombocyte count, CBC, APRI score or FIB4 index
advanced fibrosis APRI>1.5, FIB4>3.25
Ultrasound of liver
signs of cirrhosis
no signs of advanced fibrosis APRI<1.5, FIB4<3.25
no signs of cirrhosis
Assess the kidney function: creatinine level, creatinine clearance
severe functional damage GFR <30ml/min/1.73m2
no severe damage
Screening for Hep B: HBsAg, anti-HBc
positive
Refer to specialized care
negative
Assessment of possible drug interactions
likely
not likely
Rx: Sofosbuvir/Daclatasvir or Sofosbuvir/Velpatasvir for 12 weeks
First day of treatment: adherence counselling, dispense 4 weeks of medication
When visiting OATP: assessment of Hep C treatment adherence
At 4 and 8 weeks following treatment initiation: assessment of treatment adherence and counselling, discuss side effects, administer 4 weeks of medicines
side effects present
12 weeks following treatment initiation: complete treatment
12 weeks following completion of treatment:
SVR assessment -- HCV RNA test (PCR) – qualitative or quantitative
no
yes
12 months following completion of treatment:
assessment of the risk of reinfection -- HCV RNA test (PCR) – qualitative or quantitative